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Original Research Article

Predictive value of ovarian reserve markers for clinical pregnancy in women with diminished ovarian reserve

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Abstract

Background: To evaluate the predictive value of anti-Mullerian hormone (AMH) and Antral follicle count (AFC) for clinical pregnancy rates and achieving embryo transfer in women with diminished ovarian reserve (DOR) undergoing in vitro fertilization (IVF) treatment.
Materials and Methods: The study included 480 DOR patients who underwent IVF treatment. Serum levels of AMH and follicle-stimulating hormone (FSH) were measured, and AFC was determined through ultrasound examination. Patients were divided into embryo transfer-positive and -negative groups based on the outcome of their treatment cycles. Clinical pregnancy rates were compared among quartiles of AMH, FSH, and AFC. Logistic regression and receiver operating characteristic (ROC) curve analysis were performed to assess the predictive value of AMH and AFC.
Results: The study found that AFC was a more valuable for predicting positive results (OR: 2.7, R2=0.324, p<0.001), while AMH was more valuable for predicting negative results (OR: 4.6, R2=0.324, p=0.02) regarding achieving embryo transfer in DOR patients. The clinical pregnancy rates did not differ significantly among quartiles of AMH and FSH levels. However, there was a significant difference in clinical pregnancy rates among quartiles of AFC (p=0.015). The ROC analysis revealed that AFC had a higher area under the curve compared to AMH, indicating better predictive value.
Conclusion: The study indicated that AFC had greater predictive value for positive outcomes, whereas AMH proved more beneficial in predicting negative outcomes in the context of achieving embryo transfer among DOR patients. These findings suggest that AFC may be a valuable marker for predicting treatment outcomes in DOR patients undergoing IVF.

Keywords: Anti-mullerian hormone, Embryo transfer, Fertilization in vitro, Ovarian reserve.

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1. Introduction

Diminished ovarian reserve is defined as a decrease in oocyte quality and quantity in the ovaries of patients with infertility.[1] The prevalence of diminished ovarian reserve is 26% among infertile patients treated with assisted reproductive technology (ART).[2] Assessment of ovarian reserve involves using biochemical markers in the blood and ultrasound imaging of the ovary.[1] Markers such as basal estradiol (E2), follicle-stimulating hormone (FSH), inhibin B, Anti-Müllerian hormone (AMH), and Antral follicle count (AFC) are used to evaluate ovarian reserve.[1] Various reproductive medicine societies have issued similar recommendations regarding the use of ovarian reserve markers in infertile patients.[1,3,4] While ovarian reserve markers may not predict reproductive potential in the general population, they can help predict the success of ovarian stimulation in infertile patients.[1] Using ovarian reserve markers outside the context of infertility treatment may lead to unnecessary interventions and cause anxiety and depression among patients. These markers should not be used to exclude patients from undergoing in vitro fertilization (IVF) treatment, even if their AMH levels are extremely low.[5] However, studies utilizing these markers may help clinicians set realistic expectations to patients with diminished ovarian reserve regarding the outcomes of IVF therapy. Although definitive criteria for

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diminished ovarian reserve do not exist, certain organizations define cut-off values to identify this patient group. These include an AMH value <1 ng/mL, AFC <5-7, FSH >10 IU/L, and a history of poor response to IVF stimulation, as described by the American Society for Reproductive Medicine (ASRM).[3]

This study aims to investigate the relationship between ovarian reserve markers and clinical pregnancy outcomes in women with diminished ovarian reserve treated with IVF therapy.

2. Material and Methods

A cohort of 480 women diagnosed with diminished ovarian reserve received follow-up and treatment at the IVF Center of Training and Research Hospital Gynecology and Obstetrics Clinic from January 2010 to August 2019. Data were retrospectively gathered from patient files and the hospital's electronic database. Ethical approval was secured from the university's committee (1978-13.09.2019), aligning with the principles of the Helsinki Declaration, and informed consent was obtained from all participants.

Diminished ovarian reserve, excluding advanced maternal age (≥40 years), was defined based on BOLOGNA criteria. All participants were aged between 20 to 40 years, selected for their history of poor ovarian response (≤3 oocytes with conventional stimulation) and abnormal ovarian reserve tests (AFC <5-7 follicles or AMH <0.5-1.1 ng/mL). Clinical pregnancy confirmed by transvaginal ultrasound 4-5 weeks post-embryo transfer. Patients were divided into two groups based on clinical pregnancy status. Both groups exhibited normal hormone levels, a healthy uterine cavity, and confirmed bilateral tubal patency via hysterosalpingography (HSG). Additionally, they had no history of pelvic surgery or systemic disease, and their partners demonstrated normal semen analysis (according to the WHO 2010 criteria).

Blood samples collected on day 3 (±1) of the menstrual cycle, one month before IVF, and used for AMH level measurement through enzymatically amplified two-sided immunoassay (AMH Gen 2 Elisa A79765; Beckman Coulter, Ireland, 2011). Serum levels of estradiol (E2), luteinizing hormone (LH), and FSH were measured using a Siemens Immulite 2000 automated immunoassay analyzer. The sensitivities of LH, FSH, and E2 were 0.05 mIU/mL, 0.1 mIU/mL, and 15 pg/mL, respectively.

A GnRH antagonist protocol was employed for patients with diminished ovarian reserve in our infertility clinic. The stimulation protocol involving recombinant FSH (Gonal F; Merck Serono, Switzerland) alone or in combination with human menopausal gonadotropin (Menogon; Ferring, Istanbul, Turkey) starting on day 3 of menstrual cycle. GnRH antagonist (Cetrotide; Asta Medica, Frankfurt, Germany) was initiated on day 3 of menstruation and continued until the follicles reached 14 mm. After the dominant follicle reached 18 mm, recombinant hCG (Ovitrelle 250 mcg, Serono, Switzerland) was administered for oocyte maturation. Oocytes were aspirated 36 hours later under transvaginal ultrasound guidance, and intracytoplasmic sperm injection (ICSI) was performed using fresh spermatozoa. Embryo transfer was performed on day 3. Followed by the transfer, all patients received vaginal progesterone (Crinone 8%; Merck Serono) for luteal phase support. Pregnancy assessment was performed with β-human chorionic gonadotropin (β-hCG) testing 12 days post-embryo transfer and fetal heartbeat confirmation via transvaginal ultrasound 4-5 weeks later.

IBM SPSS 26.0 software was used for database creation and statistical analysis. Descriptive statistics, such as the mean, median, and standard deviation, were used for continuous variables. The Pearson Chi-square and Fisher's exact tests were used to compare categorical variables. The distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. Student's t-test was used to compare independent variables with a normal distribution, while the Mann-Whitney U test was used for those that did not follow a normal distribution. Multiple logistic regression analysis was performed to identify independent variables that predicted the dependent variable in multivariate analyses. A p-value of less than 0.05 was considered statistically significant.

3. Results

From the data records, 480 patients were identified, and 48 (10%) of them did not reach the dominant follicle after ovarian stimulation, resulting in the cancellation of oocyte pick-up (OPU). OPU was performed on 432 (90%) patients, but 68 (13.5%) of them had failed procedures due to the inability to retrieve oocytes. Embryo transfer (ET) was not performed in 25 (5.2%) patients due to fertilization failure. ET was carried out in 342 (71.2%) patients, and 83 patients achieved clinical pregnancies. The clinical pregnancy rate was 17.3% in all patients and 24.2% in the ET group. The age and serum biochemical marker distributions of patients according to clinical pregnancy status are shown in **Table 1**. There were no significant differences between the clinical pregnancy groups in terms of age, AMH, FSH, and E2 ($p > 0.05$). The mean AFC numbers were 3.9 ± 1.4 in the positive clinical pregnancy group and 3.4 ± 1.5 in the negative clinical pregnancy group, with a statistically significant difference ($p = 0.009$). From the data records, 480 patients were identified, and 48 (10%) of them did not reach the dominant follicle after ovarian stimulation, resulting in the cancellation of oocyte pick-up (OPU). OPU was performed on 432 (90%) patients, but 68 (13.5%) of them had failed procedures due to the inability to retrieve oocytes. Embryo transfer (ET) was not performed in 25 (5.2%) patients due to fertilization failure. ET was carried out in 342 (71.2%) patients, and 83 patients achieved clinical pregnancies. The clinical pregnancy rate was 17.3% in all patients and 24.2% in the ET group. The age

and serum biochemical marker distributions of patients according to clinical pregnancy status are shown in **Table 1**. There were no significant differences between the clinical pregnancy groups in terms of age, AMH, FSH, and E2 ($p > 0.05$). The mean AFC numbers were 3.9 ± 1.4 in the positive clinical pregnancy group and 3.4 ± 1.5 in the negative clinical pregnancy group, with a statistically significant difference ($p = 0.009$). The groups were divided into quartiles based on AMH and FSH levels, as well as AFC numbers. The clinical pregnancy rates for each group are shown in **Table 2**. The clinical pregnancy rates did not differ significantly among the quartiles of AMH and FSH levels when comparing all three groups (<25th percentile, 25th-75th percentile, >75th percentile) ($p > 0.05$). However, there was a significant difference in clinical pregnancy rates among the quartiles of AFC numbers (p=0.015).

The age and serum biochemical marker distributions of patients according to the status of embryo transfer are presented in **Table 3**. The mean AFC numbers and AMH levels were significantly higher in the ET-positive group (p=0.000). The mean E2 and FSH levels were significantly lower in the ET-positive group. In the regression analysis, AFC was found to be a predictor of positive results (OR: 2.7, R2=0.324, p<0.001), while AMH was found to be a predictor of negative results (OR: 4.6, R2=0.324, p=0.02) related to achieving embryo transfer in DOR patients. The receiver operating characteristic (ROC) curve is shown in Figure 1 for AMH and AFC to predict the success of embryo transfer, with an area under the curve (AUC) of 0.72 and 0.78 for AMH and AFC, respectively (p=0.000). Using a cutoff value of 0.425 ng/mL for AMH, the sensitivity, specificity, positive predictive value, and negative predictive value were found to be 67.8%, 67.4%, 30.3%, and 90.9%, respectively.

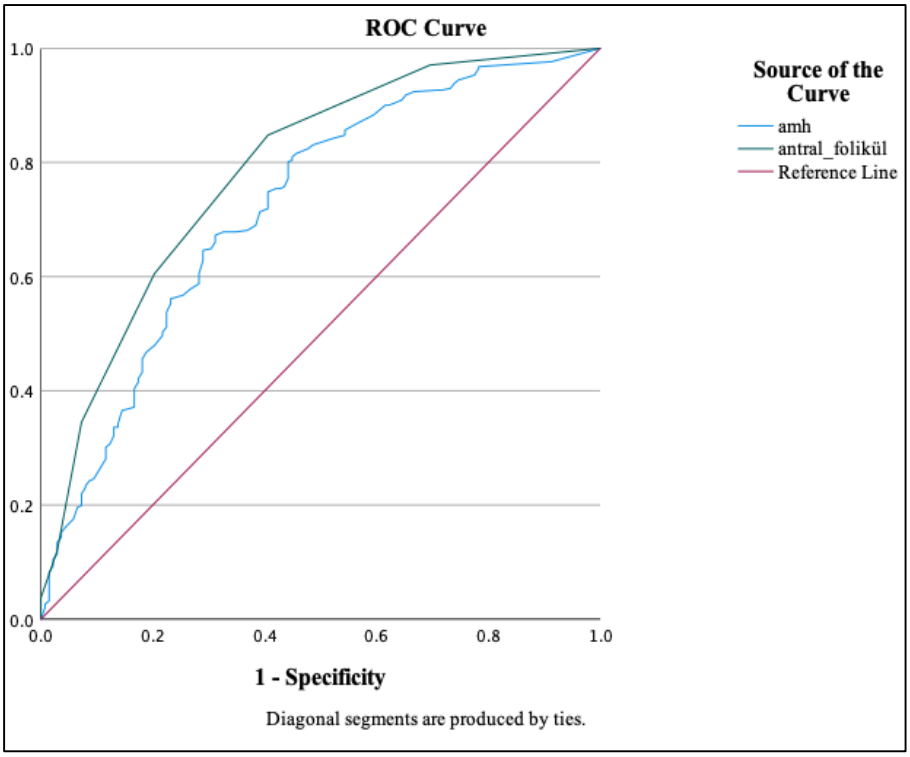

Figure 1: ROC curve for AMH levels and AFC numbers in the prediction of ET achievement in diminished over patients

Table 1: Comparison of demographical parameters and ovarian reserve markers level in pregnant and non-pregnant groups

	Mean ± SD		
Variable	**Pregnancy (+) (n=83) (17,3%)**	**Pregnancy (-) (n=397) (82.7%)**	**p value**
Age (years)	34.3±4.6	34.7±4.1	0.158
AMH (ng/mL)	0.50±0.33	0.51±0.33	0.947
AFC (n)	3.9±1.4	3.4±1.5	0.009
FSH (mIU/mL)	12.1±5.1	13.8±10	0.784
E2(pg/mL)	62.3±35	69.7±29.3	0.163

Table 2: Comparison of pregnancy rates per cycle according to the quartiles of AMH, AFC and FSH

	< 25%			25-75%				>75%		p value
	Range	n	CPR%	Range	n	CPR%	Range	n	CPR%	
AMH (ng/ml)	<0.2	22	17.6	0.2-0.79	43	17.8	>0.79	18	15.1	0.760
FSH (mIU/ml)	<8.3	19	16.2	8.3-14.6	49	20.4	>14.6	15	12.2	0.138
AFC (number)	<2	2	3.8	2-5	70	18.2	>5	11	24	0.015

Chi square test
CPR: Clinical pregnancy rate

Table 3: Comparison of age and ovarian reserve markers level in ET and non-ET groups

	Mean ± SD		
	ET (+) (n=342) (71.2%)	ET (-) (n=138) (28.8%)	p value
Age (years)	34.2±4.3	.9±3.7	0.125
AMH (ng/mL)	0.58±0.31	0.33±0.31	0.000
AFC (n)	3.9±1.4	2.4±1.3	0.000
FSH (mIU/mL)	11.5±4.9	18.2±14.6	0.000
E2(pg/mL)	67.1±25.9	74.7±38.6	0.002

ET: Embryo transfer

4. Discussion

The use of AMH and other ovarian reserve markers for predicting fertility potential, the success of assisted reproductive technology (ART), and ovarian response remains controversial. Current recommendations from reproductive medicine societies suggest that AMH and AFC are the most sensitive markers of ovarian reserve. However, these markers should not be used to predict oocyte quality, clinical pregnancy rates, or live birth rates.

In the present study, we found that the clinical pregnancy group had significantly higher mean AFC among patients with diminished ovarian reserve (DOR). Additionally, patients who achieved embryo transfer had significantly higher mean AMH levels and AFC counts, while FSH and E2 levels were significantly lower. The mean age of women was similar between groups when stratified by clinical pregnancy and embryo transfer outcomes. This similarity minimized the confounding effect of age on IVF success and allowed us to more accurately assess the predictive performance of ovarian reserve markers independent of age.

Managing DOR patients is challenging, and reported pregnancy rates after IVF treatment range from 15%.[7] Numerous studies have investigated the association between ovarian reserve markers and the prediction of clinical pregnancy. Some studies have found a correlation between AMH and live birth rates after assisted conception.[8] However, many others have not found a predictive value of AMH for clinical pregnancy rates or live birth after IVF treatment in DOR patients. Arce et al. found that AMH levels correlated with oocyte yield and cumulative live birth rates.[9] Broer et al. reported that ovarian reserve markers were useful for predicting poor ovarian response, but not for predicting ongoing pregnancy after IVF.[10]

AFC and AMH have been compared in many studies regarding their ability to predict poor ovarian response and live birth rates after IVF. Some studies have reported a correlation between AMH and AFC, which is reasonable since the majority of AMH is secreted by pre-antral and early antral follicles.[11] Lukaszuk et al. reported that AMH was a better prognostic marker than AFC and other ovarian reserve markers in terms of accuracy and robustness.[12] Iliodromiti et al. found that AFC and AMH had similar predictive value for ovarian response in assisted conception, but AMH was considered more accurate and robust, since AFC was highly dependent on operator experience.[13] Aslan et al. reported that patients with high AMH levels (≥1.1 ng/mL) and low AFC (<7) had better ovarian response compared to patients with low AMH and high AFC, based on their retrospective analysis of ovarian response in DOR patients with discordant AMH and AFC results.[14]

In a prospective study, Majumder et al. evaluated the correlation between AFC, AMH, and the number of oocytes retrieved and fertilized. They found that both markers were positively correlated with oocyte retrieval and fertilization rates. However, neither marker was associated with embryo quality, implantation rates, or clinical pregnancy rates.[15]

The first milestone in an IVF cycle is the successful formation of an embryo. After this step, several factors influence the achievement of a successful pregnancy. Failures following embryo transfer may not accurately reflect the true value of these markers, as success in implantation can be influenced by various other factors.[16] To evaluate this in the present study, we also assessed the relationship between ovarian reserve markers and the achievement of embryo transfer.

The diagnosis of DOR is increasing due to the widespread use of ovarian reserve markers.[17] When counseling DOR patients, balancing unrealistically high pregnancy expectations and unnecessary concerns arising from laboratory results presents a challenging aspect of patient management. The findings emphasized the

significance of AFC and AMH as markers indicative of ovarian reserve. However, neither marker could predict pregnancy outcomes in patients with DOR. Within the limited range of AMH values, no specific cut-off limit emerged to determine pregnancy success. Additionally, the study revealed that AFC is a more dependable predictor of achieving embryo transfer in patients with DOR compared to AMH. ROC analysis also indicated that AFC had a higher AUC compared to AMH, further supporting its predictive value.

5. Conclusion

In conclusion, the present study found that AFC was a positive predictor, while AMH was a negative predictor for achieving embryo transfer in DOR patients. However, the clinical pregnancy rates did not differ significantly among quartiles of AMH and FSH levels. These findings suggest that AFC may be a more reliable marker than AMH for predicting treatment outcomes in DOR patients undergoing IVF. Further research is needed to better understand the predictive value of ovarian reserve markers in this patient population and to identify other factors that may influence treatment success.

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The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

7. Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

8. Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article if more information needed please contact karolette@gmail.com.

9. Authors' Contributions

Görkem ARICA wrote the manuscript and made the analysis and interpretation of the data. Karolin OHANOGLU CETINEL helped with the language and revised it critically and made the submission. Fatma Verit was the supervisor of the work. All authors have participated to drafting the manuscript. All authors read and approved the final version of the manuscript.

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Not applicable

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