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Original Article

The role of anti-Mullerian hormone in predicting the response to clomiphene citrate in unexplained infertility☆

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ABSTRACT

Objective: To determine the role of anti-Mullerian hormone (AMH) levels in predicting the response to clomiphene citrate (CC) therapy for ovulation induction in women with unexplained infertility.
Materials and methods: For this retrospective study, fifty consecutive patients who responded to CC were taken as Group 1, while fifty consecutive patients who failed to show adequate ovulatory response with CC were taken as Group 2. We compared the AMH levels of the two groups and receiver operating characteristic (ROC) curve was used to determine the threshold for AMH in predicting the ovulatory response to CC therapy.
Results: Mean age, body mass index, luteinizing hormone, prolactin, and thyroid-stimulating hormone values were similar in the two groups. AMH and antral follicle count (AFC) values were higher in Group 1 than in Group 2 ($p = 0.001$ and $p = 0.001$, respectively). There was a statistically significant negative correlation between FSH and AFC ($r = -0.339$, $p = 0.001$), while AFC and AMH displayed a statistically significant positive correlation ($r = 0.713$ and $p = 0.001$). AMH values and AFC were found to be predictors of the adequate ovulatory response to CC. The area under the ROC curve was 0.86 vs 0.80, respectively. At an AFC cutoff value of 14, the sensitivity and specificity for prediction of ovulation were 68% and 80%, respectively.
Conclusion: The AMH and AFC cut-off values for the prediction of positive ovarian response to CC in patients with unexplained infertility were 2.78 ng/mL and 14, respectively. If further prospective and randomized studies confirm our results, these thresholds may be useful to predict successful ovulation induction and reduce the unresponsive cycles.

Introduction

Infertility and its associated problems are known to affect 15% of couples [1]. Anovulation, tubo-peritoneal factors and male infertility are the main causes of infertility. Among infertility patients no causative factor can be detected with a rate of 16–20% when current infertility work-out is used and these patients are classified as unexplained infertility [2]. Ovulation induction followed by intrauterine insemination is usually the first-line treatment in patients with unexplained infertility. Clomiphene citrate (CC) has been used as the first-line agent for ovulation induction [3]. The empiric use of clomiphene citrate with or without intrauterine insemination in women with unexplained infertility was proposed for correction of the subtle ovulatory dysfunction and/or ovulation of more than 1 oocyte [4]. In comparison to superovulation with gonadotropins, CC has fewer side effects, lower cost, and acceptable success rates [5].

During the last decade, the importance of anti-Mullerian hormone (AMH) in the assessment of the ovarian reserve has become

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better understood [6]. AMH, which is a member of the transforming growth factor family is secreted to the blood stream after its production from the granulosa cells of the pre-antral and antral follicles. AMH concentrations reflect the quantity of follicular pool and thus is used as a sensitive marker of the ovarian reserve. The value of AMH in prediction of ovarian response in gonadotropin stimulated cycles has been studied at the beginning of last decade. Seifer et al. found a relationship between early follicular phase serum AMH levels and the number of oocytes developed during ovulation induction [7]. The number of oocytes collected was particularly high in the presence of high serum AMH levels, leading to a higher yield of mature oocytes. The serum AMH level was found to be valuable in prediction of the number of oocytes collected at controlled hyperstimulation during in vitro fertilization (IVF) cycles [7].

In this study, in addition to previous studies that focused on the predictive value of AMH in gonadotropin induced ovulation induction cycles, we investigated the value of AMH levels in predicting the response to CC administration in patients with unexplained infertility and analyzed the correlation between antral follicle count (AFC) and serum AMH, a cycle day 3 follicle stimulating hormone (D-3 FSH) and estradiol (E2) levels.

Material and method

This retrospective study included 100 patients who were admitted to Ministry of Health Etlik Zubeyde Hanim Woman's Health Teaching and Research Hospital. All patients were diagnosed with unexplained infertility after routine infertility assessment and were scheduled for ovulation induction using CC followed by intrauterine insemination. This study was approved of by local ethical committee, Education Planning Committee. The study is a retrospective study and the investigators aimed to recruit participants to both the study and the control group from the computarized records of the patients who were scheduled for their first CC + IUI cycle at the "Reproductive Endocrinology Outpatient Clinic" of the hospital between the given dates (January–December 2015). From the first day of the initiation of the study, patients with unexplained infertility who met the inclusion criteria but did not have the exclusion criteria from both the responders (N:50) and non-responders (N:50) were included. We recruited 50 consecutive patients for each group. No patients were skipped in order to avoid the bias. The recruitment process was completed after reaching the targeted number for each group. The inclusion and exclusion criteria were strictly followed-up. After analyzing the patient records, patients who did not meet the inclusion criteria [being <36 years of age, failing to become pregnant despite regular sexual intercourse for 1 year without any contraceptive use, having regular menstrual cycles, ovulation confirmed by mid-luteal progesterone (serum progesterone level >3 ng/dl) measurement, with patent uterine tubes on hysterosalpingography, and a basal FSH <10 IU/mL.] or had one or more of the exclusion criteria [patients who had polycystic ovarian disease, endocrinological problems, chronic diseases, myomas, endometriosis, previous history of pelvic surgery or male infertility with 2 abnormal male semen analysis according to the World Health Organization (WHO) criteria [8]] were not included to the study. No other factors played a role in the selection process. All the patients had their first treatment cycle. They were put on to CC (Klomen 50 mg, Kocak Farma, Turkey) for ovarian stimulation, and the treatment was started on day 3 of menstrual cycle with a dose of 50 mg twice daily for 5 days. The patients had daily ultrasonographic examination and 10,000 U hCG (Pregnyl 5000 IU/amp. 1 × 2, im, Organon, Turkey) was administered to trigger ovulation when at least one follicle was observed to exceed a diameter of 18 mm. IUI was performed 36 h after hCG administration.

On the morning of day 3 of the treatment cycle, 8 mL of venous blood was collected from cubital vein, the samples were centrifuged at 3500 rpm and blood serum was refrigerated at −20 °C. Quantitative serum FSH, TSH, LH, E2 and Prolactin measurements were done by using the chemiluminescent microparticle immunoassay (CMIA) method (Abbott Laboratories, Illinois, USA), while quantitative AMH measurements were carried out using the enzyme-linked immunosorbent assay (ELISA) method (Diagnostic Systems Laboratories, Webster, Texas, USA).

Baseline transvaginal ultrasonography (USG) in the early follicular phase was performed before treatment to measure the sizes of the uterus and ovaries, as well as the number and diameter of follicles. The AFC was defined as the total number of follicles with a diameter of 2–10 mm in both ovaries on day 3 before the ovarian stimulation. Baseline TVUSG assessment and follicle development was followed up by using a General Electric Logiq P5 Ultrasound (6.5 MHz microconvex) vaginal probe. The patients were followed until the 21st day, and the patients who developed at least one follicle of >16 mm in diameter were considered as a positive ovarian response and had intrauterine insemination 36 h after recombinant hCG administration (Ovitrelle 250 mcg Merck) (Group 1, $n = 50$). The patients who failed to develop at least a follicule <16 mm in diameter were taken as the nonresponsive group (Group 2, $n = 50$). AMH levels were compared between the two groups and the value of the AMH level in predicting the outcome of CC therapy was calculated. Moreover, in both groups, the correlation between the AMH level and body mass index (BMI), basal serum FSH, LH, estradiol (E2), thyroid-stimulating hormone (TSH), prolactin levels, and antral follicle count (AFC) were evaluated.

The sample size of the study was calculated with G*Power (G*Power Ver. 3.1.9.2, Franz Faul, Üniversität Kiel, Germany) statistical packages. The required sample size for 88% power, $\alpha = 0.05$ Type I error, $\beta = 0.20$ Type II error and $f = 0.70$ effect size was calculated as 26 for each group. The study data was analyzed with SPSS version 17 using definitive statistics, the Student's *t*-test, the Mann–Whitney U test, Pearson correlation analysis, the analysis of variance (ANOVA) test, Bonferroni correction, and receiver operating characteristic (ROC) curve analysis. *P*-value < 0.05 was considered as statistically significant.

Results

The demographic and laboratory features of both groups were shown in Table 1. Both groups had similar mean age, BMI, serum LH, prolactin, and TSH values ($p > 0.05$). Serum AMH values and AFC were significantly higher in Group 1 than in Group 2 ($p = 0.001$ and $p = 0.001$, respectively). Serum FSH and E2 values were significantly

Table 1
Comparison of demographic and laboratory features of study population.

	Group 1 (n = 50) (responders)	Group 2 (n = 50) (non-responders)	p-value
Age (year)	26.3 ± 4.7	27.9 ± 3.6	0.063
BMI (kg/m^2)	24.8 ± 2.4	24.4 ± 2.7	0.489
FSH (IU/l)	6.1 ± 1.2	6.8 ± 1.4	0.005
LH (U/l)	5.3 ± 2.1	6.2 ± 2.5	0.096
Estradiol (pg/ml)	33.7 ± 13.6	42,6 ± 15.4	0.003
TSH (mIU/l)	1.90 ± 0.77	1,98 ± 0.81	0.694
Prolactin (ng/ml)	12.4 ± 5.0	14.4 ± 5.5	0.063
AMH (ng/ml)	3.01 ± 0.52	2.23 ± 0.50	0.001
AFC	15.2 ± 1.6	13.1 ± 1.8	0.001

Data are given as mean ± standard deviations. Body mass index (BMI); follicle stimulating hormone (FSH); luteinizing hormone (LH); thyroid stimulating hormone (TSH); anti-Mullerian hormone (AMH); antral follicle count (AFC).

lower in Group 1 than in Group 2 ($p = 0.005$ and $p = 0.003$, respectively).

The ROC curve was drawn for the AMH and AFC levels by calculating sensitivity and specificity of AMH and AFC in showing the CC response. At an AMH cutoff value of 2.78 ng/mL, the sensitivity and specificity to CC response were 74% and 86%, respectively. The sensitivity and specificity of AMH measured for other values are shown in Table 2. At an AFC cutoff value of 14, the sensitivity and specificity were 68% and 80%, respectively. The ROC curve is shown in Fig. 1. AMH and AFC values were found to be significantly valuable in predicting response to CC. The area under the curve (AUC) was 0.862 for AMH, while it was 0.792 for AFC. In this study, AMH had a higher area under the ROC curve than AFC. Therefore, AMH was more effective in predicting the response to CC. The AUC and statistical significance values for AMH and AFC are shown in Table 3.

Moreover, in both groups, the correlation of the serum AMH levels with age, basal serum FSH levels, and antral follicle count (AFC) were evaluated. On the other hand, there was a significant negative correlation between D-3 serum FSH and AFC (r = −0,339, p = 0,001); while there was a significant positive correlation between the AFC and serum AMH levels (r = 0.713, p = 0.001) (Table 4). Table 4 shows pairwise comparisons of each parameter (FSH, AFC, AMH and age) with correlation coefficient (r) and significance value (p).

The ANCOVA (analysis of covariance) showed that serum AMH levels alone had statistically significant value in predicting ovulatory response to CC (p = 0.001).

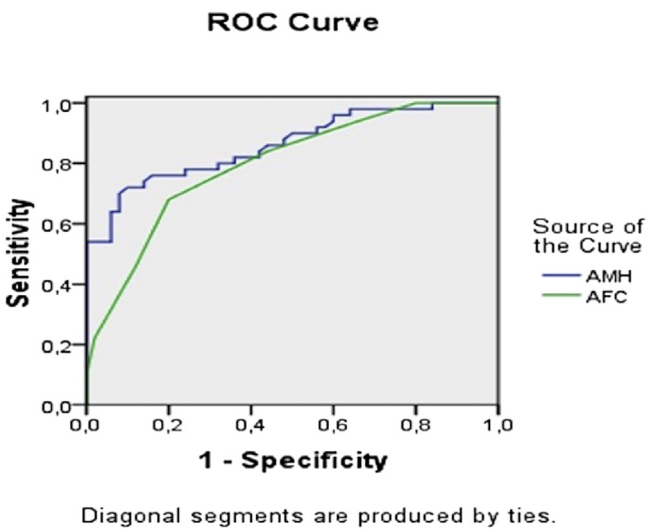

Fig. 1. ROC curve of AMH and AFC values according to response to clomiphene citrate.

Discussion

A cause for a subtle ovulatory disfunction was investigated in patients with unexplained infertility, however an abnormality in pulastile GnRH secretion or sensitivity to GnRh was not shown in the early studies [9]. Hormonal monitoring and measurement of physiological response to GnRh in women with unexplained infertility pointed out “diminished ovarian reserve” as a possible cause of unexplained imfertility [9,10]. Ekka et al. reported lower AMH values in women with unexplained infertility on comparison to age-matched fertile women [11]. AMH levels were evaluated in patients with unexplained infertility who were followed-up for 5 years as a predictor for future live birth and a cut of value of ≤10 pmol/L in combination with age and presence of ovulatory cycles was found to have high predictive value [12]. However Casadei et al. reported that AMH did not have a predictive value in predicting spontaneous pregnancy in patients with unexplained infertility [13]. Satwick et al. reported a more absolute cut-off level of 2 pmol/L (98% specificity, 20% sensitivity) for prediction of negative ovarian response while the AMH levels had a huge variation between 2 and 10 pmol/L in average responders in patients who underwent IVF-ET cycles [14]. Rigon et al. reported an association between normo-ovulatory infertility and AMH and AMH receptor type II (AMHRII) polymorphisms that might be speculated to be a possible reason for the discordance between the AMH levels and reproductive outcome in some patients [15].

Ovulation induction or augmentation is with or without IUI, gonadotropins and IVF is used for treatment of women with unexplained infertility [16]. Despite advances in the assisted reproductive technologies, there is an ongoing discussion on diagnostic tests that predict poor ovarian respond for each treatment modality [17]. Fanchin investigated the correlation between serum AMH; FSH; LH; E2, inhibin B levels of 75 infertile women and the early AFC performed on cycle Day 3. While only AMH, inhibin B and FSH were significantly correleted with early AFC, the strongest correlation was between AMH and early AFC (r = 0.74, P < 0.0001) [18]. In the presented study, in women with unexplained infertility D-3 FSH and AFC values had a statistically significant negative correlation (r = −0.339, p = 0.001); while AFC and AMH values had a statistically significant positive correlation (r = 0.713, p = 0.001).

A previous study from Turkey demonstrated that in 180 patients who had their first IVF cycle a cut-off value of 2.97 ng/mL for AMH was found to predict the poor ovarian response with a sensitivity of 100.0% and a specificity of 89.6 [19]. Lee et al. reported a cut-off value of 1.05 ng/mL for nonpregnancy and 0.68 ng/mL for cycle cancellation in 116 infertile patients ≥40 years of age who had IVF/ICSI [20]. In 90 women who had their first IVF/ICSI cycle, a baseline Day-3 serum AMH level below 2.74 ng/mL had a sensitivity of 69% and specificity of 70.5% in prediction of poor ovarian response [21]. Sahmay et al. used FSH, E2, and AMH levels in addition to AFC on day 3 of the menstrual cycle in order to predict ovarian response to COH treatment and reported that AMH was significantly more successful in predicting the response in comparison to serum FSH, E2 levels and AFC. They reported that an AMH cutoff value of ≤2 (ng/mL) predicted poor response with a sensitivity and a specificity of 78.9% and 73.8% respectively [22]. Nardo et al. investigated the role of AMH in prediction of response to ovarian hyperstimulation

Table 2
Sensitivity and specificity rates for AMH levels in response to clomiphene citrate.

Anti-Mullerian hormone (ng/ml)	Sensitivity	Specificity
2.72	0.76	0.80
2.75	0.76	0.84
2.78	**0.74**	**0.86**
2.80	0.72	0.86
2.82	0.72	0.88

A maternal serum anti-mullerian cut-off 2.78 ng/ml was found to be optimal for determination of response to CC with a sensitivity of 74% and specificity of %86.

Table 3
Statistical significance values and AUC of the AMH and AFC.

	Cut-off	ROC AUC	95% CI	p-value	Sensitivity	Specificity
AMH (ng/ml)	2.78	0.862	0.791–0.933	0.001	74%	86%
AFC	14	0.792	0.711–0.883	0.001	68%	80%

AMH, anti-Mullerian hormone; AFC, antral follicle count; ROC AUC, receiving operator curve area under curve.

Table 4
The correlation coefficients and significant values between the FSH, AFC, AMH and age of the patients.

		AFC	AMH (ng/ml)	Age (year)
FSH (IU/l)	r	−0.339	−0.551	0.138
	p	0.001	0.001	0.172
AFC	r		0.713	−0.279
	p		0.001	0.005
AMH (ng/ml)	r			−0.331
	p			0.001

FSH, follicle stimulating hormone; AFC, antral follicle count; AMH, anti-Mullerian hormone; r, correlation coefficient; $p < 0.05$ statistically significant.

with gonadotropins in IVF cycles. The stimulation was predicted by 88% sensitivity and 70% specificity at an AMH cut-off value of >3.5, while poor response was predicted by 87% sensitivity and 67% specificity with a cut-off value of <1 [23]. In the presented study, in CC cycles the cut-off value for AMH was found to be 2.78 ng/mL for prediction of poor ovarian response with a sensitivity and specificity of 74% and 86%, respectively. The presented cut-off value obtained in CC cycles was compatible with the studies in the literature although gonadotropins were used for ovulation induction in these studies [19,21].

The predictive value of AFC in ovarian response have been subject to various studies. In the presented study an AFC cutoff value of 14 was found to be predictive of ovarian response with a sensitivity and specificity of 68% and 80%, respectively. Adibi et al. reported a cutoff value of 15.5 for predicting ovarian responsiveness in clomiphene citrate cycles and stated that AFC had a better predictive value than ovarian volume and hormonal tests [24]. In a study that aimed to determine the basal value of AFC in subfertile and fertile Indian population a large percentage (86.7%) of the fertile population was found to have an AFC > 10 [25]. The AFC level was statistically significantly lower in the non-responsive group (13.1 ± 1.8 vs 15.2 ± 1.6, $p = 0.001$).

Eldar-Geva et al. analyzed AFC, serum inhibin-B, AMH, and FSH levels in 56 women going under COH with recombinant FSH. They showed that while AFC, follicular AMH and induced inhibin B levels had a predictive value for poor ovarian response only serum AMH (either follicular or luteal) had a predictive value in achieving pregnancy; a cut-off basal AMH (either follicular or luteal) of 2.52 ng/mL had a positive predictive value of 67% and a negative predictive value of 61% for achieving an ongoing pregnancy ($p < 0.01$) [26]. Hazout et al. found a strong relationship between basal serum AMH levels and the number of mature oocytes, embryos and even clinical pregnancy rates. In 109 IVF patients under 42 years of age, women who became pregnant had a mean serum AMH value of 2.4 ng/mL (38 patients) and while this was 1.1 ng/mL in nonpregnant women (71 patients) [27].

In the literature, studies investigating the efficacy of serum AMH level in prediction of ovarian response to CC have been conducted only in infertile women with polycystic ovary syndrome [28–30]. Mahran et al. reported a significantly lower serum AMH level in 187 PCOS patients who were responsive to CC (AMH levels for the responsive and nonresponsive groups were 2.5 ± 0.1, 5.8 ± 0.7, respectively, $p < 0.001$) [28]. Ellakwa et al. and Xi et al. also stated that serum AMH levels might be useful in prediction of ovarian response to clomiphene citrate in patients with PCOS [31,32].

The underlying reason of the negative correlation between serum AMH levels and response to ovulation induction with CC was associated with increasing serum AMH levels in relation to growing number of ovarian preantral and small antral follicles in polycystic ovary syndrome in response to CC [32]. This is thought to be related to be the inhibitory effect of AMH on FSH-stimulated follicle growth and eventually this will alter the follicular growth by decreasing FSH responsiveness [33]. In the presented study, unlike other studies in the literature, the patients diagnosed with PCOS were not included. In this study normoovulatory patients with unexplained infertility received ovulation induction with CC and both the serum AMH levels and AFC values were found to be significantly higher in responders, while serum FSH and E2 in the same group.

In conclusion, despite the well-recognized association between AMH and the ovarian reserve, the correlation between serum AMH levels and response to ovulation induction with CC in patients unexplained infertility needs further investigation In the presented study, a serum AMH cut-off value of 2.78 ng/mL was found to be optimal for predicting the response to CC treatment for ovulation induction in patients with unexplained fertility and we recommend using gonadotropin for ovulation induction at values below this cut-off value. Routine serum AMH level measurement may be useful for individualization of treatment modality in unexplained infertility patients. However, due to a limited number of patients recruited to the study, further prospective and randomized studies with larger patient groups are required.

Ethic committee

Ethic committee approval was received for this study.

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Conflict of interest

The authors declared no conflict of interest.

Informed consent

Written informed consent was obtained from patients who participated in this study.

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