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Clinical uses of anti-Müllerian hormone assays: pitfalls and promises

THESE

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par

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Rapport de synthèse

Utilisation clinique de l'hormone anti-müllérienne : pièges et promesses

OBJECTIF : étudier si les fluctuations sériques du taux d'hormone anti-müllérienne (AMH) sont liées à des différences méthodologiques entre les deux tests ELISA commercialement disponibles : le kit de Beckman Coulter Immunotech (Fullerton, CA) et le kit de Diagnostic Systems Laboratories (Webster, TX).

DESIGN : étude prospective au sein de deux services universitaires de médecine de la reproduction.

POPULATION ETUDIEE : cent soixante-huit échantillons sanguins provenant de trois populations différentes ainsi que des dosages itératifs au cours du même cycle menstruel dans une population de dix volontaires.

INTERVENTIONS : doubles mesures en aveugle des taux sériques d'AMH dans les 168 sera avec les deux kits commercialement disponibles. Sept dosages itératifs au cours du même cycle menstruel chez 10 volontaires normo-ovulantes.

ANALYSE STATISTIQUE : régression linéaire pour l'étude de la corrélation entre les deux méthodes de dosage. Analyse des variances pour les dosages sériés en cours de cycle menstruel.

RESULTATS : nous avons démontré une relation linéaire entre les deux méthodes, avec un coefficient de corrélation de 0,88 ainsi qu'une diminution faible mais statistiquement significative et concomitante avec l'ovulation du taux d'AMH sérique.

CONCLUSION : les variations en cours de cycle menstruel rapportées par certains auteurs ne sont pas liées à des problèmes méthodologiques. La chute du taux d'AMH lors de l'ovulation est faible mais statistiquement significative. Les variations observées en cours de cycle restent toutefois inférieures aux variations intercycles et ne représentent de ce fait pas un obstacle au dosage de l'AMH à n'importe quel jour du cycle menstruel.

A Monsieur le Professeur D. de ZIEGLER

Nous avons eu le privilège de bénéficier de votre enseignement.
C'est pour nous un honneur que vous ayez accepté de diriger nos travaux.
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A Monsieur le Professeur O. IRION

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C'est un grand privilège que d'avoir pu apprendre à vos côtés.

A Monsieur le Professeur J.B. DUBUISSON

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MEMENTO AUDERE SEMPER

Gabriele d'Annunzio, 1918

CONTROVERSY

Clinical uses of anti-Müllerian hormone assays: pitfalls and promises

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Objective: To investigate whether the controversy about fluctuations of anti-Müllerian hormone (AMH) levels during the menstrual cycle results from differences between the immunoassays currently available: the Beckman Coulter Immunotech kit (Fullerton, CA) and the Diagnostic Systems Laboratories kit (Webster, TX).
Design: Prospective trial.
Setting: Fertility clinics of two tertiary university hospitals.
Patient(s): One hundred sixty-eight blood samples from three different populations. Serial samples at set intervals from the LH surge were taken in a fourth population of 10 volunteers.
Intervention(s): We remeasured AMH levels by using the Diagnostic Systems Laboratories kit in 168 blood samples in which AMH initially had been measured by using the Beckman Coulter assay. We also conducted serial AMH measurements (n = 7) during the menstrual cycle of 10 women.
Main Outcome Measure(s): Linear regression of AMH levels determined by using 2 different assays and analysis of variance of serial measurements in the menstrual cycle.
Result(s): We found a linear relationship between the 2 methods, with a correlation coefficient of 0.88. When repeated individual AMH measures were longitudinally analyzed in relation to the LH surge, a slight but significant decrease was observed after ovulation.
Conclusion(s): Differences in AMH fluctuations during the menstrual cycle reported in recent publications do not result from the use of different AMH assays. The changes in AMH levels after ovulation are slight, yet statistically significant. However, the fluctuations observed are smaller than intercycle variability and therefore are not clinically relevant as far as AMH measurements for clinical purposes are concerned. In daily practice, AMH therefore can be measured anytime during the menstrual cycle. (Fertil Steril® 2008; ■: ■–■. ©2008 by American Society for Reproductive Medicine.)

Key Words: Anti-Müllerian hormone, AMH/MIS, menstrual cycle, contraception, Beckman Coulter assay, Diagnostic Systems Laboratories assay, DSL assay

In recent years, it has been established that plasma anti-Müllerian hormone (AMH) levels, which correlate with the number of antral and preantral follicles in mice (1), can be used for assessing ovarian reserve (2). Anti-Müllerian hormone also has been proposed as a surrogate marker of the antral follicular count (AFC) in polycystic ovary syndrome (3).

One of most appealing advantages of AMH is that its levels have been shown to be stable under various influences such as hormonal contraception (4, 5), the menstrual cycle (5–7), and pregnancy (8), and measurements can therefore be made anytime during the menstrual cycle. Remarkably, in women affected by polycystic ovary syndrome, prolonged treatment with oral contraceptives, leading to a significant reduction of ovarian volume, did not modify AMH levels (5). Further supporting the contention that AMH is FSH independent (within the limits of FSH fluctuations encountered clinically), exogenous FSH administered to women who regularly ovulate (9) or have polycystic ovary syndrome (10) did not alter plasma AMH levels. Likewise, prolonged suppression of gonadotropins by GnRH-a failed to affect circulating levels of AMH (11).

Contrasting with the host of publications indicating that AMH levels are not affected by commonly encountered hormonal changes, two reports recently contended that AMH levels actually fluctuate during the menstrual cycle (12, 13). These two studies therefore challenged the primary advantage of AMH, which, contrary to other markers of ovarian function such as FSH or inhibin B, could be measured at any

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particular time. Of note, the two studies reporting changes in AMH levels during the menstrual cycle (12, 13) used the Diagnostic Systems Laboratories (DSL) (Webster, TX) kit, whereas all the publications showing no changes used the other commercially available assay, the Beckman Coulter Immunotech kit (BC) (Fullerton, TX) (5–7).

We are aware of two publicly available studies that compared AMH measurements obtained by using DSL and BC ultrasensitive assays (14, 15). Both studies observed important differences in AMH readings obtained with the two methods. The teams of Fréour et al. (14) and Bersinger et al. (15) independently reported AMH results that were markedly lower, by factors of 4.6 and 3.1, when measured with the DSL kit as compared with the BC kit, respectively. Both groups concurred, however, in reporting that the two methods correlated well throughout the measuring range (14, 15).

The reported differences between the DSL and BC assays cannot readily explain the fact that fluctuations in AMH levels were observed during the menstrual cycle only with one (DSL) but not the other assay (BC). Yet neither of the two available comparisons between the two assays was conducted during the menstrual cycle. This therefore leaves unanswered questions about a possible role of the AMH assay in the existing controversy. Consequently, we queried whether methodological issues might have caused the difference observed during the menstrual cycle between the teams that used one (5–7) or the other kit (12, 13). This prompted us to conduct our own comparison. For this, we remeasured AMH by using the DSL kit in 168 serum specimens in which it previously had been measured with the BC method. We also measured serum AMH serially in 10 women, at seven set intervals before and after the LH surge.

MATERIALS AND METHODS

To compare AMH measurements obtained using the two commercial ultrasensitive immunoassays currently available, BC and DSL, we remeasured AMH by using the DSL kit in 168 blood samples in which AMH had already been measured with the BC method. These samples came from 95 women in three different populations.

Population 1

This group included 24 young, ovulatory women. All were studied at two consecutive intercycle intervals (n = 24) and on day 16–18 and 23–25 of either the menstrual cycle (n = 10) or while receiving hormonal contraception orally (n = 7) or vaginally (n = 7). Of 96 samples, 1 was missing. Results from these 95 AMH measurements were the basis of an institutional review board–approved study published elsewhere by our team (5).

Population 2

This group included 58 individuals from a heterogeneous population, including women in whom AMH previously had been measured during fertility workups at our institution between April 2005 and March 2007. Samples were randomly chosen in our blood bank, as part of quality-assessment measures approved by our local institutional review board.

Population 3

Fifteen samples from 13 women, whose prior AMH measurements were below the level that allows reliable detection with the BC method (<0.4 ng/mL), also were included for remeasurement with the DSL kit. This included four samples from two women who were the subject of a case report published by Fraisse et al. (16).

Furthermore, we conducted a longitudinal analysis of repeated (n = 7) AMH measures in 10 healthy normally ovulating volunteer women who had undergone a previous extensive assessment of the menstrual cycle. These evaluations were approved by our institutional review board. Daily blood samples were available for each of these women. Recent publications elsewhere (12, 13) reporting fluctuations of AMH levels in the periovulatory period led us to measure AMH levels in these samples at time intervals around the LH surge. In each woman, AMH was measured in seven samples, at intervals before (LH –10, –5, –2, and –1) and after the LH surge (LH +1, +2, +10), by using the BC kit only.

All blood samples had been stored frozen at–18°C and were thawed only once for AMH measurement, using DSL (populations 1–3; n = 168) or BC (serial analysis in relation to the LH surge; n = 70).

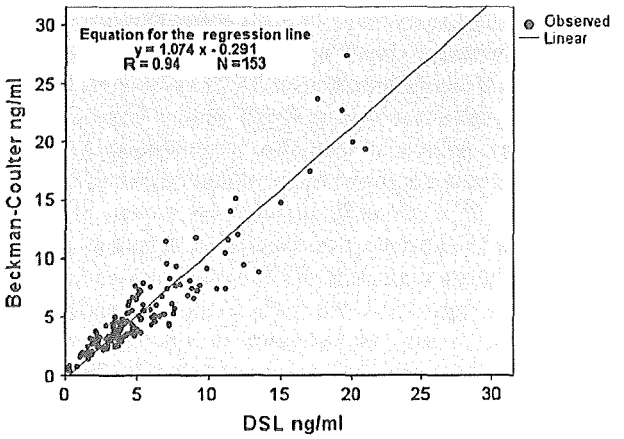
We analyzed AMH levels measured by using the two methods, BC and DSL, in study populations 1 and 2 by using linear regression analysis and Student's *t*-test. In our regression analysis, AMH DSL was defined as the independent variable *x*, and AMH BC, as the dependent variable *y*. Statistical analysis was performed by using SPSS software version 14.0 (SPSS, Inc., Chicago, IL). Power analysis was performed by using Medcalc version 9.3.1. Our study had a sufficient number of samples to show a correlation coefficient of 0.3 with a power of 0.8 and a type I error of 0.05. Levels of AMH in the menstrual cycle at seven intervals of the LH surge, conducted in 10 women, were analyzed by using analysis of variance for repeated measures.

RESULTS

In population 1, the regression equation of AMH by DSL over AMH by BC was $y = 0.79\ x + 3.24$ ng/mL (Pearson's correlation coefficient $r = 0.87$; $n = 95$), indicating similar AMH results with the two assays (BC and DSL). Levels of AMH were in the range commonly encountered in female physiology (1.4–15 ng/mL). Changes in AMH levels measured by DSL that were observed during menstrual and hormonal contraception cycles were inferior to intercycle variability, as observed elsewhere by using the BC assay (4).

FIGURE 1

Linear regression analysis of the Beckman Coulter assay vs. the DSL assay for AMH measurements.



Streuli. AMH measurement issues. Fertil Steril 2008.

In population 2, AMH was measured in a heterogeneous population with a broader range of values, from 0.4 to 36 ng/mL. The regression equation was as follows: $y = 1.17\ x + 0.57$ (Pearson's correlation coefficient, $r = 0.98$; $n = 58$).

Results of populations 1 and 2 were subsequently regrouped, and a global regression was conducted for the 153 measurements. Findings illustrated in Figure 1 show y = 1.074 × −0.291 ng/mL where y = AMH BC and x = AMH DSL (Pearson's correlation coefficient, $r = 0.88$; $n = 153$). As illustrated, the results obtained with the BC and DSL AMH kits were similar (P=.81).

In population 3, the DSL assay confirmed undetectable AMH levels in all 15 samples, as previously observed with the BC assay, including in those of two women with an ongoing pregnancy.

Serum AMH levels measured with the BC kit in our serial analysis, conducted in the menstrual cycle at set intervals (n = 7) before and after the LH surge, were plotted in relation to the LH surge (Fig. 2). Analysis of variance revealed that AMH levels were significantly lower during the early luteal phase, as compared with early follicular-phase and late luteal-phase levels (Fig. 2; analysis of variance, P=.0159 and P=.0197, respectively).

DISCUSSION

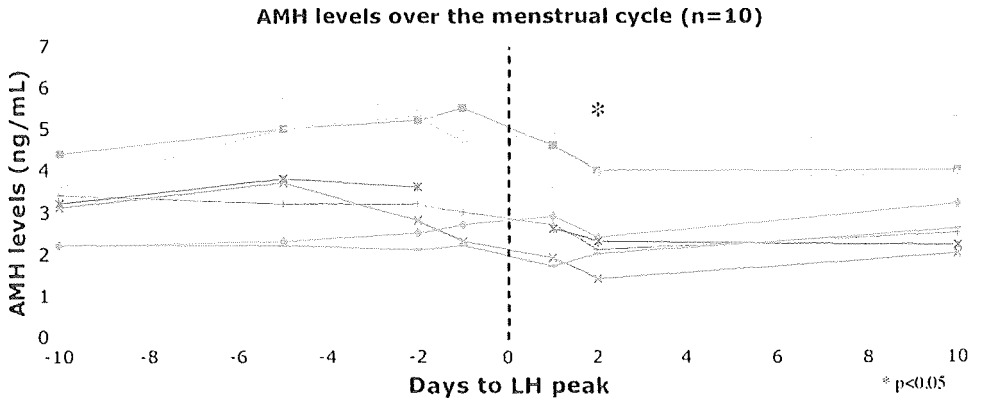
Our comparative analysis of 168 blood samples in which AMH was measured with DSL and BC ultrasensitive assays provided highly similar results. Our data therefore suggest that the differences between the studies that showed (12, 13) or did not show (5, 6) fluctuations of AMH levels during the menstrual cycle using the DSL and BC assays, respectively, are not rooted in methodological issues linked to the type of AMH assay used.

In their report, Bersinger et al. (15) observed a lesser difference between AMH results obtained with the BC and DSL techniques than Fréour et al. (14) reported elsewhere. In the discussion of their results, Bersinger et al. (15) alluded to problems inherent to AMH measurements that stem from residual matrix effects and instabilities of certain antigenic determinants. Our current data, which resulted from measurements that all were conducted in 2007, failed to report any difference between serum AMH results obtained using BC or DSL assays. This therefore suggests that the above-mentioned methodological problems have been addressed and solved by the assay manufacturers.

In their report, Wunder et al. (12), using the DSL kit, observed a statistically significant decrease in AMH levels,

FIGURE 2

Fluctuation of AMH over the menstrual cycle in 10 healthy, normally ovulating volunteers (Beckman Coulter assay).



Streuli. AMH measurement issues. Fertil Steril 2008.

reaching a nadir in the early luteal phase. This pattern of changes in AMH levels parallels the description made by Lalhou et al. (13) and our current findings that were observed in 10 patients who were serially sampled (n = 7) at set intervals before and after the LH surge (Fig. 2). Yet in all cases, the fluctuations in AMH levels were of small amplitude. In our own study, the maximum mean upward and downward excursions of AMH levels were of +6% (95% confidence interval, −72% to +85%) and −19% (95% confidence interval, −37% to +75%), respectively, by reference to a mean value of 3.48 ng/mL. The large confidence intervals are a consequence of the small sample size. In the Wunder et al. report (12), AMH fluctuated in the menstrual cycle between a mean maximum increase in the late follicular phase and a mean maximum decrease 4 days after the LH surge of +3% and −16%, respectively, by reference to a mean AMH value of 3.19 ng/mL. In the abstract presentation of Lalhou et al. (13), the upward and downward excursions of AMH levels were of +11 and −18%, respectively, by reference to a mean value of 3.29 ng/mL. In all these studies, AMH fluctuations, observed during the menstrual cycle above and below the mean value, were of the same or lesser amplitude than the intercycle variability of 28% (95% confidence interval, −23.2 to +80.3%) that we reported elsewhere (5).

The pattern of AMH fluctuations in the menstrual cycle independently seen by us, Wunder et al. (12) and Lalhou et al. (13) parallels the changes that Fanchin et al. (17) reported in controlled ovarian hyperstimulation cycles. Yet the fluctuations observed in the menstrual cycle were of much smaller amplitude than those seen in controlled ovarian hyperstimulation. These changes may reflect a decreased production of AMH by antral and preantral follicles and/or an abrupt reduction in the size of this cohort of follicles that would occur soon after ovulation. Theoretically, this follicular inhibition could result from direct adverse effects of the developing follicles and/or corpus luteum on the small preantral and antral follicles. The observation that prolonged hormonal contraception in women with polycystic ovary syndrome failed to alter AMH levels despite a nearly 50% decrease in ovarian size (8) renders this latter explanation of changes in AMH levels during the menstrual cycle an implausible one, however. The mechanism of this slight periovulatory decrease in AMH levels has not yet been elucidated. A hypothesis could be the presence of one or more putative concealing mechanisms interfering with the recognition of serum AMH after ovulation, thereby resulting in a false, rather than true, drop in AMH levels. This putative mechanism that accounts for the masking of AMH after ovulation could be the release of soluble AMH receptors into the blood circulation. In support of the hypothesis of a concealing phenomenon rather than a true drop is the rapid kinetic of the changes that has been observed by us and others (12, 13). From our current understanding of ovarian physiology, it is unlikely that the population of small preantral follicle changes in such a short time (18). Similarly, the observation that changes in ovarian volume in response to prolonged use of oral contraceptives failed to induce a change in AMH levels (4) speaks against a short-term change in AMH production by preantral follicles. However, the existence of this concealing factor remains unknown and could be the subject of future investigations.

Our comparison of the results obtained by the BC and DSL assays also confirms the equal performance of these two assays at measuring very low AMH levels, including those below detection level (<0.4 ng/mL). Among the 15 low AMH samples, 4 came from two women who carried a normally developing pregnancy and who have been the object of a case report (17). Remeasurement of AMH in these two women with the DSL kit confirmed AMH levels below detection level and indicated that the original finding (16) did not result from a methodological fluke.

In conclusion, our results reveal that the two ultrasensitive assays for AMH measurements, BC and DSL, provide similar serum AMH results. Our results also confirm the slight changes in AMH levels reported by Wunder et al. (12) in the menstrual cycle.

In all three reports studying the periovulatory drop in AMH levels, the maximal fluctuations reported were smaller than or equal to the variability of AMH levels between two menstrual cycles shown in a report elsewhere (5). We therefore conclude that the fluctuations found in the early luteal phase are not greater than variations between two early follicular phase measurements. Measurements of AMH performed in the early luteal phase consequently also can be used for clinical purposes. The results of our assay comparison therefore confirm that either the DSL or BC assay can be used to measure serum AMH, at any particular time during the menstrual cycle or while taking either oral or vaginal hormonal contraception.

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