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ORIGINAL ARTICLE PEDIATRICS

The effect of subclinical hypothyroidism on ovarian volume in prepubertal girls

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ABSTRACT

OBJECTIVE: Enlargement and cystic changes in ovaries of patients with long-standing overt hypothyroidism have been described in numerous case reports. However, there are limited data about the effect of subclinical hypothyroidism (SH) on ovarian volume. The aim of the study is to evaluate the relationship between serum thyroid stimulating hormone (TSH) level and ovarian volume in prepubertal girls with SH.

METHODS: Patients who were aged between 6 and 10 years and diagnosed with SH and age-matched healthy euthyroid controls were enrolled in the study. All subjects were prepubertal.

RESULTS: Thirty-five children with SH (mean age; 7.6±1.0 years) and 50 euthyroid healthy girls (mean age; 7.7±1.2 years) were enrolled in the study. TSH and LH levels and both ovarian volumes were significantly higher in SH group than controls ($p<0.05$). In addition, TSH was positively correlated with ovarian volumes and LH in patients with SH ($p<0.05$).

CONCLUSION: The results of this study showed that ovarian volumes of prepubertal girls with SH were significantly greater than those with normal thyroid function. Although ovarian enlargement and cyst formation is well recognized in long-standing overt hypothyroidism, it has been shown for the 1st time in patients with SH.

Keywords: Ovarian volume; prepubertal girls; subclinical hypothyroidism; thyroid-stimulating hormone.

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Subclinical hypothyroidism (SH) is characterized biochemically by an elevated thyroid-stimulating hormone (TSH) level and normal free thyroxine (fT4) [1]. Most endocrinological references use a cutoff of TSH >4.5 mIU/L to diagnose SH [1]. While, natural course of SH is unclear, current data suggest that growth, development, and neurocognitive functions are not affected in untreated patients with SH [2, 3].

It is well known that thyroid hormones are essential for normal pubertal growth and development [4]. Although hypothyroidism is typically associated with delayed puberty, some children with long-standing overt hypothyroidism present with signs of the early puberty [5]. It is characterized by breast development, vaginal bleeding, lack of pubic hair, and delayed bone age in females and macroorchidism in males [5]. Enlargement with or without multicystic changes in ovaries of patients with long-standing overt hypothyroidism has been described in numerous case reports [6, 7]. Moreover, ovarian enlargement that is observed in primary hypothyroidism could be present as a large ovarian cyst, multicystic ovaries, polycystic ovaries, or spontaneous hyperstimulation.

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However, there are limited data about the effect of SH on ovarian volume. Therefore, the aim of this study was to evaluate, if any, the relationship between TSH level and ovarian volume in prepubertal girls with SH.

Highlight key points

- The results of this study demonstrated that the ovarian volumes of prepubertal girls with SH were significantly greater than those with normal thyroid function.
- The molecular mechanism of thyroid hormones action on ovarian tissue and functions is still required to be investigated.
- Close monitoring of SH for the early pubertal development may be clinically useful.

MATERIALS AND METHODS

Study Design and Participants

This prospective case-control study was conducted on patients attending to the pediatric endocrinology clinic of our hospital. Prepubertal girls with SH (SH group) and prepubertal euthyroid healthy girls (control group) were enrolled in the study. SH was diagnosed on the basis of elevated TSH (4.5–10 μIU/L) and normal range of serum fT4 levels. Only patients with stable elevated TSH and normal fT4 levels in at least two different measurements 4–6 weeks apart were included in the study. Pubertal stages were determined using the criteria and definitions described by Marshall and Tanner [8]. Only the girls that have Tanner stage 1 breast development and aged between 6 and 10 years old included in the study. The threshold level assessed prepubertal for the basal LH level was taken as <0.3 mIU/mL [9]. Patients and control subjects with a chronic disease, a history of drug use, an endocrine pathology, and obesity were excluded from the study. Subjects were also excluded if they have Hashimoto's thyroiditis, premature thelarche and/or premature adrenarche.

Clinical and Biochemical Measurements

Anthropometric and laboratory measurements were performed in all subjects. Height was measured using a Seca stadiometer with a sensitivity of 0.1 cm. Weight was measured using a Seca scale with a sensitivity of 0.1 kg. Height and weight were obtained with participants in light clothes and without shoes. BMI was calculated by dividing weight (kg) by height squared (m^2). All patients and control subjects underwent a detailed suprapubic pelvic ultrasonography examination to evaluate the ovarian volume and ovarian cyst formation.

In all participants fasting, peripheral venous blood samples were taken from an antecubital vein between 08.00 and 10.00 a.m. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), TSH, and fT4 levels were measured on the same day with suprapubic pelvic ultrasonography. Samples were separated by centrifugation and stored protected from light at -80 C until analysis. Competitive electro-chemiluminescence immunoassays on the cobas® 6000 analyzer (Roche Diagnostics, Rotkreuz, Switzerland) were used to quantify serum LH, FSH, and E2. The lowest limits of detection were 0.1 mIU/mL for LH, 0.1 mIU/mL for FSH, and 18.4 pmol/L for E2. Serum TSH and fT4 levels were analyzed with Beckman Coulter DxI 800 Access® immunoassay system (Beckman Coulter, USA).

Suprapubic Pelvic Ultrasonography

Ovarian volume was measured as described by Campbell et al. [10]. Sonographic examinations using 13 MHz abdominal transducers (Toshiba Aplio 500 Ultrasound, Japan), were carried out by the same operator. The longitudinal size and transverse diameter of ovaries were measured. After turning transducer 90 degrees, anteroposterior diameter was measured where it is the thickest diameter. The right and left ovarian volumes were calculated by the formula (V=D1 x D2 x D3 x 0.523/1000, D1 is transvers, D2 is anteroposterior, and D3 is longitudinal diameter).

Ethics Approval

This study was conducted in accordance with the declaration of Helsinki and initiated after the approval of the Bagcilar Training and Research Hospital Clinical Research Ethics Committee of our hospital (approval number: 2018.04.1.04.040). Written informed consent of the subjects and/or parents was obtained before the study.

Statistical Analysis

In addition to descriptive statistics (mean, median, and standard-deviation), Kolmogorov-Smirnov test was used for normally distributed variables. Mann-Whitney U-test is used for non-normally distributed variables. A correlation analysis was performed using Spearman's correlation analysis. Variables with P-value <0.05 in the bivariate correlation analysis were included in a multivariate lin-

Table 1. Clinical characteristics and laboratory findings of the study groups

	Subjects with SH (n=35) Median (IQR)	Control subjects (n=50) Median (IQR)	p
Age, year	7.4 (6.7–8.0)	7.2 (6.7–8.9)	0.926
Height-SDS	-0.3 (-0.7-0.3)	0.4 (-0.4–0.7)	0.153
Weight-SDS	0.0 (-0.9–0.9)	-0.3 (-0.6–0.2)	0.409
BMI, kg/m^2	15.8 (15–18.1)	15.4 (14.3–16.)	0.256
BMI-SDS	-0.1 (-0.8–0.9)	-0.4 (-1.0–0.2)	0.154
TSH, mIU/L	6.0 (5.3–7.2)	2.2 (1.5–3.2)	0.000
FT4, ng/dL	1.02 (0.9–1.32)	0.97 (0.9–1.04)	**0.077**
LH, mIU/mL	0.12 (0.09–0.28)	0.01 (0–0.03)	**0.000**
FSH, mIU/mL	1.7 (1.4–2.5)	1.7 (1.0–2.3)	0.424
E2, pmol/L	4.8 (2.0–14.0)	5.1 (4.0–7.0)	0.782
ROV, mL	1.0 (0.6–1.5)	0.5 (0.3–0.8)	**0.000**
LOV, mL	1.0 (0.6–1.8)	0.5 (0.3–0.8)	**0.000**

SH: Subclinical hypothyroidism; IQR: Interquartile range; BMI-SDS: Standard deviation score of body mass index; TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; E2: Estradiol; ROV: Right ovarian volume; LOV: Left ovarian volume.

Table 2. Correlation between TSH and the other variables

	Pearson's correlation coefficient (r)	p
Age, years	0.041	0.706
Height-SDS	-0.303	**0.005**
Weight-SDS	0.154	0.156
BMI-SDS	0.370	**0.000**
FT4, ng/dL	0.090	0.408
LH, mIU/mL	0.478	**0.000**
FSH, mIU/mL	0.154	0.156
E2, pmol/L	0.108	0.322
ROV, mL	0.318	**0.003**
LOV, mL	0.373	**0.000**

BMI-SDS: Standard deviation score of body mass index; TSH: Thyroid-stimulating hormone; FT4: Free thyroxine; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; E2: Estradiol; ROV: Right ovarian volume; LOV: Left ovarian volume.

ear regression analysis model to assess the independent determinants. P<0.05 was considered statistically significant. Statistical analysis was performed using the program SPSS 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 35 prepubertal girls with SH (SH group, mean age of 7.6±1.0 years) and 50 euthyroid prepubertal healthy girls (control group, mean age of 7.7±1.2 years) were enrolled in this study. There was no statistically significant difference between the groups in terms of age, height and BMI (p>0.05). As expected, serum TSH levels were significantly higher in the SH group than in the control group (p<0.001). Serum LH levels were also significantly higher in the SH group than in the control group (p<0.001). Minimum LH level was 0.0 and maximum LH level was 0.29 in the SH group, whereas minimum LH level was 0.0 and maximum LH level was 0.17 in the control group. There was no significant difference in serum fT4, FSH, and E2 levels between the groups (p>0.05). On comparison of bilateral ovarian volumes, the right and the left ovarian volumes of the subjects with SH were significantly greater than in the control group (p<0.001). Clinical characteristics and laboratory findings of the study groups are displayed in Table 1.

In Spearman's correlation analysis, serum TSH levels were positively correlated with BMI-SDS (r=0.370, p=0.000), LH (r=0.478, p=0.000), right ovarian volume (r=0.318, p=0.003), and left ovarian volume (r=0.373, p=0.000), while there was a negative correlation with height-SDS (r=-0.303, p=0.005). No significant correlation was found between serum TSH levels and FSH (r=0.154, p=0.156) and E2 (r=0.108, p=0.322), as shown in Table 2. The correlation between TSH levels and ovarian volumes is also introduced in Figure 1.

DISCUSSION

This study examined the effect of SH on ovarian volume and it is observed that ovarian volumes of prepubertal girls with SH were significantly greater than those with prepubertal girls with normal thyroid function.

The pathogenesis of ovarian enlargement and/or cyst formation or precocious puberty that seen in hypothyroidism remains unclear. Several mechanisms have been considered, such as increased ovarian sensitivity to gonadotropins through PRL, an over production of multiple pituitary hormones as a result of a lack of specificity in the thyroid feedback mechanism or from an overlap in glycoprotein hormone synthesis [11, 12]. Since, an elevated TSH level is the only consistent finding in this disorder, studies focused on high levels of TSH acting through the FSH receptor causing the gonadal stimula-

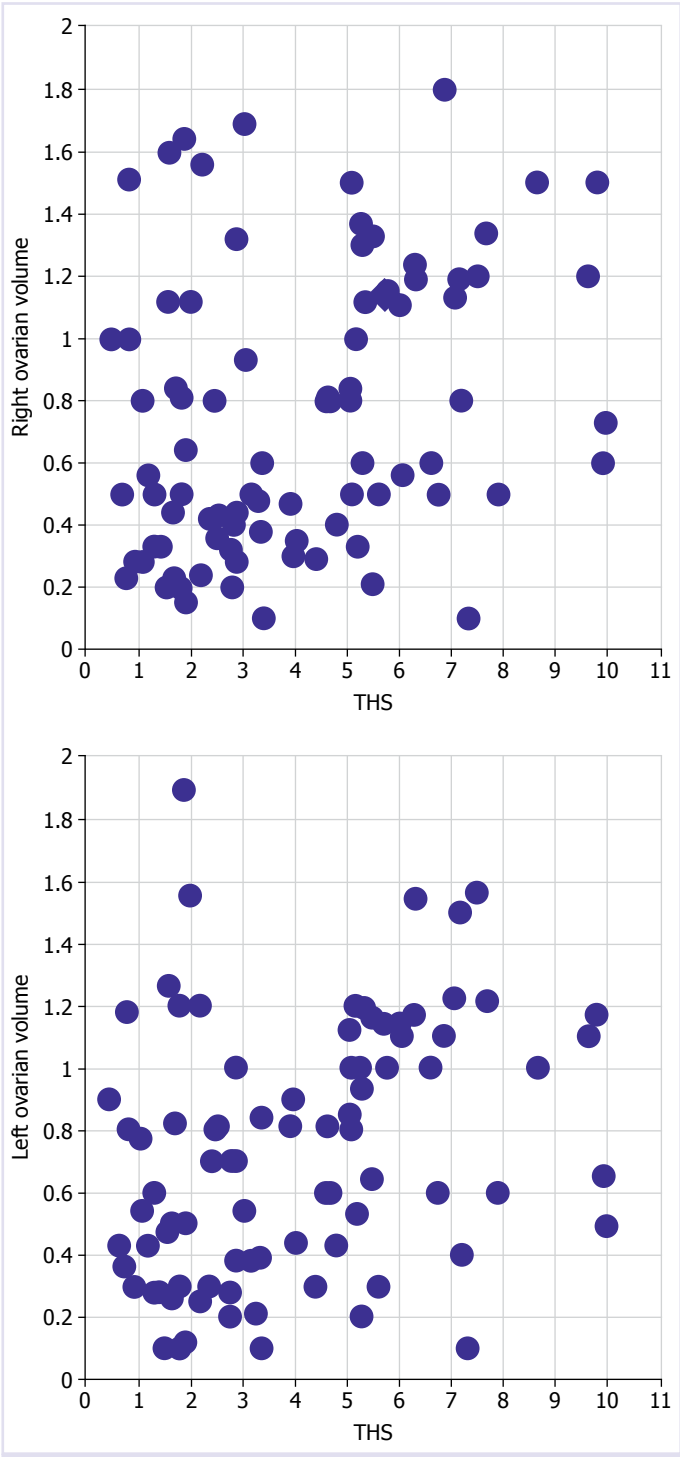

FIGURE 1. The correlation between TSH levels and ovarian volumes.

tion due to similar alpha-subunit [13, 14]. In a recent study, Ryan et al. [13] examined the hFSHR gene in eight pediatric patients (seven girls and one boy) displaying gonadal hyperstimulation due to primary hypothyroidism and demonstrated a dose-dependent and specific rhTSH-dependent increase in cAMP production in HEK293 cells expressing the wild-type hFSHR. In that study, pediatric gonadal hyperstimulation associated with severe primary hypothyroidism has been suggested to result from the actions of the elevated concentrations of TSH on the wild-type hFSHR. Anasti et al. [14] have previously reported similar findings as a potential novel mechanism for precocious puberty in juvenile hypothyroidism. However, although no cutoff is given in that study, very high TSH levels are proposed to stimulate FSH receptors. Since our study is not an experimental in vitro study, we cannot predict the effect of slightly elevated TSH levels in stimulating FSH receptors. However, we have sonographically demonstrated that there is an ovarian enlargement in patients with SH.

Recently, Muderris et al. [15] reported similar findings to our study in adult patients with hypothyroidism. In that study, ovarian volumes of patients with hypothyroidism were significantly greater than the controls and a significant decrease was found in ovarian volume after initiating thyroid hormone replacement therapy [15]. The relationship between thyroid hormones and ovarian size was also shown in a rat model study [16]. In this study, the concentration of LH/hCG receptors in ovaries of hypo-and hyperthyroid rats was estimated and the ovaries of the hyperthyroid group were diminished in size, and the number of receptors per ovary was also reduced [16]. In contrast, the ovaries of the hypothyroid group were higher in size, and the number of receptors per ovary was increased. The relation of this change is not clear, but may cause to ovarian sensitization to gonadotropins [16]. In our study, we also found a statically significant correlation between TSH levels and ovarian volumes. However, we might conclude that this correlation was relatively weak.

In the present study, LH levels were also significantly higher in prepubertal girls with SH than control group. It is possible that the ovarian enlargement/cysts seen in hypothyroid girls result from chronic LH stimulation since an association between high LH concentration and cyst formation has been reported [17]. McNatty et al. [18] found that cysts occurred in many women whose follicular fluid had increased amounts of LH. Furthermore, elevated LH in the presence of normal FSH has been implicated in the etiology of polycystic ovary disease [19, 20]. However, the fact that LH is within normal limits in many cases suggesting that other factors may have an effect besides this mechanism [6]. In addition, in our study, in which girls up to 10 years of age were included, there

may be some patients who were in the very early stage of puberty, when the LH level started to increase. Ovaries may have started to grow with slight and fluctuating increase in gonadotropin levels, but estrogen may not yet be produced at a level to enlarge the breast tissue. Perhaps chronic and mild TSH stimulation in the gonads may cause intermittent estrogen spikes with relatively early stimulation of the hypothalamus-pituitary-gonad axis and a shift to earlier onset of puberty than genetically programmed time.

Although, all these mechanisms listed above are considered in patients with long-standing overt hypothyroidism, the effectiveness of this mechanism is not known in patients with SH. Therefore, more study is needed. In addition, there is a limitation of this present study that needs to be addressed; prolactin was not measured and hence its relationship with other parameters could not be evaluated. However, based on findings of our study, we conclude that TSH may have an effect on ovarian volume even in slightly elevated levels.

In conclusion, the results of this study demonstrated that ovarian volumes of prepubertal girls with SH were significantly greater than those with normal thyroid function. Although ovarian enlargement and cyst formation are well recognized in longstanding overt hypothyroidism, it has been shown for the 1st time in patients with SH. Hence, close monitoring of SH for early pubertal development may be clinically useful.

Ethics Committee Approval: The Bagcilar Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 13.04.2018, number: 2018.04.1.04.040).

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