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Original Article

The predictive effect of serum AMH and FSH levels alone or in combination on fertility outcome

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ABSTRACT

Objective: To explore the roles of anti-mullerian hormone (AMH) and follicle stimulating hormone (FSH) in predicting clinical pregnancy.

Materials and Methods: Forty patients who were decided on IVF/ICSI due to different infertility etiologies were included in the study. The patients were divided into two groups according to their AMH and FSH values as having a good prognosis or a poor prognosis. The clinical pregnancy and miscarriage rates of 33 cycles with good prognosis and 17 cycles with poor prognosis were compared.

Results: In the good prognosis group, the FSH value was significantly lower than the poor prognosis group (5.98±1.04 mIU/mL vs. 13.6±3.07 mIU/mL, p<0.01), while the serum AMH level was significantly higher. (3.80±1.32 ng/mL vs 0.54±0.02 ng/mL, p<0.01). The rate of chemical pregnancy in the group with good prognosis was twice as high and significant compared to the group with poor prognosis (12 (36.3%) vs 5 (29.4%), p<0.02). In terms of clinical pregnancy rates, the group with good prognosis showed a higher frequency (33.3% vs. 23.5%, p<0.001), while miscarraige rates were higher in the group with poor prognosis (9.0% vs. 25%, p<0.003).

Conclusions: Evaluation of AMH and FSH together is critical in determining clinical pregnancy rates.

Keywords: AMH; FSH; clinical pregnancy; age; BMI

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Introduction

Although many serum and radiological markers are used to determine functional reserve of ovary in women of reproductive age, AMH and FSH are considered the best indicators of ovarian reserve. The main problem with AMH and FSH is that there is no specific cut-off value for both hormones. Obtaining pregnancies with low AMH and high FSH values in rare cases has led to the questioning of the effects of these two hormones on fertility outcome. Despite their significant effects on ovarian reserve, the weaker effects on pregnancy rates have made the combined use of these two hormones widespread [1,2].

Anti-Mullerian hormone (AMH) is a glycoprotein hormone belonging to the transforming growth factor beta family and is synthesized and secreted by granulosa cells. It continues to be released from the primary follicle to the early-stage antral follicle. As the follicles respond to FSH, AMH release also decreases and disappears. Preovulatory follicle, atretic follicles, and corpus luteum are the stages in which AMH activity is completely absent. No AMH activity has been reported in follicles larger than 8 mm [1,2]. Considering the efficiency of AMH to be superior to FSH in determining ovarian reserve has led to the predictive use of this molecule in many areas. Determining the fertility outcome according to AMH values is one of these areas [3]. Since there is no marker to measure the primordial follicle pool directly, the primary follicles indirectly show the primordial pool.

Functional ovarian reserve can be modeled in three different ways according to the number of quality embryos, FSH and AMH values. The common feature of all three models is that maternal age is the determinant.

The higher the number of embryos in the embryo model, the higher the improvement in fertility outcome linearly. In FSH modeling, fertility outcome and AMH values are inversely proportional. The higher the FSH, the more negatively the fertility outcome will be affected. The relationship between AMH values and fertility outcome shows a polynomial course. Mid-range values of AMH give the best fertility results. Low and very high AMH values, on the other hand, decrease the occurrence of pregnancy and increase the risk of abortion [4,5]. The combined use of AMH and FSH is critical in identifying groups with good or poor prognosis. AMH>1.1 ng/ml and FSH <10 mIU/ml suggest good ovarian reserve. Deviation of AMH and FSH values from the above values indicates poor ovarian response [6,7]. This study was planned to determine the clinical pregnancy rates of patients who were divided into groups as ovarian reserve with good or poor prognosis according to AMH and FSH values.

Material and methods

Medical files of 100 patients who were treated for infertility at Gözde Akademi Hospital IVF Center between 2019 and 2021 were retrospectively analyzed. A total of 40 patients with serum AMH and FSH values, who completed their cycles, had fresh or FET cycles, and had demographic data, and 50 cycles were included in the study. The participants were divided into two groups according to their AMH and FSH values as good prognosis (n=33 cycle) and poor prognosis (n=17 cycle). Cases with AMH greater than 1.0 ng/ml and FSH smaller than 10 mIU/ml were included in the group with good prognosis [4,5].

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Cases with AMH less than 1.0 ng/ml and FSH bigger than 10 mIU/ml constituted the group with poor prognosis. Serum follicular stimulating hormone levels were measured with chemiluminescent enzyme immunoassay. Serum AMH levels were measured by using AMH ELISA kit. Informed consent was not obtained because the study was retrospective. Ethical approval was obtained from Diyarbakır Gazi Yaşargil Training and Research Hospital on 30.12.2022 with protocol number 250.

An antagonist protocol was applied to all participants and frozen embryo transfer was performed following artificial endometrial preparation. Serum beta-hCG, clinical pregnancy rate (CPR) and miscarriage rates were calculated. Serum beta-hCG levels were measured 12 days after the transfer. The presence of a gestational sac on ultrasonography at the fourth gestational week was considered clinical pregnancy. Fetal losses before the 20th gestational week were considered miscarriage.

Statistical analysis

SPSS 21 (SPSS Inc., Chicago, IL, USA) program was used for whole data analysis. The t-test was used for normally distributed parameters, and Mann-Whitney U was used for non-normal ones. If the frequencies were smaller than expected, the Fischer exact test was preferred. $p<0.05$ was considered significant.

Results

Demographic, laboratory and fertility outcome data of groups with good (AMH ≥1 ng/ml; FSH <10 mIU/mL) and poor (AMH <1 ng/ml; FSH ≥10 mIU/mL) prognosis are detailed in Table 1.

Table 1. Comparison of demographic, laboratory and fertility data of groups with good and poor prognosis.

	Good prognosis	Poor prognosis	P
Cycle, n(%)*	33 (66%)	17 (34%)	*<0.01*
Age (years) *	26.4±6.2	29.3±8.4	0.02
BMI (kg/m^2) *	25.3±8.3	26.1±5.0	>0.05
FSH (mIU/mL) *	5.9±1.0	13.6±3.0	<0.01
AMH (ng/mL) *	3.8±1.3	0.54±0.02	<0.01
Embryo transferred	1	1	>0.05
Beta hCG, n(%)	12 (36.3%)	5 (29.4%)	0.02
Clinical Pregnancy, n(%)	11 (33.3%)	4 (23.5%)	<0.001
Miscarriage, n(%)	1 (9.0%)	1 (25%)	0.003

**Data are presented as Mean±SD*

The number of cycles of the good prognosis group was approximately two times higher than the number of cycles of the group with poor prognosis (66% vs 34%, $p<0.01$). The mean age of the participants in the poor prognosis group was significantly higher than the good prognosis group. BMI values of both groups were found to be similar. FSH value measured in the group with good prognosis was approximately 2.5 times lower than the group with poor prognosis (5.98±1.04 mIU/mL vs. 13.6±3.07 mIU/mL, $p<0.01$). The serum AMH level of the good prognosis group was found to be significantly higher than the poor prognosis group (3.80±1.32 ng/mL vs 0.54±0.02 ng/mL, $p<0.01$). The number of embryos transferred in both groups was similar. The number of patients with positive pregnancy test in the group with good prognosis was twice as high as in the group with bad prognosis, and the difference was recorded as significant (12 (36.3%) vs 5 (29.4%), $p<0.02$). Clinical pregnancy rates were significantly higher in the good prognosis group than in the poor prognosis group (33.3% vs 23.5%, $p<0.001$). Miscarriage rates were found to be significantly higher in the poor prognosis group (9.0% vs 25%, $p<0.003$)

Discussion

AMH is superior to FSH in showing ovarian reserve and fertility outcome [8]. However, when we used AMH and FSH in combination, these two hormones were more predictive than AMH alone or FSH alone in determining clinical pregnancy rates. However, we do not know clearly whether the hormone that increases the predictive value in the combined use of these two markers is AMH or FSH. In order to make a comment on this issue or to say which of the two hormones is more predictive, analysis using generalized additive mixed models is required. Only by using such a statistical method we can reveal the nonlinear fixed and predictive effect of FSH and AMH on clinical pregnancy rates [9]. The total number of 50 cycles in our study did not provide enough power for us to conduct such an analysis. In a recent study using generalized additive mixed models, when FSH and AMH were used together, AMH provided a significant advantage over FSH in determining fertility outcome (1].

We can classify the possible reasons why AMH is superior to FSH in determining the fertility outcome as follows. While AMH defines functional ovarian reserve, FSH determines the amount of granulosa cell mass capable of synthesizing estrogen. FSH has no feature to define functional ovarian reserve. Neither AMH nor FSH can identify the primordial follicle pool. AMH activity begins with the growth of primordial follicles. Since the growing follicle pool reflects the active granulosa cell mass for AMH, AMH is superior to FSH in determining fertility outcome. Sometimes, despite the sufficient growing follicle pool, FSH may be elevated because insufficient estrogen will be synthesized due to failed follicle development. For this reason, high FSH does not always indicate that ovarian reserve and fertility outcome are bad (10,11].

Both the number of hCG positive pregnant women and clinical pregnancy rates were significantly higher in the good prognosis group compared to the poor prognosis control group. Micarriage rates were higher in the poor prognosis group. While FSH values were >13 mIU/mL in the poor prognosis group, AMH values were recorded as 0.54 ng/mL. In infertile women (>0.6 ng/mL) with AMH values above a certain cut-off, a FSH >10 mIU/mL may not be very important. Büyük et al [10] reported that the oocyte count and clinical pregnancy rates were higher in cases with AMH>0.6 ng/mL despite high FSH compared to cases with AMH<0.6 ng/mL [1,12]. When the literature data and our findings are evaluated together, we can argue that the high FSH value in cases with high AMH levels does not affect the fertility outcome much [4,5]. The inverse relationship of FSH levels with fertility outcome, and the polynomial pattern of AMH will enable the functional ovarian reserve to be determined more clearly when both markers are used together. Thus, the predictivity of FSH and AMH association will increase more significantly [5]. However, we can reach a definite conclusion with more comprehensive studies, after which value of FSH affects the fertility outcome. We could not establish a link between increased miscarriage rates and elevated FSH or decreased AMH in the poor prognosis group. High FSH and low AMH are indicators of deterioration in follicle development quality. For this reason, abortion rates may also be high, as an embryo with a high risk of DNA damage will have a higher chance of being transferred.

The small number of cases is an important limitation of our

study. Also, since AMH is affected by both oral contraceptive use [13] and BMI [14], these two parameters need to be considered. Since the BMI values of our patients were similar, this does not constitute a discrepancy. However, the use of oral contraceptives by the participants was not taken into account. This study is important in terms of showing that the combination of AMH and FSH is more effective than AMH and FSH alone in determining the fertility outcome.

Disclosure

Authors have no potential conflicts of interest to disclose.

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