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The effect of anti mullerian hormone and follicle stimulating hormone discordance on oocyte quality and live birth rates

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Abstract

Evaluating ovarian reserve is crucial in infertility treatment to determine the appropriate approach and predict success rates. Anti-Müllerian Hormone (AMH) and Follicle-Stimulating Hormone (FSH) are key parameters commonly used for this purpose, and they usually yield consistent results. A good ovarian reserve is typically indicated when FSH is below 10 IU/ml and AMH is 1 ng/ml or higher. However, in clinical practice, these parameters often conflict, with one suggesting a good ovarian reserve while the other indicates a diminished one. AMH is known to predict oocyte count effectively, but its ability to predict live births is weaker. This study aimed to investigate which parameter is more useful in predicting oocyte count, quality, and live birth outcomes in cases of discordance. This retrospective study was conducted on 82 patients who sought infertility treatment at Assisted Reproductive Techniques Center of Gülhane Training and Research Hospital between January 1, 2016, and December 31, 2020. Data collected included age, AMH and FSH levels, number of retrieved oocytes, mature (M2) oocytes, pregnancy outcomes, and embryos obtained. Statistical analyses were performed using SPSS 25.0. Normal distribution was assessed using the Kolmogorov-Smirnov test and graphical methods. Independent t-tests and One-Way ANOVA were used for normally distributed data, with a significance level set at p=0.05. Patients were divided into two groups: AMH <1 ng/ml & FSH ≥10 IU/ml, and AMH ≥1 ng/ml & FSH <10 IU/ml. Patients with AMH <1 ng/ml were older and shorter (p<0.05). This group also had fewer retrieved oocytes and M2 oocytes (p<0.05). However, no significant differences were observed between the groups regarding live births, miscarriages, or embryo counts(p>0.05). In cases of discordance, AMH is more reliable for predicting oocyte quantity and quality, while neither AMH nor FSH is superior in predicting live birth outcomes. Both markers have limitations in estimating live birth probabilities.

Keywords: Anti-Müllerian Hormone, Follicle-Stimulating Hormone, ovarian reserve, live birth, oocyte quality

Introduction

Infertility is characterized as the failure to conceive after 1 year of regular (at least twice a week) and unprotected sexual intercourse [1]. Approximately 85-90% of healthy young couples conceive within 1 year, mostly within the first 6 months [2]. Infertility is estimated to affect 8 to 12% of couples of reproductive age worldwide [3].

Infertility is a prevalent and significant issue that has psychological, economic, demographic, and medical repercussions for many couples. Community awareness that infertility is a treatable condition with the development of assisted reproductive techniques, developments in contraception and family planning, increasing maternal age and the tendency to postpone childbearing in western countries have led to an increase in the demand for infertility services [4].

The key causes of infertility consist of male factors, diminished ovarian reserve, ovulatory disorders, tubal damage or blockage, uterine factors, pelvic factors, and unexplained infertility. Male

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factors can consist hypothalamic-hypophyseal disorders, primary gonadal disorders, anatomical defects, congenital anomalies of the ejaculatory system, abnormal spermatogenesis, abnormal motility and sexual dysfunction. In women, decreased ovarian reserve, ovulation disorders, tubal damage or obstruction, peritoneal and tubal adhesions associated with endometriosis may play an important role. Uterine and pelvic factors may also contribute to infertility. However, unexplained infertility can be diagnosed in some cases [5].

Ovarian reserve defines the number, quality and adequacy of follicles to fulfill the function of folliculogenesis and steroidogenesis in the ovaries. It indicates a woman's reproductive potential. A good test showing ovarian reserve is a marker of the probability of conception in a woman receiving or not receiving treatment, as well as guiding the clinician in adjusting treatment doses in the infertile population [6].

In addition to all these, an optimal ovarian reserve test should be easy to perform, reproducible, inexpensive, have minimal inter- or intra-cycle variability, diagnose reduced ovarian reserve, which is among the most important causes of female infertility, with high specificity and sensitivity, and predict the risk of development of ovarian hyperstimulation syndrome (OHSS) in infertility treatment [7].

Despite all these values, no definite standardization has been made worldwide in determining ovarian reserve. Discussions continue about the most reliable parameter [2]. In our research, we evaluated Follicle Stimulating Hormone (FSH) and Anti-Müllerian Hormone (AMH), which are two important parameters used in the evaluation of ovarian reserve. Incompatibility between these two variables, which are generally compatible with each other, may occur and this is quite common. The clinical manifestations of such discrepancies are not clearly known.

In our study, we aimed to predict which parameter is more valuable in predicting live birth rates and the yield or quality of oocytes obtained when there is a mismatch between AMH and FSH, that is, when FSH value indicates good ovarian response while AMH value shows decreased ovarian response for the same patient or vice versa.

Material and Methods

Our study is a retrospective descriptive study. Between 01.01.2016 and 31.12.2020, 82 patients who met the study criteria among 1495 patients who applied to Gülhane Training and Research Hospital (GTRH) Department of Obstetrics and Gynecology Assisted Reproductive Techniques Center with the desire for a child and were diagnosed with infertility and planned In Vitro Fertilisation (IVF) were determined as the study population.

Patients who applied to the GTRH Gynecology and Obstetrics Assisted Reproductive Techniques Center with the complaint of inability to achieve pregnancy after one year of regular sexual activity without employing any contraceptive methods, whose AMH and FSH values from ovarian reserve tests were studied and oocyte pick up was performed were evaluated.

Firstly, two groups were determined based on AMH and FSH values.

- Patients with AMH <1ng/ml and FSH <10 IU/ml
- Patients with AMH ≥1 ng/ml and FSH ≥10 IU/ml

The study also included patients with normal sperm parameters in the male and normal paterns of at least one fallopian tube in the female, documented by hysterosalpingography or laparoscopic chromotubation, without uterine or other infertility factors.

Patients with AMH ≥1 ng/ml and FSH <10 IU/ml were excluded because both parameters were suggestive of good ovarian reserve; likewise, patients with AMH <1ng/ml and FSH ≥10 IU/ml were excluded because both parameters were suggestive of decreased ovarian reserve.

The ethics committee approval of the study was obtained from the Gülhane Scientific Research Ethics Committee of the University of Health Sciences, with the registration number 2021/172. Then, the results of the patients in the hospital information system, file and archive scans were examined by observing patient privacy and keeping patient identity information confidential, and a single-center retrospective descriptive study was conducted.

The following parameters were collected from the patients included in the study;

Age, height, weight, AMH value, FSH value, number of oocytes collected, number of mature oocytes collected, pregnancy status resulting in live birth or miscarriage, number of embryos obtained

Data analysis was conducted using IBM SPSS 25.0 (Armonk, NY: IBM Corp.) and MedCalc 15.8 (MedCalc Software bvba, Ostend, Belgium) statistical software. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, minimum-maximum) and the Chi-Square (χ^2) test were employed to compare qualitative data. The normality of the data was assessed using the Kolmogorov-Smirnov test, alongside skewness, kurtosis, and graphical methods (such as histogram, Q-Q Plot, Stem and Leaf, and Boxplot). For quantitative data demonstrating normal distribution, Independent Samples t-test and One-Way ANOVA (one-way analysis of variance) were utilized. The level of statistical significance was set at p=0.05.

Results

Age, weight, height, body mass index, AMH, FSH levels, number of oocytes and M2 oocytes collected, live birth, miscarriage and embryo characteristics were recorded (Table 1).

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Table 1. Characteristics of the participants

		Mean±SD	Median (Min-Max)
Age(year)		34.3±4.4	35.0 (23.0–42.0)
Weight (kg)		67.8±11.6	68.0 (45.0–105.0)
Height (cm)		162.9±6.1	162.5 (145.0–178.0)
BMI (kg/m²)		25.6±4.7	25.1 (17.1–40.0)
AMH		0.8±0.6	0.7 (0–3.1)
FSH		8.0±3.0	8.3 (1.0–16.9)
Number of oocytes collected		5.3±3.8	5.0 (0–15.0)
M2 oocyte count		3.9±3.1	3.0 (0.0–12.0)
		n	**%**
Group	**AMH<1**	60	73.2
	FSH<8	36	43.9
	8≤FSH<10	24	29.3
	AMH≥1	22	26.8
	8≤FSH<10	10	12.2
	FSH≥10	12	14.6
Live birth	**Absent**	67	81.7
	Present	15	18.3
Miscarriage	**Absent**	76	92.7
	Present	6	7.3
Embryo	**No oocytes**	8	9.8
	POQ	15	18.3
	TFC	12	14.6
	Day 2 embryo	6	7.3
	Day 3 and later embryo	41	50.0

BMI: body mass index, AMH: anti- müllerian hormone, FSH: follicle stimulating hormone, POQ: poor embryo quality, TFF: total fertilization cancellation, M2: metaphase 2

In the group comparisons, it was found that there was no statistically significant difference in weight and BMI values between the groups (p>0.05), whereas a statistically significant difference was observed in terms of age and height values (p=0.004, p=0.003), AMH<1 patients were found to be older and shorter. It was found that there was a statistically significant difference between the groups in terms of AMH and FSH values (p=0), and in both cases where there was a difference, the AMH<1 patient group had lower values; there was a significant difference between the groups regarding the number of collected Oocytes and M2 (Metaphase 2) Oocytes (p=0.019, p=0.039), and in both cases where there was a difference, the AMH<1 patient group had lower values (Table 2).

Table 2. Comparison of patient characteristics, AMH and FSH, and number of collected oocytes and M2 oocytes by groups

	Group		**P***
	AMH<1	**AMH≥1**	
	(n=60)	**(n=22)**	
Age (year)	35.1±3.9	32.0±4.8	**0.004**
Weight (kg)	67.8±12.7	67.6±8.2	**0.951**
Height (cm)	161.7±5.7	166.1±6.0	**0.003**
BMI (kg/m²)	25.9±5.0	24.6±3.7	**0.238**
AMH	0.5±0.3	1.6±0.6	**0**
FSH	6.9±2.4	11.0±2.6	**0**
Number of oocytes collected	4.8±3.4	7.0±4.4	**0.019**
M2 oocyte count	3.4±2.6	5.3±3.8	**0.039**

*: independent samples t test (Mean±SD); BMI: body mass index, AMH: anti- müllerian hormone, FSH: follicle stimulating hormone, M2: metaphase 2

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In the comparisons conducted between the groups, it was determined that there was no statistically significant difference in terms of live birth, miscarriage, and embryo values (p>0.05). In the group comparisons, no statistically significant difference was observed regarding the number of oocytes retrieved (p>0.05), a statistically significant difference was observed between the groups concerning the number of M2 oocytes (p:0.039). Post-hoc tests were applied to determine the source of the difference, and it was found that there was a difference between the patient groups with AMH<1 - FSH<8 and AMH≥1 - FSH≥10, with the AMH<1 - FSH<8 group having lower values. In the intra-group comparisons, it was found that there was no statistically significant difference between the subgroup values in either group (AMH<1, AMH≥1) for all variables (p>0.05) (Table 3).

Table 3. Comparison of the number of collected oocytes and M2 oocytes between and within groups

		AMH<1		AMH≥1		P*	Difference
		FSH<8 (n=36)[1]	8≤FSH<10 (n=24)[2]	8≤FSH<10 (n=10)[3]	FSH≥10 (n=12)[4]		
Number of oocytes collected		4.4±3.4	5.3±3.4	6.4±4.8	7.4±4.2	0.082	--
	P**	0.318		0.602			
M2 oocyte count		3.0±2.4	3.9±2.9	4.9±4.2	5.6±3.6	**0.049**	1 and 4
	P**	0.187		0.686			

*: one-way Anova (Mean±SD), **: independent samples t test (Mean±SD), M2: metaphase 2

In the group comparisons, it was determined that there was no statistically significant difference (p>0.05) between the groups regarding live birth, abortion and embryo values. In intragroup comparisons revealed that there was no statistically significant difference (p>0.05) between subgroup values in both groups (AMH<1, AMH≥1) in terms of all variables (Table 4).

Table 4. Comparison of live birth - miscarriage - embryo by groups

		AMH<1		AMH≥1		P*
		FSH<8 (n=36)[1]	8≤FSH<10 (n=24)[2]	8≤FSH<10 (n=10)[3]	FSH≥10 (n=12)[4]	
Live birth	**Absent**	29 (80.6%)	21 (87.5%)	7 (70.0%)	10 (83.3%)	0.680
	Present	7 (19.4%)	3 (12.5%)	3 (30.0%)	2 (16.7%)	
	P*	0.725		0.624		
Miscarriage	**Absent**	35 (97.2%)	22 (91.7%)	8 (80.0%)	11 (91.7%)	0.318
	Present	1 (2.8%)	2 (8.3%)	2 (20.0%)	1 (8.3%)	
	P*	0.558		0.571		
Embryo	**No oocytes**	5 (13. 9%)	1 (4.2%)	2 (20.0%)	0 (0%)	0.656
	POQ	7 (19.4%)	4 (16.7%)	1 (10.0%)	3 (25.0%)	
	TFC	5 (13.9%)	3 (12.5%)	2 (20.0%)	2 (16.7%)	
	Day 2 embryo	2 (5.6%)	4 (16.7%)	0 (0%)	0 (0%)	
	Day 3 and later embryo	17 (47.2%)	12 (50.0%)	5 (50.0%)	7 (58.3%)	
	P*	0.518		0.365		

*: Chi-Square Test (n (%)); POQ: poor embryo quality, TFF: total fertilization cancellation

Discussion

Infertility is a prevalent and significant issue that has psychological, economic, demographic, and medical implications for many couples. It impacts 10-15% of reproductive-aged couples in the population. [2]. Evaluation of ovarian reserve is necessary to analyze the individual characteristics of patients selected for treatment and to select appropriate treatment protocols. However, it is observed that the tests currently used to evaluate ovarian reserve are still inadequate and a definite standardization has not been achieved [8]. It has been noted that even the most reliable ovarian reserve tests can yield false positive results in 10-20% of cases [9]. Traditionally, FSH has been the primary tool used; however, AMH has recently gained prominence. In fact, numerous studies now regard AMH as more specific for predicting ovarian reserve and the ovarian response to gonadotropin stimulation [10].

In a study carried out by Leader et al. for female infertility, it was shown that there was a discordance between AMH and FSH in 1 out of every 5 evaluations and there was no difference in gonadotropin-stimulated cycle results and oocyte yield in patients with these discordant values [11]. In our study, AMH and FSH values obtained from the same patient were compared and we aimed to determine which ovarian reserve marker is more valuable in predicting oocyte quality and live birth outcomes in patients with AMH and FSH mismatch.

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La Marca et al. attributed the more constant and consistent serum AMH levels to the independence of AMH release from endogenous gonadotropins. It has been suggested that AMH can be used as a marker for ovarian aging and ovarian response to controlled ovarian stimulation and that AMH is the best marker to reflect the oocyte/folicle pool when compared with other ovarian tests [12]. Fanchin et al. showed that AMH was more compatible with early antral follicle numbers compared with other markers of follicular status and development [13]. In the study by Tremellen et al., it was mentioned that AMH correlated well with AFC but had no association with live birth or miscarriage, making it a useful marker of quantitative but not qualitative ovarian reserve [14]. Many studies have also concluded that there is a strong correlation between AMH and ovarian response to gonadotropins and that AMH is the most discriminating hormonal marker of ovarian response in assisted reproductive techniques [15,16]. In the study of Muttukrishna et al. AMH was found to have the most significant relationship with the number of oocytes collected when compared with FSH or inhibin B in patients with poor response. They reported that AMH as a single marker was the best indicator of ovarian response in patients with poor ovarian response, while combining FSH, inhibin B and AMH increased the predictive value only slightly [17]. In our study, a significantly higher number of oocytes were obtained in the AMH ≥1 ng/ml group, which has a reassuring AMH in terms of the number of oocytes collected, compared with the AMH <1 ng/ml group, which suggests decreased ovarian response.

In studies conducted in young women with normal AMH levels but high FSH levels, the superiority of AMH over FSH has often been proven [18,19]. In our study, it was statistically observed that the patients in the AMH <1 ng/ml group were older and the decrease in the oocyte pool with advancing age is more clearly seen with AMH. In other words, AMH predicts the decreasing oocyte/folicle pool in the ovary with advancing age better than FSH.

Barad et al. compared AMH and FSH values according to the number of oocytes and number of pregnancies in patients undergoing IVF cycles. In 76 IVF cycles investigated, AMH was clearly superior in predicting IVF outcomes compared with FSH [20]. AMH is a more reliable predictor of live birth in patients undergoing IVF when FSH and AMH values are inconsistent. Low AMH levels are independently linked to reduced live birth rates and increased IVF cycle cancellation rates compared to high FSH levels in patients with discordant values. [21]. However, in our study, when two groups with reassuring AMH and reassuring FSH were compared, no statistically significant difference was found between the two groups when pregnancy, live birth and day 3 embryos were compared.

Husain et al. analyzed the data of 107 women who underwent IVF/ICSI (Intra-Cytoplasmic Sperm Injection). They divided the patients into four groups according to AMH/FSH levels and examined the relationship between AMH and FSH. While 57% of the women had concordant values (both normal and abnormal AMH/FSH), 43% of the women had discordant values (one hormone normal and one abnormal AMH/FSH). They discovered that group 1 (with AMH and FSH levels within the normal range) and group 2 (normal AMH but elevated FSH) were younger than group 3 (low AMH and normal FSH) and group 4 (both AMH and FSH levels abnormal), with group 1 demonstrating the highest oocyte yield. Groups 3 and 4 required greater doses of gonadotropins for controlled ovarian stimulation. There were no differences in cycle cancellation, clinical pregnancy and live birth/ongoing pregnancy rates in all groups. These tests are useful in predicting ovarian response, but whether AMH is a significantly better predictor is yet to be determined [22]. In our study, in the group of patients with AMH≥1 ng/ml, we firstly screened the group with FSH≥10 IU/ml and the other group showing discordance, and after obtaining the data, since FSH≥8 IU/ml and each 1 IU/ml FSH elevation decreases the spontaneous pregnancy rate by 7% in subfertile individuals, we also included FSH ≥10 IU/ml according to FSH in patients with AMH≥1 ng/ml. We compared our data by obtaining two groups with 8≤FSH<10 IU/ml and 4 groups with FSH <8 IU/ml and 8≤FSH<10 IU/ml in patients with AMH <1ng/ml. We also compared the obtained patient groups according to age, BMI, number of oocytes collected, number of M2 oocytes collected, oocyte quality and live birth rates. At the end of the comparison, AMH <1ng/ml and 8≤FSH<10 IU/ml groups were older than the other groups, which once again showed that AMH and FSH are effective in showing ovarian aging.

Likewise, when all groups were compared in terms of number of oocytes, it was observed that there was no statistically significant difference, but the group with AMH<1 ng/ml and FSH<8 IU/ml had lower values in terms of M2 oocytes. It has been suggested that M2 oocytes may be associated with more clinical pregnancies and better quality embryos according to previous studies [1].

When we examine the values of AMH<1 ng/ml and FSH<8 IU/ml groups separately, although FSH<8 IU/ml values suggest that ovarian reserve is very good when evaluated with current publications, it is not understood whether AMH<1 ng/ml is more effective on the ovary or whether this decrease in the quality of the oocytes obtained is a pathology related to the genetics of the ovary. More data and studies are needed to fully understand this situation. The underlying cause also needs to be evaluated from a genetic point of view. When these four groups were evaluated in terms of clinical pregnancy, live birth and abortion, no statistically significant difference was observed. Therefore, although antral follicle counts and AMH are increasingly appealing to clinicians, FSH still represents the most widely used tool in routine daily practice and AMH and FSH should be studied together in patients undergoing infertility treatment to further identify groups showing discordance.

Conclusion

As a result of our study in cases with AMH and FSH discordance; AMH is more valuable in ovarian reserve evaluations, in predicting the number of oocytes, and in the evaluation of

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oocyte quality, AMH is more valuable when the collected M2 oocyte ratios are evaluated, so AMH is important because it is a more successful predictive value in cases with discordance. However, we concluded that there was no difference between the two parameters in terms of live birth, embryo retrieved and pregnancy rates. Thus, while AMH and FSH demonstrate clear clinical value for prognosis prediction in infertility patients, neither marker alone nor in combination is sufficient to accurately predict a patient's likelihood of achieving a live birth.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

The ethics committee approval of the study was obtained from the Gülhane Scientific Research Ethics Committee of the University of Health Sciences, with the registration number 2021/172.

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