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e-mail: tduratra@cfnavarra.es**Short title:** Clinical data and basal LH for CPP prediction**Key words:** Bone age. Central precocious puberty. Premature thelarche. Predictors of puberty. Unstimulated luteinizing hormone. Gonadotropin-releasing hormone stimulation test.**Word count:** 2465

Abstract

Objective. The objective of this study was to analyze whether some auxological characteristics or a single basal gonadotropin measurement will be sufficient to distinguish the prepubertal from pubertal status.

Methods. Auxological characteristics were recorded and serum LH and FSH were measured by immunochemiluminescence assays before and after GnRH stimulation test in a sample of 241 Caucasian girls with breast budding between 6- to 8- years old. Peak LH levels higher than 5 IU/L were considered a pubertal response. Area under the curve, cut-off points, sensitivity, and specificity for auxological variables and basal gonadotropins levels were determined by receiver operating curves.

Results. There were no significant differences in age at onset, weight, height, BMI and height velocity between both groups. Bone age was significantly higher in pubertal girls ($p < 0.05$), although with limited discriminatory capacity. The sensitivity and specificity for the basal LH levels were 89% and 82% respectively, for a cut off point of 0.1 IU/L. All girls in the pubertal group had a basal LH higher than 1.0 IU/L (positive predictive value of 100%). There was a wide overlap of basal FSH and LH/FSH ratio between prepubertal and pubertal girls.

Conclusions. Auxological characteristics should not be used only in the differential diagnosis between prepubertal from pubertal status in 6- to 8-year-old girls. We found a high specificity of a single basal LH sample and it would be useful for establishing the diagnosis of puberty in this age group, **reducing** the need for GnRH stimulation testing.

Introduction

Central precocious puberty (CPP) is defined as the premature activation of the hypothalamic-pituitary-gonadal axis (HPG) with the onset of breast development before 8 years of age in girls and an increase in testicular size in boys younger than 9 years of age that is progressive and accompanied by advancement of skeletal age and accelerated linear growth (1-3). The phenomenon is much more common in girls than in boys (4, 5). On the other hand, idiopathic premature thelarche (PT) is relatively frequent and refers to the isolated development of the breasts before the age of 8 in girls without the activation of the HPG axis. Although most girls with premature thelarche will show spontaneous regression, there is a possibility of progression to true precocious puberty; therefore, it would be mandatory to discriminate between the puberty (precocious puberty) and prepubertal (premature thelarche) values of gonadotropins (6).

Laboratory measurement of gonadotropins, in particular luteinising hormone (LH), after stimulation with GnRH or GnRH analog (GnRHa) is the standard method to confirm HPG activity (2, 3, 7). Currently, the value of 5 IU/L is accepted as the cut-off point when LH is determined by immunochemiluminescence assay (8-12). However, the development of additional sensitive immunoassays that measure gonadotropins in serum has motivated several authors to consider the utility of basal LH as a screening method (9, 13-15).

The objective of this study was to analyze whether some auxological characteristics or a single basal gonadotropin measurement will be sufficient to distinguish the prepubertal from pubertal hypothalamic-pituitary-gonadal axis in girls with breast budding between 6- to 8- years old; and therefore the current method of gonadotropin response to GnRH stimulation could be omitted in many cases.

Material and methods

Participants

This is a retrospective study carried out in a sample of 241 Caucasian girls aged 6- to 8- years who were evaluated for early signs of puberty, such as breast budding, in the Pediatric Outpatient Endocrine Clinic of the Navarra Hospital Complex in Pamplona, Spain, between years 2015 and 2019. Breast development was assessed by both inspection and palpation and rating according to Tanner stage. All participants presented with Tanner stage 2 in breast development (appearance of the breast bud), and were followed up to at least 9 years of age.

The sample of girls was divided into two groups according to the GnRHa stimulation test results. Girls who had a peak LH values ≥ 5 IU/l were considered as having a pubertal activation of the HPG axis (CPP group), and girls who had lower values were considered prepubertal or premature thelarche (PT group). Patients previously diagnosed with gonadotropin-independent or peripheral precocious puberty were excluded.

Information recorded from every patient included family (paternal and maternal height, age of maternal menarche) and personal data (age at onset of breast budding, weight and height, BMI, and bone age), and GnRHa-stimulation testing

results. Weight and height of all the participants had been previously recorded by the pediatrician at the Primary Health Care Center (periodical health checkup), and allowed the calculation of growth velocity 6-12 months before the current clinical evaluation. Target height was calculated in centimetres using the formula: $(\text{maternal height} + \text{paternal height} - 13)/2$. Bone age (BA) and height-prognosis was determined using RUS-TW2 method (16).

Weight and height measurements were taken with participants wearing only undergarments and barefoot. Weight was measured using an Año-Sayol scale (reading interval 0 to 120 kg and a precision of 100 g), and height was measured using a Holtain wall stadiometer (reading interval 60 to 210 cm, precision 0.1 cm). BMI was calculated according to the following formula: $\text{weight (kg)}/\text{height}^2 \text{ (m)}$.

The SDS values for the weight, height, BMI, and HV were estimated by applying the program Aplicación Nutricional, from the Spanish Society of pediatric gastroenterology, hepatology and nutrition (Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica, available at <https://www.gastroinf.es/nutritional/>). The graphics from Ferrández et al. (Centro Andrea Prader, Zaragoza 2002) were employed as reference charts (17).

GnRH test

GnRH test was accomplished at least once after 4 months of follow-up in both groups. GnRH stimulation test was performed by determining serum LH and FSH at baseline (between 8:00 am and 9:00 am after an overnight fast) and 4 hours post subcutaneous administration of GnRH analog (leuprorelin, 500 mcg). LH and follicular stimulating hormone (FSH) were measured by highly sensitive immunochemiluminescence assays (Immulite 2500) with a sensitivity of <0.1 U/L for LH and FSH. Intra-assay coefficients of variation at 0.3 IU/L for LH were 3.5% and FSH 5%. Baseline LH/FSH ratio and LH/FSH ratio

post leuprorelin administration were calculated.

Statistical analysis

The parametric Student's t-test was used to compare the differences in variables recorded between PT and CPP groups. The receiver operating curves (ROC) were constructed after using the exact logistic regression models in order to evaluate the sensitivity and specificity of the auxological variables and basal gonadotropin levels based on predicted probability, and the area under the curve (AUC) was measured for each curve. Youden's J index, defined as $(\text{sensitivity} - \text{specificity}) - 1$, was used to determine the optimal cut point from the ROC curves to discriminate between PT from CPP girls. Statistical analyses were performed using the program Statistical Packages for the Social Sciences version 20.0 (Chicago, IL, USA). Statistical significance was accepted when p-value was <0.05 .

Parents and/or legal guardians were appropriately informed and gave consent for the participation of the participants in this study in all cases. This study was approved by the Ethics Committee for Human Investigation of the Navarra Hospital Complex, Pamplona, Spain (code: 19/07) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and later amendments.

Results

Table 1 shows and compares mean values of family and personal data registered between PT (prepubertal) and CPP girls. Bone age advancement (BA-CA) are significantly higher in CPP girls ($p < 0.05$). There were no significant differences in target height, height prognosis, and maternal menarche, age at onset, weight, height, and BMI and height velocity between both groups.

The AUCs for bone age advancement (0.59, 95% CI: 0.51–0.67, $p = 0.016$) were significantly higher than 0.5. Maximal Youden's J index was reached based on specificity of 52% and sensitivity of 64% for bone age advancement, and bone age advancement cut off point of 1.65 years was chosen to discriminate between PT (prepubertal) and CPP girls. In fact, 69.5% of the girls in the CPP group had a bone age advancement higher than 1.65 years (positive predictive value), while 52.6% of the girls in the prepubertal group had a bone age advancement lower than 1.65 years (negative predictive value). Table 2 displays and compares the average values for basal and stimulated serum concentrations of gonadotropins (LH, FSH, and LH/FSH ratio) between PT (prepubertal) and CPP girls. Both basal LH and FSH and LH/FSH ratio means as well as the stimulated concentration of LH and FSH and the LH/FSH ratio were significantly higher in the CPP group than in the PT group ($P < 0.01$).

The AUCs and the optimal cut off point for discriminating PT (prepubertal) from CPP girls using a non-stimulated gonadotropin sample, (basal LH, FSH, and LH/FSH ratio) and based on sensitivity and specificity are shown in Table 3. The AUCs for basal LH, FSH and LH/FSH ratio were significantly higher than 0.5, but the maximum predictability was reached using the basal LH with an AUC of 0.89 (Figure 1). Maximal Youden's J index was reached based on specificity of 82% and sensitivity of 89% for basal LH, and LH cut off point of 0.1 IU/l was chosen to discriminate between CPP and prepubertal girls. In fact, 83% of the girls in the CPP group had a basal LH higher than 0.1 IU/L (positive predictive value), while 85% of the girls in the prepubertal group had a basal LH lower than 0.1 IU/L (negative predictive value). All girls in the CPP group had a basal LH higher than 1.0 IU/L (positive predictive value of 100%). The basal FSH yielded less favourable performances such as sensitivity of 63% and specificity of 80% for a cut off point of 2.5 IU/l. The sensitivity and specificity for the basal LH/FSH ratio values were 73 and 74% respectively, for a cut off point of 0.05. That is, there was a wide overlap of basal FSH and LH/FSH ratio between prepubertal and pubertal girls.

Discussion

This study features that auxological characteristics represent a weak predictor for GnRH-dependent PP and should not be used only in the differential diagnosis between PT and CPP in 6- to 8-year-old girls. However, we found a high specificity of a single basal LH sample and it would be useful for establishing the diagnosis of CPP in this age group.

Most cases of premature thelarche present in the first four years of life and regress before puberty, but girls who present

later may be accompanied by accelerated growth and advanced bone age. The name given to this condition by several authors was "slowly progressive variant of precocious puberty" associated with both basal and GnRH-stimulated serum LH levels of prepubertal characteristics (2, 10). Our data show that most of the auxological characteristics recorded overlapped between girls with PT and CPP aged 6 to 8 years. In fact, there were no significant differences in weight, height, BMI, and growth velocity between both groups; only advanced bone age emerged as a significant predictor of CPP in this age group, although with limited discriminatory capacity (positive predictive value: 69.5%). Therefore, an exclusive measurement of the auxological characteristics would not be sufficient to diagnose or exclude CPP in girls with breast budding in this age range (18). In addition, it should be noted that the prognosis of adult height of the CPP girls, which at the time of diagnosis is usually overvalued by clinical and auxological conditions (19), did not differ from that calculated for the PT girls.

Diagnosis of CPP is based on clinical evaluation and laboratory hormonal assessment. Different hormone assays with high sensitivity to measure gonadotropins levels are currently available, such as immunofluorometric, immunochemiluminiscence (ICMA) or electrochemiluminescence. But ICMA is the most commonly used -it has also been used in this study- and allows reasonable discrimination between prepubertal and pubertal status using a single basal LH level (11). The distinct cut-off values of basal LH assessed by ICMA that indicate HPG axis activation varies according to the different authors, and oscillate between 0.1 and 1.1 IU/l (9, 10, 13, 20, 21). Caution should be used when interpreting gonadotropin concentrations in girls in the first three years of life, because basal gonadotropin concentrations are usually high in this age group (22). Our results, carried out in a larger cohort in girls aged 6 to 8 years, confirm the high sensitivity (82%) and specificity (90%) of a single basal LH sample for establishing the diagnosis of CPP when basal LH sample was higher than 0.1 IU/L, with a positive predictive value of 83%. However, the positive predictive value of 100% obtained in this study from a single baseline LH sample was obtained with a cut-off point of 1.0 IU/L. Since the sensitivity and specificity of a single basal LH sample for the diagnosis of CPP varies in relation to cut-off value and laboratory methodology (11, 12), several authors have recommended blood sample collection to obtain normal basal values of gonadotropins in clinical centers that care for girls with CPP (7-9).

As both gonadotropin determinations (basal LH, FSH and LH/FSH ratio) are supposed to be increased in the HPG axis activation, they have been routinely measured during the evaluation of CPP and, in fact, both have discriminatory capacity between CPP and prepubertal girls. However, as several authors have described (9, 10, 13-15), this study found that the measurement of basal FSH concentrations or basal LH/FSH ratio do not improve diagnostic sensitivity over basal LH alone in girls aged 6-8 years undergoing evaluation for CPP. This lower discriminatory capacity observed in basal FSH and LH/FSH ratio seems to derive from the overlap of the FSH levels observed in girls with and without CPP. Serum levels of estradiol are not used to diagnose CPP, considering their low sensitivity and large overlap between normal prepubertal and pubertal children (11). Nevertheless, novel laboratory techniques such as tandem mass spectrometry

might improve the sensitivity and specificity of estradiol assays (23). In fact, different authors have described that GnRHa-stimulated serum estradiol level at 24 h may be a useful indicator of pubertal activation, regardless of the LH values (21, 24). However, GnRH-stimulated serum LH level provides the best clinical model due to its practicality and convenience when evaluating puberty in girls.

In the present study, we found that a basal LH level greater than 0.1 IU/L would be suggestive of central pubertal activation (positive predictive value of 83%) in those girls who have breast budding accompanied by physical suspicion of precocious puberty (accelerated growth rate and, especially, bone age advancement). However, if LH level was greater than 1.0 IU/L (positive predictive value of 100%), a diagnosis of CPP can be made, avoiding the inconvenience, costs and time of the GnRH stimulation test. Thus, a sample for basal LH measurement could be obtained by the primary care physician for initial management: a LH level higher than 0.1 IU/L, would mean a reasonable suspicion of puberty status that should be confirmed by GnRH stimulation; if basal LH level was higher than 1.0 IU/L, the girl should be referred for additional assessment concerning the aetiology of precocious puberty and to determine adequate treatment by the paediatric endocrinologist. In contrast, baseline LH levels are not sufficiently sensitive to rule out CPP in girls whose baseline LH levels are <0.1 IU/L; furthermore, even if the basal levels of LH were undetectable in the presence of clinical signs of progressive pubertal development, the stimulation test would be necessary for the identification of hypothalamic-pituitary-gonadal axis activation. In this way, an algorithm for the diagnosis of CPP was proposed for our endocrinology unit (figure 2) based on the data obtained in this study. Patients should be followed on a quarterly basis until at least 9 years of age in order to exclude possible advanced puberty.

There are certain limitations in the diagnostic sensitivity of basal LH levels. Indeed, 17% of the girls who had CPP in our cohort had an initial LH concentration of <0.1 IU/L. This absence of concordance between the GnRHa stimulation tests with the basal level of LH could be due to the fact that the girls had been evaluated at an early stage of puberty, since in the first months of pubertal development hypothalamic-pituitary-gonadal axis activation is progressive and even oscillating (10). In fact, in 15 cases out of the 108 girls with CPP included in this study (14%), a previous GnRHa test was performed with a prepubertal result, but with a subsequent pubertal progression. However, it is possible that some of our patients who presented with PT represent slowly progressing variants of CPP (2). Another limitation is that girls with peripheral sexual precocity have suppressed basal LH levels. That is, the presence of a high concentration of estradiol with low basal gonadotropins together with a rapid development of secondary sexual characteristics should compel to investigate for peripheral causes (adrenal or ovarian tumours, exposure to exogenous sex steroids, etc.). Furthermore, due to the diurnal fluctuation of gonadotropin levels, especially in early puberty, the evaluation of basal serum LH levels would be debatable (15). Despite these restrictions, we found that a basal LH level greater than 0.1 IU/L in girls is highly suggestive of central pubertal activation, whereas an undetectable LH value does not exclude a GnRHa test.

In conclusion, we support that, in the majority of girls aged 6- to 8 years presenting with premature thelarche, a single

basal LH determination would be of high diagnostic usefulness in identifying girls who have CPP, so reducing the need for GnRH stimulation testing. Basal FSH concentrations or basal LH/FSH ratio do not improve diagnostic sensitivity in girls undergoing evaluation for CPP. However, clinical judgment and follow-up continue to be of greater importance in the evaluation of this entity.

Declaration of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article (none declared).

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Author contribution statement

TDT and FGV participated in study design and data analysis, and wrote the first draft of the manuscript. MMC, LAM, SBZ and MCG participated in data collection and analysis. All authors participated in manuscript preparation and approved its final version.

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LEGENDS OF FIGURES

Figure 1. ROC curves used to evaluate the sensitivity and specificity of basal gonadotropin (LH, FSH and LH/FSH ratio)

Figure 2.

Algorithm proposed for the diagnosis of central precocious puberty

Table 1. Family and personal data of TP (prepubertal) and CPP girls (M \pm SDS)

| Items | PT girls (n=133) | CPP girls (n=108) | p-values* |
|---------------------------|---------------------|----------------------|-----------|
| Target height (cm) | 162.0 \pm 5,1 | 161.1 \pm 5.5 | 0.227 |
| Height prognosis (cm) | 167.5 \pm 4.9 | 166.5 \pm 5.2 | 0.238 |
| Maternal menarche(years) | 12.1 \pm 1.5 | 11.8 \pm 1.3 | 0.464 |
| Age at onset (years) | 7.3 \pm 0.4 | 7.4 \pm 0.3 | 0.238 |
| Weight (kg) | 30.4 \pm 6.6 | 31.0 \pm 6.0 | 0.520 |
| Weight Z-score | 1.02 \pm 0,7 | 1.03 \pm 0,9 | 0.470 |
| Height (cm) | 130.3 \pm 7.6 | 132.1 \pm 8.2 | 0.218 |
| Height Z-score | 1.23 \pm 1.04 | 1.36 \pm 1.2 | 0.367 |
| BMI (kg/m ²) | 18.1 \pm 2.7 | 17.4 \pm 2.4 | 0.090 |
| BMI Z-score | 0.83 \pm 0.9 | 0.91 \pm 0,9 | 0.480 |
| Height velocity (cm/year) | 6.8 \pm 1.3 | 7.0 \pm 1.6 | 0.666 |
| Height velocity Z-score | 1.67 \pm 1,41 | 1.90 \pm 1.73 | 0.272 |
| BA-CA (years) | 1.61 \pm 0.67 | 1.82 \pm 0.71 | 0.024 |

* Student's t test.

TP: thelarche premature. CPP: central precocious puberty. BMI: body mass index. BA: bone age. CA: chronological age

Table 2. Basal and stimulated serum concentrations of gonadotropin of PT (prepubertal) and CPP girls (M \pm SDS)

| Hormone | PT girls (n=133) | CPP girls (n=108) | p-values* |
|------------------------|---------------------|----------------------------------|-----------|
| Basal LH (UI/L) | 0.06 \pm 0.09 | 0.61 \pm 0.94 | 0.001 |
| (range) | (0.01-1.03) | (0.01-4.14) | |
| LH peak (UI/L) | 2.20 \pm 1.14 | 12.89\pm5.34 | 0.001 |
| (range) | (0.01-4.75) | (6.09-28.42) | |
| Basal FSH (UI/L) | 1.49 \pm 0.92 | 3.34 \pm 1.82 | 0.001 |
| (range) | (0.10-4.85) | (0.44-0.91) | |
| FSH peak (UI/L) | 15.03 \pm 6.48 | 18.90 \pm 6.73 | 0.001 |
| (range) | (0.27-29.53) | (8.24-34.71) | |
| Basal LH/FSH ratio | 0.042 \pm 0.388 | 0.16 \pm 0.155 | 0.001 |
| (range) | (0.01-0.24) | (0.01-0.8) | |
| LH peak/FSH peak ratio | 0.156 \pm 0.131 | 0.755 \pm 0.53 | 0.001 |
| (range) | (0.04-1.36) | (0.19-3.30) | |

* Student's t test

Table 3. Sensitivity and specificity for selected cut off point values of basal gonadotropin level discriminating CPP from PT girls, calculated by ROC.

| Hormone | AUC (95% CI) | p | Cut off point values | Sensitivity (95% CI) | Specificity (95% CI) |
|--------------|---------------------|-------|----------------------|----------------------|----------------------|
| LH | 0.89 (0.84-0.93) | 0.001 | 0.1 | 0.82 (0.76-0.88) | 0.90 (0.83-0.97) |
| FSH | 0.80 (0.75-0.85) | 0.001 | 2.5 | 0.63 (0.53-0.73) | 0.80 (0.73-0.87) |
| LH/FSH ratio | 0.82 (0.76-0.88) | 0.001 | 0.05 | 0.73 (0.63-0.83) | 0.74 (0.66-0.82) |

Figure 1



