



Adequacy of basal luteinizing hormone levels in the diagnosis of central precocious puberty

Santral puberte prekoks tanısında bazal lütenizan hormon düzeyinin yeterliliği

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The known about this topic

In the differentiation of central precocious puberty and premature thelarche, ultrasonography findings, basal and stimulated gonadotropin levels, and basal estradiol levels should be evaluated, as well as clinical findings such as growth velocity and bone age. The gold standard test used to demonstrate activation of the hypothalamo-pituitary-gonadal axis is the gonadotropin-releasing hormone stimulation test. Currently, the efficacy is not clear and standardization has not been performed for any alternative approaches to be used instead of the gonadotropin-releasing hormone stimulation test.

Contribution of the study

In girls presenting with premature breast development, basal luteinizing hormone level (≥ 0.65 IU/L) and luteinizing hormone/ follicle-stimulating hormone ratio (≥ 0.25) are sensitive methods that can be used in demonstrating the activation of the hypothalamo-pituitary-gonadal axis and in making a diagnosis of central precocious puberty. Among these methods, the variable that gives the best sensitivity and specificity is the measurement of basal luteinizing hormone (≥ 0.65 IU/L), which is a sensitive test that can be used as a screening test in the diagnosis of central precocious puberty.

Abstract

Aim: To determine the clinical, anthropometric, and laboratory parameters that could be used for differentiating central precocious puberty from premature thelarche in girls who had breast development between the ages of 3 and 8 years.

Material and Methods: The study included 344 girls (196 girls with idiopathic central precocious puberty, 148 girls with premature thelarche) who underwent gonadotropin-releasing hormone stimulation tests for breast development. Age at diagnosis, bone age, anthropometric measurements, basal/stimulated hormone levels were recorded. Univariate regression analysis was performed to determine the parameters that could be used for differentiating precocious puberty from premature thelarche. Significant parameters in univariate analyses were grouped according to the thresholds determined using receiver operating characteristic curves and reevaluated through multivariate analysis.

Results: The bone age, height-standard deviation score, body mass index-standard deviation score, and growth velocity-standard deviation score at diagnosis were found to be higher; pubertal stages were found to be more advanced; uterus and ovary volumes were found to be larger; and the basal/peak luteinizing hormone, follicle-stimulating hormone,

Öz

Amaç: Bu çalışmada 3–8 yaş arasında meme gelişimi başlayan santral puberte prekoks ve prematür telarş tanılı kız olguların klinik, antropometrik ve laboratuvar bulguları incelenerek santral puberte prekoks ve prematür telarş ayırımında kullanılabilir ölçümlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya meme gelişimi nedeniyle gonadotropin-salğılatıcı hormon uyarı testi yapılmış 344 kız olgu (196 idiyopatik santral puberte prekoks, 148 prematür telarş) alındı. Olguların tanı yaşı, kemik yaşı, antropometrik ölçümleri, bazal/uyarılmış hormon düzeyleri kaydedildi. Santral puberte prekoks ve prematür telarş ayırımında kullanılabilir ölçümleri belirlemek için tek değişkenli regresyon analizi yapıldı. Anlamlı gelen ölçümler işlem karakteristik eğrisiyle saptanan eşik değerlere göre gruplandırıldı ve çok değişkenli analiz ile değerlendirildi.

Bulgular: Santral puberte prekoks olguların tanıda kemik yaşı, boy-standart sapma skoru, vücut kitle indeksi-standart sapma skoru, büyüme hızı-standart sapma skoru prematür telarşlılardan daha yüksek, puberte evreleri daha ileri, uterus-over hacimleri daha büyük, bazal/

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luteinizing hormone/follicle-stimulating hormone levels were found to be higher in the subjects with precocious puberty. There was no difference between estradiol levels between the two groups. The best thresholds to differentiate the two groups were found as 0.65 IU/L (78% sensitivity, 100% specificity), 1.9 IU/L (100% sensitivity, 72% specificity), 0.25 (67% sensitivity, 100% specificity) and 1.1 (69% sensitivity, 71% specificity), respectively, for basal luteinizing hormone, follicle-stimulating hormone, luteinizing hormone/follicle-stimulating hormone ratio, and the growth velocity-standard deviation score.

Conclusion: In girls presenting with early breast development, a basal luteinizing hormone level of ≥ 0.65 IU/L and a luteinizing hormone/follicle-stimulating hormone ratio of ≥ 0.25 are sensitive ways to demonstrate activation of the hypothalamo-pituitary-gonadal axis. Among these, the variable that gives the best sensitivity and specificity is the measurement of basal luteinizing hormone levels (≥ 0.65 IU/L), which can be used as a screening test in the diagnosis of central precocious puberty.

Keywords: Central precocious puberty, gonadotropin-releasing hormone, precocious puberty, premature thelarche, puberty

Introduction

Central precocious puberty (CPP) is the initiation of puberty signs before the age of 8 years in girls as a result of activation of the hypothalamo-pituitary-gonadal (HPG) axis. Premature thelarche (PT) is the term used for unilateral or bilateral isolated breast development in the absence of the other secondary sex characteristics before the age of 8 years (before activation of the axis). Sixty percent of subjects with premature thelarche are below the age of 2 years, and the other subjects peak between the ages of 5 and 7 years (1). In these subjects, the growth velocity is normal, the bone age is compatible with the chronologic age, and basal gonadotropin (Gn) and estradiol (E_2) levels are compatible with the levels found before puberty in contrast to CPP (2). Premature thelarche is considered a normal variant and is not a pathologic condition (3). In these children, the follicle-stimulating hormone (FSH) level is increased, but no change is observed in the level of luteinizing hormone (LH).

Premature thelarche is divided into two groups according to clinical and laboratory characteristics. Classic PT occurs before the age of 2 years, generally regresses spontaneously or does not show progression (4–6). Puberty and menarche occurs at the normal time and final adult height is not expected to be influenced negatively. Non-classic PT, which is called thelarche variant or exaggerated thelarche and shows an extraordinary course, generally occurs before the age of 3–4 years, breast development does not show regression, and is a precursor of precocious puberty; the possibility of precocious puberty is high (2, 7). Approximately 13–14% of subjects with premature thelarche may progress to CPP and they should be monitored in this aspect (2, 3).

In the differentiation of CPP and premature thelarche, ultrasonography findings, basal and stimulated Gn lev-

el, and basal E_2 levels should be evaluated, as well as clinical findings such as growth velocity and bone age. The HPG axis is active in CPP, whereas there is no axis activation in premature thelarche. The gold standard test used to demonstrate HPG axis activation is stimulation tests performed using gonadotropin-releasing hormone (GnRH) or GnRH analogue (GnRHa) (8, 9). However, the GnRH stimulation test is a long and troublesome test that causes anxiety in patients because it requires establishment of vascular access and obtaining numerous blood samples at different times. Therefore, there are various studies that recommend alternative use of clinical findings, ultrasonography findings, and hormone measurements such as basal Gn and E_2 levels in place of the GnRH test in differentiating cases of CPP from cases of PT (10–12). However, the efficiency is not clear and standardization has not been performed for any of the alternative approaches to be used in place of GnRH stimulation test. In different studies, it was attempted to find thresholds with high sensitivity and specificity by evaluating basal and stimulated LH levels (12–17).

Çıkarımlar: Erken meme gelişimi ile gelen kızlarda bazal lütenizan hormon $\geq 0,65$ IU/L, lütenizan hormon/folikül uyarıcı hormon $\geq 0,25$ olması hipotalamo-hipofiz-gonad ekseninin harekete geçmesini göstermede kullanılacak duyarlı yöntemlerdir. Bu yöntemler arasında en iyi duyarlılık ve özgüllük veren değişken bazal lütenizan hormon ölçümüdür. Bazal lütenizan hormon $\geq 0,65$ IU/L olması santral puberte prekoks tanısında tarama testi olarak kullanılacak duyarlı bir testtir.

Anahtar sözcükler: Gonadotropin-salgılatıcı hormon, prematür telarş, puberte, puberte prekoks, santral puberte prekoks

els, and basal E_2 levels should be evaluated, as well as clinical findings such as growth velocity and bone age. The HPG axis is active in CPP, whereas there is no axis activation in premature thelarche. The gold standard test used to demonstrate HPG axis activation is stimulation tests performed using gonadotropin-releasing hormone (GnRH) or GnRH analogue (GnRHa) (8, 9). However, the GnRH stimulation test is a long and troublesome test that causes anxiety in patients because it requires establishment of vascular access and obtaining numerous blood samples at different times. Therefore, there are various studies that recommend alternative use of clinical findings, ultrasonography findings, and hormone measurements such as basal Gn and E_2 levels in place of the GnRH test in differentiating cases of CPP from cases of PT (10–12). However, the efficiency is not clear and standardization has not been performed for any of the alternative approaches to be used in place of GnRH stimulation test. In different studies, it was attempted to find thresholds with high sensitivity and specificity by evaluating basal and stimulated LH levels (12–17).

In this study, it was aimed to determine measurements that could be used in the differentiation of CPP–PT by examining the clinical, anthropometric, and laboratory findings in female subjects with a diagnosis of CPP and PT whose breast development started at the age of 3–8 years. In girls, plasma Gn levels increase a few days after birth, and are reduced to low levels before puberty, after the age of 2–3 years (18). In the first 3 years of life, both the level of basal LH and peak LH response against GnRH test show great variance in healthy individuals. Therefore, children below the age of 3 years were not included in this study.

Material and Methods

Three hundred forty-four girls aged between 3 and 8 years who presented to pediatric outpatient clinics

because of breast development and had undergone a GnRH stimulation test in the last 15 years were included in the study. The data were evaluated retrospectively by examining patient records. The chronologic age (CA) at the time of diagnosis; age at the time of onset of symptoms; puberty stage at the time of diagnosis; growth velocity in the last 6 months, if present; bone age (BA) at the time of diagnosis; anthropometric measurements [body weight, height, body mass index (BMI)]; pelvic ultrasonography findings (uterine longitudinal diameter, mean ovarian volume); basal and stimulated Gn levels; and basal E_2 levels were recorded.

A diagnosis of idiopathic CPP (iCPP) was made with breast development before the age of 8 years (Tanner stage ≥ 2) in association with BA/CA > 1 , a basal serum E_2 level of ≥ 10 pg/mL, a peak LH level of ≥ 5 IU/L in GnRH test, and normal pituitary magnetic resonance imaging (MRI) (19). Subjects who had isolated breast development, BA \leq CA, a peak LH value of < 5 IU/L in the GnRH test, and those who were not found to have progression in puberty signs and BA as a result of clinical follow-up of at least one year, were considered as having PT.

The GnRH test was performed by obtaining venous blood sample at the 20th, 40th, 60th, and 120th minute for measurement of FSH and LH following intravenous administration of 100 $\mu\text{g}/\text{m}^2$ LHRH (gonadorelin acetate, Ferring®) (19). Follicle-stimulating hormone, LH, and E_2 were measured using commercial kits (ARCHITECT System, Abbott Laboratory Diagnostics, USA) with immunochemiluminometric (ICMA) method. The lowest values for FSH, LH, and E_2 that could be measured were found as 0.3 IU/L, 0.07 IU/L, and 10 pmol/L, respectively.

A nurse trained in auxology measured the subjects' body weights in kg using an electronic scale (SECA) that could measure in intervals of 0.1 kg, and measured heights in meters using a Harpenden stadiometer that could measure in intervals of 0.1 cm in the standing position. The height-standard deviation score (height-SDS) was calculated according to CA and bone age using the Centers for Disease Control and Prevention (CDC) tables. The BMI was calculated by dividing body weight in kilograms by height in meters squared. The BMI-standard deviation score (BMI-SDS) was calculated according to the LMS method using CDC tables (20). The growth velocity-standard deviation score (growth velocity-SDS) was calculated using the data of Kelly et al. (21). Puberty stages were determined using the Marshall and Tanner (22) staging system. Bone age was calculated according to the Greulich and Pyle (23) method using the bone age atlas.

The subjects whose data were deficient in file records, subjects with peripheral precocious puberty, subjects with CPP who were found to have organic pathology on central nervous system imaging, and subjects with comorbidities that could influence onset of puberty such as hypothyroidism, growth hormone deficiency, and congenital adrenal hyperplasia, were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki principles. Approval was obtained from Hacettepe University Ethics Committee for the study (Date of approval: 24.04.2019, Approval number: 16969557-923). Patient consent was not obtained because the study was conducted retrospectively.

Statistical Analysis

The SPSS 21.0 (SPSS Inc., Chicago, IL, USA) program was used in statistical analyses. All data are expressed as mean \pm standard deviation (SD). The distribution of the data was examined using Kolmogorov–Smirnov test. Student's t-test was used for the comparison of groups and the Chi-square test was used for the comparison of group percentages. A p value of < 0.05 was considered statistically significant. Univariate logistic regression analysis was performed to determine the factors to be used in the differentiation of CPP and PT. Threshold values were found using receiver operating characteristics (ROC) curves for the parameters that were found to be significant in univariate analyses. The factors that were found to be significant in univariate analyses were grouped by the threshold values found with ROC analysis, and were evaluated using multivariate regression analysis.

Results

One hundred ninety-six female subjects who were initiated on GnRH analogue treatment with a diagnosis of CPP and 148 female subjects who were followed up with a diagnosis of PT were included in the study. Age at the time of onset of symptoms and age at the time of diagnosis were similar in both groups, whereas the BA at the time of diagnosis was found to be markedly advanced in the CPP group compared with the PT group ($p < 0.001$). In the subjects with CPP, the height-SDS, BMI-SDS, and growth velocity-SDS values were found to be higher compared with the subjects with PT, whereas the height-SDS adjusted for BA values were found to be lower compared with the subjects with PT. The puberty stage was found to be more advanced, uterine and ovarian volumes were found to be greater, basal LH, FSH levels and basal LH/FSH ratios, peak FSH, LH values, and peak LH/FSH ratios were found to be significantly higher in the subjects with CPP, whereas no significant difference was found between basal E_2 levels (Table 1).

Table 1. Clinical, anthropometric and laboratory characteristics of the subjects with central precocious puberty and premature thelarche

	Central precocious puberty (n=196) Positive response to GnRH test	Premature thelarche (n=148) Negative response to GnRH test	p
Chronologic age at the time of diagnosis (years)	7.2±1.3	7.3±1.2	0.262
Age at the time of onset of symptoms (years)	6.2±1.2	6.4±1.3	0.146
Bone age (years)	9.2±1.1	7.9±1.3	<0.001
BA-CA (years)	2.0±1.1	0.6±1.1	<0.001
Body mass index-SDS	0.7±0.7	0.4±0.8	<0.001
Height-SDS	1.4±1.6	0.6±1.2	<0.001
Height-SDS adjusted for BA	-0.6±0.8	0.1±1.1	<0.001
Growth velocity-SDS	1.6±2.4	0.1±2.0	<0.001
Puberty stage			<0.001
Tanner stage 2	82 (41.8%)	81 (54.7%)	
Tanner stage 3	84 (42.9%)	67 (45.3%)	
Tanner stage 4	30 (15.3%)		
Mean ovarian volume (mL)	2.1±0.9	1.8±0.8	<0.001
Uterine longitudinal diameter (mm)	38.5±8.3	26.1±11.8	<0.001
Basal FSH (IU/L)	3.5±1.4	1.6±0.8	<0.001
Basal LH (IU/L)	0.9±0.8	0.2±0.2	<0.001
Basal LH/FSH ratio	0.3±0.3	0.1±0.1	<0.001
Basal E ₂ (pg/mL)	31.2±15.4	28.6±13.8	0.061
Peak FSH (IU/L)	14.6±5.6	11.6±5.8	<0.001
Peak LH (IU/L)	13.6±8.4	2.1±1.2	<0.001
Peak LH/FSH ratio	1.1±0.8	0.2±0.1	<0.001

E₂: Estradiol; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; BA: Bone age; LH: Luteinizing hormone; CA: Chronologic age

The aim of our study was to determine the clinical and laboratory findings that could be used as an alternative for the GnRH test and make the differentiation between CPP and PT. The intravenous GnRH test was used as the gold standard method in the differential diagnosis of these two groups. Therefore, only basal hormone levels were considered in the next analyses rather than the peak hormone levels obtained in the GnRH test. The factors determined with univariate logistic regression are shown in Table 2. The threshold values of these factors found in ROC analyses are shown in Table 3. The results of multivariate analysis performed by grouping the factors that were found to be significant in univariate analyses according to the threshold values found through ROC curve analyses are shown in Table 4 and Table 5. Among the factors that were found to be significant in univariate analyses, basal LH and basal LH/FSH ratio were correlated with each other. Therefore, they were not included in the same multivariate analysis, and were examined separately with two different models.

Discussion

This study showed that basal LH, basal LH/FSH ratio and growth velocity, if known, were sufficient in demonstrating activation of the HPG axis. Early recognition of activation of the gonadal axis will enable early differentiation of cases of CPP and PT, timely initiation of GnRH_a treatment in subjects with CPP, and obtaining sufficient height gain. In the diagnosis of CPP, various hormonal methods such as measurements of basal and stimulated Gn levels are currently being used in addition to clinical findings including growth velocity and advanced BA. However, there is no diagnostic method that can definitely differentiate CPP from PT.

In our study, different clinical and anthropometric findings that could be used in the differentiation of CPP and PT were examined. The findings that subjects with CPP had more advanced BA, higher growth velocities, and higher height and body weight values compared with the

Table 2. Univariate logistic regression analysis of the measurements to be used in the differentiation of central precocious puberty and premature thelarche

Variables	Odds ratio	95% CI		p
		Lower limit	Upper limit	
Bone age advancement (BA-CA)	5.325	2.611	8.632	<0.001
Body mass index-SDS	2.246	1.087	4.639	0.059
Height-SDS adjusted for BA	3.410	1.814	6.411	<0.001
Growth velocity-SDS	4.609	2.148	9.889	<0.001
Puberty stage (T3 and 4 vs. T2)	1.706	0.721	4.038	0.224
Mean ovarian volume (mL)	1.849	0.987	3.464	0.055
Uterine longitudinal diameter (mm)	1.194	1.106	1.290	<0.001
Basal FSH (IU/L)	24.126	13.862	31.671	<0.001
Basal LH (IU/L)	30.532	5.889	58.294	<0.001
Basal LH/FSH	13.145	8.438	18.902	<0.001
Basal E ₂ (pg/mL)	1.018	0.982	1.056	0.320

CI: Confidence interval; E₂: Estradiol; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; BA: Bone age; LH: Luteinizing hormone; CA: Chronologic age

Table 3. Thresholds that give the best sensitivity and specificity in the differentiation of central precocious puberty and premature thelarche

Variables	Sensitivity (%)	Specificity (%)	Threshold	AUC	p
Bone age advancement (BA-CA)	100	68	0.75	0.782	<0.001
Height for BA-SDS	72	74	-0.3	0.738	<0.001
Growth velocity-SDS	69	71	1.1	0.723	<0.001
Uterine longitudinal diameter (mm)	74	100	38.2	0.894	<0.001
Basal FSH (IU/L)	100	72	1.9	0.814	<0.001
Basal LH (IU/L)	100	32	0.10	0.912	<0.001
	78	68	0.30		
	78	100	0.65		
Basal LH/FSH	67	100	0.25	0.754	<0.001

FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; BA: Bone age; CA: Chronologic age

Table 4. Multivariate logistic regression analysis of the measurements to be used in the differentiation of central precocious puberty and premature thelarche (Primary model)

Variables	Odds ratio	95% CI		p
		Lower limit	Upper limit	
BA-CA ≥0.75	1.896	1.136	3.044	0.726
Height-SDS adjusted for BA ≥-0.3	1.824	1.286	2.964	0.268
Growth velocity-SDS ≥1.1	1.598	1.124	4.256	<0.001
Uterine longitudinal diameter ≥38.2 (mm)	4.675	2.425	7.124	0.120
Basal LH ≥0.65 (IU/L)	16.348	4.654	28.120	<0.001

CI: Confidence interval; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; BA: Bone age; CA: Chronologic age

subjects with PT were expected because of the increased sex hormone levels. The fact that the height and BA values were higher in the subjects with CPP with the influ-

ence of increased sex hormone levels, while height-SDS adjusted for BA values were lower compared with the subjects with PT, showed that the difference between the

Table 5. Multivariate logistic regression analysis of the measurements to be used in the differentiation of central precocious puberty and premature thelarche (Secondary model)

Variables	Odds ratio	95% CI		p
		Lower limit	Upper limit	
BA-CA ≥ 0.75	1.948	1.194	3.122	0.605
Height-SDS adjusted for BA ≥ -0.3	1.842	1.144	2.529	0.141
Growth velocity-SDS ≥ 1.1	2.145	1.249	4.563	<0.001
Uterine longitudinal diameter ≥ 38.2 (mm)	4.838	2.368	6.752	0.056
Basal LH/FSH ≥ 0.25	5.195	1.684	8.162	<0.001

CI: Confidence interval; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; BA: Bone age; CA: Chronologic age

height-SDS values arose from the difference in BAs. While the puberty stages were more advanced and uterine and ovarian dimensions were greater on ultrasonographic examination compatible with advanced puberty stage in patients with CPP, multivariate logistic regression analysis showed that none of these factors were significant criteria to be used in the differentiation of CPP and PT. Similar to our study, Della Manna et al. (24) showed that increased height, increased growth velocity, advanced BA and increased uterine and ovarian volume were found in the precocious puberty group. In multivariate regression analyses, the growth velocity-SDS was found to be the only significant anthropometric finding that could be used in the differentiation of the two groups. In conclusion, it is difficult to determine activation of the HPG axis based on clinical findings alone, though various clinical findings can be used in the differentiation of CPP and PT.

The gold standard finding used in the evaluation of activation of the HPG axis, is a peak LH level of ≥ 5 IU/L and/or a stimulated peak LH/FSH ratio of >0.6 in the standard GnRH stimulation test (25, 26). Currently, it is being proposed that measurement of basal Gn levels will be sufficient in determining activation of the HPG axis, and pubertal and prepubertal values can be defined for basal Gn levels with use of new immunokits that can perform more sensitive measurement for serum Gn levels. In this study, it was shown that the basal LH and basal LH/FSH ratio could be used as a screening test that could predict a positive response in the GnRH test in a large cohort including 344 female subjects from a single center who presented with early breast development.

In our study, the threshold value that was found for basal LH to be used in the differentiation of CPP and PT was similar to the value reported by Houk et al. (10). When the threshold value for basal LH was considered as 0.65 IU/L in our study, it was observed that it had a sensitivity of 78% and a specificity of 100%. When this threshold value was considered as 0.1 IU/L, the sensitivity reached

100%, but the specificity was reduced to 32%. This finding showed that the possibility of obtaining a positive response in the GnRH test increased as the basal LH level increased. Houk et al. (10) measured the basal serum LH levels in 55 subjects who were clinically suspected of having CPP using third-generation immunokits (Architect and Delfia), and found the threshold value as 0.83 IU/L for basal LH for the Architect kit with a sensitivity of 93% and a specificity of 94%. Pasternak et al. (15) showed that a basal LH level of ≤ 0.1 IU/L excluded the diagnosis of CPP in 94.7% of 38 prepubertal girls with a sensitivity of 64% and a specificity of 94%. Suh et al. (27) reported that a basal LH threshold value of 0.22 IU/L predicted a positive response in the GnRH test in 540 girls with a sensitivity of 87.8% and a specificity of 20.9%. Lee et al. (12) determined the basal LH level to predict pubertal response in the GnRH test as 1.1 IU/L with a sensitivity of 69.1% and a specificity of 50.5%. Physicians should specify their local threshold values to be used in the diagnosis of CPP according to the kit they use because different threshold values have been found in different studies.

In previous studies, the threshold values for basal FSH were found to range between 1.9 and 2.25 IU/L (15, 28). However, it has been reported that basal FSH values were not sufficiently reliable and discriminative in the differentiation of CPP and PT, because these threshold values had low sensitivity and specificity. In our study, a basal FSH level of ≥ 1.9 IU/L was found to have a sensitivity of 100%, whereas it was found to have a low specificity (72%). It is known that FSH dominance is present in subjects with premature thelarche and LH dominance is present in subjects with CPP. However, the mean FSH level in the subjects with CPP in this study was found to be higher compared with those with PT (3.5 ± 1.4 vs. 1.6 ± 0.8 IU/L). This finding suggests that it would be more appropriate to decide according to the LH/FSH ratio rather than basal FSH value when differentiating CPP and PT. In different studies, different threshold values (0.04–0.2) have been reported for the basal LH/FSH ratio to be used

in the diagnosis of CPP (13, 16). In our study, it was found that a basal LH/FSH ratio of ≥ 0.25 was a finding in favor of CPP with a sensitivity of 67% and a specificity of 100%.

In our study, it was shown that basal LH levels and the basal LH/FSH ratio should be evaluated primarily in the diagnosis of CPP, and the GnRH test should be performed in selected cases, if clinically suspected, similar to the study conducted by Lee et al. (13). In our study, the area under the curve (AUC) value found for basal LH with ROC curve analysis was found to be higher compared with the values found for the basal LH/FSH ratio. This finding shows that the basal LH value is more valuable compared with the LH/FSH ratio value in the differentiation of CPP and PT. In addition, the basal LH value (≥ 0.65) was found to be the most sensitive and most specific variable in the diagnosis of CPP. Some authors propose that the basal LH/FSH ratio is also an important criterion that can be used in the diagnosis of CPP (16). However, basal FSH levels may influence the LH/FSH ratio because they may overlap in prepubertal and pubertal girls, and this may limit the use of this measurement in the diagnosis of CPP. Mogensen et al. (29) showed that basal LH levels were better in predicting the peak LH level in the GnRH test compared with basal FSH, E_2 , and inhibin B levels.

Higher basal or stimulated LH levels and LH/FSH ratio compared with the specified threshold values show that the HPG axis is activated, and may be used in differentiating cases of CPP from cases of PT. However, growth velocity, target height loss, and progression in BA and pubertal stage should be evaluated in a follow-up time of at least 3–6 months before deciding to initiate treatment in subjects who are thought to have CPP, and GnRH treatment should be initiated only in cases of CPP with a rapid course. In subjects who are considered to have CPP, one should be careful when initiating GnRH treatment, especially if there is an incompatibility between the basal LH value and basal LH/FSH ratio and the GnRH test results.

The most important limiting factor in our study was that it was conducted retrospectively. The subjects whose data could not be reached because of deficient data in patient records were excluded from the study. This resulted in the inclusion of a limited number of patients. In spite of this, our study is one of the more comprehensive studies in terms of subject numbers when compared with the other studies in the literature.

In conclusion, measurements of basal LH levels (≥ 0.65) and basal LH/FSH ratios (≥ 0.25) in girls presenting with early breast development are sensitive methods that can

be used in demonstrating activation of the HPG axis and diagnosing CPP. Among these methods, the variable that gives the best sensitivity and specificity is the measurement of basal LH. The basal LH value (≥ 0.65 IU/L) is a sensitive test that can be used as a screening test in the diagnosis of CPP. Clinical findings such as growth velocity-SDS are supportive data that can be used in the differentiation of CPP and PT in addition to laboratory findings.

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