DOI: 10.59213/TP.2024.149
Trends in Pediatrics 2024;5(3):79-84

Original Article

The relationship between serum anti-mullerian hormone levels and puberty in girls with obesity

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Cite this article as: Sarıkaya E, Çiçek D, Kara L, et al. The relationship between serum anti-mullerian hormone levels and puberty in girls with obesity. Trends in Pediatrics. 2024;5(3):79-84.

ABSTRACT

Objective: The purpose of this study was to assess the serum anti-Mullerian hormone (AMH) levels and related factors in overweight and obese girls during their prepubertal, pu-bertal, and post-menarcheal periods.

Method: Anthropometric measurements, physical examination features, laboratory findings, and serum AMH levels were evaluated in girls with overweight and obesity admitted be-tween March and April 2021 in the Pediatric Endocrinology Clinic at Erciyes University Faculty of Medicine.

Results: Serum AMH levels were evaluated in a total of 40 girls: 12 (30%) prepubertal, 12 (30%) pubertal, and 16 (40%) post-menarcheal. Their ages were 7.7 (±1.7), 10.3 (±2.1), and 15.4 (±1.8) years, and their serum AMH measurements were 2.4 (±2.4), 2.1 (±1.1), and 4.6 (±3.7) ng/mL, respectively. The serum AMH levels between prepubertal and pubertal girls and post-menarcheal girls were significantly different (p=0.020). There was no significant difference when compared to normal AMH levels for their age (p=0.722).

In the age-adjusted correlation analysis of the patients, no significant relationship was found between AMH levels and anthropometric measurements (height, weight, weight-SD, BMI, BMI-SD, neck circumference-SD, mid-upper arm circumference-SD, waist circumference-SD, waist-to-height ratio, and waist-to-hip ratio). A positive correlation was found only in height-SD (r=0.334, p=0.038).

Conclusion: The study found that the serum AMH levels of girls with overweight and obesi-ty increased moderately during the prepubertal period, specifically several years preceding puberty, slightly decreased during the onset of puberty, and significantly increased during the post-menarcheal period, like healthy girls.

Keywords: Anti-Mullerian hormone, body mass index, body measurements, obesity, puber-ty

INTRODUCTION

Anti-Mullerian hormone (AMH, formerly also called Mullerian inhibiting substance; MIS) is a homodimeric disulfide-linked glycoprotein and a member of the transforming growth factor-beta (TGF-b) superfamily secreted by the granulosa cells in the ovaries.[1,2] Antral follicles, which contain a large number of granulosa cells, are considered to be the primary source of circulating AMH. Since AMH is secreted exclusively from ovarian follicles, its serum concentrations in females are thought to reflect the size of the ovarian follicle pool.[3,4]

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Received: 10.05.2024 **Accepted:** 01.08.2024

Lee et al. first described normal levels of AMH in humans from infancy to adulthood. AMH values in females were lowest and typically undetectable during infancy, with a mini-mal rise throughout childhood and puberty. The mean serum AMH values rise during late puberty and then decline as a function of age.[5] In later investigations with larger case numbers, it was discovered that while the AMH level was undetectable in the cord blood, it slightly increased in the infantile period in accordance with the mini-puberty phase, then fell and stayed at consistent levels until around 6–8 years of age. AMH levels were found to rise after the aforementioned ages (about 2-3 years before the onset of puberty development) and to decrease moderately with the onset of pubertal development. It has been demonstrated that AMH levels rise once more, reaching a peak in the mid-twenties and falling off until menopause.[6-10] In addition, while there was an inverse correlation between AMH and both follicle-stimulating hormone (FSH) and luteinizing hor-mone (LH) levels before puberty, it was noticed that this relationship disappeared with the onset of puberty.[7,10,11]

While researches in reproductive-age women with obesity found an inverse relation-ship between AMH levels and body mass index (BMI), studies in adolescent girls with obesi-ty found a favorable relationship.[12-16] Some of these studies have suggest-ed that the relationship between BMI and AMH levels in the context of obesity is more closely related to increased central adiposity, the presence of polycystic ovary syndrome (PCOS), or having a mother with PCOS.[13,14,16] In the first known study of adolescents by Hart et al., girls with PCOS were found to have significantly higher AMH levels, BMI, and BMI-SD values.[14] However, in certain studies involving girls and women with obesity, no link was found between AMH levels and BMI.[17-19]

Previous studies in obese women have also investigated the relationship between AMH and glucose metabolism parameters such as glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR).[2,20,21] In this respect, we wanted to elucidate this relationship, which has not been previously examined in children and adolescents with obesity.

The aim of this study is to evaluate AMH levels in girls with overweight and obesity during their prepubertal, pubertal, and post-menarcheal periods, compare them to normal values, and demonstrate the accompanying features.

METHODS

The anthropometric measurements and laboratory data of girls between the ages of 4 and 18 who were overweight or obese (BMI ≥ 85%) and had their AMH levels measured during their visit to the university hospital's pediatric endocrinology clinic in March and April 2021 were obtained retrospectively from the archives. Anthropometric measurements, including height and weight without shoes, were performed by a single experienced nurse. The meas-urement devices had an accuracy of 0.1 cm for height and 0.05 kg for weight. BMI was cal-culated using the formula weight/height^2 (kg/m^2). The anthropometric measurements of the patients were evaluated according to the auxological references of Turkish children, and BMI standard deviation (SD) values were calculated for all ages compared to normal.[22] The patient's physical examination and neck, waist circumference, hip circumference, and mid-upper arm circumference (MUAC) measurements were performed by pediatric endocrinology fellows using a non-flexible measuring tape with a precision of 0.1 cm as previously described.[23,24]

AMH, FSH, LH, estradiol, testosterone, and insulin levels were analyzed using the electrochemiluminescence method with the Roche Diagnostics Cobas® e801 module (Roche Diagnostic, Mannheim, Germany). Glucose levels were analyzed using the enzymatic (hexo-kinase) spectrophotometric method in the Roche Diagnostics Cobas® c701 module (Roche Diagnostic, Mannheim, Germany). Glycosylated hemoglobin (HbA1c) levels were analyzed using the turbidimetric inhibition method in the Roche Diagnostics Cobas® c501 module (Roche Diagnostic, Mannheim, Germany).

To evaluate our data, we divided them into two categories: those that showed a nor-mal distribution and those that did not. We used ANOVA and Kruskal-Wallis tests to evalu-ate our independent variables. To evaluate our dependent variables, we used paired sample t-tests for those that showed a normal distribution and Wilcoxon signed rank tests for those that did not. We used partial correlation analyses to evaluate the relationship between de-pendent quantitative variables. Statistical evaluation of the findings was performed using Statistical Packages for the Social Sciences version 25.0 software (SPSS, Chicago, IL, USA).

RESULTS

Serum AMH levels were studied from a total of 40 girls, 12 (30%) prepubertal, 12 (30%) pubertal, and 16 (40%) post-menarcheal. Their ages were 7.7 (±1.7), 10.3 (±2.1), and 15.4 (±1.8) years, and their serum AMH measurements were 2.4 (±2.4), 2.1 (±1.1), and 4.6 (±3.7) ng/mL, respectively (Table 1 and Figure 1). There was a significant difference in terms of AMH levels among the three groups (p=0.020), but no significant difference was observed when the patients' AMH levels were compared with their age averages (p=0.722) (Table 2).

Table 1. Comparison of the characteristics of patients according to pubertal periods				
	Prepubertal	Pubertal	Post-menarcheal	P
Age (year)	7.7 (±1.7)	10.3 (±2.1)	15.4 (±1.8)	<0.001[1]
Weight-SD	2.52 (±0.86)	2.03 (±1.15)	1.59 (±1.02)	0.072[1]
Height-SD	1.38 (±1.22)	0.01 (±1.28)	-0.58 (±0.94)	<0.001[1]
BMI-SD	2.2 (±0.5)	2.2 (±0.7)	1.9 (±0.6)	0.403[1]
Neck Circumference (cm)	30.9 (±3.8)	31.5 (±2.7)	34.0 (±1.8)	0.012[1]
Neck Circumference-SD	3.75 (±2.16)	2.21 (±1.47)	2.13 (±1.23)	0.028[1]
Mid-Upper Arm Circumference (cm)	24.9 (±4.6)	28.3 (±3.8)	30.3 (±2.7)	0.002[1]
Mid-Upper Arm Circumference-SD	3.87 (±1.33)	4.37 (±1.06)	3.47(±1.32)	0.187[1]
Waist Circumference (cm)	76.4 (±9.7)	82.8 (±10.6)	86.9 (±7.2)	0.017[1]
Waist Circumference-SD	4.00 (±1.50)	3.06 (±1.35)	1.6 (±1.23)	<0.001[1]
Waist-to-Height Ratio	0.57 (±0.04)	0.58 (±0.06)	0.55 (±0.04)	0.235[1]
Waist-to-Hip Ratio	0.89 (±0.05)	0.87 (±0.05)	0.83 (±0.06)	0.050[1]
AMH (ng/mL)	2.42 (±2.4)	2.14 (±1.1)	4.62 (±3.7)	0.020[2]
FSH (mIU/mL)	1.02 (±0.3)	8.6 (±17.7)	4.64 (±1.5)	<0.001[2]
LH (mIU/mL)	0.62 (±1.0)	4.12 (±8.9)	12.08 (±7.4)	<0.001[2]
Estradiol (pg/mL)	10.01 (±16.6)	19.3 (±21.3)	89.2 (±91.3)	<0.001[2]
Glucose (mg/dL)	87.5 (±10.4)	87.8 (±9.9)	88.3 (±9.4)	0.976[1]
Insulin (µU/mL)	17.52 (±10.6)	20.79 (±9.6)	26.85 (±26.3)	0.371[2]
HOMA-IR	3.89 (±2.4)	4.59 (±2.3)	6.17 (±6.7)	0.696[2]
HbA1c (%)	5.23 (±0.2)	5.35 (±0.1)	5.27 (±0.3)	0.302[2]

BMI: body mass index. AMH: Anti-Mullerian hormone. FSH: follicle-stimulating hormone. LH: luteinizing hormone. HOMA-IR: homeostasis model assessment of insulin resistance. HbA1c: glycosylated hemoglobin. [1] One-Way Anova Test p-value. [2] Kruskal-Wallis Test p value. p<0.05 was considered statistically significant.

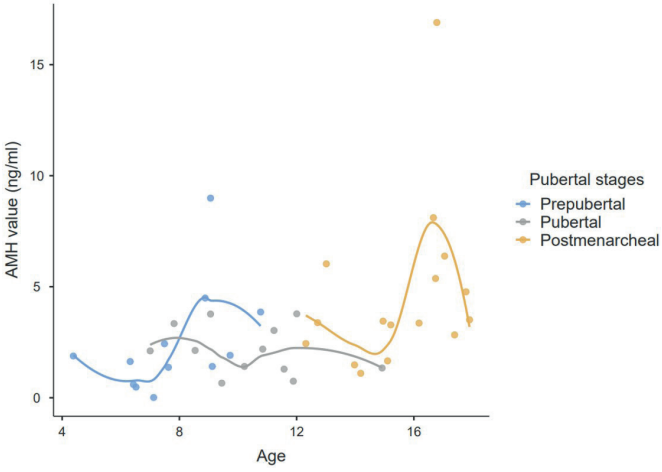

Figure 1. Trend of AMH levels according to age and pubertal stages

The results indicated no age-adjusted correlation between AMH levels and various body measurements, such as weight-SD, BMI-SD, neck circumference-SD, mid-upper arm circumference-SD, waist-to-height ratio, and waist-to-hip ratio (Table 3). A positive correla-tion was observed between serum AMH levels and height-SD (r = 0.167, p = 0.038). In addi-tion, no significant age-adjusted correlation was found between serum AMH and FSH, LH, estradiol, testosterone, glucose, insulin, HbA1c, and HOMA-IR measurements (Table 3).

DISCUSSION

In this study, the AMH levels of girls with overweight and obesity were found to be con-sistent with previous studies in the prepubertal, pubertal, and post-menarcheal periods. As in these studies, a moderate decrease in AMH levels compared to the prepubertal period with the onset of the pubertal period and then an increase in the post-menarcheal period were de-tected.[5,7-10] In addition, when the AMH levels of the patients

Table 2. Comparison of AMH measurements with age-specific norms			
	The mean AMH (ng/mL) value by age according to our study	The mean AMH (ng/mL) value by age, according to the study by Lee et al. (1996)	P[1]
Prepubertal	2.42 (±2.44)	2.60 (±0.50)	0.347
Pubertal	2.14 (±1.11)	2.85 (±0.64)	0.117
Post-menarcheal	4.62 (±3.78)	3.00 (±1.09)	0.234
Total	3.22 (±2.98)	2.83 (±0.82)	0.722

[1] Wilcoxon Signed Ranks Test p-value. p<0.05 was considered statistically significant.

Table 3. Age-adjusted correlation evaluation of AMH measurements with other parameters					
	Number	Mean	SD	r	P[1]
Weight-SD	40	2.00	1.06	0.158	0.335
Height-SD	40	0.18	1.38	0.334	0.038[a]
BMI-SD	40	2.09	0.66	0.009	0.955
Neck Circumference-SD	40	2.64	1.75	0.147	0.372
Mid-Upper Arm Circumference-SD	40	3.86	1.28	-0.090	0.586
Waist Circumference-SD	40	2.76	1.67	0.244	0.135
Waist-to-height ratio	40	0.56	0.05	0.023	0.889
Waist-to-hip ratio	40	0.86	0.06	0.224	0.169
FSH (mIU/mL)	35	4.64	9.65	-0.222	0.208
LH (mIU/mL)	35	6.20	8..27	-0.096	0.590
Estradiol (pg/mL)	34	45.12	70.02	-0.124	0.492
Testosterone (ng/dL)	19	25.95	19.35	0.020	0.938
Glucose (mg/dL)	40	87.9	9.6	-0.180	0.272
Insulin (µU/mL)	36	22.4	18.6	0.054	0.760
HOMA-IR	36	5.07	4.74	0.040	0.821
HbA1c (%)	36	5.28	0.28	-0.179	0.303

BMI: body mass index. AMH: Anti-Mullerian hormone. FSH: follicle-stimulating hormone. LH: luteinizing hormone. HOMA-IR: homeostasis model assessment of insulin resistance. HbA1c: glycosylated hemoglobin. SD: standard deviation. [1] p value for age-adjusted partial correlation test. [a] Statistically significant. p<0.05 was considered statistically significant.

were com-pared with the mean AMH levels of their age stated in previous studies, no difference was found.[5,11]

In the presented study, there was no age-adjusted correlation between serum AMH levels and various body measurements such as weight-SD, BMI-SD, waist circumference-SD, waist-to-height ratio, and waist-to-hip ratio in girls with overweight and obesity. There was a significant age-adjusted correlation only between AMH levels and height-SD. A recent research of 83 prepubertal and pubertal girls (23.6% of whom were overweight or obese) demonstrated that those with a greater waist-to-height ratio had higher AMH_{log} levels.[25] A prior study with women of repro-ductive age demonstrated that AMH levels were inversely associated with waist circumfer-ence and waist-to-height ratio, both of which are central obesity markers and BMI.[26] While there is an inverse relationship between BMI and AMH levels in research conducted with women of reproductive age, there are studies that show a positive correlation in research conducted during adolescence.[12-16,27] A previous study reported an inverse correlation between AMH levels and BMI-SD in girls with premature adrenarche.[28] Yet, some research with adolescents and adults found no link between BMI and AMH levels, which is in line with our study.[17-19,29,30] Another study found that in girls with central precocious puberty, AMH levels were negatively correlated with height-SD and BMI-SD.[31]

No significant age-adjusted correlation was found between serum AMH levels and FSH, LH, estradiol, testosterone, glucose, insulin, HOMA-IR, and HbA1c measurements of girls with overweight and obesity. In contrast to our outcomes, an earlier study in adolescent girls reported a negative relationship between serum AMH levels and estradiol levels.[32] A previous study on adolescents with PCOS reported a positive correlation between AMH levels and total testosterone levels.[16] Furthermore, studies in women with PCOS found a favorable association between total testosterone, LH, and AMH levels.[13,15] Unlike our study, investigations in adult women reported that individuals with high AMH levels have higher HOMA-IR.[2,20,21]

We believe that comparing the parameters of girls with overweight and obesity at dif-ferent stages of adolescence would not be reliable due to the limited number of cases in our study. Another important limitation is that serum AMH levels were not studied simultane-ously with an age-matched control group due to the retrospective nature of the study. None-theless, we assert that the similarity of AMH levels in girls with overweight and obesity in our research to the findings of investigations that reveal the normal AMH levels according to age is valuable. Undoubtedly, future studies with a larger sample size will make greater con-tributions to this field.

CONCLUSION

The study revealed that the serum AMH levels in girls with overweight and obesity increased moderately during the prepubertal period, specifically several years preceding puberty, slightly decreased during the onset of puberty, and significantly increased during the post-menarcheal period, similar to healthy girls. In addition, there was no age-adjusted correlation between serum AMH levels and various body measurements such as weight-SD, BMI-SD, waist circumference-SD, waist-to-height ratio, and waist-to-hip ratio of prepubertal, pubertal, and post-menarcheal girls with overweight and obesity.

Ethical approval

The study was approved by the Ethics Committee of Erciyes University Faculty of Medicine (Protocol no. 2021-757/11.24.2021).

Author contribution

Study conception and design: ÜGŞ, and NH; data collection: ES, DÇ, LK, ESG, UB, and SM; analysis and interpretation of results: ES, ÜGŞ, NH; draft manuscript preparation: ES, ÜGŞ, and NH. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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