Comparison of antimüllerian hormone levels and antral follicle count as predictor of ovarian response to controlled ovarian stimulation in good-prognosis patients at individual fertility clinics in two multicenter trials

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Objective: To compare antimüllerian hormone (AMH) and antral follicle count (AFC) as predictors of ovarian response to controlled ovarian stimulation at individual fertility clinics.
Design: Retrospective analysis of individual study center data in two multicenter trials. Centers that provided >10 patients were included in the analysis.
Setting: A total of 19 (n = 519 patients) and 18 study centers (n = 686 patients) participating in a long GnRH agonist trial (MERIT) and a GnRH antagonist trial (MEGASET), respectively.
Patient(s): Infertile women of good prognosis.
Intervention(s): Long GnRH agonist or GnRH antagonist cycles.
Main Outcome Measure(s): Correlation between AMH and AFC, and oocyte yield by each study center for each trial.
Results(s): Antimüllerian hormone was more strongly correlated with oocyte yield than AFC: $r = 0.56$ vs. $r = 0.28$ in the GnRH agonist cohort, and $r = 0.55$ vs. $r = 0.33$ in the GnRH antagonist cohort. The correlation was numerically higher for AMH than for AFC at a significantly higher proportion of study centers: 17 (89%) and 15 (83%) centers in the long GnRH agonist and GnRH antagonist trial, respectively. Assessment of the relative capacity of AMH and AFC for predicting oocyte yield demonstrated that AMH dominated the model: AMH, $R^2 = 0.29$ and 0.23; AFC: $R^2 = 0.07$ and 0.07; AMH + AFC: $R^2 = 0.30$ and 0.23 for long GnRH agonist and GnRH antagonist trials, respectively.
Conclusions(s): Antimüllerian hormone was a stronger predictor of ovarian response to gonadotropin therapy than AFC at the study center level in both randomized trials utilizing GnRH agonist and GnRH antagonist protocols. Antral follicle count provided no added predictive value beyond AMH. (Fertil Steril® 2015;103: 923–30. ©2015 by American Society for Reproductive Medicine.)
Key Words: Antimüllerian hormone, antral follicle count, IVF clinic, multicenter randomized controlled trial, ovarian response

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The ovarian response resulting from controlled ovarian stimulation (COS) in IVF with standard doses of gonadotropins is associated with a large interindividual variability. Individualization of the starting dose of gonadotropin according to ovarian reserve parameters has been proposed as a means of improving safety and efficacy of COS (1–3). To date, a number

of markers of ovarian response have been used and evaluated (4), such as age, FSH, and inhibin B; however, antral follicle count (AFC) and antimüllerian hormone (AMH) are the two biomarkers that have consistently provided the best performance in terms of predicting ovarian response to gonadotropins (5, 6).

Antral follicle count has been shown to possess similar performance as AMH in predicting the number of oocytes retrieved in the majority of single-center observational cohort studies in IVF/intracytoplasmic sperm injection (ICSI) patients treated with GnRH agonist protocols (7–11), whereas a few studies have suggested either AFC (12, 13) or AMH (14, 15) as being a better predictor. Two meta-analyses of a number of these relatively small, single-center studies indicated that AMH and AFC have similar levels of accuracy and clinical value for the prediction of poor (16) as well as excessive response (17). In marked contrast to these reports, three recent large, prospective, multicenter trials in IVF/ICSI patients of good prognosis consistently concluded that AMH was a better predictor of ovarian response than AFC in GnRH agonist (18) and antagonist (19, 20) cycles, regarding the number of oocytes retrieved as well as categorization of low and high responders. Furthermore, in models of ovarian response AFC did not provide any additional predictive value beyond that provided by AMH (18–20).

The overall superior performance of AMH over AFC in these multicenter trials may have been attributed to considerable sonographer-dependent variability across centers. Furthermore, such interoperator variability between different IVF clinics may also explain the different performance of AFC in single-center and multicenter studies. Therefore, it would be important to explore whether the findings in multicenter trials are determined by the integrated data evaluation rather than by the actual performance at each study center, because AMH was analyzed centrally and AFC locally. This is essential to clarify, given the perception that each fertility clinic believes that their ultrasound evaluation of AFC is robust, and because AFC has been considered the gold standard biomarker for the prediction of ovarian response.

The aim of the present study was to compare the values of AMH and AFC for prediction of oocyte yield at a study center level for fertility clinics participating in two large, multicenter trials: one conducted with the long GnRH agonist protocol (21) and the other with a GnRH antagonist protocol (22). Consistent with previous systematic reviews and individual patient data meta-analyses (4, 23, 24), other predictors of ovarian response to gonadotropin stimulation, such as FSH, were shown to be less predictive than AMH in both trials (18, 19) and therefore not considered for this evaluation.

MATERIALS AND METHODS

Study Population and Study Centers

This study is a retrospective analysis of data prospectively collected in two randomized, controlled, multicenter trials in IVF/ICSI patients of good prognosis undergoing COS with highly purified hMG (Menopur; Ferring Pharmaceuticals) or recombinant FSH (follitropin alfa [Gonal-F, Merck Serono] or follitropin beta [Puregon, MSD]) after a long GnRH agonist protocol (MERIT trial) (21) or a GnRH antagonist protocol (MEGASET trial) (22). The women included in each trial had been infertile for at least 1 year and had a regular menstrual cycle, a transvaginal ultrasound documenting presence and adequate visualization of both ovaries without evidence of abnormality, and an early follicular-phase serum level of FSH within normal limits (1–12 IU/L). Women with polycystic ovary syndrome and/or a poor response in a previous COS cycle were excluded in both trials. In the GnRH antagonist trial, women with an AFC <10 (diameter 2–10 mm) at screening were excluded. At each study center, the patients were randomized in a 1:1 ratio to treatment with either highly purified hMG or rFSH.

The trials were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and local regulatory requirements, and were approved by the local regulatory authorities and the independent ethics committees covering all participating study centers. Written informed consent was provided by each of the subjects.

Stimulation Regimens

In the long GnRH agonist trial, pituitary suppression was initiated with 0.1 mg/d of triptorelin (Decapeptyl, Ferring Pharmaceuticals) 5–7 days before the estimated start of next menses and continued until the end of gonadotropin administration. Gonadotropin treatment started when down-regulation was confirmed, and the dose was fixed at 225 IU/d for the first 5 days of COS, followed by individual dose adjustments according to the patient's follicular response. In the GnRH antagonist trial, treatment with a daily dose of 150 IU of gonadotropin started on day 2–3 of the menstrual cycle and was fixed for the first 5 days of COS, followed by individual dose adjustments according to the patient's follicular response. Treatment with 0.25 mg/d of ganirelix (Orgalutran, MSD) was initiated on stimulation day 6 and continued throughout the gonadotropin treatment period. In both trials, the criteria for giving hCG (Ovitrelle, Merck Serono) was development of at least three follicles with a diameter ≥ 17 mm. Oocyte retrieval took place 36 ± 2 hours later, followed by IVF or ICSI and embryo/blastocyst transfer. Detailed descriptions of ovarian stimulation regimens, cohort assessments, and procedures in the long GnRH agonist and antagonist trials are provided in Nyboe Andersen et al. (2006) (21) and Devroey et al. (2012) (22), respectively.

Endocrine Assays and Antral Follicle Count

In both trials, circulating concentrations of AMH were analyzed in serum samples collected on stimulation day 1 before the start of stimulation by a central laboratory (Hormone Laboratory, Universitair Ziekenhuis, Brussels, Germany for the agonist trial and Laboratory for Clinical Research, Kiel, Germany for the antagonist trial). Serum samples were immediately frozen to $-18^{\circ}C$ for the first 2 weeks until transport to a central facility, followed by storage at $-70^{\circ}C$. Antimüllerian hormone was analyzed by