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Clinical and Analytical Presentation of Central Precocious Puberty: A 20-Year Cross-Sectional Study

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Abstract

Objectives – This study aims to compare the clinical and analytical presentation of Central precocious puberty (CPP), considering age. **Methods** – An observational, cross-sectional study was conducted on children diagnosed with CPP at a level III hospital, between January 2002 and April 2022. Clinical, auxological, sociodemographic, laboratory, and imaging parameters were analyzed. **Results** – Out of the 52 children studied, the majority were girls (N=44). The median age of puberty onset in girls was 6.79 years and the mean age at first consultation of 8.13 years, with a significantly lower age at hospital referral (7.65 years; P=0.045) compared to boys. Idiopathic etiology was predominant in both. In girls, breast development appeared at older mean ages (P=0.009), while pubic hair growth and accelerated growth were associated with younger ages at puberty onset (P=0.021; P=0.018, respectively). Basal and peak levels of gonadotropin hormones were higher in girls, although not statistically significant. In girls, age at puberty onset correlated negatively with standard deviation of body mass index (P=0.023), while age at first consultation correlated positively with bone age (P<0.001), and was associated with younger ages at Gonadotropin-Releasing Hormone stimulation test (P=0.020). **Conclusion** – This study provides innovative and relevant findings that enhance understanding of CPP presentation according to age, thereby improving clinical management of this condition.

Key Words: Puberty ▪ Precocious Puberty ▪ Central Precocious Puberty.

Introduction

Puberty is a complex biological process that starts with the appearance of secondary sexual characteristics and progresses to full sexual maturation and reproductive capacity. Typically, the first sign of puberty is the development of breast buds (thelarche) in girls and testicular enlargement in boys (1). The appearance of pubic hair (pubarche) typically occurs simultaneously, although it can sometimes appear slightly earlier or later (2). Tanner described normal pubertal development in five stages, known as the Tanner stages. Stage 2 marks the onset of puberty in both sexes, occurring between the ages of 8-13 in girls and 9-14 in boys (1-3).

Precocious puberty (PP) is characterized by the onset of puberty before age 8 in girls and age 9 in boys, resulting in premature development of secondary sexual characteristics, accelerated growth, and advanced bone maturation due to early epiphyseal closure, leading to reduced final height (2, 4).

At the beginning of puberty, the activation of the hypothalamic-pituitary-gonadal (HPG) axis results in increasing levels of luteinizing hormone

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(LH), follicle-stimulating hormone (FSH), and sex hormones. When its activation occurs prematurely, it is called central precocious puberty (CPP) (3-5).

In 80% of PP cases, the etiology is central. However, CPP is rare, with a prevalence of 1:5000-10000 in caucasians. It is more common in girls (1:10), and in these cases, 80%90% are idiopathic. In boys, it is more often associated with organic causes, particularly lesions in the central nervous system (CNS) (3, 5-7). CPP can result from congenital or acquired CNS alterations, genetic syndromes, endocrine disruptors, and early exposure to sex steroids (3, 7). In recent years, understanding of the genetic factors involved has increased, with mutations identified in the KISS1 gene and its receptor, as well as in DLK1 and MKRN3 genes (5, 8). Adoption, family history of CPP, overweight/obesity, and hypothyroidism are also risk factors mentioned in the literature (8-12).

The gonadotropic response to stimulation with gonadotropin-releasing hormone (GnRH) is the standard diagnostic test. (1, 5) However, this test is expensive and time-consuming, so basal LH measurement has been used for diagnosing CPP (13, 14). Regarding imaging tests, brain Magnetic Resonance Imaging (MRI) is notable for ruling out anatomical lesions, left hand and wrist radiography for confirming bone age (BA), and pelvic ultrasound for evaluating girls reproductive organs (3, 5, 15, 16). Treatment with GnRH analogs (aGnRH) is widely used in CPP and has proven to be both effective and safe. These treatments suppress the HPG axis, helping to stabilize pubertal progression, delay skeletal maturation, and maintain appropriate growth (6, 14).

This study aims to clarify the different forms of CPP presentation and determine if there are differences in clinical and analytical presentation according to age.

Methods

A cross-sectional study was conducted on children with central precocious puberty (CPP), evaluated during their first pediatric endocrinology consultation between January 1st, 2002, and April 30th, 2022, at a level III hospital. The diagnosis of CPP was defined by the simultaneous presence of the following clinical and analytical criteria. Clinical criteria: appearance of secondary sexual characteristics before age 8 in girls, presenting as thelarche or pubarche; and before age 9 in boys, presenting with a testicular volume of ≥4mL or pubarche. Analytical criteria: basal LH >0.2 IU/L; or LH >5 IU/L or LH/FSH ratio >0.66 after GnRH stimulation test. Children without follow-up in this consultation or lacking the necessary clinical records were excluded. Of the 77 children selected with suspected precocious puberty (PP), 24 children were excluded due to early thelarche or adrenarche/pubarche, and one child was excluded due to incomplete medical records, resulting in a final sample of 52 children. The data were obtained through consultation of the computerized clinical records.

Ethical Considerations

This study was approved by the Ethics Committee for Research in Life and Health Sciences of the University of Minho with identification number CEICVS 069/2022, and by the Ethics Committee of the Hospital of Braga with identification number 97_2022. The anonymity and confidentiality of the patients were ensured.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics (International Business Machine, Statistical Package for the Social Sciences), version 28. A P-value <0.05 was considered statistically significant. A descriptive study was conducted according to sex, followed by a comparison between the sexes. For the comparison of qualitative variables, the Chi-square test ($\chi 2$) or Fisher's exact test was used when the percentage of cells with an expected count <5 exceeded 20%. Phi (Φ) or Cramer's V (Φc) was used as a measure of effect size for 2×2 or larger tables, respectively. For the comparison of quantitative variables, the independent samples t-test (t) or Mann-Whitney test (U) was used. Effect size was estimated using Cohen's d (d) for parametric tests

and r for non-parametric tests. One Way ANOVA was used to compare three or more groups regarding quantitative variables, with eta squared (η2) calculated as a measure of effect size. Pearson (rp) or Spearman (rs) correlation coefficients were used to evaluate the correlation between quantitative variables. In boys, given the small sample size (N=8), non-parametric tests were used.

Results

A total of 52 children were diagnosed with CPP. The majority were girls (N=44; 84.6%), with a median pubertal onset (PO) age of 6.79 years (IQR=1.23) and a mean age at the first consultation of 8.13±0.91 years. Descriptive analysis and comparison between sexes are presented in Table 1.

Table 1. Descriptive Analysis of Clinical, Sociodemographic, Auxological, Analytical, and Imaging Variables, and Comparison between Sexes

Variable	Gender		Test statistics	P	Effect size
	Girls (N=44)	Boys (N=8)			
Gestational age, weeks[b]	38.44±2.02	38.72±0.70	t (50) = 0.38	0.708	d=0.15
Prematurity[a]					
Yes (< 37w)	5 (11.4)	0 (0.0)	Fisher's exact test	>0.990	Φ=-0.14
No (≥ 37w)	39 (88.6)	8 (100.0)			
Birth weight, SD[b*]	-0.08±1.17	0.53±0.67	t (49) = 1.34	0.186	d=0.55
Length at birth, SD[b*]	-0.30±1.70	0.54±0.66	t (47) = 128	0.208	d=0.52
Birth weight classification[a]					
SGA	7 (15.9)	0 (0.0)	Fisher's exact test	0.713	Φc=0.18
AGA	30 (68.2)	7 (87.5)			
LGA	7 (15.9)	1 (12.5)			
Birth length classification[a]					
SGA	10 (23.8)	0 (0.0)	Fisher's exact test	0.415	Φc=0.22
AGA	25 (59.5)	6 (75.0)			
LGA	7 (16.7)	2 (25.0)			
Nationality[a]					
Portuguese	38 (86.4)	8 (100.0)	Fisher's exact test	>0.990	Φc= 0.15
Brazilian	4 (9.1)	0 (00)			
Spanish	1 (2.3)	0 (0.0)			
French	1 (2.3)	0 (0.0)			
Maternal menarche, years[b*]	11.74±1.83	11.81±0.84	t (50) = 0.11	0.912	d=0.04
Family history of PP[a]					
Yes	18 (40.9)	0 (0.0)	Fisher's exact test	0.039	Φ=0.31
No	26 (59.1)	8 (100.0)			
Personal history[a]					
Yes	15 (34.1)	6 (75.0)	Fisher's exact test	0.049	Φ=-0.30
No	29 (65.9)	2 (25.0)			
Development changes	5 (33.4)	2 (33.4)	-	-	-
Epilepsy	2 (13.4)	1 (16.7)	-	-	-
Costello syndrome	0 (0.0)	1 (16.7)	-	-	-
Myofibromatosis	1 (6.7)	0 (0.0)	-	-	-
Neurofibromatosis type 1	1 (6.7)	0 (0.0)	-	-	-
Spastic cerebral palsy	2 (13.4)	0 (0.0)	-	-	-
Congenital adrenal hyperplasia	0 (0.0)	1 (16.7)	-	-	-

Continuation of Table 1. Descriptive Analysis of Clinical, Sociodemographic, Auxological, Analytical, and Imaging Variables, and Comparison between Sexes

Variable	Gender		Test statistics	P	Effect size
	Girls (N=44)	Boys (N=8)			
Micropenis	0 (0.0)	1 (16.7)	-	-	-
Fetal growth restriction	3 (20.0)	0 (0.0)	-	-	-
Overweight	4 (26.7)	4 (66.8)	-	-	-
Dyslipidemia	1 (6.7)	1 (16.7)	-	-	-
Hypothyroidism	2 (13.4)	2 (33.4)	-	-	-
Number of initial pubertal signs[a]					
1	34 (77.3)	2 (25.0)	U = 87.00	0.023	r=-0.39
2	9 (20.5)	6 (75.0)			
3	1 (2.3)	0 (0.0)			
Initial clinical manifestations[a]					
Thelarche	27 (61.4)	0 (0.0)	-	-	-
Pubarche	22 (50.0)	8 (100.0)			
Testicular enlargement	0 (0.0)	3 (37.5)	-	-	-
Accelerated growth rate	6 (13.6)	3 (37.5)			
Additional clinical manifestations[a]					
Thelarche	15 (38.5)	0 (0.0)	-	-	-
Pubarche	20 (51.2)	0 (0.0)			
Testicular enlargement	0 (0.0)	5 (100.0)			
Accelerated growth rate	15 (38.5)	0 (0.0)			
Menarche	4 (10.3)	0 (0.0)			
Number of pubertal signs[a]					
1	(4.5)	0 (0.0)	U=157.50	0.645	r=-0.07
2	20 (45.5)	5 (62.5)			
3	21 (47.7)	3 (37.5)			
4	1 (2.3)	0 (0.0)			
Tanner stage - breast[a]					
≤ 2	20 (45.5)	-	-	-	-
> 2	24 (54.5)	-	-	-	-
Tanner stage - pubic hair[a]					
≤ 2	25 (56.8)	6 (75.0)	Fisher's exact test	0.449	Φ=0.13
> 2	19 (43.2)	2 (25.0)			
Tanner stage - gonads[a]					
≤ 2	-	2 (28.6)	-	-	-
> 2	-	5 (71.4)	-	-	-
GnRH test[a]					
Yes	15 (34.1)	4 (50.0)	Fisher's exact test	0.443	Φ=-0.12
No	29 (65.9)	4 (50.0)			
Pelvic ultrasound classification[a]					
Pubertal	28 (75.7)	-	-	-	-
Prepubertal	9 (24.3)	-			
Neuroimage exam[a]					
MRI	19 (95.0)	7 (100.0)	Fisher's exact test	>0.990	Φ=-0.12
CT	1 (5.0)	(0.0)			

Continuation of Table 1. Descriptive Analysis of Clinical, Sociodemographic, Auxological, Analytical, and Imaging Variables, and Comparison between Sexes

Variable	Gender		Test statistics	P	Effect size
	Girls (N=44)	Boys (N=8)			
Neuroimage[a]					
Yes	20 (45.5)	7 (87.5)	Fisher's exact test	0.051	Φ=-0.30
No	24 (54.5)	1 (12.5)			
Neuroimagem abnormalities[a]					
Sim	7 (35.0)	3 (42.9)	Fisher's exact test	>0.990	Φ=-0.07
Não	13 (65.0)	4 (57.1)			
Hypothalamic hamartoma	1 (14.3)	0 (0.0)	-	-	-
Hypoxic-ischemic encephalopathy	2 (28.6)	0 (0.0)	-	-	-
Arachnoid cyst	1 (14.3)	0 (0.0)	-	-	-
Arnold-Chiari malformation type 1	0 (0.0)	1 (33.3)	-	-	-
Pineal gland cyst	1 (14.3)	2 (66.6)	-	-	-
Rathke's cleft cyst	1 (14.3)	0 (0.0)	-	-	-
Pituitary microadenoma	1 (14.3)	0 (0.0)			
PPC classification[a]					
Idiopathic	40 (90.9)	7 (87.5)	Fisher's exact test	>0.990	Φ=-0.04
Secondary	4 (9.1)	1 (12.5)			
Secondary PPC causes[a]					
Congenital adrenal hyperplasia	0 (0.0)	1 (100.0)	-	-	-
Type 1 neurofibromatosis	1 (25.0)	0 (0.0)	-	-	-
Hypoxic-ischemic encephalopathy	2 (50.0)	0 (0)	-	-	-
Hypothalamic hamartoma	1 (25.0)	0 (0.0)	-	-	-
Arachnoid cyst	1 (25.0)	0 (0.0)	-	-	-
Treatment[a]					
Yes	31 (70.5)	8 (100.0)	Fisher's exact test	0.177	Φ=-0.25
No	13 (29.5)	0 (0.0)			
aGnRH[a]					
Triptorrelin	28 (90.3)	6 (75.0)	Fisher's exact test	0.268	Φ=0.19
Leuprorrelin	3 (9.7)	2 (25.0)			
Administration[a]					
Quarterly	30 (96.8)	8 (100)	Fisher's exact test	>0.990	Φ=-0.08
Monthly	1 (3.2)	0 (0)			
Age at treatment-1st consultation, months[b*]	3.42 (3.39)	7.86 (7.56)	t (8) = 1.33	0.221	d=0.81
Pubertal onset, years[c]	6.79 (1.23)	7.63 (1.64)	U=92.00	0.032	r=-0.30
Referral age, years[b]	7.65±1.12	8.50±0.74	t (50)=2.05	0.045	d=0.79
Age at first consultation, years[b]	8.13±0.91	8.77±0.64	t (50)=1.90	0.063	d=0.73
Referral age-pubertal onset, years[b]	1.16±1.01	1.54±1.65	t (50)=0.89	0.380	d=0.34
Weight, DP[b]	1.41±1.35	2.37±1.71	t (50)= 0.78	0.082	d=0.68
Length, DP[b*]	1.33±1.37	1.70±1.60	t (49)=0.70	0.489	d=0.27
BMI, DP[b*]	1.19 ±0.92	1.93±1.65	t (8)=1.24	0.253	d=0.70
BMI classification[a]					
Normal	14 (32.6)	3 (37.5)	Fisher's exact test	0.209	Φc=0.24
Weight excess	18 (41.9)	1 (12.5)			
Obesity	11 (25.6)	4 (50.0)			

Continuation of Table 1. Descriptive Analysis of Clinical, Sociodemographic, Auxological, Analytical, and Imaging Variables, and Comparison between Sexes

Variable	Gender		Test statistics	P	Effect size
	Girls (N=44)	Boys (N=8)			
TFH, SD[b]	-0.48±0.86	-0.10±1.05	t (50) = 1.11	0.270	d=0.43
PAH, cm[b*]	157.84±7.38)	180.13±14.99	t (8) = 4.11	0.004	d=2.50
PAH, SD[b*]	-0.79±1.12	0.53±2.01	t (8) = 1.80	0.110	d=1.03
PAH-TFH, SD[b*]	-0.31±0.93	0.62±1.83	t (48) = 2.19	0.034	d=0.84
Growth rate, cm/year[b]	8.30±1.83	7.39±1.92	t (42) = -1.26	0.214	d=-0.49
BA, SD[b]	2.44±0.98	2.57±1.02	t (48) = 0.34	0.733	d=0.13
BA-real age, years[b]	2.09±0.93	2.30±1.04	t (48) = 0.57	0.572	d=0.22
BA classification[a]					
Similar	16 (38.1)	2 (25.0)	Fisher's exact test	0.694	Φ=-0.10
Advanced	26 (61.9)	6 (75.0)			
Basal FSH, IU/L[b]	6.14±3.34	2.34±2.28	t (49) = -3.07	0.003	d=-1.18
Basal LH, IU/L[b]	2.30±2.12	0.81±0.64	t (38) = -3.78	<0.001	d=-0.75
Peak FSH, IU/L[b]	16.53±6.81	3.99±1.91	t (17) = -3.57	0.002	d=-2.01
Peak LH, IU/L[c]	17.11 (17.81)	5.70 (8.64)	U = 53.00	0.002	r=0.53
Peak LH/FSH[b]	1.34±0.91	3.25±4.17	t (3) = 0.91	0.430	d=0.98
Estradiol, pmol/L[c]	121.62 (109.49)	45.02 (25.35)	U = 226.00	0.002	r=0.42
Testosterone. ng/dL[c]	18.24 (12.16)	50.04 (80.07)	U = 39.00	0.002	r=-0.48
Uterine length. cm[b]	43.74±13.09	-	-	-	-

[a]Results expressed as absolute frequency and relative frequency (N (%); [b]Results expressed as mean ± SD (standard deviation); [c]Results expressed as median ± IQR (interquartile range); *N may vary depending on missing data.

Boys had a significantly higher median PO age (Mdn=7.63; IQR=1.64; P=0.032) and a mean age at the first consultation of 8.77±0.64 years. The number of initial pubertal signs was lower in girls (P=0.023), with 77.3% exhibiting only one sign. Initially, 61.4% of girls showed thelarche, while all boys presented pubarche. Among additional pubertal signs, pubarche appeared in 51.2% of girls, and all boys had testicular enlargement. Hospital referral occurred at a significantly younger age in girls (7.65±1.12 vs. 8.50±0.74; P=0.045), with a shorter average referral delay, though not statistically significant (1.16±1.01 vs. 1.54±1.65; P=0.380).

A higher percentage of boys had relevant personal history compared to girls (75% vs. 34.1%; P=0.049), with overweight being the most prevalent (N=4; 66.8%). Regarding the presence of a family history of PP, a difference was detected between groups, with 40.9% in girls vs. 0% in boys (P=0.039).

No differences were found regarding growth velocity (GV) or auxological parameters, except for the difference between the predicted adult height (PAH) and target familial height (TFH) (P=0.034), which was positive in boys (0.62 SD). Both sexes had a high percentage of children with advanced bone age (61.9% vs. 75%).

Basal LH (2.30±2.12 IU/L; P<0.001) and FSH (6.14±3.34 IU/L; P=0.003) values were higher in girls, as were peak LH (Mdn=17.11; IQR=17.81 IU/L; P=0.020) and FSH (16.53±6.81 IU/L; P=0.0.002) values. Either estradiol and testosterone showed sex differences, with higher estradiol in girls (Mdn=121.62; IQR=109.49 pmol/L; P=0.002) and higher testosterone in boys (Mdn=50.04; IQR=80.07 ng/dL; P=0.002), as expected.

Imaging studies showed alterations in 42.9% of boys and 35% of girls. Idiopathic etiology was most prevalent in both (90.9% in girls vs. 87.5% in boys). All boys and 70.5% of girls received

treatment with aGnRH. Boys had a longer average delay in starting treatment, though not statistically significant (7.86±7.56 vs. 3.42±3.39 months; P=0.221).

Comparison of Puberty Onset Age with Sociodemographic and Clinical Variables in Girls

Differences were identified between PO age and thelarche as the first pubertal sign, with a higher mean age in girls who presented with thelarche initially (6.79±0.91 vs. 6.02±0.89 years; P=0.009) (Table 2). Conversely, thelarche as an additional sign occurred at younger ages (6.07±0.91 vs. 6.71±0.94 years; P=0.034). PO age was significantly lower when the first signs of puberty were pubarche (Mdn=6.29; IQR=1.13 vs. Mdn=7.00; IQR=1.06 years; P=0.021) and increased GV (Mdn=5.92; IQR=0.81 vs. Mdn=7.00; IQR=1.19 years; P=0.018). Initial presentation with more than one pubertal sign occurred at younger mean ages but without statistical significance (6.29±0.83 vs. 6.55±1.01 years; P=0.463). Imaging and the presence of alterations occurred at younger mean ages but without statistical significance. Secondary PPC etiology also presented with a younger mean PO age compared to idiopathic PPC (5.63±1.11 vs. 6.58±0.93 years; P=0.060).

Table 2. Comparison of Pubertal Onset Age with Sociodemographic and Clinical Variables in Girls

Variable	Pubertal onset age	Test statistics	P	Effect size
Prematurity[b]				
Yes (< 37w) (N=5)	6.67±0.66	t (42) = 0.42	0.674	d = 0.20
No (≥ 37w) (N=39)	6.47±1.01			
Birth weight classification[b]				
SGA (N=7)	6.51±1.01			
AGA (N=30)	6.56±0.93	F (2. 41) = 0.47	0.630	η2 = 0.02
LGA (N=7)	6.17±1.17			
Birth length classification[b]				
SGA (N=10)	6.57±0.97			
AGA (N=25)	6.61±0.81	F (2. 39) = 1.58	0.219	η2 = 0.07
LGA (N=7)	5.89±1.40			
Immigrant[b]				
Yes (N=6)	6.18±0.85	t (42) = 0.85	0.403	d = 0.37
No (N=38)	6.54±0.99			
Personal history[b]				
Yes (N=15)	6.34±1.00	t (42) = 0.72	0.474	d = 0.23
No (N=29)	6.57±0.96			
Development changes[b]				
Yes (N=5)	6.95±0.57	t (13) = -1.80	0.096	d = -0.98
No (N=10)	6.04±1.05			
Weight excess[b]				
Yes (N=4)	6.21±0.98	t (13) = 0.31	0.762	d = 0.18
No (N=11)	6.39±1.05			
Family history of PP[b]				
Yes (N=18)	6.24±0.98	t (42) = 1.45	0.155	d = 0.44
No (N=26)	6.67±0.94			

Continuation of Table 2. Comparison of Pubertal Onset Age with Sociodemographic and Clinical Variables in Girls

Variable	Pubertal onset age	Test statistics	P	Effect size
BMI classification[b]				
< 2SD (Normal/weight excess) (N=32)	6.68±0.88	t (41) = 1.77	0.085	d = 0.62
≥ 2SD (Obesity) (N=11)	6.12±0.98			
BA classification[b]				
Similar (N=16)	6.66±0.73	t (40) = 0.45	0.656	d = 0.14
Advanced (≥ 2SD) (N=26)	6.52±1.01			
Number of initial pubertal signs[b]				
1 (N=34)	6.55±1.01	t (42) = 0.74	0.463	d = 0.27
>1 (N=10)	6.29±0.83			
Thelarche as firs sign[b]				
Yes (N=27)	6.79±0.91	t (42) = -2.76	0.009	d = -0.85
No (N=17)	6.02±0.89			
Pubarche as firs sign[c]				
Yes (N=22)	6.29 (1.13)*	U = 144.00	0.021	r = -0.35
No (N=22)	7.00 (1.06)*			
Increased growth rate as firs sign[c]				
Yes (N=6)	5.92 (0.81)*	U = 46.50	0.018	r = -0.35
No (N=38)	7.00 (1.19)*			
Thelarche as additional sign[b]				
Yes (N= 15)	6.07±0.91	t (42) = 2.19	0.034	d = 0.70
No (N=29)	6.71±0.94			
Pubarche as additional sign[b]				
Yes (N=20)	6.71±1.01	t (42) = 1.39	0.172	d = -0.42
No (N=24)	6.31±0.92			
Accelerated growth as additional sign[b]				
Yes (N=15)	6.63±1.02	t (42) = -0.69	0.494	d = -0.22
No (N=29)	6.42±0.95			
Menarche as additional sign[b]				
Yes (N=4)	6.38±1.11	t (42) = 0.25	0.804	d = 0.13
No (N=40)	6.50±0.97			
Number of pubertal signs[b]				
≤ 2 (N=22)	6.54±0.98	t (42) = 0.33	0.742	d = 0.10
> 2 (N=22)	6.44±0.98			
Tanner stage – breast[b]				
≤ 2 (N=20)	6.42±1.04	t (42) = -0.47	0.640	d = -0.14
> 2 (N=24)	6.56±0.92			
Tanner stage - pubic hair[b]				
≤ 2 (N=25)	6.50±1.10	t (42) = 0.08	0.936	d = 0.03
> 2 (N=19)	6.48±0.80			
GnRH test[b]				
Yes (N=15)	6.57±0.74	t (42) = -0.39	0.699	d = -0.12
No (N=29)	6.45±1.08			
Pelvic ultrasound classification[b]				
Pubertal (N=28)	6.51±0.94	t (35) = 0.06	0.951	d = 0.02
Prepubertal (N=9)	6.53±0.80			

Continuation of Table 2. Comparison of Pubertal Onset Age with Sociodemographic and Clinical Variables in Girls

Variable	Pubertal onset age	Test statistics	P	Effect size
Neuroimage[b]				
Yes (N=20)	6.26±1.16	t (31) = 0.14	0.171	d = 0.44
No (N=24)	6.68±0.74			
Neuroimage exam[b]				
MRI (N=19)	6.20±1.16	---	---	---
CT (N=1)	---			
Neuroimage abnormalities[b]				
Yes (N=7)	6.13±1.15	t (18) = 0.39	0.719	d = 0.17
No (N=13)	6.33±1.21			
PPC classification[b]				
Idiopathic (N=40)	6.58±0.93	t (42) = 1.94	0.060	d = 1.02
Secondary (N=4)	5.63±1.11			
Treatment[b]				
Yes (N=31)	6.56±0.91	t (42) = -0.76	0.453	d = -0.25
No (N=13)	6.32±1.11			
aGnRH[b]				
Triptorrelin (N=28)	6.59±0.87	t (29) = -0.52	0.607	d = -0.32
Leuprorrelin (N=3)	6.30±1.47			
Administration[b]				
Quarterly (N=30)	6.58±0.92	-	-	-
Monthly (N=1)	---			

[a] Results expressed as absolute frequency and relative frequency (n (%)); [b] Results expressed as mean ± SD (standard deviation); [c] Results expressed as median ± IQR (interquartile range); * N may vary depending on missing data.

Comparison of Age at First Consultation with Sociodemographic and Clinical Variables in Girls

The number of initial and total pubertal signs did not show significant differences with age at the first consultation (Table 3). Despite the small sample of girls with menarche as an additional sign (N=4 vs. N=40), the mean age at the first consultation was higher in these cases (9.40±0.94 vs. 8.00±0.82 years; P=0.002). Tanner stage ≤2 for pubarche was associated with younger mean ages (7.83±0.71 vs. 8.53±1.01 years; P=0.010). Girls undergoing GnRH stimulation test (N=15; 34.1%) had a significantly younger age at the first consultation (7.69±0.68 vs. 8.36±0.94 years; P=0.020). Treatment with aGnRH occurred at younger mean ages (8.08±0.72 vs. 8.26±1.29 years), with triptorelin being the most used formulation (N=28; 90.3%) and leuprorelin used at older mean ages (8.36±0.31 vs. 8.04±0.75 years), with no statistically significant differences identified.

Table 3. Comparison of Age at First Consultation with Sociodemographic and Clinical Variables in Girls

Variable	Age at 1st consultation (N=44)	Test statistics	P	Effect size
Prematurity[b]				
Yes (< 37w) (N=5) No (≥ 37w) (N=39)	8.22±0.49 8.12±0.96	t (42) = 0.23	0.823	d=0.11
Birth weight classification[b]				
SGA (N=7)	8.60±1.09	F (2. 18) = 2.18	0.126	η2=0.10
AGA (N=30)	8.14±0.89			
LGA (N=7)	7.61±0.62			

Continuation of Table 3. Comparison of Age at First Consultation with Sociodemographic and Clinical Variables in Girls

Variable	Age at 1st consultation (N=44)	Test statistics	P	Effect size
Birth length classification[b]				
SGA (N=10)	8.41±0.97	F (2. 39) = 0.60	0.553	η2=0.03
AGA (N=25)	8.02±0.97			
LGA (N=7)	8.11±0.76			
Immigrant[b]				
Yes (N=6)	8.17±1.12	t (42) = -0.11	0.914	d=-0.05
No (N=38)	8.12±0.89			
Personal history[b]				
Yes (N=15)	8.06±1.30	t (18) = 0.29	0.776	d=0.11
No (N=29)	8.16±0.66			
Development changes[b]				
Yes (N=5)	8.85±1.15	t (13) = -1.79	0.096	d=-0.98
No (N=10)	7.67±1.24			
Weight excess[b]				
Yes (N=4)	8.75±1.78	t (13) = -1.26	0.229	d=-0.74
No (N=11)	7.81±1.08			
Family history of PP[b]				
Yes (N=18)	8.41±0.86	t (42) = -1.75	0.087	d=-0.54
No (N=26)	7.93±0.91			
BMI classification[b]				
< 2SD (Normal/weight excess) (N=32)	8.02±0.81	t (41) = -1.89	0.066	d=-0.66
≥ 2SD (Obesity) (N=11)	8.59±1.02			
BA classification[b]				
Similar (N=16)	8.22±0.67	t (40) = -0.10	0.919	d=-0.03
Advanced (≥ 2SD) (N=26)	8.24±0.85			
Number of initial pubertal signs[b]				
1 (N=34)	8.15±0.91	t (42) = 0.31	0.761	d=0.11
>1 (N=10)	8.05±0.97			
Thelarche as firs sign[b]				
Yes (N=27)	8.30±0.87	t (42) = -1.63	0.111	d=-0.50
No (N=17)	7.85±0.94			
Pubarche as firs sign[c]				
Yes (N=22)	7.93 (0.90)	t (42) = 1.48	0.146	d=0.45
No (N=22)	8.33 (0.90)			
Increased growth rate as firs sign[c]				
Yes (N=6)	7.79 (1.13)	t (42) = 0.97	0.336	d=0.43
No (N=38)	8.18 (0.88)			
Thelarche as additional sign[b]				
Yes (N= 15)	7.99±0.72	t (42) = 0.70	0.486	d=0.22
No (N=29)	8.20±1.00			
Pubarche as additional sign[b]				
Yes (N=20)	8.24±0.77	t (42) = -0.75	0.459	d = -0.23
No (N=24)	8.03±1.03			

Continuation of Table 3. Comparison of Age at First Consultation with Sociodemographic and Clinical Variables in Girls

Variable	Age at 1st consultation (N=44)	Test statistics	P	Effect size
Accelerated growth as additional sign[b]				
Yes (N=15)	8.50±1.09	U = 144.50	0.070	r=0.27
No (N=29)	8.08±1.04			
Menarche as additional sign[b]				
Yes (N=4)	9.40±0.94	t (42) = -3.22	0.002	d=-1.69
No (N=40)	8.00±0.82			
Number of pubertal signs[b]				
≤ 2 (N=22)	7.90±0.85	t (42) = -1.69	0.099	d=-0.51
> 2 (N=22)	8.36±0.94			
Tanner stage – breast[b]				
≤ 2 (N=20)	7.93±0.83	t (42) = -1.34	0.188	d=-0.41
> 2 (N=19)	8.30±0.96			
Tanner stage - pubic hair[b]				
≤ 2 (N=25)	7.83±0.71	t (42) = -2.70	0.010	d=-0.82
> 2 (N=19)	8.53±1.01			
GnRH test[b]				
Yes (N=15)	7.69±0.68	t (42) = 2.42	0.020	d=0.77
No (N=29)	8.36±0.94			
Pelvic ultrasound classification[b]				
Pubertal (N=28)	8.16±0.81	t (35) = -0.75	0.458	d=-0.29
Prepubertal (N=9)	7.88±1.44			
Neuroimage[b]				
Yes (N=20)	7.93±1.03	t (42) = 1.36	0.181	d=0.41
No (N=24)	8.30±0.78			
Neuroimage exam[b]				
MRI (N=19)	7.87±1.03	-	-	-
CT (N=1)	-			
Neuroimage abnormalities[b]				
Yes (N=7)	7.51±1.21	t (18) = 1.35	0.194	d=0.63
No (N=13)	8.15±0.89			
PPC classification[b]				
Idiopathic (N=40)	8.29±1.06	U = 34.50	0.062	r=-0.28
Secondary (N=4)	7.17±2.58			
Treatment[b]				
Yes (N=31)	8.08±0.72	t (42) = 0.60	0.554	d=0.20
No (N=13)	8.26±1.29			
aGnRH[b]				
Triptorrelin (N=28)	8.04±0.75	t (29) = 0.71	0.481	d=0.43
Leuprorrelin (N=3)	8.36±0.31			
Administration[b]				
Quarterly (N=30)	8.06±0.73	-	-	-
Monthly(N=1)	-			

[a] Results expressed as absolute frequency and relative frequency (N (%)); [b] Results expressed as mean±SD (standard deviation); [c] Results expressed as median±IQR (interquartile range); * N may vary depending on missing data.

Correlation between Puberty Onset Age and Age at First Consultation with Clinical and Analytical Parameters in Girls

PO age correlated negatively with body mass index (BMI) SD (P=0.023) (Table 4). Older bone age was associated with an older age at the first consultation (P<0.001). Both PO age and age at the first consultation correlated with referral age. Thus, the later a child started puberty, the later they were referred and subsequently had their first consultation (P<0.001). It was found that the younger the PO age, the longer the time to referral (P=0.017). A positive correlation was found between age at the first consultation and the time interval between puberty onset and referral (P<0.001). No association was found between peak FSH and LH values, basal FSH and LH values, and PO age. Additionally, no association was found between uterine longitudinal length and both ages.

Table 4. Correlation Between Age of Pubertal Onset and Age at First Consultation with Clinical and Analytical Variables in Girls

Variables	N	Pubertal Onset Age (rp)	P	Age at 1st Consultation rp	P
Gestational age, weeks	44	0.03	0.868	0.04	0.779
Birth weight, SD	44	-0.12	0.432	-0.12	0.442
Birth length, SD	42	-0.06	0.721	-0.15	0.346
Maternal menarche, years	44	0.13	0.391	-0.13	0.387
TFH, SD	44	-0.01	0.966	-0.02	0.924
Weight 1st consultation, SD	44	-0.05	0.731	0.21*	0.166
Height 1st consultation, SD	43	-0.12	0.441	0.24	0.122
BMI, SD	43	-0.35	0.023	0.14	0.372
Growth rate, cm/year	36	-0.26	0.120	0.06	0.733
BA, years	42	-0.19	0.229	0.58	<0.001
BA, SD	42	-0.27	0.083	0.02	0.900
BA-real age, years	42	-0.27	0.084	-0.07	0.657
PAH, SD	42	-0.07	0.662	0.14	0.370
PAH-TFH. SD	42	-0.08	0.617	0.17	0.276
Referral age, years	44	0.54	<0.001	0.77	<0.001
Age at 1st consultation, years	44	0.26	0.085	-	-
Referral age-PO age, years	44	-0.36	0.017	0.61	<0.001
Basal FSH, IU/L	43	-0.24	0.114	-0.17*	0.290
Basal LH, IU/L	44	-0.23	0.127	0.09	0.565
FSH peak, IU/L	15	-0.15	0.597	-0.38	0.159
LH peak, IU/L	15	-0.28	0.306	-0.17	0.536
LH/FSH peak	15	-0.06	0.835	0.18	0.520
Estradiol, pmol/L	43	0.06	0.720	0.29	0.059
Testosterone, ng/dL	32	-0.33*	0.063	0.09	0.614
Uterine length, cm	38	0.11	0.499	0.30	0.069
Age at treatment-1st consultation, months	31	0.13*	0.472	-0.02	0.901

* N may vary depending on missing data. (rs)=The Spearman's rank correlation coefficient.

Comparison of Puberty Onset Age and Age at First Consultation with Sociodemographic, Clinical, and Analytical Parameters in Boys

Table 5 presents the statistical analysis of the boys' sample. This is an exploratory analysis due to the small sample size (N=8).

Table 5. Comparison of the Onset Age of Puberty and Age at First Consultation with Sociodemographic, Clinical, and Analytical Variables in Boys

Variables	Pubertal onset age (N=8)	Test statistics	Variables	Age at 1st consultation (N=8)	Test statistics
	Mdn (IQR)			Mdn (IQR)	
Prematurity			Prematurity		
Yes (N=0)	-	-	Yes (N=0)	-	-
No (N=8)	7.63 (1.64)		No (N=8)	8.46 (1.15)	
Birth weight classification			Birth weight classification		
SGA (N=0)	-		SGA (N=0)	-	
AGA (N=7)	7.50 (2.00)		AGA (N=7)	8.42 (0.92)	-
LGA (N=1)	-	-	LGA (N=1)	-	
Birth length classification			Birth length classification		
SGA (N=0)			SGA (N=0)	-	
AGA (N=6)	-	-	AGA (N=6)	8.84 (1.35)	-
LGA (N=2)			LGA (N=2)	8.38 (-)	
Immigrant			Immigrant		
Yes (N=0)	-	-	Yes (N=0)	-	-
No (N=8)	7.63 (1.64)		No (N=8)	8.46 (1.15)	
Personal history			Personal history		
Yes (N=6)	7.75 (2.75)	U = 7.00; P=>0.990	Yes (N=6)	8.84 (1.18)	U=12.00; P=0.071
No (N=2)	7.59 (-)	r = 0.12	No (N=2)	8.21 (-)	r=0.71
Development changes			Development changes		
Yes (N=2)	8.00 (0.00)	U = 7.00; P=0.267	Yes (N=2)	9.34 (-)	U=6.00; P=0.533
No (N=4)	6.75 (4.13)	r = 0.60	No (N=4)	8.46 (1.15)	r=0.38
Weight excess			Weight excess		
Yes (N=4)	6.75 (4.13)	U = 1.00; P=0.267	Yes (N=4)	8.46 (1.15)	U=2.00; P=0.533
No (N=2)	8.00 (0.00)	r = -0.60	No (N=2)	9.34 (-)	r=-0.38
Family history of PP			Family history of PP		
Yes (N=0)	-	-	Yes (N=0)	-	-
No (N=8)	7.63 (1.64)		No (N=8)	8.46 (1.15)	
BMI classification			BMI classification		
< 2SD (N=2)	7.88 (0.50)	U = 4.00; P=0.343	< 2SD (N=2)	8.71 (1.23)	U=6.00; P=0.686
≥ 2SD (N=6)	6.75 (4.13)	r = -0.42	≥ 2SD (N=6)	8.46 (1.15)	r=-0.20
BA classification			BA classification		
Similar (N=2)	7.00 (-)	U = 6.00; P=>0.990	Similar (N=2)	9.50 (-)	U=1.00; P=0.143
Advanced (N=6)	7.63 (1.69)	r =0.00	Advanced (N=6)	8.38 (0.52)	r = -0.59
Number of initial pubertal signs			Number of initial pubertal signs		
1 (N=2)	5.38 (-)	U = 3.00; P=0.429	1 (N=2)	8.34 (-)	U=3.00; P=0.429
>1 (N=6)	7.75 (0.94)	r = -0.36	>1 (N=6)	8.80 (1.27)	r = -0.25
Increased growth rate as firs sign			Increased growth rate as firs sign		
Yes (N=3)	7.50 (-)	U = 7.00; P=>0.990	Yes (N=3)	9.17 (-)	U=4.00; P=0.393
No (N=5)	7.75 (2.79)	r = -0.05	No (N=5)	8.42 (0.79)	r=-0.37
Pubarche as firs sign			Pubarche as firs sign		
Yes (N=8)	7.63 (1.64)	-	Yes (N=8)	8.46 (1.15)	-
No (N=0)	-		No (N=0)	-	
Increased growth rate as firs sign			Increased growth rate as firs sign		
Yes (N=3)	8.00 (-)	U = 4.00; P=0.393	Yes (N=3)	8.42 (-)	U=7.00; P=>0.990
No (N=5)	7.50 (3.38)	r = -0.38	No (N=5)	8.50 (1.25)	r=-0.05

Continuation of Table 5. Comparison of the Onset Age of Puberty and Age at First Consultation with Sociodemographic, Clinical, and Analytical Variables in Boys

Variables	Pubertal onset age (N=8)	Test statistics	Variables	Age at 1st consultation (N=8)	Test statistics
	Mdn (IQR)			Mdn (IQR)	
Accelerated growth as additional sign			Accelerated growth as additional sign		
Yes (N=5) No (N=3)	7.75 (2.79) 7.50 (-)	U = 7.00; P=>0.990 r = -0.05	Yes (N=5) No (N=3)	8.42 (0.79) 9.17 (-)	U = 4.00; P=0.393 r = -0.37
Pubarche as additional sign			Pubarche as additional sign		
Yes (N=0) No (N=8)	- 7.63 (1.64)	-	Yes (N=0) No (N=8)	- 8.46 (1.15)	-
Accelerated growth as additional sign			Accelerated growth as additional sign		
Yes (N=0) No (N=8)	- 7.63 (1.64)	-	Yes (N=0) No (N=8)	- 8.46 (1.15)	-
Number of pubertal signs			Number of pubertal signs		
≤ 2 (N=5) > 2 (N=3)	7.50 (3.38) 8.00 (-)	U = 4.00; P=0.393 r = -0.38	≤ 2 (N=5) > 2 (N=3)	8.50 (1.25) 8.42 (-)	U= .00; P=>0.990 r = -0.05
Tanner stage - gonads			Tanner stage - gonads		
≤ 2 (N=2) > 2 (N=5)	7.59 (-) 7.50 (3.50)	U = 5.00; P=>0.990 r =0.00	≤ 2 (N=2) > 2 (N=5)	8.21 (-) 9.17 (1.25)	U=10.00; P=0.095 r =0.73
Tanner stage - pubic hair			Tanner stage - pubic hair		
≤ 2 (N=6) > 2 (N=2)	7.63 (0.94) 5.50 (-)	U = 5.00; P=0.857 r = -0.12	≤ 2 (N=6) > 2 (N=2)	8.38 (1.35) 8.84 (-)	U=8.00; P=0.643 r =0.24
GnRH test			GnRH test		
Yes (N=4) No (N=4)	7.46 (1.33) 8.00 (3.75)	U=4.00; P=0.343 r = -0.42	Yes (N=4) No (N=4)	8.29 (1.27) 8.84 (0.98)	U=4.00; P=0.343 r = -0.41
Neuroimage			Neuroimage		
Yes (N=7) No (N=1)	7.50 (2.00) -	-	Yes (N=7) No (N=1)	8.42 (0.92) -	--
Neuroimage exam			Neuroimage exam		
MRI (N=7) CT (N=0)	7.50 (2.00) -	-	MRI (N=7) CT (N=0)	8.42 (0.92) -	-
Neuroimage abnormalities			Neuroimage abnormalities		
Yes (N=3) No (N=4)	6.00 (-) 7.88 (0.50)	U=1.00; P=0.114 r = -0.67	Yes (N=3) No (N=4)	8.50 (-) 8.34 (0.79)	U=3.00; P=0.400 r = -0.40
PPC classification			PPC classification		
Idiopathic (N=7) Secondary (N=1)	7.75 (0.58) -	-	Idiopathic (N=7) Secondary (N=1)	8.42 (1.25) -	-
Treatment			Treatment		
Yes (N=8) No (N=0)	7.63 (1.64) -	-	Yes (N=8) No (N=0)	8.46 (1.15) -	-
aGnRH			aGnRH		
Triptorrelin (N=6) Leuprorrelin (N=2)	7.63 (0.94) 5.50 (-)	U=5.00; P=0.857 r = -0.12	Triptorrelin (N=6) Leuprorrelin (N=2)	8.38 (1.35) 8.84 (-)	U=4.00; P=0.643 r = -0.24
Administration			Administration		
Quarterly (N=8) Monthly (N=0)	7.63 (1.64) -	-	Quarterly (N=8) Monthly (N=0)	8.46 (1.15) -	-

Discussion

Only girls showed a family history of CPP statistically different from boys. This finding is consistent with a recent article comparing sporadic, familial, and adoption-related CPP, which determined a similar girls/boys ratio for sporadic (219/9) and familial forms (78/4). The higher prevalence of family history in girls might be related to the predominantly female nature of CPP in all its forms. The mentioned article also detected an association between familial forms and earlier referrals, reflecting greater attention and concern from families and professionals regarding the increased risk of CPP (17). This could explain the significantly lower age at referral detected in girls (7.65 years). The anticipation in referrals for girls points to an earlier onset of puberty, contributing to the current debate on the diagnosis age. Some studies suggest bringing forward the onset age of puberty in girls to 7 years (18, 19).

The mean ages of PO in girls were identical to those reported in a recent study with the Portuguese population (6.4±1.6 years), indicating a national trend toward earlier puberty. Significant differences were noted in the median ages of PO between girls and boys, consistent with normal pubertal physiology (20).

Boys exhibited a high percentage of idiopathic cases (87.5%), approaching the girls' value, showing no differences in etiology. Recent literature suggests an increase in male CPP cases, mainly due to a rise in idiopathic cases. A recent study reported 79% idiopathic CPP cases, much higher than previously reported. This trend might be linked to increased awareness of this pathology, leading to greater detection. Despite not being significant, boys showed a greater delay in referral, possibly due to the harder-to-identify pubertal signs in boys, such as increased testicular volume (21, 22).

Regarding the difference between the SDS of height prediction and final height, a significantly higher value was found in boys, primarily associated with the high height prediction (180.13 cm) and its SDS (0.53). This result aligns with a study on boys, which found that during the diagnosis of precocious puberty, the height prediction was higher than the final height, and this relationship persisted throughout treatment with aGnRH. The authors explained this result by the greater delay in bone maturation in boys, with a dissociation between the increase in sex hormones and their effect on bone age. Thus, they believe that bone age is less advanced at diagnosis, contributing to an exaggerated height prediction calculation using the Bayley-Pinneau method. This sex difference might indicate a more pronounced impact of precocious puberty on height prediction in girls; however, more studies are needed to confirm this assertion (23).

A study evaluated baseline gonadotropin levels in non-CPP children across different pubertal stages, finding higher baseline LH values from Tanner stage 3 and baseline FSH values at all stages in girls. In this study, baseline LH and FSH values were also significantly higher in girls, just like LH and FSH peak values. However, more studies are needed to evaluate the need for establishing different reference values for these laboratory data for both sexes (24, 25).

Regarding treatment initiation, boys showed a 7-month delay from the first consultation compared to the 3-month delay in girls, a non-significant difference. Literature indicates that boys are more associated with organic causes of CPP, recommending cerebral MRI in all cases, possibly delaying treatment initiation (1, 8).

Concerning initial clinical manifestations, thelarche showed an association with PO age, suggesting that later thelarche is more likely associated with CPP. This finding is consistent with studies suggesting an association between older thelarche presentation ages and progression to CPP. However, this topic remains controversial, with no consensus in the literature, and some studies do not find this association. Conversely, pubarche and growth acceleration as initial clinical manifestations are associated with earlier puberty onset ages. These findings are crucial as CPP in girls is sometimes mistakenly defined only by thelarche, potentially delaying investigation in these children (26, 27).

Data from the first consultation showed menarche in 4 girls at significantly older ages. On average, menarche occurs 2 years after puberty onset,

and given the CPP definition, menarche around 10 years would be expected, consistent with the results obtained (7). It was expected that with increasing age, clinical presentation would be more complex, but no association was found between age and the number of initial or total pubertal signs. A observational study on girls with CPP found no differences in PO age based on the number of pubertal signs, similar to our results. These findings may support the idea that there is no relationship between the number of pubertal signs and age (28).

It was also observed that the earlier the first signs of puberty, the longer the time interval to referral. This association might reflect a more expectant attitude in younger children, opting for surveillance over time to assess pubertal sign progression.

The increase in sex hormones significantly impacts bone maturation, causing a gap between chronological age and BA. CPP progression in children can be rapid, with accelerated bone maturation, or slower with less advanced maturation (16). This study found a positive correlation between chronological age at first consultation and BA, indicating no significant gap between them, pointing to slower CPP progression.

Several studies report a decreasing trend in pathological findings in cerebral MRI with increasing age. From 6 years old, few girls have abnormalities, making neuroimaging controversial. These MRI findings and secondary CPP causes are often associated with younger puberty onset ages. However, this study found no differences between PO ages and the first consultation regarding imaging abnormalities. Despite discordant data with the literature, the median PO age and mean age at the first consultation being over 6 years may have limited the sample distribution, with fewer younger girls expected to show these abnormalities. Regarding secondary etiology, it presented at younger ages, but the lack of significant results might be due to the small sample size (N=4) (1, 12, 29).

In this study, the BMI z-score was 1.19±0.92, similar to a 2014 study (1.1±0.8) for children with CPP. It was observed that the younger the PO age, the higher the BMI z-score, as described in the literature. This result aligns with studies suggesting obesity is associated with CPP, correlating with the age at which puberty occurs, despite poorly defined pathophysiological mechanisms (30-33).

The GnRH stimulation test was performed at significantly younger ages (7.69 years) at the first consultation. However, after 2019, eight girls undergoing the test had pubertal basal LH levels, raising the question of the unnecessary use of these tests. Several studies have demonstrated the diagnostic value of basal LH, considered a good predictor of a positive GnRH test. This test should be reserved for cases where, despite prepubertal basal LH values, there is high clinical suspicion, such as progressive pubertal signs, growth acceleration, and advanced BA. The reason for the continued use of this test might be the poorly defined basal LH reference values, varying between 0.1-1 IU/L in the literature, and low sensitivity and/or specificity not allowing diagnosis confirmation (7, 34-37).

Basal and peak LH and FSH values did not correlate with PO age, indicating independence from age and relating to the functioning of the HPG axis regulated by different feedback mechanisms controlling gonadotropin pulsatile release. Estradiol and testosterone also did not correlate with PO age, expected as they are regulated by gonadotropins (2).

Regarding treated girls, the mean age at the first consultation was 8.08 years, with treatment initiated about 3 months later. Studies show that after 8 years, the benefit of GnRH analogs is reduced, with better results when started at younger ages. Untreated girls had a higher mean age, albeit not significant, demonstrating progress in attempting to timely initiate treatment for better results (5, 14).

Conclusion

This study demonstrated an association between PO age and initial clinical manifestations such as thelarche, pubarche, growth acceleration, and BMI z-score. The age at the first consultation was associated with the GnRH test, BA, and along with

PO age, correlated with referral age and the interval between referral and the onset of pubertal signs. Additionally, no differences were found between ages and birth anthropometry, gestational age, number of pubertal signs, auxological parameters at the first consultation, growth velocity, laboratory parameters, and CPP etiology, demonstrating the independence of these variables.

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