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Predicting fertility with antimüllerian hormone: Is a cutoff value adequate?

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Antimüllerian (AMH) has become a popular measure of ovarian reserve. The assumption is that a single measurement of AMH has predictive value for fertility, independent of the day of the menstrual cycle. Indeed, several studies have demonstrated its consistency within and between cycles (for review, see reference [1] and references therein). AMH has been shown to correlate with antral follicle count and predict response to ovarian stimulation in assisted reproductive technologies (ART) and has been suggested as a predictor of time to menopause (1). However, there are factors that affect AMH that may, or may not, directly reflect the primordial follicular reserve. There is a higher rate of decline of AMH in smokers compared to nonsmokers, and antineoplastic treatment may decrease levels of AMH. Conversely, polycystic ovarian syndrome has been associated with elevated levels of AMH, as would be expected with a large number of immature follicles (1). Despite the abundance of literature concerning AMH, there have been few fecundity studies involving AMH outside of ART.

Fecundity, the likelihood of achieving pregnancy, is often quantified using a time-to-pregnancy (TTP) analysis. TTP studies have been used to examine the effects of specific exposures on fertility and may also be helpful in evaluating the predictive value of markers of fecundity. Furthermore, there may be a relationship between increased TTP and adverse pregnancy outcomes, including preterm delivery, low birth weight, and cesarean section (2). Thus, TTP is useful not only as a predictive measure of fecundity but may have clinical implications for the resulting pregnancy as well. In the evaluation of AMH and fecundity, TTP studies are unique because they allow for a more thorough interpretation of the significance of AMH values. In addition to demonstrating the cumulative proportions of women achieving pregnancy at certain time intervals, TTP studies may reveal a range of AMH values within which fecundity is optimal. Recognition of this range, rather than focusing on a “cutoff value” of AMH indicative of subfertility, is a conceptually different interpretation of the test. Fertility specialists must know the values that define this range to appropriately counsel patients regarding fertility.

To date, there are only two studies that have analyzed AMH and fecundity in noninfertility patients (3, 4), and the results are conflicting. In this issue of *Fertility and Sterility*, Hagen et al. (4) conducted a prospective cohort study in which AMH was measured in 186 young, healthy women who planned to discontinue contraception and begin attempts at first pregnancy. Results showed that high levels of AMH were associated with a 38% reduction

in fecundity ($P < .05$), while the fecundity of women with low values was not statistically different from that of women in the medium AMH group (4). Of note, findings persisted after adjustment for covariates. There was a trend toward reduced fecundity in patients with low AMH; however, statistical significance was not reached. In brief, the findings demonstrate that a TTP approach identified optimal fertility within a range of AMH values and not simply levels above a single cutoff value.

In 2011, Steiner et al. (3) reported a study of AMH using a TTP design. Results showed significantly reduced fecund-ability in women with low AMH (3). Differences in patient characteristics and study designs make direct comparison between the two studies difficult; however, there are several points to consider. The patients in the study by Steiner et al. (3) were 30–42 years of age and had been attempting pregnancy for no more than 3 months; 63% were nulliparous. Semen analyses were not performed, but couples with known male factor infertility were excluded. Conversely, Hagen et al. (4) included nulliparous patients aged 25–30 years who had been using contraception and controlled for oligo-zoospermia. It is possible that Steiner et al. (3) found a significant correlation between low AMH and decreased fecundity because a larger proportion of their older patient population had low AMH. Furthermore, there may have been more subfertile or infertile patients in their study, as some women had been attempting pregnancy for up to 3 months before enrollment.

Differences in pregnancy and contraceptive history between the two studies may have contributed to the conflicting results. There have been inconsistent findings in the literature regarding trends of AMH during and after oral contraceptive pill (OCP) use and pregnancy. Some studies have demonstrated that AMH values are unaffected by OCPs, while others have found a correlation between OCP use and decreased AMH. Women in the study by Hagen et al. (4) were enrolled after discontinuing birth control, with an average time of 4 weeks between discontinuing contraception and enrollment. Some, but not all, women in the study by Steiner and coworkers (3) used contraception before enrollment. It is possible that more fecund women had low AMH in the study by Hagen et al. (4) because of the higher incidence of recent OCP use. This may explain why the time to pregnancy was not significantly increased in women with low AMH. The literature regarding AMH in pregnancy has similarly provided inconclusive results. While some studies have shown that AMH values do not significantly change throughout pregnancy or after delivery, others have demonstrated reduced AMH with advancing gestation and subsequent recovery in the early puerperium (5). Without details on the timing of previous pregnancies in relation to the study period in the report by Steiner et al. (3), one cannot exclude past pregnancy as a possible confounder in their study.

Despite the differences between the two studies, the TTP approach has revealed what astute clinicians have suspected all along: if the outcomes of interest are fertility and pregnancy outside of ART, AMH values should not be conceptualized as dichotomous, either above or below a specific threshold. Rather, AMH levels must be within a critical range for optimal fecundability. Future studies are needed to define the high and low values of AMH above which, and below which, pregnancy is less likely.

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