

THE RELATIONSHIP BETWEEN BODY MASS INDEX (BMI) AND SERUM ANTI-MULLERIAN HORMONE (AMH) LEVELS

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ABSTRACT

Background and objective: Reduced ovarian reserve is associated with a decrease in quality and quantity of oocytes and thus adverse effects in IVF cycles. Anti-Mullerian Hormone (AMH) has been accepted as a prognostic marker of ovarian reserve. The relationship between BMI and serum AMH levels has not been well documented. The main purpose of this study is to determine the relationship between BMI and AMH level in IVF candidate infertile women referred to an infertility clinic.

Materials and methods: through a cross-sectional study, IVF candidates were recruited. BMI and serum AMH were measured. Then, stimulation of ovulation began on days 3-4. Patients were assigned to three groups with poor ovarian response (≤ 3 oocytes), adequate ovarian response (4-12 oocytes) and excessive ovarian response (>12 oocytes) based on the number of oocytes retrieved.

Results: The results of linear regression showed no significant relationship between AMH levels and BMI ($P = 0.8$). Only in overweight individuals, the likelihood of forming an oocyte was 10% higher than those with normal BMI, and this relationship was not observed for obese subjects ($P = 0.3$). In obese people, there is no relationship between AMH levels and poor and excessive ovarian responses.

Discussion and conclusion: this study showed that AMH does not correlate with BMI. In obese infertile women, AMH is not an appropriate indicator of ovarian response.

Keywords: ovarian reserve, Anti-Mullerian Hormone (AMH), IVF candidate, infertile women.

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Introduction

In the recent decades, socioeconomic and cultural changes taken place in society and tendency of women to continue their education and employment lead to delayed pregnancy in families and consequently problems caused by decline in fertility in older ages. Moreover, prevalence of overweight and obesity in modern society and reduced response to assisted reproductive techniques in obese patients require further studies in this regard. Awareness of ovarian reserve and factors associated with reduced ovarian reserve as well as factors which influence the results of ovarian reserve screening tests provide the physician with an opportunity to judge

appropriately about the patient and her fertility ability, and provide appropriate interventions and strategies to the patient. Obesity is one of the major health problems worldwide, including Iran. Recent studies have shown that prevalence of obesity and overweight is increasing alarmingly. This increase is observed both in developing countries and in developed countries. Based on recommendation of the International Association for Obesity, overweight is^(1,2) defined as Body Mass Index (BMI) >25 and BMI <30 and obesity is defined as BMI ≥ 30 ⁽³⁾. Overweight and obesity are not only risk factors of diseases such as hypertension, diabetes, cardiovascular disease and cancers, they are associated with poor outcomes of assisted reproductive techniques

such as reduced oocyte count and increased IVF cancelled cycles^(4,5,6). Understanding the ovarian reserve and ovarian response is one of the goals of physicians in fertility treatment and allows them to obtain the best outcome with the lowest complications⁽⁹⁾. Anti-Mullerian Hormone (AMH) has been accepted as a prognostic marker for ovarian reserve^(10,11,12,13). The relationship between serum levels of this hormone and response to infertility treatment has been evaluated in patients⁽⁹⁾. In some studies, there is a negative correlation between BMI and AMH level^(14,15,16); however, other studies have questioned this correlation^(16,17,18).

AMH level has a strong correlation with the number of antral follicles and successful reproductive cycles, and has been introduced as a predictor of successful assisted reproductive techniques^(19,20,21). Therefore, it is important to identify the factors which influence the serum level of this hormone. Serum AMH level is not influenced by menstrual cycle⁽²²⁾; however, the level of this hormone decreases with age⁽²³⁾. There are contradictory results about the relationship between BMI and serum AMH levels; while some studies support lower levels of this hormone in obese women with high BMI^(24,16,15), some questions have questioned this correlation^(25, 23). So far, the correlation between BMI and serum AMH level has not been well documented. Skałba et al. evaluated the relationship between serum AMH and BMI in two groups of women with and without polycystic ovary syndrome (87 women in the first group in which 54 women had normal BMI and 33 women had high BMI, 51 women in the second group in which 28 women had normal BMI and 22 women had high BMI). They reported that AMH levels were not related to BMI in both groups⁽²⁶⁾.

Malhotra et al.⁽²⁷⁾ evaluated the relationship between Inhibin B and AFC and BMI in 183 infertile women. Ignoring the effect of age, they reported that the level of Inhibin B was significantly lower in obese women; however, there is no significant relationship between BMI and AFC.

The main objective of this study was to determine the relationship between body mass index (BMI) and AMH levels in infertile IVF candidates referred to an infertility clinic. In this regard, it is important to consider obesity as an effective risk factor on ovarian reserve, which was considered in this study.

Materials and methods

Through a cross-sectional study, infertile IVF candidate women referred to infertility clinic of the Mahdiah Hospital with no history of previous medical disease, no previous ovarian surgery, no hormonal medication during the last three months and IVF candidates were recruited for the study. BMI and serum AMH level were measured. The patients entered the long-term standardized cycle with GnRH agonist. Then, the baseline ultrasonography was performed at the beginning of the cycle (day 1-3) to ensure that there is no underlying pathology. Ovulation stimulation began on days 3-4 with HMG (human-urinary type: Merional-AMP-IBSA-75IU/ml) according to protocol of infertility clinic of the Mahdiah Hospital based on age of the patient. Controlled ultrasonography was performed every 3-4 days and the treatment was continued based on ovarian response. By observing the dominant follicle (size 16-18 mm), final intervention was performed by injecting HCG and 36 hours later oocytes retrieved.

The results of all tests, ultrasonography and ovarian response of each patient (number of oocytes retrieved) and dose of the drug administered in each cycle were recorded in patient file. Based on the number of oocytes retrieved, the patients were divided into three groups with poor ovarian response (≤ 3 oocytes), adequate ovarian response (4-12 oocytes) and excessive ovarian response (> 12 oocytes)⁽⁹⁾; based on BMI, the patients were divided into four groups with BMI < 18.5 , BMI = 18.5-24.9, BMI = 25-29.9 and BMI > 30 .

Data was analysed statistically in different weight groups. All quantitative variables were expressed as mean and standard deviation; qualitative variables were expressed as number (percentage). All statistical tests were two-tailed ($p < 0.05$). SPSS18 software was used to analyse the data. In addition to descriptive analysis by mean and standard deviation, significance of the difference between tests was measured by Independent t-test and Chi-square. Sample size was calculated based on type 1 error ($\alpha = 5\%$) and test power (power = 80%) and minimum difference ($d = 30\%$), which was clinically significant.

Results

Distribution of Age and BMI

This study used data of 500 women referred to infertility clinic of the Mahdiah Hospital in Tehran. Table 1 shows age groups studied (32.4±5.3). 81% of our patient were between 25 to 40 years old. Moreover, Shapiro-Wilk test showed that age was not normally distributed (P<0.05).

Age group	N	%
20-25 years	53	10.6
25-30 years	138	27.6
30-35 years	166	33.2
35-40 years	103	20.6
40-45 years	40	8
Total	500	100

Table 1: Age groups studied.

Maximum and minimum BMI recorded was 40.6 and 15 kg/m², respectively. Pearson correlation coefficient test showed a positive and direct correlation between age and BMI; a one-year increase in age was associated with 0.18% increase in BMI (P<0.001). Table 2 presents data related to BMI in details. Table 2 shows that BMI of 50% of subjects was more than 27 and BMI of the rest 50% was less than this value. This finding indicates that 50% of people are overweight or obese.

Percentile	BMI	Mean (SD)
1	18.9	27.6±4.7
5	21.2	
10	22.1	
25	24.5	
50 (median)	27.05	
75	30.4	
90	33.4	
95	36.3	
99	39.2	

Table 2: BMI of patients referred to the infertility clinic of the Mahdiah Hospital.

Since this variable was not normally distributed and the mean BMI fell within the same range, distribution of the variable had no skewness and some kurtosis.

In classifying people to low weight, normal, overweight and obese groups, the results showed that 3 (0.6%) had low weight, 122 (24.6%) had normal weight, 237 (47.4%) were overweight and 133 (26.6%) were obese. Table 3 shows BMI of people based on age groups. Since only 3 patients had BMI<18.5, they were discarded in analysis.

Age group	BMI (n%)		
	Normal (18.5-24.9)	Overweight (25-29.9)	Obese (≥30)
20-25 years	20 (16.4)	25 (10.5)	6 (4.5)
25-30 years	37 (30.3)	70 (29.5)	28 (21.1)
30-35 years	40 (32.8)	75 (31.6)	50 (37.6)
35-40 years	18 (14.8)	45 (19)	38 (28.6)
40-45 years	7 (5.7)	22 (9.3)	11 (8.3)

Table 3: BMI based on different age groups.

Distribution of AMH

Further analyses showed mean and standard deviation of AMH (3.75±4.3). As shown in previous studies, natural logarithm of these values was used for the next analyses considering the skew nature of this hormone. Figure 1 shows logarithmic distribution of AMH.

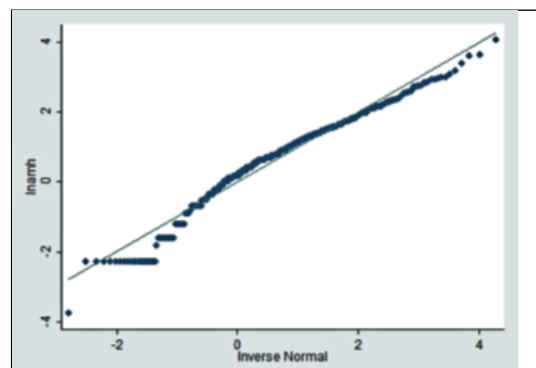


Fig. 1: Logarithmic distribution of AMH.

Relationship between AMH and BMI

The results of linear regression showed no significant relationship between AMH levels and BMI (P = 0.8). Table 4 supports this finding.

Figure 2 well indicates that there is no relationship between these two variables.

Once people were classified in terms of BMI to normal, overweight and obese people, one-way analysis of variance (ANOVA) showed no difference in mean of AMH for these three groups (F=1.17, p=0.3).

Source	SS	df	MS			
Model	0.78661779	1	0.78661779		Number of obs=	500
Residual	761.298989	498	1.52855487		F(1,498)=	0.05
Total	761.298989	499	1.52564928		Prob>F=	0.8206
					R-squared=	0.0001
					Adj R-squared=	-0.0019
					Root MSE=	1.2363
Inamh	Coef.	Std. Err.	t	P>	[95& Conf.	Interval]
Bmi	-0.0028133	0.0124017	-0.23	0.821	-0.0271794	0.0215528
_cons	0.8039954	0.346181	2.32	0.021	0.1238401	1.484151

Table 4: The relationship between natural logarithm of AMH and BMI of patients referred to infertility clinic.

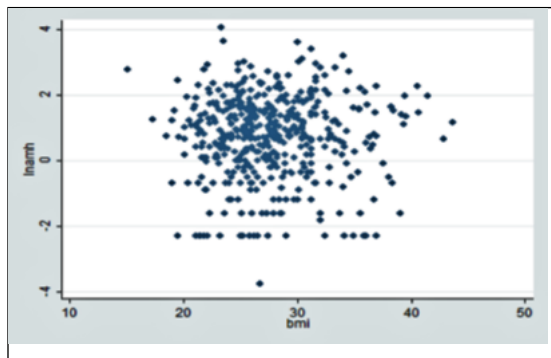


Fig. 2: Relationship between AMH and BMI.

Relationship between AMH and Age

The results also showed a linear and significant relationship between age and AMH level; by increasing 1 year to age, hormone level decreases by a coefficient of 0.159 (p<0.001). Figure 3 shows this relationship and table 5.

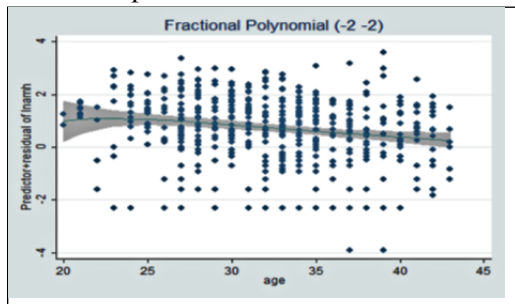


Fig. 3: Relationship between logarithm of AMH and age of patients referred to the infertility clinic.

Source	SS	df	MS			
Model	26.2594975	1	26.2594975		Number of obs=	500
Residual	735.039492	498	1.47598292		F(1,498)=	17.79
Total	761.298989	499	1.52564928		Prob>F=	0
					R-squared=	0.0345
					Adj R-squared=	0.0326
					Root MSE=	1.2149
Inamh	Coef.	Std. Err.	t	P>	[95& Conf.	Interval]
Bmi	-0.0430013	0.0101948	-4.22	0	-0.0630314	-0.022971
_cons	2.119369	0.3346696	6.33	0	1.46183	1.484151

Fig. 5: Linear regression analysis of the relationship between AMH level and age of patients referred to infertility clinic.

Relationship between BMI and Number of Oocytes Formed

Evaluating the effects of BMI on the number of released oocytes, Poisson regression analysis indicated a significant correlation between BMI and the number of oocytes formed. Table 6 shows the results of this model.

Considering people with normal BMI as reference, it is observed that likelihood of forming an oocyte was 10% higher in overweight people than those with normal BMI; this relationship was not seen for obese people (p = 0.3). It is also observed that one year increase in age reduced the likelihood of forming an oocyte after treatments by 3%.

Relationship between Ovarian Response and AMH in Normal, Overweight and Obese People

By dividing ovarian responses to poor, normal and excessive, the effects of different variables were examined on them. In this analysis, normal ovarian response was considered as reference and analysis was done for normal, overweight and obese BMI separately. These results are listed in the table below. In people with normal BMI considering the normal ovarian response as reference, Table 7 shows that one unit of increase in AMH concentration increases the chance of excessive ovarian response by 31% compared to normal ovarian response. Note that this analysis did not provide significant results for poor ovarian response to normal response. Second, this analysis was done for overweight people. In these people, one unit of increase in AMH significantly increased the chance of excessive ovarian response by 22%. For obese people, this analysis showed no relationship between AMH levels and poor and excessive ovarian responses. This finding suggests that AMH level is not a good predictor of ovarian response in obese people.

Discussion

In this study, AMH levels were compared in three normal, overweight and obese groups and no significant differences were found between three groups. In fact, once people were divided into normal, overweight and obese people, one-way ANOVA showed no difference in mean of AMH for these three groups. The results of linear regression showed no significant relationship between

Iteration 0:	Log likelihood=	-1881.5397					
Iteration 1:	Log likelihood=	-1881.5179					
Iteration 2:	Log likelihood=	-1881.5179					
Poisson	regression				Number of obs=	492	
					LR chi2(4)	349.82	
Log	Likelihood=	-1881.5179				Prob>chi2=	0
					Pseudo R2=	0.0851	
oo	IRR	Std. Err.	z	P>	[95& Conf.	Interval]	
bmicat							
2	1.107695	0.0362528	3.13	0.002	1.038872	1.181077	
3	1.036614	0.039443	0.95	0.345	0.9621193	1.116876	
Age	0.97532	0.0025029	-9.74	0	0.9704267	0.9802379	
Amh	1.040211	0.002866	14.31	0	1.034609	1.045843	
_cons	21.2744	1.804328	36.05	0	18.01628	25.12174	

Table 6: Poisson regression analysis for effects of BMI on the number of oocytes formed.

AMH levels and BMI. Semi et al.⁽⁴¹⁾ and Singh et al.⁽⁴³⁾ found no significant correlation between AMH level and BMI, which is consistent with current study. In contrast, Ellakwa (2015) claimed that BMI and AMH are interrelated and can be used to predict ovarian response to clomiphene in PCOD patients⁽⁴⁵⁾. Studying European women, Moy et al discarded the effect of age and showed an inverse relationship between BMI and AMH; this relationship was not observed in women belonging to other races⁽⁴⁴⁾. Freeman et al. (2007) also measured AMH level in healthy obese and non-obese women at late reproductive age (over 40 years) and found that AMH was significantly lower in obese women than non-obese women⁽¹⁴⁾. These studies are not consistent with current study.

Variables	RR	p-value	95% CI
BMI normal			
Ovary Weak	0.64	0.155	0.34-1.18
Ovary overstimulate	1.31	0.001	1.12-1.53
Overweight (25-30)			
Ovary Weak	0.66	0.054	0.44-1.00
Ovary overstimulate	1.22	<0.0001	1.11-1.35
Obese (>30)			
Ovary Weak	0.83	0.21	0.63-1.10
Ovary overstimulate	1.05	0.18	0.97-1.14

Table 7: Effects of AMH on poor and excessive ovarian responses in normal, overweight and obese people. Independent t-test showed no relation between AMH level and pregnancy test result (P>0.05).

Moreover, current study found a linear and significant relationship between age and AMH level; one year increase in age slightly reduced AMH level. Although this reduction is very linear and slight, it can cause a significant difference in older people; this is consistent with Lamarka⁽³⁶⁾ and Moy⁽⁴⁴⁾. Another finding addressed in current study is predictive value of AMH for ovarian response in obese people. The results showed that increase in AMH level increases the chance of excessive ovarian response in people with normal BMI and overweight people. However, there is no relationship between AMH level and poor ad excessive ovarian response in obese people. In fact, AMH is not a good predictor of ovarian response in obese people.

Evaluating the effects of BMI on the number of oocytes retrieved, the results show a significant relationship between BMI and the number of oocytes retrieved. Considering people with normal BMI as reference, likelihood of forming an oocyte was 10% higher in overweight people than those with normal BMI. However, Buick et al. found an inverse relationship between BMI and AMH level and the number of oocytes retrieved in a group of women with reduced ovarian reserve (FSH>10IU/L), while this relationship was not found in the group of women with normal ovarian reserve⁽³⁹⁾.

Zang et al. showed that the number of oocytes retrieved during IVF cycle is lower in obese and overweight women than those with normal weight⁽⁵⁾; this is inconsistent with current study. In current study, patients with polycystic ovary syndrome were not included, while they were addressed in other studies. Skafba et al. examined the relationship between serum AMH level and BMI in two groups of women with and without polycystic ovarian syndrome. In both groups, AMH level was not associated with BMI⁽⁴⁰⁾.

Finally, the present study which was conducted with appropriate sample size showed no significant relationship between BMI and AMH. Moreover, no relationship was found between AMH level and ovarian response in BMI>30 group; thus, it can be concluded that AMH is not a good predictor of ovarian response in obese people.

Conclusion

Reduced ovarian reserve is associated with a decrease in quality and quantity of oocytes and thus adverse effects in IVF cycles. Anti-Müllerian Hormone (AMH) has been accepted as a prognostic marker of ovarian reserve. The relationship between BMI and serum AMH levels has not been well documented. This study tended to determine the relationship between BMI and AMH level in infertile IVF candidates. This study compared AMH level in normal, overweight and obese groups and found no significant difference in three groups. In fact, once people were divided into normal, overweight and obese people, one-way ANOVA showed no difference in mean of AMH for these three groups. The results of linear regression showed no significant relationship between AMH levels and BMI.

The results showed that one year increase in age slightly reduced AMH level, indicating a linear and significant relationship between age and AMH level. Although this reduction is very slight, it can cause a significant difference in older people. Evaluating the effects of BMI on the number of oocytes released, the results showed a significant relationship between BMI and the number of oocytes formed. Considering people with normal BMI as reference, likelihood of forming an oocyte was 10% higher in overweight people than those with normal BMI.

The results showed no significant relationship between AMH and BMI. In obese people, AMH is not a good predictor of ovarian response. Since 50% of the studied population was overweight or obese, it seems essential to consider change in lifestyle and weight loss in infertile patients.

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