

# Impact of the COVID-19 pandemic on central precocious puberty: a retrospective cohort study from Türkiye

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## ABSTRACT

**Objective:** This study aimed to investigate the clinical and demographic characteristics of girls diagnosed with central precocious puberty (CPP) before and during the COVID-19 pandemic to identify potential changes in incidence and contributing factors.

**Methods:** A retrospective cohort study was conducted in two pediatric endocrinology centers in Türkiye. Girls treated with GnRH Gonadotropin-Releasing Hormone (GnRH) analogs between March 2018 and March 2022 were categorized into two groups: the pre-pandemic group (2018–2020) and the pandemic group (2020–2022). Clinical, anthropometric, and hormonal data were analyzed. Patients with organic lesions, genetic disorders, or medications affecting puberty were excluded.

**Results:** CPP diagnoses increased significantly during the pandemic, rising from 0.5% (32/6,446) in the pre-pandemic period to 2.1% (160/7,436) during the pandemic. Basal, peak LH, and peak LH/peak FSH levels were significantly higher in the pandemic group ( $p < 0.01$ ), while BMI and Tanner stages showed no significant differences.

**Conclusion:** The study highlights a marked increase in CPP diagnoses during the pandemic. Elevated basal and peak LH levels suggest a more pronounced hormonal activation, potentially influenced by pandemic-related factors. Further research is necessary to elucidate the underlying mechanisms, including environmental and psychological contributors.

**Keywords:** central precocious puberty, COVID-19 pandemic, GnRH analogs, pediatric endocrinology, lifestyle changes

## INTRODUCTION

Various measures have been implemented to mitigate the impact of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, which has affected the entire world. In line with these measures, stay-at-home orders and school closures have had both physiological and psychological effects on children.<sup>1</sup> Moreover, obesity rates have increased due to reduced physical activity, disrupted sleep patterns, and altered eating habits.<sup>2</sup> As the

pandemic's impact lessens over time, our understanding of how it affected puberty is improving.

Puberty is a critical period that leads to complex endocrinological changes and enables the attainment of reproductive capacity. Some mechanisms that initiate the pubertal period have not yet been elucidated. However, it is known that changes in energy balance, neurotransmitters, and neuropeptide expression, and genetic and epigenetic factors, contribute to the beginning of pubertal signals.<sup>3</sup>



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Early pubertal maturation could lead to rapid skeletal development and premature epiphyseal closure, which may be associated with a psychological burden due to potential short stature.<sup>4</sup>

Several studies have shown that admissions due to early pubertal changes have increased in different countries during the COVID-19 pandemic.<sup>5,6</sup> Although some studies from Türkiye have shown that the age of onset of pubertal changes started earlier, no differences were found in others.<sup>7,8</sup> Several mechanisms, such as the direct effect of SARS-CoV-2 infection, electronic device use, sedentary lifestyles, obesity, and sleep disturbances, have been hypothesized to explain increased precocious puberty, but the entire mechanism needs clarification.<sup>6,8</sup> This study aimed to compare the clinical and demographic properties of patients with precocious puberty admitted before and after the pandemic.

## METHODS

The study included patients admitted to the Pediatric Endocrinology Departments of Ümraniye Training and Research Hospital and Süleyman Demirel University, located in two different cities in Türkiye. These patients were diagnosed with precocious puberty and treated with GnRH analogs before and after the COVID-19 pandemic. The patients were categorized into two groups: the pre-pandemic group (admitted and started GnRH analog treatment between March 2018 and March 2020) and the pandemic group (admitted and started GnRH analog treatment between March 2020 and March 2022), covering 24 months before and after the start of the pandemic lockdown. The participants' medical records were reviewed retrospectively.

Clinical data, including Tanner staging, anthropometric measurements, and hormonal profiles, were collected. Hormonal profiles included luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), estradiol (E2), and, if available, other hormones such as dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone (17-OHP), prolactin (PRL), and free thyroxine (FT4). Pediatric endocrinologists assessed all patients for pubertal staging according to the Marshall and Tanner criteria.<sup>9</sup> Bone age was determined using left-hand X-rays analyzed with the Greulich-Pyle method.<sup>10</sup> Height, weight, and body mass index data were taken retrospectively from patient files. Body mass index (BMI), height SDS, and weight SDS were calculated using

an online calculator based on Turkish children's growth standards.<sup>11</sup>

Overweight and obesity were defined as BMI values between the 85<sup>th</sup> and 95<sup>th</sup> percentiles and  $\geq 95^{\text{th}}$  percentile for age and gender, respectively.

Central precocious puberty (CPP) in girls was defined as the onset of secondary sexual characteristics before 8 years of age, accompanied by advanced bone age ( $\geq 1$  year above chronological age) and a pubertal response to GnRH stimulation (peak LH  $> 5$  IU/L, peak LH/FSH ratio  $> 1$ , or basal LH  $> 0.3$  IU/L).<sup>6,8,12</sup>

If pubertal changes began after eight years of age but progressed faster than six months between two pubertal stages, these cases were classified as accelerated pubertal development. Only patients diagnosed with CPP and who were initiated on GnRH analogue therapy were included in the study. Cases with slow progression that did not require immediate treatment were excluded.

Patients with organic lesions (e.g., hypothalamo-pituitary tumors), congenital malformations, oncological diseases, neurosurgical or genetic disorders, or medications affecting puberty were excluded from the study.

Serum levels of LH (mIU/mL), FSH (mIU/mL), and estradiol (pg/mL) were measured using the immunochemiluminescence method (ICMA, ADVIA Centaur XPT, Siemens, USA). Samples for FSH and LH during GnRH stimulation tests were obtained at 20, 40, and 60 minutes following intravenous administration of 100  $\mu\text{g}/\text{m}^2$  (maximum 100  $\mu\text{g}$ ) LHRH (LHRH Ferring ampule) if basal FSH and LH levels were inconclusive.

## Ethical approval

This study was approved by the Clinical Research Ethics Committee of the Ministry of Health, University of Health Sciences, Ümraniye Training and Research Hospital on August 25, 2022 (Ethics Committee No: 19659). The study was conducted in accordance with the principles of the Declaration of Helsinki.

## Statistical analysis

The statistical analysis was performed using the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of the data was assessed using the Kolmogorov-Smirnov test. As the data followed a normal distribution, they were expressed as mean  $\pm$  standard deviation. For the comparison of normally distributed data

between two groups, the Independent Samples t-test was used. Categorical variables were analyzed using the Chi-square test. A p-value of <0.05 was considered statistically significant for all tests.

## RESULTS

During the pre-COVID-19 period, 6,446 patients presented various complaints, compared to 7,436 patients during the COVID-19 period. Of these, CPP diagnoses accounted for 32 cases pre-pandemic (0.5%) and 160 cases during the pandemic (2.1%). Notably, the incidence of new CPP cases requiring GnRH analog therapy nearly quadrupled during the pandemic compared to the pre-pandemic period.

The demographic, anthropometric, and clinical characteristics of patients were compared based on their admission periods (pre-pandemic vs. pandemic) (Table 1, Table 2).

Among Tanner stages, stage IV was the most frequent in the pandemic group (26.3%), whereas stage III was the most common in the pre-pandemic group (62.5%). Menarche was reported in 20 (12.5%) patients in the pandemic group and 4 (12.5%) in the pre-pandemic group. Although no statistically significant difference was found in BMI category distribution, the proportion of normal-weight patients was higher in the pandemic group (15.0% vs. 6.3%).

No significant differences were observed between the groups in terms of bone age ( $10.0 \pm 1.7$  vs.  $10.08 \pm 1.4$  years,  $p = 0.33$ ) or BA/CA ratio ( $1.22 \pm 0.13$  vs.  $1.20 \pm 0.12$ ,  $p = 0.26$ ). Additionally, estradiol, basal and peak FSH, prolactin, DHEAS, and TSH levels were similar between groups. However, basal LH ( $2.08 \pm 1.89$  vs.  $1.37 \pm 1.03$  IU/L),

peak LH ( $20.5 \pm 9.1$  vs.  $10.7 \pm 6.5$  IU/L), and peak LH/FSH ratio ( $1.45 \pm 0.35$  vs.  $1.10 \pm 0.30$ ) were significantly higher in the pandemic group (all  $p < 0.01$ ), indicating a more pronounced hormonal activation.

## DISCUSSION

This study observed an increase in the number of admissions, in the diagnosis of CPP, and in the requirement for GnRH therapy during the pandemic compared to the pre-pandemic period. Consistent with our findings, several studies from Italy confirmed the association between the pandemic and the increased incidence of precocious puberty.<sup>8,13,14</sup> Stagi et al. compared cases of precocious puberty during the pandemic period with the same timeframe over the preceding five years and reported a significantly higher rate of newly diagnosed cases during the pandemic (37 cases per year versus  $17.8 \pm 1.3$  cases per year pre-pandemic).<sup>6</sup> Similarly, Verzani et al. found an increase in suspected precocious puberty cases during the pandemic in a retrospective review of consultation reports (215 vs. 87 patients).<sup>13</sup> Studies from Türkiye also support this trend, with Yüksek Acinikli et al. reporting a threefold increase in CPP and rapidly progressive early puberty diagnoses after the pandemic<sup>7</sup>, and Acar et al. documenting that CPP cases more than doubled after the pandemic compared to the previous three years.<sup>15</sup> As supported by this study, a multicenter study by Yeşiltepe Mutlu et al. also reported that the onset of puberty occurred earlier and the need for pubertal suppression therapy increased during the pandemic period compared to the previous year in Turkish children.<sup>8</sup> These findings suggest that the global pandemic, while primarily affecting respiratory health, also had significant effects on the endocrine system.<sup>16</sup>

**Table 1.** Demographic and anthropometric characteristics of CPP patients, comparing pre-pandemic and pandemic groups

Variable	Pre-pandemic (n=32)	Pandemic (n=160)	p-value
Age (years)	$8.35 \pm 1.21$	$8.16 \pm 0.98$	0.27
Weight SDS	$1.04 \pm 0.70$	$1.07 \pm 0.90$	0.34
Height SDS	$0.79 \pm 0.74$	$1.12 \pm 0.94$	0.11
BMI SDS	$0.87 \pm 0.78$	$0.77 \pm 0.98$	0.15
Obesity (%)	62.5	58.8	0.27
Overweight (%)	31.3	26.3	0.23
Normal Weight (%)	6.3	15.0	0.16
Bone Age (years)	$10.0 \pm 1.7$	$10.08 \pm 1.4$	0.33
BA/CA Ratio	$1.22 \pm 0.13$	$1.20 \pm 0.12$	0.26

BA: Bone age, CA: Chronologic age

Pre-pandemic group: patients diagnosed between March 2018 and March 2020 (n = 32).

Pandemic group: patients diagnosed between March 2020 and March 2022 (n = 160).

**Table 2.** Clinical and hormonal features of CPP patients in the pre-pandemic and pandemic groups

Variable	Pre-pandemic (n=32)	Pandemic (n=160)	p-value
Tanner Stage II n (%)	4(12.5)	34(21.3)	0.27
Tanner Stage III n (%)	20(62.5)	64(40.0)	0.31
Tanner Stage IV n (%)	4(12.5)	42(26.3)	0.21
Tanner Stage V n (%)	4(12.5)	20(12.5)	0.47
Menarche n (%)	4(12.5)	20(12.5)	0.45
Basal LH (mIU/mL)	1.37 ± 1.03	2.08 ± 1.89	<0.01*
Peak LH (mIU/mL)	10.7 ± 6.5	20.5 ± 9.1	<0.01*
Estradiol (pg/mL)	28.5 ± 23.2	26.8 ± 20.5	0.33
Peak FSH (mIU/mL)	10.06 ± 6.2	14.3 ± 5.2	0.27
Basal FSH (mIU/mL)	3.83 ± 2.02	4.43 ± 4.74	0.36
Peak LH/ peak FSH	1.10 ± 0.30	1.45± 0.35	<0.01*
<b>17-OHP (ng/mL)</b>	<b>1.2 ± 0.4</b>	<b>1.4 ± 0.5</b>	0.07
DHEAS (µg/dL)	112 ± 26	116 ± 29	0.32
Prolactin (ng/mL)	14.0 ± 3.5	13.2 ± 3.0	0.22
FT4 (ng/dL)	1.15 ± 0.18	1.18 ± 0.20	0.45
TSH (mIU/L)	2.1 ± 0.6	2.3 ± 0.7	

\*p<0.05 (Independent samples T test)

The values corresponding to Tanner stages and menarche represent the number of patients (n) and the percentage (%) within each group.

Abbreviations: LH = Luteinizing Hormone; FSH = Follicle-Stimulating Hormone; 17-OHP = 17-Hydroxyprogesterone; DHEAS = Dehydroepiandrosterone sulfate; FT4 = Free Thyroxine; TSH = Thyroid-Stimulating Hormone.

Pandemic-related restrictions, including school closures, changes in eating habits, reduced physical activity, increased screen time, poor sleep quality, and elevated stress levels, are potential factors influencing pubertal timing and progression.<sup>14</sup> Several studies have linked the rise in precocious puberty cases during the pandemic to an increase in BMI, potentially driven by higher food consumption and decreased physical activity.<sup>8</sup> Interestingly, our study found that while BMI in the pandemic group was comparable to the pre-pandemic group, the need for GnRH therapy increased. Stagi et al. observed a notable increase in Δ BMI-SDS in the pubertal progression group, suggesting a possible link between weight changes and pubertal progression.<sup>6</sup> Accelerated weight gain during the pandemic may explain the significantly higher number of precocious puberty cases observed in our study. On the contrary, there was no significant difference in weight and BMI among groups in our study. However, we were unable to investigate the body composition, which could impact puberty onset, due to a lack of lean mass and fat mass measurements. Certain studies from Türkiye also showed that BMI-SDS was similar in patients with CPP diagnosed before and after the pandemic,<sup>6,14</sup> indicating that increased admissions for precocious puberty cannot be solely attributed to BMI changes. This may be explained by reduced physical activity,

which can lead to increased body fat without altering BMI.<sup>5</sup> Our study found that the admission age of the two groups was similar, aligning with findings from Türkiye and other countries.<sup>7,17</sup> However, Yeşiltepe Mutlu et al. reported that patients with precocious puberty were younger during the pandemic compared to the pre-pandemic period.<sup>8</sup> These conflicting results may reflect differences in the timing of enrollment after the onset of clinical signs, as fear of illness during the pandemic likely led to delayed admissions.<sup>18</sup> In our study, the relatively higher rate of normal-weight cases in the pandemic group, though not statistically significant, may reflect increased parental vigilance and altered referral patterns during lockdown periods, rather than a true shift in the weight–puberty relationship.

Similar to our findings, Stagi et al. observed elevated basal and peak LH levels in the pandemic group<sup>6</sup>, although some studies did not find significant differences in LH levels.<sup>5,19</sup> Reduced melatonin secretion, potentially linked to increased screen and electromagnetic field exposure, may lead to disinhibition of GnRH secretion and contribute to earlier onset of puberty.<sup>20,21</sup> It is well established that SARS-CoV-2 infections can impact the central nervous system (CNS) through ACE-2 receptor binding, using olfactory or hematogenous pathways, as well as via the cytokine

storm.<sup>22</sup> Given that ACE-2 receptors are also expressed in the ovaries and testes, it is plausible that SARS-CoV-2 may play a role in triggering early puberty through direct viral effects and additional influencing factors.

Lastly, the presence of endometrial rhyme is a highly specific marker of estrogenic secretion and significant pubertal activation.<sup>19</sup> It is plausible that the estrogenic surge was more pronounced in patients who experienced pubertal onset during the lockdown period. This heightened estrogenic activity may have contributed to the development of endometrial rhyme, even in the presence of similar laboratory findings.

### Limitations

This study recognizes several limitations that may have influenced the findings and interpretations. One notable limitation is the lack of data regarding participants' exposure to electronic devices, which has been hypothesized to play a significant role in the increase of precocious puberty cases during the pandemic. Without quantifying screen time or electromagnetic field exposure, it remains challenging to fully assess their impact on pubertal development.

Additionally, stress—an established trigger for hormonal changes and pubertal onset—was not directly measured in this study. Pandemic-related factors such as fear of illness, prolonged social isolation, and school closures likely heightened stress levels in children, which may have contributed to the observed rise in precocious puberty cases. However, cortisol levels or other biomarkers of stress were not evaluated, limiting the study's ability to establish a clear connection.

Finally, the retrospective nature of the study and reliance on existing medical records might have introduced selection biases or inconsistencies in data collection. Future prospective studies that account for these variables, including stress and electronic device usage, are essential to better understand the mechanisms driving the increase in precocious puberty cases during the pandemic.

### CONCLUSION

This study highlights a significant rise in central precocious puberty (CPP) cases during the COVID-19 pandemic, indicating a potential interplay between environmental, psychological, and biological factors. While lifestyle changes such as reduced physical activity, increased screen time, and altered eating habits have been widely implicated, our

findings suggest that hormonal activation may have played a crucial role beyond these behavioral shifts. The observed increase in basal, peak LH, and peak LH/peak FSH levels reinforces the need to explore potential neuroendocrine triggers, including stress-related and viral mechanisms. Given the long-term implications of early puberty on metabolic and psychosocial health, further studies are essential to unravel the precise mechanisms and develop effective preventive and therapeutic strategies.

### Ethical approval

This study has been approved by the Clinical Research Ethics Committee of the Ministry of Health, University of Health Sciences, Ümraniye Training and Research Hospital (approval date 25.08.2022, number 19659). Written informed consent was obtained from the participants.

### Author contribution

The authors declare contribution to the paper as follows: Study conception and design: GS, MA; data collection: GS, MA; analysis and interpretation of results: GS, MA; draft manuscript preparation: GS. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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