Original Article

# Evaluation of Clinical and Laboratory Findings in the Differential Diagnosis of Central Precocious Puberty and Premature Thelarche

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## Abstract

**Aim:** In this study, it was aimed to examine the clinical and laboratory findings that can be used to predict central precocious puberty (CPP) in cases whose breast development started before the age of 8. **Materials and Methods:** The chronological age, anthropometric measurements, bone age (BA), hormone test results and pelvic ultrasonography findings of the cases were recorded. Those with a peak luteinizing hormone (LH) level of ≥5 IU/L in the gonadotropin-releasing hormone (GnRH) stimulation test were classified as CPP and those with a peak LH level of <5 IU/L were classified as prepubertal cases. A receiver operating characteristic (ROC) analysis was performed to determine the diagnostic accuracy of laboratory variables. **Findings:** A total of 297 female cases were included in the study. The age at the time of admission, height-standard deviation score (SDS), BA, the long axis of the uterus and the volumes of the right and left ovaries of the cases diagnosed with CPP were found to be significantly higher than those of the prepubertal group. The cut-off value providing the best sensitivity (99%) and specificity (99%) for the peak LH was found to be 4.55; the cut-off value providing the best sensitivity (94%) and specificity (85%) for the peak LH/follicle-stimulating hormone (FSH) ratio was found to be 0.32 and the cut-off value providing the best sensitivity (47%) and specificity (93%) for the basal LH was found to be 0.13. **Conclusion:** We believe that in female cases with early breast development, a peak LH level of ≥4.55 may possibly indicate CPP and a basal LH level of <0.13 can significantly rule out CPP.

**Keywords:** Central precocious puberty, GnRH stimulation test, puberty

## Introduction

Puberty is a transitional period from childhood to adulthood, in which reproductive functions and sexual maturity are acquired.[1,2] During this period, the decrease in the inhibitory mechanisms of the hypothalamic gonadotropin-releasing hormone (GnRH) neurons activates the hypothalamic-pituitary-gonadal (HHG) axis. The gonadotropins (Gn), which increase with the activation of the axis, cause more sex steroid release in the gonads compared with the prepubertal period. Increased sex steroids lead to the appearance of puberty symptoms and acceleration in growth.[3] Central precocious puberty (CPP) is the onset of puberty symptoms before the age of 8 as a result of the activation of the HHG axis in girls. Its incidence is between 1: 5000 and 1: 10.000, and its prevalence is increasing all over the world.[4,5] The onset of puberty and menarche at an early age causes the cases with CPP to remain short when they reach adult height and this brings negative psychosocial effects. Therefore, early diagnosis is very important to achieve adequate height gain in cases with CPP.[6] CPP is diagnosed by identifying the activation of the HHG axis in cases with increased growth rate and BA, whose puberty symptoms have started before the age of 8. Today, the gold standard used in identifying the activation of the HHG axis is the stimulation tests using GnRH or GnRH analogues (GnRHa).[7,8] However,

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the GnRH stimulation test is a long and labouring process. The necessity of creating a vascular access in the cases and collecting multiple blood samples at different times causes anxiety. Therefore, in various studies, it was attempted to determine the cut-off values that provide the best sensitivity and specificity by using clinical and ultrasonographic findings and hormone measurements such as basal and stimulated Gn levels in the diagnosis of cases with CPP.[9-12]

In this study, we aimed to determine the measurements with high diagnostic sensitivity that can be used in the diagnosis of CPP by examining the clinical and laboratory findings of cases with breast development before the age of 8.

## Materials and Methods

In the study, a total of 297 female cases between the ages of 3 and 8, who presented to Dicle University Faculty of Medicine Pediatric Endocrinology Polyclinic with early breast development in the past 9 years and underwent the GnRH stimulation test were included. Cases with missing data in their medical records, cases who had peripheral precocious puberty, cases with organic pathology detected in the central nervous system imaging and cases with chronic diseases were excluded from the study.

The medical records of the cases included in the study were examined and the data were evaluated retrospectively. The chronological age (CA), Tanner stage of puberty, BA, anthropometric measurements (body weight [BW], height and body mass index [BMI]), pelvic ultrasonography findings (the longest diameter of the uterus, mean ovarian volume), basal and stimulated Gn levels and basal E2 levels of the cases were recorded.

The cases with breast development (Tanner stage ≥2) before the age of 8 were evaluated according to the peak LH response in the GnRH test. Those with a peak LH level of ≥5 IU/L were classified as CPP, and those with a peak LH level of <5 IU/L were classified as prepubertal cases.[10]

Following the intravenous administration of 100 μg/m$^2$ LHRH (gonadorelin acetate, Ferring®) for the gonadotropin-releasing hormone test, venous blood samples were collected at 0, 30, 45 and 60 min for measuring the follicle-stimulating hormone (FSH) and LH.[13] In measuring the FSH, LH and E2 levels with the immunochemiluminometric assay (ICMA) method, commercial kits (ARCHITECT System, Abbott Laboratory Diagnostics, USA) were used.

The body weight of the cases was measured in kilograms with a SECA brand digital scale with 0.1 kg graduation, and the height was measured in metres with a Harpenden stadiometer with 0.1 cm graduation. The BMI was calculated by dividing the body weight in kilograms by the square of the height in metres. The height, weight and BMI standard deviation scores were calculated according to the national data, using the web-based Child Metrics software.[14,15] The pubertal staging was carried out using the Marshall and Tanner scale.[16] The BA was evaluated using the Greulich-Pyle atlas.[17]

### Statistical analysis

The statistical analysis of the obtained results was carried out using the SPSS 21.0 (Statistical Package for the Social Sciences – IBM®, Chicago, IL, USA) statistical software package. Whether the variables were normally distributed or not was evaluated using the Shapiro–Wilk test. In the comparison of two independent groups, if the group was normally distributed, Student's *t* test, and if the group was not normally distributed, Mann–Whitney *U* test was used. The Chi-square test was used to compare the group ratios. The categorical data were expressed as frequency (percentage) while the numerical data were expressed as median (the 25$^{th}$ and 75$^{th}$ percentiles) or mean ± standard deviation. In the comparison of the groups, a $P$ value of < 0.05 was considered statistically significant. In cases with idiopathic CPP, a receiver operating characteristic (ROC) analysis was performed to calculate the cut-off values that provide the best sensitivity and specificity for the laboratory test.

### Ethical clearance statement

The study was approved by Dicle University Faculty of Medicine vide letter no 2021/167 on 04.03.2021. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follows the guidelines laid down in Declaration of Helsinki 2008.

### Findings

In the study, a total of 297 female cases who presented with early breast development and underwent the GnRH stimulation test, were included. Following the GnRH stimulation test, 167 (56%) of the cases were diagnosed with CPP. The remaining 112 (44%) cases were evaluated as prepubertal. The ages of the cases diagnosed with CPP at the time of admission were found to be higher than those of the prepubertal cases, and the difference between them was found to be statistically significant ($P$ < 0.05). When the anthropometric measurements of the two groups were compared, the height-SDS and BA were found to be higher in the CPP group than in the prepubertal group, and the difference between them was statistically significant ($P$ < 0.05). Although BW-SDS was found to be higher in the CPP group and BMI-SDS in the prepubertal group, there was no statistically significant difference between them ($P$ = 0.053, $P$ = 0.232, respectively). When the pelvic ultrasonography (USG) results of the groups at the time of admission were compared, the long axis of the uterus and the volumes of the right and left ovaries were found to be higher in the group with CPP, and the difference between them was statistically significant ($P$ < 0.05). In the comparison of the groups in terms of laboratory variables, the basal LH, basal FSH, basal E2, basal LH/FSH, peak LH and peak LH/FSH ratios were found to be higher in the group with CPP and the difference was statistically significant ($P$ < 0.05) [Table 1].

When a ROC analysis was performed to determine the cut-off value providing the best sensitivity and specificity in the diagnosis of CPP, the variables providing the best sensitivity and specificity were found to be: basal LH (AUC = 0.728, *P* = <0.001), basal FSH (AUC = 0.782, *P* = <0.001), basal E2 (AUC = 0.655, *P* = <0.001), peak LH (AUC = 1.000, *P* = <0.001) and peak LH/FSH ratio (AUC = 0.955, *P* = <0.001). [Table 2 and Figure 1].

The cut-off value providing the best sensitivity (47%) and specificity (93%) for the basal LH was found to be 0.13, the value providing the best sensitivity (71%) and specificity (68%) for the basal FSH was found to be 1.81, the value providing the best sensitivity (50%) and specificity (80%) for the basal E2 was found to be 5.07, the value providing the best sensitivity (99%) and specificity (99%) for the peak LH was found to be 4.55 and the value providing the best sensitivity (94%) and specificity (85%) for the peak LH/FSH ratio was found to be 0.32 [Table 3].

**Table 1: The clinical, anthropometric and laboratory findings of CPP and Prepubertal cases**

| | CPP (*n*=167) | Prepubertal (*n*=112) | *P* |
|---|---|---|---|
| Chronological age (years) | 7.3 (6.7-7.5) | 6.7 (5.8-7.3) | <0.001[b] |
| Bone Age (years) | 7.85 (7.8-8.8) | 7.80 (6.8-7.8) | <0.001[b] |
| BA/CA (years) | 1.13 (1.03-1.21) | 1.15 (1.10-1.20) | 0.411[b] |
| BW-SDS | 0.46±1.15 | 0.196±1.12 | 0.053[a] |
| Height-SDS | 0.58±1.22 | 0.20±1.17 | 0.009[a] |
| BMI-SDS | 0.23±1.00 | 0.80±1.19 | 0.232[a] |
| Long axis of the uterus | 31.22±6.3 | 27.94±5.94 | <0.001[a] |
| Volume of the left ovary | 1.2 (0.9-2.2) | 1.01 (0.7-1.8) | 0.007[b] |
| Volume of the right ovary | 1.3 (0.8-2.3) | 1.08 (0.7-1.8) | 0.030[b] |
| Basal LH (IU/L) | 0.11 (0.1-0.4) | 0.1 (0.1-0.1) | <0.001[b] |
| Basal FSH (IU/L) | 2.4 (1.66-3.74) | 1.52 (1.01-1.9) | <0.001[b] |
| Basal E2 (pg/mL) | 5.1 (5.0-16.39) | 5 (5.0-5.0) | <0.001[b] |
| Basal LH/FSH | 0.07 (0.04-0.15) | 0.06 (0.05-0.1) | 0.158[b] |
| Peak LH (IU/L) | 7.23 (5.84-11.3) | 2.7 (1.96-3.3) | <0.001[b] |
| Peak LH/FSH | 0.58 (0.40-0.9) | 0.22 (0.18-0.29) | <0.001[b] |

[a]Independent Samples *t*-test, [b]Mann-Whitney *U* test. CPP: Central Precocious Puberty, CA: Chronological Age, BA: Bone Age, BW: Body Weight, BMI: Body Mass Index, SDS: Standard Deviation Score, LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone, E2: Estradiol

## Discussion

In girls with CPP, prematurely increased sex hormones lead to acceleration in growth and progression in BA. In these girls, who are initially tall, epiphyses close prematurely, resulting in short final adult height. Therefore, it is important to identify the cases of CPP who present with early breast development and to plan their treatment in a timely manner to achieve adequate height gain.[18] Today, the gold standard used in the diagnosis of CPP is the GnRH stimulation test. Due to some difficulties experienced in the GnRH stimulation test, in various studies, clinicians attempted to determine the parameters with high sensitivity that can be used in the diagnosis by examining the clinical and laboratory findings of cases with CPP.[9,13,19-22]

Several studies were conducted on the diagnostic value of clinical findings in girls with CPP and different results were obtained.[13,19,20] In a study conducted by Lee *et al*.[13] it was reported that no significant difference was found between the

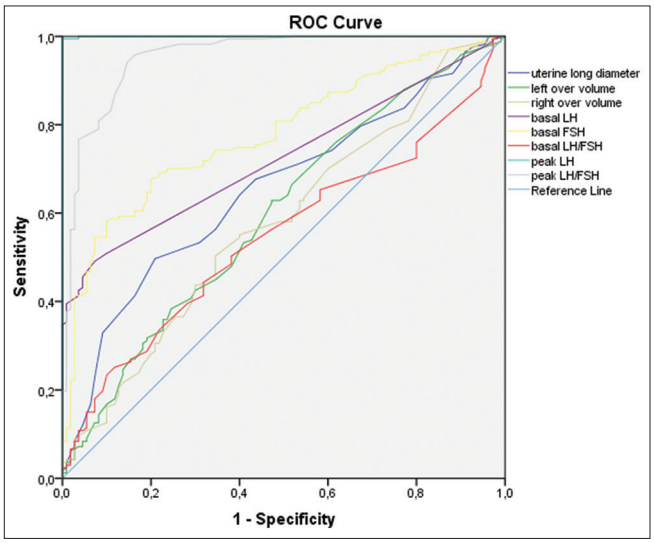


**Figure 1:** The demonstration of the laboratory variables used in the diagnosis of CPP on a ROC curve

**Table 2: The ROC analysis results of the laboratory variables in the diagnosis of CPP**

| Variables | Area (AUC) | Standard Error | *P* | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| Basal LH (IU/L) | 0.728 | 0.029 | <0.001 | 0.670 | 0.785 |
| Basal FSH (IU/L) | 0.782 | 0.061 | <0.001 | 0.728 | 0.835 |
| Basal LH/FSH | 0.548 | 0.034 | 0.176 | 0.480 | 0.616 |
| Peak LH (IU/L) | 1.000 | 0.000 | <0.001 | 0.999 | 1.000 |
| Peak LH/FSH | 0.955 | 0.012 | <0.001 | 0.931 | 0.979 |
| Long axis of the uterus | 0.654 | 0.033 | <0.001 | 0.589 | 0.718 |
| Volume of the right ovary | 0.580 | 0.035 | 0.025 | 0.511 | 0.648 |
| Volume of the left ovary | 0.598 | 0.035 | 0.006 | 0.530 | 0.666 |

ROC: Receiver Operating Characteristic, CPP: Central Precocious Puberty, AUC: Area Under the Curve LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone

**Table 3: The cut-off values providing the best sensitivity and specificity in the diagnosis of CPP**

| | Sensitivity (%) | Specificity (%) | Cut-off value |
|---|---|---|---|
| Basal LH IU/L | 47 | 93 | 0,13 |
| Basal FSH IU/L | 71 | 68 | 1,81 |
| Basal LH/FSH | 65 | 41 | 0,052 |
| Peak LH IU/L | 99 | 99 | 4,55 |
| Peak LH/FSH | 94 | 85 | 0,32 |
| Long axis of the uterus | 64 | 60 | 29,5 |
| Volume of the right ovary | 70 | 40 | 0,85 |
| Volume of the left ovary | 62 | 52 | 1,09 |

FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone, CPP: Central Precocious Puberty

pubertal and prepubertal groups in terms of height, BMI and BA. Nam *et al*.[19] reported in their study, in which 574 female cases were evaluated, that 375 cases were diagnosed with CPP and that the BMI and BAs of the cases diagnosed with CPP were more advanced than the prepubertal cases. In the study by Vurallı *et al*.[20] they compared 196 girls with CPP and 148 girls with premature thelarche, it was reported that the height, BMI, and BAs were significantly advanced in cases with CPP. In our study, as in the study of Vurallı *et al*.[20] the height and BA were found to be significantly higher in the pubertal group than in the prepubertal group. However, unlike some previous studies, no significant difference was found in terms of BMI in our study.[13,19,20] In the literature, some studies on the uterine and ovarian volume in cases with CPP reported that uterine and ovarian volumes were greater in cases with CPP than in the prepubertal group.[20,23] In our study, we found that the long axis of the uterus and the ovarian volumes were greater in the group with CPP, consistent with the literature. These different data in the studies show us that clinical findings support the diagnosis in cases with CPP, but the diagnosis cannot be made with clinical findings alone.

In cases with CPP, the gold standard used in identifying the activation of the hypothalamic-pituitary-gonadal axis is the GnRH stimulation test.[24,25] The fact that the GnRH stimulation test caused anxiety in the cases and the start of the use of new immunokits that can measure serum Gn levels with more sensitivity led to the opinion that basal Gn levels may be sufficient to identify the activation of the HHG axis.[26] In studies conducted with this purpose, the efficiency of basal LH level in distinguishing pubertal cases from prepubertal cases was examined and it was stated that cut-off values with high sensitivity and specificity that can be used in distinguishing between these two groups were determined.[9,13,20] Houk *et al*.[9] used two third-generation immunokits (Architect and Delfia) to measure the basal serum LH level of 55 patients with clinical suspicion of CPP and determined the basal LH cut-off value for the Delfia kit as 0.83 IU/L with 93% sensitivity and 100% specificity and for the Architect kit as 1.05 U/L with 100% sensitivity and 100% specificity. In another study, 121 cases with CPP and 39 prepubertal cases were examined and the basal LH cut-off value in predicting CPP was reported as 0.22 IU/L with 69.4% sensitivity and 82.1% specificity.[13] Suh *et al*.[27] reported that they found the basal LH value the same as the previous study (0.22 IU/L), but with 87.8% sensitivity and 20.9% specificity. Again, in a recent study conducted in our country in which 196 cases with CPP were examined, it was reported that the basal LH cut-off value in predicting CPP was found as 0.65 IU/L with 78% sensitivity and 100% specificity.[20] In our study, we found the basal LH value to be significantly higher in the CPP group compared with the prepubertal group, consistent with the literature.[9,13,20,27] In addition, we performed a ROC analysis for the basal LH level to predict CPP and we found the cut-off value for the basal LH as 0.13 IU/L. The sensitivity of the cut-off value (0.13 IU/L) for the basal LH in predicting CPP was found as 47%, and the specificity was found as 93%. This finding shows that a basal LH level of 0.13 IU/L and above is not a sensitive screening test to show the status of puberty. However, it shows that 93% of the cases with a basal LH level below 0.13 IU/L do not have CPP. In the diagnosis of central PP, a GnRH-stimulated peak LH level of ≥5 is accepted as a reliable indicator of pubertal response.[7,10] In our study, we found that a peak LH level of 4.55 and above in the GnRH stimulation test had 99% sensitivity and 99% specificity. Therefore, although it is accepted that the peak LH level should be ≥5 in the GnRH stimulation test in the diagnosis of CPP, we think that a peak LH level of 4.55 and above may possibly indicate CPP in our study.

Studies investigated the diagnostic value of basal FSH in predicting CPP and certain cut-off values were determined. In these studies, the authors reported different opinions on the usability of the determined cut-off values in the diagnosis of CPP.[20,22,26,28] In some studies, in which the cut-off value for the basal FSH was determined as 1.9–2.25 IU/L, it was reported that these values had low sensitivity and specificity and could not be used in the diagnosis of CPP.[20,26,28] However, Heo *et al*.[22] stated that the cut-off value for the basal FSH was determined as 1.160 IU/L with 92% sensitivity and 43% specificity, and stated that basal FSH could be used in the diagnosis of cases with CPP. In our study, we found the basal FSH level to be significantly higher in the CPP group compared with the prepubertal group, but in the ROC analysis, we found the sensitivity and specificity of the basal FSH value to be low, as in the previous studies.[20,26,28] Therefore, we think that it is not correct to predict CPP based on the basal FSH level.

Different cut-off values were reported for the basal and stimulated LH/FSH ratio in previous studies conducted on precocious puberty.[12,20] Vurallı *et al*.[20] reported that a basal LH/FSH ratio of ≥ 0.25 had 67% sensitivity and 100% specificity. In another study, the cut-off value for the basal LH/FSH in predicting CPP was reported to be 0.04 with a sensitivity of 54.4% and a specificity of 93.7%.[12] The authors of these two studies reported that the basal LH/FSH ratio can be used in the diagnosis of CPP.[12,20] In our study, although the basal LH/FSH ratio was higher in the group with CPP, the difference between them was not statistically

significant. Contrary to the abovementioned studies, we found the specificity of the basal LH/FSH ratio to be low in the ROC analysis. Studies reported that the peak LH/FSH ratio is one of the most reliable variables to be used in the diagnosis of CPP, and a peak LH/FSH ratio of >0.66 had a sensitivity of 96% and a specificity of 100%.[7,29] In another study, it was shown that a peak LH/FSH ratio of > 0.33 had a sensitivity of 80% and a specificity of 88% for the diagnosis of CPP.[28] In our study, we found the peak LH/FSH ratio to be significantly higher in the CPP group than in the prepubertal group. We found the peak LH/FSH ratio to be 0.32 with 94% sensitivity and 85% specificity, which was consistent with the literature.[28]

In this study, it was determined that the variables providing the best sensitivity and specificity that can be used in the diagnosis of CPP using a ROC analysis are the peak LH and peak LH/FSH ratios. The area under the curve (AUC) value determined for the peak LH using the ROC curve was greater than the value determined for the peak LH/FSH ratio. This finding shows that the peak LH value is more valuable than the peak LH/FSH ratio in the diagnosis of CPP.

In conclusion, in our study, as a result of the ROC analysis, the variable that provided the best sensitivity (99%) and specificity (99%) in the diagnosis of CPP was found to be the peak LH level (the peak LH cut-off value: 4.55). Therefore, we think that a peak LH level of 4.55 and above in the GnRH stimulation test may possibly indicate CPP. In addition, we believe that a basal LH level below 0.13 can significantly rule out CPP. However, laboratory findings must be supported by clinical findings and they need to be evaluated together before initiating treatment in these cases.

## Ethics approval

The study was performed in accordance with the rules of the Declaration of Helsinki and this study was initiated after the approval of the Dicle University Faculty of Medicine Ethics Committee (Approval No. 2021/167).

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## Conflicts of interest

There are no conflicts of interest.

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