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The Use of Antimüllerian Hormone in Women Not Seeking Fertility Care

ABSTRACT: Antimüllerian hormone is produced by the granulosa cells surrounding each oocyte in the developing ovarian follicle. The production and serum levels of antimüllerian hormone at any given time are reflective of a woman's ovarian reserve, and multiple studies have demonstrated that antimüllerian hormone levels decline across the reproductive lifespan. Data exist to support the use of antimüllerian hormone levels for the assessment of ovarian reserve in infertile women and to select ovarian stimulation protocols in this population; however, using serum antimüllerian hormone levels for fertility counseling in women without a diagnosis of infertility is not currently supported by data from high-quality sources. The obstetrician–gynecologist should exercise caution when considering the predictability of serum antimüllerian hormone levels in any population of women with a low prevalence of infertility, including reproductive-aged women who either have never tried to become pregnant or have become pregnant previously without assistance. Based on the current information, a single serum antimüllerian hormone level assessment obtained at any point in time in a population of women with presumed fertility does not appear to be useful in predicting time to pregnancy and should not be used for counseling patients in this regard. At this time, routine antimüllerian hormone testing for prediction of pregnancy loss is not recommended. More data are needed to determine the utility of antimüllerian hormone as a predictor of time to menopause, a biomarker for polycystic ovary syndrome, or a predictor of future menses in women who have received gonadotoxic therapy.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions:

- Serum antimüllerian hormone level assessment generally should not be ordered or used to counsel women who are not infertile about their reproductive status and future fertility potential.
- Although serum antimüllerian hormone levels are a known predictor of ovarian response to exogenous gonadotropin stimulation in infertile women undergoing assisted reproduction cycles, the use of antimüllerian hormone in women with presumed fertility is limited by a lack of international assay standards and differing assay methodologies.
- A single serum antimüllerian hormone level assessment obtained at any point in time in a population of women with presumed fertility does not appear to be useful in predicting time to pregnancy.
- The use of antimüllerian hormone levels as a predictor of the onset of menopause is unsuitable for clinical practice at this time.
- Currently, serum antimüllerian hormone levels are not part of the accepted diagnostic criteria for polycystic ovary syndrome (PCOS).
- More data on the use of serum antimüllerian hormone levels to predict postchemotherapy fertility and to guide fertility counseling in these patients are needed.
- Routine antimüllerian hormone testing for prediction of pregnancy loss is not recommended.

Case Study

A 26-year-old woman presents for a well-woman visit. As part of your routine counseling, you discuss with her the effects of aging on fertility. She tells you she is not ready to become pregnant now but would like to become pregnant in the future. She also mentions that her friend recently had a blood test done to “check her egg count, so she knows how much longer she can wait to have a baby.” Your patient asks whether you will offer her the same test.

Lifetime Ovarian Function and the Concept of Ovarian Reserve

The number of oocytes in the ovaries reaches a maximum number (typically 7–8 million) at approximately 20 weeks of gestation. From that point onward, there is a rapid atresia of oocytes within the ovary. By the age of puberty, there are approximately 500,000 oocytes remaining within both ovaries. Every month, a cohort of oocyte-containing follicles is activated, either progressing on to ovulate or becoming atretic. Thus, the number of oocytes within the ovaries decreases with increasing age (1). The total number of gonadotropin-responsive follicles and oocytes contained within an individual's ovaries at any given time is known as her “ovarian reserve.” When an individual progresses through her reproductive years toward menopause and the number of oocytes decreases, the quality of oocytes also diminishes. Poor oocyte quality is characterized by a reduction in oocyte fertilization, subsequent embryo development, and embryo implantation. In addition, age-related reductions in oocyte quality lead to an increase in embryonic aneuploidy. After *menopause* (defined as the final menstrual period resulting from the physiologic permanent decline in gonadal hormone levels confirmed by 12 months of amenorrhea in women with a uterus), there are few-to-no gonadotropin-responsive follicles contained within either ovary.

Data exist to support the use of antimüllerian hormone levels for the assessment of ovarian reserve in infertile women and to select ovarian stimulation protocols in this population. However, using serum antimüllerian hormone levels for fertility counseling in women without a diagnosis of infertility is not currently supported by data from high-quality sources (2, 3). The data and recommendations in this Committee Opinion refer to women not seeking treatment for infertility. For information regarding the use of ovarian reserve testing in infertile women and women preparing to undergo fertility treatment, see the American Society for Reproductive Medicine's *Testing and Interpreting Measures of Ovarian Reserve*, which is endorsed by the American College of Obstetricians and Gynecologists (4).

Antimüllerian Hormone

Antimüllerian hormone is produced by the granulosa cells surrounding each oocyte in the developing ovar-

ian follicle (as well as by the Sertoli cells of the testis, where it inhibits development of the müllerian ducts in males). Antimüllerian hormone is secreted primarily by the preantral and small (less than 8 mm) antral follicles of the ovary. Although the number of preantral and small antral follicles is fairly constant within a given menstrual cycle, these follicle numbers slowly decline with age. Therefore, the production and serum levels of antimüllerian hormone at any given time are reflective of a woman's ovarian reserve, and multiple studies have demonstrated that antimüllerian hormone levels decline across the reproductive lifespan (5–8).

Along with other methods of ovarian reserve assessment (including serum follicle-stimulating hormone [FSH] levels, antral follicle count, ovarian volume, menstrual cycle day 3 serum FSH and estradiol levels, and the clomiphene citrate challenge test), serum antimüllerian hormone levels are useful for prediction of the ovarian response to ovulation induction and controlled ovarian hyperstimulation. One advantage of serum antimüllerian hormone levels over other available methods, in addition to its ability to predict ovarian response, is that an antimüllerian hormone level assessment can be obtained almost any time during the menstrual cycle (unlike FSH and estradiol, which should be assessed early in the follicular phase of the menstrual cycle). However, although serum antimüllerian hormone levels do not vary extensively during the menstrual cycle, modest variations in antimüllerian hormone levels of approximately 1.3 ng/dL have been reported (9). Additionally, although antimüllerian hormone declines across the reproductive lifespan, significant intraindividual variability is observed over time, beginning as early as puberty (10–15). Moreover, when serum antimüllerian hormone levels have been studied in several different populations, many of these studies have shown a significant variability in antimüllerian hormone levels within a specific population.

Commercially Available Antimüllerian Hormone Assays

Although several commercially available assays exist, comparison of antimüllerian hormone levels across assays, or even from the same individual using the same assay, is difficult. Although the ideal antimüllerian hormone assay would have high sensitivity (the ability to correctly identify those with disease) for diminished ovarian reserve, good precision (multiple measurements would be close together), and broad range limits (the assay can accurately detect very low levels and very high levels), the currently available assays differ in their methodologies and reference ranges and can exhibit significant intraobserver variability. Moreover, there are currently no international assay standards (16–18). Thus, this information must be considered when interpreting the results of the test for an individual patient.

Antimüllerian Hormone as a Predictor of Future Fertility

The obstetrician–gynecologist should exercise caution when considering the predictability of serum antimüllerian hormone levels in any population of women with a low prevalence of infertility, including reproductive-aged women who either have never tried to become pregnant or have become pregnant previously without assistance. Several studies have demonstrated that antimüllerian hormone does not accurately predict the chance of pregnancy in women who are not infertile. A prospective study of 186 young healthy women in Denmark (ages 19–35 years) who stopped contraception to achieve pregnancy assessed the predictability of a single serum antimüllerian hormone level for pregnancy during the next six menstrual cycles. The monthly probability of pregnancy in women with *low serum antimüllerian hormone levels* (defined as less than or equal to 10 pmol/L or approximately 1.4 ng/mL) did not differ from that of women with normal serum antimüllerian hormone levels (19). More recently, a study of 750 women who were not infertile and were actively trying to become pregnant found no association between *serum antimüllerian hormone levels* (defined as 0.7 ng/dL or less) and time to pregnancy for women between the ages of 38 years and 44 years (20). In a study of women with documented fertility (a prior spontaneous pregnancy loss), there was again no significant association observed between serum antimüllerian hormone levels and time to pregnancy (21). Therefore, based on the current information, a single serum antimüllerian hormone level assessment obtained at any point in time in a population of women with presumed fertility does not appear to be useful in predicting time to pregnancy and should not be used for counseling patients in this regard.

Antimüllerian Hormone as a Predictor of Menopause

The ability to predict accurately the onset of menopause would provide important clinical knowledge. Given the known decline in antimüllerian hormone with age (serum antimüllerian hormone levels become undetectable in postmenopausal women), serum antimüllerian hormone has been explored as a marker for time to menopause. However, studies on the use of antimüllerian hormone for this purpose (or on the use of antimüllerian hormone coupled with other predictors, such as age) have yielded conflicting results. Some studies suggested that antimüllerian hormone is highly predictive for time to menopause (22) and others demonstrated that the predictive effect diminishes with increasing age (23). Even among the favorable studies, data are limited by heterogeneity in study populations (24), the trajectory of decline also appears to differ between women (2), and the use of antimüllerian hormone as a predictor of the onset of menopause is unsuitable for clinical practice at this time. In October 2018, the U.S. Food and Drug

Administration permitted the marketing (through the de novo premarket review pathway) of an antimüllerian hormone test to aid in the determination of a patient's menopausal status. The test is “meant to be used only in conjunction with other clinical assessments and laboratory findings,” and published peer-reviewed data on the accuracy and clinical performance of this specific test are not currently available (25). For more information, including the U.S. Food and Drug Administration's recommendations for clinicians, see the October 24, 2018 Press Release (25).

Antimüllerian Hormone as a Biomarker for Polycystic Ovary Syndrome

Polycystic ovary syndrome is the most common endocrine disorder in women of childbearing age and a common cause of oligo-ovulation, hyperandrogenism, and infertility. The ability to make an accurate diagnosis is important to address the metabolic and reproductive risks associated with the disorder (26). Antimüllerian hormone has been proposed as an additional biomarker for the diagnosis of PCOS. However, data conflict as to whether antimüllerian hormone is more sensitive than ultrasound-visualized antral follicle count for diagnosis of PCOS (12, 13), is less sensitive (14), or whether neither marker is superior (15). Thus, currently, serum antimüllerian hormone levels are not part of the accepted diagnostic criteria for PCOS.

Antimüllerian Hormone as an Assessment of Ovarian Reserve After Gonadotoxic Therapy

Survival rates for reproductive-aged women with cancer have continued to improve over the years. Appropriately, this has resulted in increased attention to the effects of gonadotoxic chemotherapy on long-term ovarian function and fertility potential (27). Although pretreatment antimüllerian hormone levels may help predict menses and the potential for extended amenorrhea after completion of treatment (28), posttreatment antimüllerian hormone levels are highly variable (29), and this high variability affects the usefulness of antimüllerian hormone levels after chemotherapy (28). There are no long-term data on births or fertility. More data on the use of serum antimüllerian hormone levels to predict postchemotherapy fertility and to guide fertility counseling in these patients are needed.

Antimüllerian Hormone and Risk of Miscarriage

In addition to its role as a marker of ovarian reserve, antimüllerian hormone has been investigated as a marker of oocyte competence and, therefore, pregnancy loss risk. Small retrospective studies have yielded inconsistent results, with some studies finding an association between pregnancy loss and low antimüllerian hormone (30–34), and others reporting no link between the two (35, 36).

However, in the only available large prospective cohort study of more than 1,200 women, a secondary analysis of a trial evaluating the effect of low-dose aspirin on live birth in women with a history of one or two previous pregnancy losses, prepregnancy antimüllerian hormone values were not associated with pregnancy loss (37). Thus, at this time, routine antimüllerian hormone testing for the prediction of pregnancy loss is not recommended.

Conclusion

Although serum antimüllerian hormone levels are a known predictor of ovarian response to exogenous gonadotropin stimulation in infertile women undergoing assisted reproduction cycles, the use of antimüllerian hormone levels in women with presumed fertility is limited by a lack of international assay standards and differing assay methodologies. More data are needed to determine the utility of antimüllerian hormone as a predictor of time to menopause, a biomarker for PCOS, or a predictor of future menses in women who have received gonadotoxic therapy. At this time, however, serum antimüllerian hormone level assessment generally should not be ordered or used to counsel women who are not infertile about their reproductive status and future fertility potential.

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