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Antimüllerian Hormone Levels Of Infants With Premature Thelarche

Short Title: AMH level of infants with premature thelarche

Nursel Muratoglu Sahin[1], Elvan Bayramoglu[1], Hatice Nursun Ozcan[2], Erdal Kurnaz[1], Meliksah Keskin[1], Senay Savas Erdeve[1], Semra Cetinkaya[1], Zehra Aycan[1]
[1]Dr. Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital, Pediatric Endocrinology Clinic, Ankara, Turkey
[2]Dr. Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital, Pediatric Radiology, Ankara, Turkey

What is already known on this topic?
AMH levels of mini puberty are higher than prepubertal period. Because AMH inhibits both initial follicle recruitment and FSH-dependent follicle growth, the rising levels of AMH during mini-puberty may be an ovarian response to prevent FSH-induced follicle growth. Premature thelarche has been postulated to result from transient partial activation of the hypothalamic-pituitary-ovarian axis with excessive secretion of FSH in infants.

What this study adds?
This is the first study that investigates AMH levels in infants with premature thelarche. It was concluded that a decreased level of AMH may cause premature thelarche in infants because the detected AMH levels in infants with premature thelarche are less compared to healthy controls and there exists a negative correlation between AMH and FSH.

Abstract
Objective: AMH levels in mini puberty are higher than prepubertal period. In this study we investigated AMH levels in infants with premature thelarche who were presumed to have prolonged mini puberty due to inadequate/late suppression of pubertal activation.
Methods: Forty five female infants between 1 and 3 years of age with premature thelarche were enrolled in the study and 37 healthy girls in the same age group were included in the study. Bone age, pelvic ultrasonography (USG) findings, LH (luteinizing hormone), FSH (follicle-stimulating hormone), estradiol and AMH level of the patient group and serum AMH level of the control group were evaluated.
Results: Serum AMH levels of premature thelarche [med: 1.66 ng/ml (11.85 pmol/L) min-max: 0.15-6.32 ng/ml (1.07-45.12 pmol/L)] were significantly lower than the control group's [med: 1.96 ng/ml (13.99 pmol/L) min-max: 0.60-8.49 ng/ml (4.28-60.64 pmol/L)] (p:0.025). AMH and FSH were negatively correlated (r:-0.360 p:0.015) in infants with premature thelarche. There was no correlation between AMH and uterine size, uterine volume, endometrium thickness, fundocervical ratio, over size, over volume, follicle size and follicle number.
Conclusion: This is the first study that investigates AMH levels in infants with premature thelarche. It was concluded that AMH may play a role of suppressing pubertal findings during the infancy and decreased AMH may cause premature thelarche in infants because detected AMH levels in infants with premature thelarche were less than compared to healthy controls and there exists a negative correlation between AMH and FSH.
Keywords: AMH, premature thelarche, infancy, mini-puberty

Nursel Muratoglu Sahin, MD
Dr. Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital, Pediatric Endocrinology Clinic, 06080, Ankara, Turkey
+90 312 3056515
nursel_m_sahin@yahoo.com.tr
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Introduction

Mini-puberty of infancy refers to the transient activation of the HPG axis during the first few months of life. The follicle-stimulating hormone (FSH) level of girls decreases at delivery and increases again with activation of the hypothalamic-pituitary-gonadal axis. The activation of the hypothalamo-pituitary-gonadal axis reaches a peak level approximately in the 6-8th week after delivery. In this period, the levels of sex steroids are similar to early-middle pubertal levels (so called mini-puberty), but their peripheral effects are not realized. Increased FSH in girls continues until the age of 2-4 years, although the level of estradiol is high in the 2-4th month after delivery (1).

Premature thelarche (PT) refers to the precocious appearance of breast development in girls with no other signs of sexual maturation. It is common mostly during the first 2 years of life. PT has been postulated to result from transient partial activation of the hypothalamic-pituitary-ovarian axis with excessive secretion of FSH; the physiologic baseline event in PT is the increase in FSH level (2).

In females, antimüllerian hormone (AMH) is produced by granulosa cells at primer, preantral and early antral follicles (3). AMH has at least two functions during follicular development. First, AMH plays an inhibitory role during initial recruitment, when resting primordial follicles are initiated to grow, and second, it may modify preantral and small antral follicle growth by decreasing the FSH responsiveness of the follicle. The second effect is important during cyclic recruitment, when certain large preantral and small antral follicles are recruited to grow on to the preovulatory follicle stage (4-6).

According to a few studies, AMH levels have a rise during infancy, whereas they are stable from childhood to early adulthood (7,8). In a recent study it is stated that after pubertal onset, AMH decreased 30% during the first 2 years (9). In Sahin et al.'s study, it is found that AMH levels in the central precocious puberty (CPP) group were lower than those in the PT group, and there was a negative correlation between AMH and basal gonadotropin levels (10). In light of this information, it can be thought that AMH may play a role of suppressing puberty. The high levels of AMH in the mini-puberty period when the peripheral effects of hormones are not observed despite the presence of hormonal values similar to pubertal period supports the braking mechanism of AMH. We aimed to investigate AMH levels in infants with premature thelarche who are presumed to have prolonged mini-puberty due to inadequate / late suppression of pubertal activation. We hypothesized that, the AMH related ovarian response to prevent FSH-induced follicle growth is deficient in infants with premature thelarche.

Materials and Methods

Forty five consecutive girls aged between 1 and 3 years who have been admitted to our clinic between July 2015 and September 2016 and who had PT (breast development with no other signs of sexual maturation or bone age advancement) were included to the study. All of parents received oral and written information before signing a consent form. The study was approved by Local Ethical Committee (Zekai Tahir Burak EAH, no:44/2015). Exclusion criteria were as follows: Central and peripheral PP, thyroid illnesses, intake of any medication, acute or chronic diseases, and small for gestational age.

Pubertal staging was done according to the method of Tanner and Marshall by same pediatric endocrinologist (11). If breast stages were differed between the two breasts; the higher stage was taken into an account in the evaluation. All patients were presented with breast budding as only sign of puberty. SDS values for height, weight and relative weight were calculated using national reference data (12). Bone age (BA) was evaluated using Greulich and Pyle method by same endocrinologist (13).

Blood sampling Intravenous cannula was inserted into an antecubital vein, from which venous blood samples were drawn into standard vacuum tubes at 8:00 am. For AMH assay, blood samples were centrifuged (3000 × *g* at 10 min) within 30 min and serum was analysed immediately. AMH was measured with the enzyme immunoassay method (Anshlab AMH/MIS ELISA kit). LH, FSH, and estradiol were measured using chemiluminescence method (Advia Centaur XP, Siemens AG, Munich, Germany).

All the patients were prospectively examined by pelvic ultrasonography (US) performed by the same experienced pediatric radiologist, who was blinded to their clinical and laboratory findings. US was performed using a Logiq 6 US scanner (General Electric Co.Milwaukee, WI), a 7.5-MHz linear-array small parts transducer. Patients and controls were scanned several times until a period with full bladder could be captured. Foley catheterization was not performed in any of the participants. The three dimensions of the uterus, endometrial thickness, and the three dimensions of each ovary were measured. The fundocervical ratio was assessed as >1 or ≤1 as a simple and fast expression of uterine maturation. Endometrial echogenicity was checked with the uterus scanned in the sagittal plane. Ovarian volume, as cubic centimeters, was calculated using the ellipsoid formula (longitudinal dimension × AP dimension × transverse dimension × 0.52).

As the control group, 37 healthy age-matched Tanner stage I infants are included in the study. The control group's SDS values for height, weight and relative weight were calculated and AMH levels were measured.

Statistical Analysis

The results of tests were expressed as the number of observations (n), median and min-max values. The results of the homogeneity (Levene's test) and normality tests (Shapiro Wilk) were used to decide which statistical methods to apply in the comparison of the study groups. According to those test results, parametric test assumptions were not available for variables, so the comparisons of two independent groups were performed by using Mann-Whitney U-test. The statistical significance level of $p< 0.05$ was considered significant. Parametric test preconditions matching variables to determine the relationship between two continuous variables, and then Pearson's correlation coefficient were used. In parametric test for variables that do not meet the pre-conditions, the Spearman correlation coefficient was used. All statistical analyses were performed with the SPSS software (SPSS Ver. 17.0; SPSS Inc., Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant.

Results

The anthropometric properties of the patient and the control groups are given in Table 1. The mean chronologic age (CA) of the patients was 1.76 ± 0.54 (med: 1.70 min-max, 1-3) years. The mean age of onset of breast development was 8.19±6.76 months (med: 8 min-max 0.8-22). The mean duration of breast presence was 12.39±10.29 months (med:10 min-max 1-34) and the patient's breast stages were stage 2 and stage 3. The mean (CA) and BA difference was 0.1±0.34 years (med:0.15 min -0.6 max +0.7). In the follow-up period of (mean 9 months, min-max: 6-18 months), no pubertal progression was found in any patient. Serum AMH levels of premature thelarche [med: 1.66 ng/ml (11.85 pmol/L) min-max: 0.15-6.32 ng / ml (1.07-45.12 pmol/L)] were significantly lower than the control group's [med: 1.96 ng/ml (13.99 pmol/L) min-max: 0.60-8.49 ng / ml (4.28-60.64 pmol/L)] (p: 0.025, power of test: 45%) (Table 1). When the patients were grouped according to breast stages, there was no significant difference between the AMH levels (p: 0.585). AMH was not correlated with CA and BA. There was no relationship between AMH and CA-BA difference.

Laboratory and pelvic USG findings of the infants with premature thelarche are given in Table 2. AMH and FSH were negatively correlated (r: -0.360 p: 0.015) in infants with premature thelarche (Figure 1). The correlation between FSH and AMH levels was significant after controlling the effect of age (r: -0.366 p: 0.014). No correlation was found between AMH and LH and only 4 (7.3%) patients' baseline LH levels were above the measurement limit as expected. No correlation was found between AMH and estradiol because only 16 (35.5%) patients' estradiol levels were above the measurement limit. No correlation was found between AMH and LH levels. Only 2 patients' uterine length were larger than 34 mm, and in only 5 patients uterine volume was above 2 cc. There were 4 patients that endometrium echoes were detected. There were only 6 patients with fundocervical ratio above one. There was no correlation between AMH and uterine size, uterine volume, endometrium thickness, fundocervical ratio, over size, over volume, follicle size and follicle number.

Discussion

This is the first study to investigate AMH levels in infants with premature thelarche. In this study, serum AMH levels in infants with PT were significantly lower than healthy girls' and a negative correlation between FSH and AMH was detected. According to limited studies in girls, AMH level increases gradually from 3 years before pubertal onset to the beginning of puberty, then it decreases approximately 30% during the following 2 years (9,14,15). In recent study, it is found that the AMH levels of CPP group were lower than the AMH levels of PT group aged between 4.5-8 years and a negative correlation is exist between AMH and basal and stimulated gonadotropin levels (10). AMH plays an inhibitory role during initial recruitment, when resting primordial follicles are initiated to grow, and AMH decreases the sensitivity of primordial follicles to FSH and inhibits granulosa cell aromatase, which results in a decreased chance for the follicle to move toward cyclic recruitment and estrogen biosynthesis (4-6). The decrease in the AMH level in the duration of the hypothalamus-pituitary-ovarian axis activation causes cyclic follicle recruitment. Partial activation of the hypothalamus-pituitary-ovarian axis during the so-called mini puberty in the first months of life in girls has been demonstrated. Hagen et al. have demonstrated a marked increase in AMH levels from birth to 3 months of age (7). Because AMH inhibits both initial follicle recruitment (primordial to primary follicles) and FSH-dependent follicle growth (preantral and antral follicles), they propounded that rising levels of AMH during mini puberty may be an ovarian response to prevent FSH-induced follicle growth at a time of life when further differentiation of follicles would be inappropriate. Elevated AMH levels might prevent the progress of puberty. Premature thelarche is a condition seen in the period of mini-puberty and it has been postulated to result from prolonged mini-puberty due to inadequate / late suppression of pubertal activation. (1,2). In this study, detection of somewhat lower AMH levels in infant with PT and a negative correlation between FSH and AMH support our hypothesis that AMH related ovarian response to prevent FSH-induced follicle growth is deficient in infants with premature thelarche.(power of test: 45%). However the role of AMH in the pathogenesis of PT is not known clearly. It is known that many factors have complex interactions during the mini-puberty period, and this study concluded that AMH may play a role in this complex interaction.

There are different results in 5 other studies investigating AMH levels in early pubertal development in the literature (10,16-19)(Table 3). In the Hagen et al.'s study, the number of subjects is very limited and no comparison was made with healthy controls (16). In the study of Şahin et al. the groups were consisted with girls aged 4-8 years (10). The AMH levels of the CPP group were found to be lower than the PT group's (10). This result is consistent with present study. In the study of Chen et al, compared with the slowly progressive CPP group, girls with progressive CPP have lower AMH levels (18). This result also supports that pubertal progression is associated with decreased AMH levels. In the Nam et al.'s study, there was no difference between CPP and control group of the AMH levels (17). However, the patients are older and pubertal stages are more advanced than other studies (17). In the study, it may not be possible to determine the decrease of AMH in the onset of puberty due to advanced pubertal stage of patients. In the Erdeve et al's study, serum AMH levels in girls with PT were found to be higher than the AMH levels of prepubertal girls (19). However, the comparison of AMH values of groups in this study is not appropriate because the age of the control group is significantly different than the PT group's. Although no significant difference was detected, they found that the AMH level of the CPP group was lower than the PT group's, in the study (19).

Pelvic ultrasound might be useful for diagnosis of precocious puberty. However no significant differences in uterine and ovarian ultrasound measurements were detected between children with premature thelarche and controls (2). In a recent study, they found that AMH reflected the number of small (2–3 mm) and medium (4–6 mm) follicles (20). In early puberty (Taner breast stage 1–3), the number of AMH-producing follicles (2–6 mm) correlated positively with pubertal stages, whereas AMH levels were unaffected (20). In our study, ultrasound findings of the vast majority of our patients were prepubertal as expected. Therefore, a correlation could not been determined between AMH and the findings of pelvic ultrasound.

There is an important limitation in this study in which we achieved important results. Because the study group was composed of infants, only AMH levels were measured from control group due to ethical reasons. Although a negative correlation between AMH and FSH was found in the PT group; the FSH-AMH relationship could been shown more clearly if the FSH level assayed in the control group.

In conclusion, AMH may play a role of suppressing pubertal findings during the infancy because of AMH decreases the sensitivity of primordial follicles to FSH and inhibits granulosa cell aromatase, which results in a decreased chance for the follicle to move toward cyclic recruitment and estrogen biosynthesis. Decreased AMH may cause premature thelarche in infants because detected AMH levels in infants with premature thelarche were less than compared to healthy controls and there exists a negative correlation between AMH and FSH. Although our findings support our hypothesis; the opposite hypothesis that an excessive activation of the ovary result in lower AMH production cannot be completely excluded and the influence of other factors involved in the mini-puberty period cannot be ruled out. The reason of somewhat lower AMH and the role of AMH in the etiopathogenesis of PT will be clarified by further studies evaluating AMH levels in mini- puberty and related disorders in infancy.

Ethics

Ethics Committee Approval: Zekai Tahir Burak EAH, no:44/2015

Informed Consent: All of parents received oral and written information before signing a consent form.

Authorship Contributions

Surgical and Medical Practices: Nursel Muratoglu Sahin, Elvan Bayramoglu, Hatice Nursun Ozcan, Erdal Kurnaz, Meliksah Keskin, Senay Savas Erdeve, Semra Cetinkaya, Zehra Aycan

Concept: Nursel Muratoglu Sahin

Design: Nursel Muratoglu Sahin

Data Collection or Processing: Nursel Muratoglu Sahin, Elvan Bayramoglu, Hatice Nursun Ozcan, Erdal Kurnaz, Meliksah Keskin, Senay Savas Erdeve, Semra Cetinkaya, Zehra Aycan

Analysis or Interpretation: Nursel Muratoglu Sahin, Semra Cetinkaya, Zehra Aycan

Literature Search: Nursel Muratoglu Sahin

Writing: Nursel Muratoglu Sahin

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Figure 1. The correlation figure of AMH and FSH

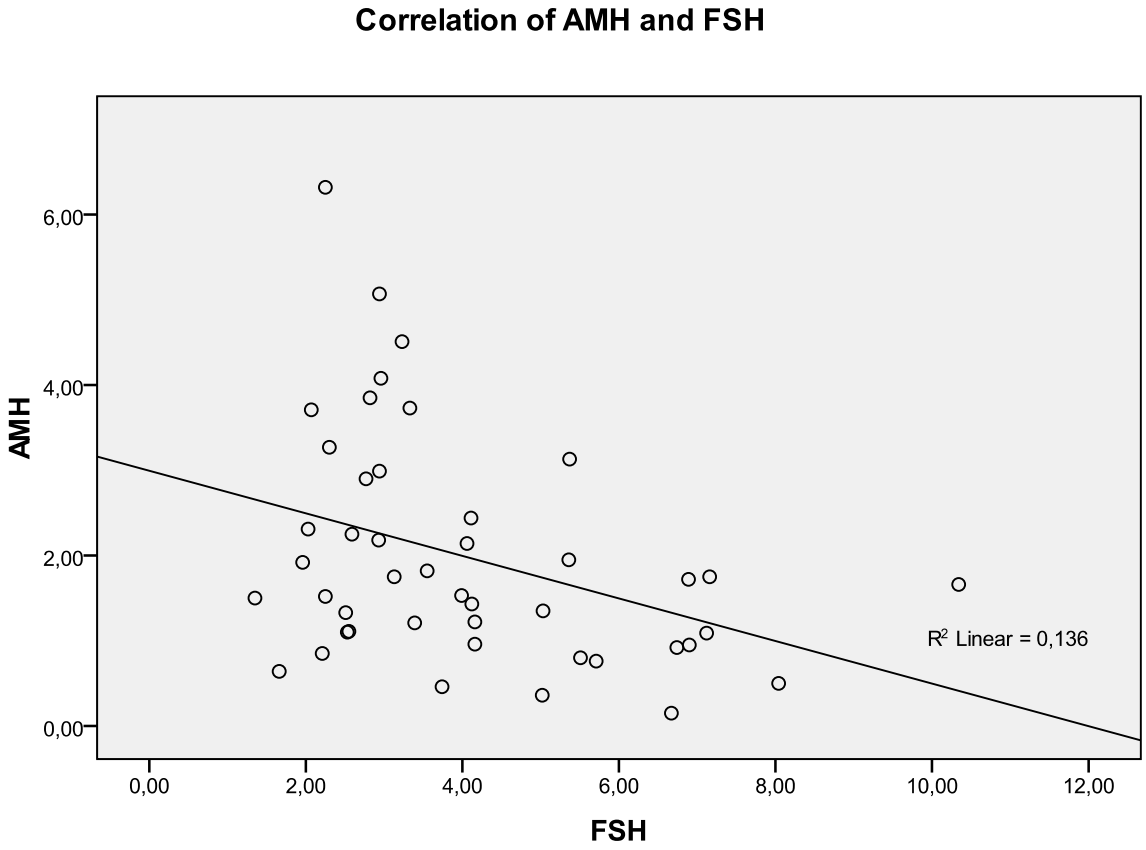

Table 1: The anthropometric properties of the infant with premature thelarche and control group

	Premature Thelarche (n:45)			Control (n:37)			
	Median	IQR	25-75p	Median	IQR	25-75p	**p**
Chronological age (year)	1.70	0.75	1.35 - 2.1	1.90	1.05	1.35 – 2.5	0.127
Height (cm)	83.20	7.6	80.40 - 88.05	84.60	10.5	79.25 – 89.75	0.621
Height SDS	0.16	1.34	-0.56 - +0.79	-0.40	1.18	-1.13 - +0.05	0.012
Weight (kg)	11.50	1.92	10.65 – 12.58	11.10	3.05	9.90 – 12.95	0.518
Weight SDS	0.21	1.47	-0.46 - +1.02	-0.34	1.49	-1.19 - +0.30	0.021
Relative weight (%)	103	15.5	96 – 111.5	99	12.5	94 – 106.5	0,08
AMH (ng/ml)	1.66	1.65	1.03 – 2.67	1.96	2.21	1.54 – 3.76	0.025

(Mann-Whitney U-test)

Table 2: Laboratory and ultrasound findings of the infants with premature thelarche

	Median	**IQR**	**25-75p**
Follicle-stimulating hormone (IU/L)	3.39	2.86	2.54 – 5.37
Luteinizing hormone) (IU/L)	0.07	0.001	0.07 – 0.07
Estradiol (pg/ml)	11.80	4.98	11.8 – 15.56
Uterine length (mm)	27.0	6.5	22.5 – 29.5
Uterine volume (cc)	1.17	0.61	0.79 – 1.54
Total ovarian volume (cc)	1.40	1.21	0.66 – 1.87

Table 3: AMH levels in early pubertal development in the literature

	Hagen et al.2012 (15) med (min-max)	Sahin et al.2015 (10) med (min-max)	Nam et al.2017 (17) mean ± sd	Erdeve et al.2017 (19) mean ± sd	Chen et al.2017 (18) med (min-max)		This study med (min-max)
Control							
n		25	55	22	20		49
Year		8.1 (2.7-10)	9.4 ± 0.5b	6.52 ± 1.10a	6,7 (5.4-7.9)		1.6±0.8(0.4-3)
FSH	-	NA	2.30 ± 1,30b	2.21 ± 1.70	0,85 (<0,1-2,13)		NA
LH		NA	0.30 ± 0.40	0.09 ± 0.78	<0,07(<0,07-0,09)		NA
AMH (ng/ml)		1.81 (0.07-8.53)a,b	5.40 ± 3,70	2.10 ± 0.85a	2,14 (0,79-4,14)		2,46 (0,60-8,49)b
PT							
n		37		24	65		55
Year		7.6 (4.7-8)		7.16 ± 0.62b	6.75 (5,2-8,0)		1,6±0,7 (0.3-3)
FSH	-	1.4 (0.23-3.88)a	-	1.84 ± 1.45	2,37 (<0,1-5,4)		4.32 ± 2.26
LH		0.05 (0-0.58)a		0.10 ± 0.64	<0,07(<0,07-0,26)		0.10 ± 0.16
AMH (ng/ml)		2.39 (0.77-8.88)a		3.70 ± 3.00b	NA		1,66 (0,15-7,28)a
CPP					Progressive CPP	Slowly Progressive CPP	
n	15	37	98	21	55	28	
Year	7.7 (7.2-8.6)	8.0 (4,5-8)	8.4 ± 0.5a	7.45 ± 0,87b	6,5 (5,0-8,0)	6,75 (5,25-8,0)	
FSH	NA	2.46 (1.05-9.31)b	3.50 ± 2.50a	2.61 ± 1.45	2,63 (0,74-7,35)	2,42 (0,79-5,46)	-
LH	NA	0.11 (0.04-4.79)b	0.40 ± 0.60	0.28 ± 0.33	0,33 (0,11-1,92)	0,25(0,12-0,41)	
AMH (ng/ml)	2.84 (0.28-4.20)	1.55 (0.48-5.52)b	5.90 ± 3.60	2.70 ± 1.61a,b	2,82 (1,04-6,16)a	5,39 (1,94-11,15)b	

PT: premature thelarche, CPP: central precocious puberty, NA: non assessment

a,b: The difference between the group means with different letters are significant ($p < 0.05$).