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ORIGINAL ARTICLE

# Trend of Central Precocious Puberty before and during SARS-CoV-2 pandemic

## Comportamiento de la pubertad precoz central antes y durante la pandemia de SARS-CoV-2

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**What do we know about the subject matter of this study?**

Since the beginning of the pandemic, several endocrinology referral centers around the world have reported a significant increase in the diagnosis of central precocious puberty, as well as an increase in cases of rapidly progressive puberty.

**What does this study contribute to what is already known?**

The main contribution of our study is that it is one of the first to address this issue in Latin America. To this end, we compared two groups of patients diagnosed with central precocious puberty (CPP): one before the pandemic and one during it. The results show a higher frequency of CPP onset in girls during the pandemic period and an earlier age of presentation in boys.

## Abstract

During the SARS-CoV-2 pandemic, there was an increase in the diagnosis of endocrine disorders, notably the onset of central precocious puberty (CPP). **Objective:** To describe and compare the frequency of precocious puberty onset in two periods, before and during the SARS-CoV-2 pandemic**. Patients and Method:** Medical records with a confirmed diagnosis of CPP were reviewed from patients treated at *Hospital Las Higueras*, in Talcahuano, during two periods: 2019-2020 (Group 1, before the pandemic) and 2021-2022 (Group 2, during the pandemic). The variables studied were age at diagnosis, sex, age at onset of puberty, Body Mass Index (BMI) Z-score, Tanner stage, bone age, Luteinizing Hormone (LH), uterine size, and ovarian volumes at diagnosis. **Results:** There were 98 cases of precocious puberty in Group 1 (96.9% females) and 162 cases in

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Group 2 (95% females), showing a significant increase in CPP cases during the pandemic period ($p < 0.001$). Females presented with a higher BMI Z score and more advanced Tanner stage and bone age at diagnosis during the pandemic ($p = 0.049$, 0.07, and 0.06, respectively). Males were younger at diagnosis of precocious puberty in Group 2 ($p = 0.019$). **Conclusions**: Our data show a higher frequency of CPP onset in females and an earlier age at presentation in males during the pandemic period.

## Introduction

Puberty is a period of transition during which secondary sexual characteristics and reproductive capacity are acquired. The activation of the hypothalamic-pituitary-gonadal (HPG) axis is caused by a change in the secretion pattern of gonadotropin-releasing hormone (GnRH), which leads to an increase in the frequency and amplitude of the pulsatile pattern of gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), ultimately leading to the production of sex hormones in the gonads responsible for pubertal changes[1,2].

Central precocious puberty (CPP) refers to the early activation of the HPG axis and manifests as breast development in girls or increased testicular volume (≥ 4 cc) in boys before the normal age, which is 8 years in girls and 9 years in boys[3]. Its estimated prevalence is approximately 1 in 5,000-10,000, being more common in girls than in boys, with studies indicating ratios ranging from 10-20:1, respectively[1,4].

In relation to the predictors of puberty onset, it has been reported that genetics explains between 50% and 80% of the variation in pubertal timing[3]. Considering that pubertal development has become increasingly earlier in recent decades, a potential role has been attributed to environmental factors such as obesity, diet, adoption, low socioeconomic status, sleep, stress, screen time, exercise, and sedentary lifestyle[5]. Additionally, during the SARS-CoV-2 pandemic, there were radical changes in lifestyle due to lockdown, with less physical activity and more time spent in front of screens, mainly for schooling and mobile device use, leading to a marked increase in CPP worldwide[6,7].

Since early 2020, and in the context of the COVID-19 pandemic, several studies have observed an increase in referrals for suspected precocious puberty[7-17], both in the number of cases of CPP and rapidly progressive puberty, mainly in girls[9]. This new trend was first reported in the literature in November 2020 at the Meyer Children's University Hospital in Florence, Italy. The medical team in charge hypothesized that this phenomenon could be explained by the factors mentioned above, such as increased BMI or screen use, which occurred during lockdown, but a causal relationship could not be established given the limitations of the study[6,10]. Subsequently, new reports emerged from different countries, such as Turkey[11], Italy[12], China[13], India[14], Spain[15], Brazil[16], and South Korea[17], where the following were identified as possible triggering factors: increased BMI, sedentary lifestyle, overuse of screens, and greater exposure to psychosocial stress[18].

The objective of this study was to determine the frequency of onset of CPP in two periods: before the pandemic (2019-2020) and during the COVID-19 lockdown (2021-2022).

## Patients and Method

### Design

Descriptive cross-sectional study, approved by the Ethical-Scientific Committee of the Talcahuano Health Service (Official Letter No. 2262), which exempted the study from the requirement to obtain informed parental consent, given the study design and the characteristics of the data used, as they do not allow identification of the participants.

### Population

The study population consisted of patients diagnosed with CPP treated at *Hospital Las Higueras* in Talcahuano, who were prescribed Triptorelin, the only drug used in our center for the treatment of this condition. Female patients who had breast development (Tanner 2 or higher) before the age of 8, associated with at least two of the following criteria, were included: basal LH ≥ 0.2 mIU/ml (ICMA), bone age advancement > 1 year or 2 standard deviations for age, pelvic ultrasound with uterus ≥ 35 mm in length with ovaries ≥ 2 cc. For male patients, the criteria used were testicular volume ≥ 4 cc associated with at least one of the following: basal LH ≥ 0.2 mIU/mL (ICMA) and/or bone age advancement > 1 year or 2 standard deviations for age (1.19).

At the same time, patients who received this drug and had a diagnosis other than precocious puberty, such as prostate cancer, puberty suppression thera-

py in cases of transsexuality, as adjuvant treatment in growth disorders, and rapidly progressive normal puberty, were excluded.

For this study, the selected sample considered two periods: the first period from April 1, 2019, to March 31, 2020 (the year before the pandemic, group 1) and the second from April 1, 2021, to March 31, 2022 (COVID-19 lockdown period, group 2).

**Variables**

The variables considered were sex, chronological age at which pubertal development events occurred (thelarche, pubarche, adrenarche, gonadarche); chronological age, body mass index (BMI) Z score, and height Z score, Tanner stage of breast and pubic hair, and bone age at diagnosis. The age at the onset of thelarche, adrenarche, and pubarche was defined as that reported by the parents and/or when detected during the visit. The age at the onset of gonadarche was defined as the presence of testicular volume ≥ 4 cc detected during the visit. In addition, the time elapsed between the chronological age at the onset of thelarche or gonadarche and the age at diagnosis was compared, as well as the difference between bone age and chronological age at the time of initial evaluation. Additionally, serum levels of LH (mIU/mL, ICMA), FSH (mIU/mL, ICMA), estradiol (pg/mL, ICMA), or testosterone (ng/mL, hexokinase) at diagnosis were reported, and in girls, uterine size (mm) and ovarian volumes (cc) were reported. The difference in all variables was analyzed according to the study subgroups: patients diagnosed before and during the pandemic.

**Statistical analysis**

The normality of the variables was analyzed using the Kolmogorov-Smirnov test. The variables were expressed as mean and standard deviation (SD). Categorical variables were expressed as absolute values and percentages. Continuous variables were compared using t-tests or Wilcoxon tests, depending on the distribution of the data. Categorical variables were compared using the chi-square ($\chi^2$) test or Fisher's exact test (F) in cases with fewer than 5 elements per cell. A p-value $< 0.05$ was considered statistically significant. All statistical analyses were performed using Stata version 17 software (StataCorp, College Station, TX, USA).

## Results

Of a total of 260 clinical records analyzed, 98 patients (37.7%) had onset of precocious puberty in the period before the pandemic, and 162 (62.3%) during the COVID-19 lockdown period ($p < 0.001$). In terms of sex distribution, 95 patients (96.9%) in group 1 and 154 (95%) in group 2 were female.

In female patients (Table 1), the mean age of diagnosis of CPP was 8.3 ± 0.8 years in group 1 and 8.3 ± 0.8 years in group 2 (p=0.380). There was no statistically significant difference in the chronological age of presentation of thelarche, with a mean of 7.4 ± 1.1 years in the first group, compared to 7.3 ± 0.9 years in the second group ($p = 0.113$). However, a more advanced Tanner stage was evident at diagnosis in group 2 ($p = 0.007$).

A total of 19 girls (8%) had menarche before diagnosis, 4 (4%) in the pre-pandemic group, while 15 (10%) were in the group diagnosed during lockdown ($p = 0.110$). In addition, the age of menarche was lower in the group diagnosed during the pandemic compared to the group diagnosed previously (8.8 ± 0.6 vs. 9.4 ± 0.5 years; $p = 0.109$).

Regarding the difference between bone age and chronological age at diagnosis, a median of 1.8 (1.3, 2.3) years was observed for group 1 and 2.2 (1.5, 2.7) years for group 2 ($p = 0.006$).

A higher BMI z-score was found during the pandemic in girls (1.2 ± 1.0 vs. 1.1 ± 0.9, $p = 0.049$), with a higher proportion of obesity diagnoses compared to the pre-pandemic period. Other variables related to pubertal development in females did not reach statistical significance, including the chronological age of pubarche ($p = 0.138$) and adrenarche ($p = 0.191$).

In group 1, the mean LH, FSH, and estradiol levels were 0.95 ± 1.32 mIU/mL, 22.7 ± 18.2 mIU/mL, and 3.0 ± 2.2 pg/mL, respectively, while in group 2, the values were 1.35 ± 3.14 mIU/mL, 21.6 ± 18.9 mIU/mL, and 3.4 ± 2.4 pg/mL, respectively, with no statistical significance. When analyzing girls who had LH ≥ 0.2, 74% reached this value in the pre-pandemic period and 75% during the pandemic.

In pre-pandemic girls, the mean right ovarian volume was 2.6 ± 1.3 cc, and the left ovarian volume was 2.4 ± 1.4 cc. 71% reached values ≥ 2 cc in the right ovary, and 60.2% in the left ovary. The mean uterine size was 42.6 ± 9.0 cm, with a size ≥ 35 mm in 83.5%. In group 2, girls had a mean right ovarian volume of 3.0 ± 4.6 cc and left ovarian volume of 2.5 ± 1.8 cc. 66% reached values ≥ 2 cc in the right ovary, and 62.2% in the left ovary. The mean uterine size was 45.2 ± 10.5 cm, and those with a size ≥ 35 mm were 90.7%.

In relation to male patients (Table 2), the mean age at diagnosis of CPP was 10.3 ± 0.5 years in group 1, while in group 2 it was 8.6 ± 0.9 years ($p = 0.019$). The onset of gonadarche, adrenarche, and pubarche was not significant. There was no statistical difference in bone age ($p = 0.472$) or the difference between bone age and chronological age ($p = 0.305$).

**Table 1. Characteristics of girls with precocious puberty at diagnosis**

| Variable | Total N = 249[1] | Before pandemic N = 95 (38%)[1] | After pandemic N = 154 (62%)[1] | P value |
|---|---|---|---|---|
| Age at diagnosis (years) | 8.3 (0.8) | 8.3 (0.8) | 8.3 (0.8) | 0.380 |
| Age at thelarche (years) | 7.3 (1.0) | 7.4 (1.1) | 7.3 (0.9) | 0.113 |
| Age at adrenarche (años) | 6.9 (1.2) | 7.0 (1.4) | 6.8 (1.1) | 0.191 |
| Age at pubarche (años) | 7.7 (1.0) | 7.8 (1.1) | 7.6 (1.0) | 0.138 |
| Menarche at diagnosis | 19 (8%) | 4 (4%) | 15 (10%) | 0.110 |
| Age at menarche | 9.0 (0.6) | 9.4 (0.5) | 8.8 (0.6) | 0.109 |
| Anthropometry | | | | |
| Height Z score | 0.7 (1.1) | 0.7 (1.1) | 0.7 (1.1) | 0.906 |
| BMI Z score | 1.2 (0.9) | 1.1 (0.9) | 1.2 (1.0) | 0.049 |
| Nutritional diagnosis | | | | 0.090 |
| Malnutrition | 3 (1%) | 1 (1%) | 2 (1%) | |
| Risk of malnutrition | 2 (1%) | 1 (1%) | 1 (1%) | |
| Normal | 83 (33%) | 37 (39%) | 46 (30%) | |
| Overweight | 119 (48%) | 47 (49%) | 72 (47%) | |
| Obesity | 42 (17%) | 9 (9%) | 33 (21%) | |
| Breast Tanner stage | | | | 0.007 |
| I | - | - | - | |
| II | 36 (14%) | 20 (21%) | 16 (10%) | |
| III | 162 (65%) | 64 (67%) | 98 (64%) | |
| IV | 48 (19%) | 10 (11%) | 38 (25%) | |
| V | 3 (1%) | 1 (1%) | 2 (1%) | |
| Pubic hair Tanner stage | | | | 0.235 |
| I | 95 (38%) | 40 (42%) | 55 (36%) | |
| II | 81 (33%) | 34 (36%) | 47 (31%) | |
| III | 65 (26%) | 18 (19%) | 47 (31%) | |
| IV | 8 (3%) | 3 (3%) | 5 (3%) | |
| V | - | - | - | |
| Bone age (years) | 10.5 (10.0. 11.0) | 10.5 (10.0. 11.0) | 10.5 (10.0. 11.0) | 0.192 |
| Bone age – Chronological age | 2.1 (1.5. 2.6) | 1.8 (1.3. 2.3) | 2.2 (1.5. 2.7) | 0.006 |
| Right ovarian volume (cc) | 2.8 (3.7) | 2.6 (1.3) | 3.0 (4.6) | 0.530 |
| < 2 cc | 78 (32.1%) | 27 (29.0%) | 51 (34.0%) | 0.480 |
| ≥ 2 cc | 165 (67.9%) | 66 (71.0%) | 99 (66.0%) | |
| Left ovarian volume (cc) | 2.5 (1.7) | 2.4 (1.4) | 2.5 (1.8) | 0.540 |
| < 2 cc | 93 (38.6%) | 37 (39.8%) | 56 (37.8) | 0.787 |
| ≥ 2 cc | 148 (61.4%) | 56 (60.2%) | 92 (62.2%) | |
| Uterine lenght (cm) | 44.2 (10.0) | 42.6 (9.0) | 45.2 (10.5) | 0.170 |
| < 35 mm | 29 (12.0%) | 15 (16.5%) | 14 (9.3%) | 0.105 |
| ≥ 35 mm | 213 (88.0%) | 76 (83.5%) | 137 (90.7%) | |
| Basal LH (mUI/ml) | 1.20 (2.6) | 0.95 (1.32) | 1.35 (3.14) | 0.828 |
| LH < 0,2 | 60 (25%) | 24 (26%) | 36 (25%) | 0.879 |
| LH ≥ 0,2 | 177 (75%) | 68 (74%) | 109 (75%) | |
| FSH (mUI/ml) | 22.0 (18.6) | 22.7 (18.2) | 21.6 (18.9) | 0.319 |
| Estradiol (pg/ml) | 3.2 (2.3) | 3.0 (2.2) | 3.4 (2.4) | 0.296 |

[1]Mean (SD); n (%). BMI: Body mass index. P value among group participants: < 0,001.

The mean pre-pandemic LH was 1.0 ± 0.2 mIU/mL, and those who reached a value ≥ 0.2 were 100%. During the pandemic, the mean was 0.5 ± 0.6 mIU/mL, and 75% reached a value ≥ 0.2.

No patients had elevated levels of BHCG or alpha-fetoproteins. In addition, all had normal serum concentrations of 17 OH progesterone, DHEAS, androstenedione, and testosterone (data not shown).

## Discussion

Our study showed a higher incidence of CPP during the COVID-19 lockdown period compared to the pre-pandemic period. This phenomenon was also described in other reviews from countries such as Spain, Italy, Turkey, China, and Brazil, which showed an increase in the incidence of CPP during the pandemic[7,8,18,20,21].

The results of our research suggest that female patients diagnosed with CPP during the pandemic had a more advanced Tanner stage at diagnosis compared to the pre-lockdown group, even though the age of thelarche was similar in both groups. In addition, in patients who had their CPP onset with menarche, it occurred at an earlier age in the group during the pandemic, which could be due not only to a delay in diagnosis but also to a more rapid progression of puberty. In a study conducted in Brazil, a shorter interval was reported between the perception of thelarche by parents and the diagnosis of CPP, possibly due to increased observation by caregivers due to the lockdown

**Table 2. Characteristics of boys with precocious puberty at diagnosis**

| Variable | Total N = 11[1] | Before pandemic N = 3 (27%)[1] | After pandemic N = 8 (73%)[1] | P value |
|---|---|---|---|---|
| Age at diagnosis (years) | 9.1 (1.1) | 10.3 (0.5) | 8.6 (0.9) | 0.019 |
| Age at gonadarche (years) | 8.7 (1.1) | 9.6 (1.1) | 8.4 (1.0) | 0.260 |
| Age at adrenarche (years) | 7.9 (1.8) | 9.3 (1.6) | 7.4 (1.7) | 0.381 |
| Age at pubarche (years) | 8.4 (1.3) | 9.3 (0.7) | 7.5 (1.2) | 0.200 |
| Anthropometry | | | | |
| Height Z score | 0.5 (1.3) | -0.5 (1.4) | 0.9 (1.1) | 0.194 |
| BMI Z score | 1.8 (0.7) | 1.2 (0.8) | 2.0 (0.5) | 0.194 |
| Nutritional diagnosis | | | | 0.079 |
| Malnutrition | - | - | - | |
| Risk of malnutrition | - | - | - | |
| Normal | 2 (18%) | 2 (67%) | 0 (0%) | |
| Overweight | 4 (36%) | 0 (0%) | 4 (50%) | |
| Obesity | 5 (45%) | 1 (33%) | 4 (50%) | |
| Pubic hair Tanner stage | | | | 0.152 |
| I | 5 (45%) | 0 (0%) | 5 (63%) | |
| II | 2 (18%) | 1 (33%) | 1 (13%) | |
| III | 3 (27%) | 1 (33%) | 2 (25%) | |
| IV | 1 (9%) | 1 (33%) | 0 (0%) | |
| V | - | - | - | |
| Testicular volumen at diagnosis (cc) | 4 (5.1) | 12 (8) | 5.3 (2.3) | 0.046 |
| Bone age (year) | 11.3 (2.0) | 12.0 (1.7) | 11.0 (2.1) | 0.472 |
| Bone age – Chronological age | 2.2 (1.3) | 1.7 (1.3) | 2.4 (1.3) | 0.305 |
| Basal LH (mUI/ml) | 0.6 (0.5) | 1.0 (0.2) | 0.5 (0.6) | 0.261 |
| LH < 0.2 | 2 (20%) | 0 (0%) | 2 (25%) | 0.999 |
| LH ≥ 0.2 | 8 (80%) | 2 (100%) | 6 (75%) | |
| FSH (mUI/ml) | 1.2 (0.5) | - | 1.2 (0.5) | - |
| Testosterone (ng/ml) | 1.7 (5.0) | 0.3 (0.0) | 2.1 (5.6) | 0.145 |

[1]Mean (SD); n (%). P value among group participants: 0,131

and/or a faster rate of puberty progression[16]. However, other hypotheses suggest the involvement of environmental factors that trigger or favor the progression of CPP, such as higher BMI, increased exposure to electronic devices, reduced physical activity, psychological stress, and changes in sleep and eating habits[5,7]. This phenomenon was also demonstrated in a study conducted at Meyer Children's University Hospital[20], which reported more advanced Tanner stages at diagnosis after lockdown. At the same time, another study conducted in Turkey reported an increase in cases of menarche at diagnosis[21], which is relevant given that early menarche is associated with an increased risk of metabolic comorbidities, cardiovascular disease, and breast cancer[22-25].

Economic and transportation barriers to accessing healthy food contributed to a marked increase in obesity rates during the pandemic[6,26]. Several studies have hypothesized that factors involved in obesity and insulin resistance generate greater expression and release of GnRH, alterations in sex hormone-binding globulin (SHBG), and overproduction of aromatase, among other effects[27]. However, studies show dissimilar results regarding the relationship between obesity and the diagnosis of precocious puberty[7,18]. Reports from Turkey and China recorded statistically significant differences in relation to the increase in BMI between the pre- and during-pandemic periods[7,28,29], which is consistent with our findings in girls. In contrast, there are studies that did not report significant changes in BMI[8,13]. Although in boys, in our report, the BMI z-score almost doubled, it was not significant, which is probably explained by the small number of boys in our study.

Regarding the use of electronic devices, studies describe that prolonged exposure to them and the disruption of melatonin levels secondary to their use, together with poor sleep hygiene, could have a proportional correlation with the onset of puberty. This theory is reinforced by an Italian study that indicates that patients with CPP have a higher rate of sleep disturbances and go to bed later than the control group after quarantine[30]. Due to the pandemic, there was a significant increase in screen use among school children internationally[31] and a decrease in the quality of their sleep hygiene[32], which can also be extrapolated to our population[33].

Another relevant factor is psychosocial stress, which is thought to intensify GnRH secretion in predisposed females. In addition, a direct correlation has been observed between increased anxiety symptoms and an increase in cases of CPP[34.35]. In the context of lockdown, factors such as isolation, social exclusion, and widespread fear have had a significant psychological impact on children and adolescents, increasing their susceptibility to acute stress disorders[36]. This phenomenon has also affected the school population in Chile[37].

Other factors that have been reported to be associated with precocious puberty during the pandemic are vitamin D deficiency[10] and a direct effect of SARS-CoV-2 infection[5,7].

An Italian study of girls reported lower baseline LH concentrations and slower bone age advancement during the onset of the pandemic compared to subsequent years[8]. This is similar to what we observed in our study, although the LH levels did not reach statistical significance.

Regarding our study, it is worth mentioning that the lowest basal LH cut-off value reported in the literature was used for the diagnosis of CPP. This approach was adopted because lower levels than the suggested cut-off do not allow this diagnosis to be ruled out, and because LHRH stimulation testing is not available at our center[1,2,19, 38].

Regarding precocious puberty in males, we found that its incidence increased more than doubled during the second period and that the age of diagnosis was earlier, as in other reports[7]. However, a limitation of our study is the small number of male patients.

## Conclusions

The findings of our study are similar with those reported in international literature regarding the increase in cases of precocious puberty during the pandemic. Although the exact cause of this phenomenon is not known, several reviews suggest the role of triggering or facilitating factors in the progression of CPP, such as increased BMI, use of electronic devices, and psychosocial stress. Further studies with larger samples are needed to evaluate this increase on a larger scale and correlate it with specific pathogenic factors.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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