Review Article

Iraqi Experience in the Assessment of Anti-Müllerian Hormone Utilization in Clinical Practice: An Overview

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Abstract

Anti-Müllerian hormone (AMH) is a dimeric glycoprotein, first recognized due to its action in male sex development. In women, it is synthesized by granulosa cells, pre-antral, and antral follicles; its main function in the ovary appears to be the inhibition of the early steps of folliculogenesis. Measurement of serum AMH made the assessment of ovarian reserve possible for more than 30 years. Its use has been expanded for many clinical implications, including assisted reproductive techniques, menopause, reproductive dysfunctions, the degree of ovarian damage/toxicity, and others. Numerous studies executed in this field concluded that AMH declines with aging; it has a positive correlation with oocyte yield in assisted reproduction; it is upregulated in polycystic ovarian syndrome and decreases in ovarian surgery and cancer therapy. This review aims to highlight the Iraqi experience in the implication of AMH assessment in clinical practice. We reviewed the PubMed database regarding the most recent literature in the assessment of AMH in Iraqi Clinical Practice; studies in polycystic ovarian syndrome (PCOS) patients were excluded. The review results show the importance of AMH assessment in many clinical fields especially for the evaluation of ovarian reserve of an infertile woman either to begin treatment strategists or follow-up patients and oncofertility counseling; yet studies must be encouraged in Iraq about it.

Keywords: Anti-Müllerian hormone, Iraq, menopause, ovarian damage, ovarian reserve testing

Introduction

Jost[1] mentioned anti-Müllerian hormone (AMH) since 1940 when he ended to the point that a portentous material, produced in the testes of mammals and men which is not testosterone, is blamed for the reversion of Müllerian ducts, originally called "Müllerian Inhibiting Substance." It is a member of the transforming growth factor-beta (TGF-β) superfamily, its major function is sex determination and differentiation during embryonic development.[2] Anti-Müllerian hormone secretion may be altered by the stage of gonadal growth, as it is upregulated from hardly existing levels at birth to increased levels after puberty. Anti-Müllerian hormone is produced by primary to antral follicles,[3] and has autocrine and paracrine functions as a regulator of follicular maturation[4] [Figure 1]. After follicle stimulating hormone-dependent selection, AMH expression is nearly undetectable.[5] For this reason, it can be used as a marker for ovarian function regarding follicular activity and maturation. Measuring AMH levels has become a routine practice in assisted reproduction centers and is more sensitive than other methods.[3] Many studies have awarded its role in predicting premature ovarian failure (POF) and menopause.[6,7] Serum AMH levels contribute to clinical scenarios and diagnoses relating to polycystic ovarian syndrome (PCOS).[8] Many factors have been blamed for influencing AMH serum levels, of these hormonal contraception uses and vitamin D serum levels.[9] In this review, we look at the Iraqi utilization of AMH in clinical practice to highlight its importance as a diagnostic and therapeutic marker.

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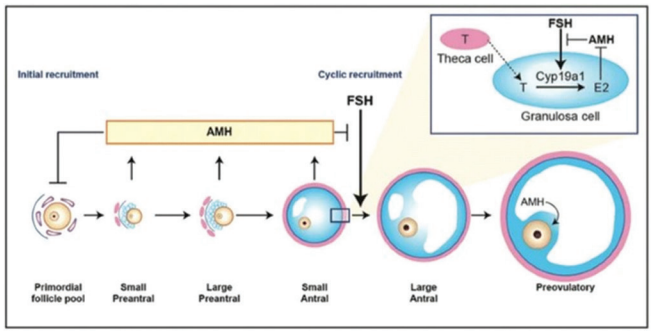

Figure 1: Schematic representation of anti-Müllerian hormone (AMH) actions. T: testosterone, Cyp19a1: aromatase. [Dewilly *et al*. 2014[10]]

Variability of serum AMH in healthy women in Iraqi study with body mass index

Till now the relation between AMH and obesity is still controversial.[11] Research team in Karbala concluded that no association was found between AMH serum level and body mass index (BMI) as part of their research results.[12] The same finding was reached by Altaee *et al*.[13] in Al Najaf city through a study done in 2012 in the fertility center of Al Sader Teaching Hospital. Hussein *et al.*[14] in Erbil city in a sample of Kurdish women, study the association between BMI and ovarian reserve taking AMH as a marker, concluded that there were no relation between them. In Baghdad city, Hussein and Majeed[15] reached different findings when they found a positive relation between BMI and AMH serum level. Shareif and Abd[16] in Al Basra City have concluded that obese women have lower AMH levels compared to normal women in the late reproductive years reflecting that increased body weight may affect the ovarian reserve in the premenopausal age group. These controversies in results may be attributed to sample size, age groups in each study, or the type of study design.

Evaluation of female fertility—AMH and ovarian reserve testing and assisted reproductive techniques outcome

The anti-Müllerian hormone has been used as an index of fertility in the last years since it correlates well with growing follicles in a menstrual cycle.[17] A PubMed search done by Cedars in this regard, and the results were published in February 2022, he concluded that AMH is a useful indicator of ovarian reserve in reproductive-aged women, and increased screening of non-infertile women requires a good knowledge of factors that may affect AMH serum levels; still, age is the strongest predictor in deciding success rates in fertility treatments.[18] Many Iraqi works have approved that although AMH estimation is very important for the evaluation of ovarian reserve for fertility workup, age will still be the best marker to predict natural as well as assisted ovulation and *in vitro* work including Intra Cytoplasmic Sperm Injection (ICSI) outcome.[19] Al-Quzwini in 2016 studied 100 infertile couples attending an infertility center in a maternity hospital in Babylon city, she found that age and AMH are correlated negatively, and about 20% of the infertile women have an AMH serum level of less than 1 ng/mL.[20] Alsafi[21] from Holy Karbala reported that with the increase age of women, they need larger doses of gonadotropin stimulation and have a lower pregnancy rate than younger women following ICSI and have poor response and a higher cancelation rate. Hussein *et al*. work in Erbil, in a study of a convenience sample of 300 infertile women of different age groups, concluded the same results.[14] Mature oocytes in woman decline when serum AMH levels decline.[22] Abed *et al*.,[23] in Al-Sammeraii Hospital in 2019, have compared AMH and FSH serum levels in a case–control study by using the Receiver Operator Characteristic curve. They found that AMH is more sensitive and accurate than FSH in detecting poor ovarian response when comparing the POF patients to healthy fertile controls. As AMH levels have minimal within-menstrual cycle variation they can, therefore, be assessed whenever necessary and may hold a more useful clue in the early detection of POF.[23] On the other hand, Khudheir *et al*.[24] found that there is a significant negative relation between AMH with antral follicle count. A study done in Baghdad by Jawad *et al*.[25] concluded that females whose age <33 years and AMH level of >1.63 ng/mL are the best markers of pregnancy in women undergoing ICSI.

Assessment of ovarian damage from chemotherapy, radiotherapy, and bariatric surgery

Ovarian damage by chemotherapy assessed by AMH serum level

The advanced detection methodology of cancer and the use of anticancer therapy all over the world have resulted in the rise of cancer survivors.[26] The use of chemotherapy helped to increase the survival rate, despite reducing life pleasure by remote side effects such as POF and infertility in young women.[27] Breast cancer (BC) is the most common cancer in females, about 2.3 million new cases all over the world. Sung et al., in 2021, in their meta-analysis found that ovarian reserve, taking AMH as a marker, falls after Chemotherapy in patients with BC. For this reason, they recommended that during oncofertility counseling, cryopreservation of oocytes, embryos, and ovarian cortex may help females with cancer-induced infertility to become pregnant.[28,29]

In Iraqi women, the incidence rates of BC have increased from 2000 to 2019, risk factors may include increased weight, diet, recumbent life, smoking, and marriage in old age. BC has the highest percentage and mortality rate of cancer (22.58% and 6.22/100,000, respectively) (Iraqi Cancer Board, 2019).[30] Since chemotherapy affects a woman's whole body, many sites may be affected, and this

effect differs from woman to woman.[31] Recent evidence has shown that age and the use of cyclophosphamide-based chemotherapy are the main factors influencing ovarian failure and amenorrhea.[32-34]

In Iraq, an increasing build of literature has been written on the effect of chemotherapy on the ovarian reserve in women with BC evaluated by AMH. Al-Janabi *et al*.[35] in Babylon and Al-Rawi and Al-Naqqash[36] in Baghdad conducted studies in which they used chemotherapy for treating BC patients who were recently diagnosed, they were below 50 years of age and they followed them for 4 months. Both studies concluded that there was a significant decrease in serum AMH levels in women after initiation of chemotherapy, although the regimen is different both used cyclophosphamide as an anticancer drug. The menstrual cycle pattern has changed to either amenorrhea or oligomenorrhea. Both studies concluded that AMH is a sensitive marker of follicular changes in young women during and after chemotherapy.[35,36]

Chemotherapy usually hits actively dividing cells, so that it destroys mature ovarian follicles by inducing apoptosis in granulosa cells.[37,38] Histologically: ovarian atrophy, exhaustion of the primordial follicle stockpile, decreased ovarian weight, and stromal fibrosis may result after treatment.[39] Abdulla *et al*.[40] in Baghdad city concluded that the negative impact of chemotherapy on ovarian function can be short-term ovarian dysfunction like menstrual cycle irregularities or longer-term fertility and the risk of early menopause. Bone function, cardiovascular, and neurological health are also important features of the long-term ramifications of chemotherapy in women.[41,42]

Ovarian damage by radiotherapy assessed by AMH serum level

Cancer cells can be killed or decrease their capacity to replicate by radiotherapy.[43] When an organ is exposed to radiation, the intimated damage will be by absorbing radiation at the cellular level which has a harmful effect on DNA; this can cause mutation and apoptosis.[44] This DNA damage can happen to the ovaries when a female pelvis is exposed to irradiation for cancer treatment; the follicles will be harmed, atrophied, and ovarian hormone and reserve will be affected as well. The insult to the ovary depends on the age of the patient, the amount and duration of the exposure.[45-49]

In a study done in Sulymania, Iraq, in 2021 by Ahmed et al.,[50] they concluded that special attention should be paid to young ladies with breast mass, after reviewing 100 cases of women who underwent treatment for BC, and one of the treatment modalities is radiotherapy, which has been used in 70% of the cases; and they recommend that counseling a woman regarding fertility preservation prior to chemotherapy and radiotherapy is important, especially for those young and who did not complete their families. This can be done through discussing with them the options of fertility preservation procedures which is called oncofertility counseling. These techniques may include oocyte cryopreservation, embryo freezing, and ovarian tissue cryopreservation, as it appears to be a promising way to provide cancer patients with a realistic way to preserve fertility.[51,52]

Anti-Müllerian hormone following bariatric surgery

Obesity prevalence has increased in the last three decades, and in 2016 one-third of females were reported to be overweight or obese. Obesity has a deleterious impact on female fertility and pregnancy and its outcome, as proved by many studies.[53-55]

Severe obesity is usually difficult to respond to diet and lifestyle modification; because of that many women seek fast alternatives of bariatric surgery.[56,57] This procedure decreases menstrual irregularities and polycystic ovary syndrome signs and symptoms,[58] improves fertility but it decreases AMH serum level.[59] This may be due to the idea that fast weight loss could lead to the release of toxic materials and fat-soluble endocrine disrupters which could have deleterious effects on ovarian function, or it may be due to malabsorption of nutrients necessary for the female reproductive system and/or affect the regulation of expression of AMH gene.[60] Al Kabbi *et al*.[61] in Karbala city suggested that AMH decreases after bariatric surgery in reproductive-age women, and there is improvement in cycle regularity; they followed the women for 6 months after surgery, and they recommended doing a larger sample size study and for a longer period of time to confirm or disregard their conclusion. If a deleterious effect is confirmed, oocyte cryopreservation before surgery could be discussed.[62] Noori *et al*.[63] have discussed this topic under the title "Fertility outcomes following bariatric surgery" and concluded that although BS for an obese woman may solve her infertility problem; the safety of these techniques used, and the long-term consequences on neonates and childhood have been not yet elucidated.

Conclusion

The review results show the importance of AMH assessment in many clinical fields especially for the evaluation of ovarian reserve of an infertile woman either to begin treatment strategists or follow-up patients and oncofertility counseling; yet studies must be encouraged in Iraq about it.

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Conflicts of interest

There are no conflicts of interest.

Authors contribution

Al-Taee made data gathering and revision; Al-Sallami wrote and revised the manuscript.

Ethical approval

The manuscript was approved by the Medical Ethical Committee of Babylon University, College of Medicine.

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