

# Has the Frequency of Precocious Puberty and Rapidly Progressive Early Puberty Increased in Girls During the COVID-19 Pandemic?

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## What is already known on this topic?

The timing of puberty is under the control of several factors, such as environmental and nutritional factors, endocrine disruptors, sleep, stress, and bone maturation. However, which one of these factors is the main determinant is not known.

## What this study adds?

We found that the incidence of newly diagnosed central precocious puberty and rapidly progressive early puberty cases increased during the Coronavirus disease-2019 pandemic period.

## Abstract

**Objective:** Early puberty is development of secondary sex characteristics earlier than the expected normal age range. We subjectively observed an increased frequency of early puberty during the Coronavirus disease-2019 (COVID-19) lockdown and aimed to show the clinical, demographic characteristics of the cases and the change in its incidence.

**Methods:** Female patients with central precocious puberty (CPP, n = 28) and rapidly progressive early puberty (RPEP, n = 61), presenting to our clinic before (January 2019-March 2020) and during the COVID-19 pandemic (April 2020-June 2021) were included.

**Results:** Among 28 CPP cases, six (21%) presented before the pandemic lockdown, whereas 22 (79%) were diagnosed during the COVID-19 pandemic lockdown. While RPEP was seen in 16 (26%) patients before the pandemic, 45 (74%) patients were diagnosed during the lockdown period. Presentation with menarche was seen in 15 RPEP patients; two (13%) were in the pre-pandemic period and 13 (87%) were in the lockdown period. Chronological age, bone age, bone age to chronological age ratio, height, weight, and body mass index standard deviation scores of patients with RPEP and CPP were similar between the pre-pandemic and pandemic period.

**Conclusion:** In this cohort, the frequency of CPP and RPP cases were significantly ( $p < 0.001$ ) increased during the COVID-19 pandemic, possibly due to environmental changes.

**Keywords:** LHRH, physical inactivity, distance education, school closures, quarantine

## Introduction

Puberty starts with the elimination of inhibition of the hypothalamic-pituitary axis as a result of the interaction of complex factors. Activation of the gonadotropin-releasing hormone (GnRH) pulse generator occurs with the interaction of kisspeptin and kisspeptin 1 receptor, synchronized operation of neurokinin-B, glutamate, leptin, and androgens. Inhibitory systems are endogenous opioid peptides, such as dynorphin A, gamma-aminobutyric acid (GABA), and macrorin ring finger protein-3 (MKRN3) (1). While various hypothalamic genes including KISS1,

KISS1R, MKRN3, DLK1 regulate the rate of puberty, micro RNAs provide epigenetic control of puberty by regulating GnRH gene transcription. The timing of puberty is under the control of several factors such as environmental and nutritional factors, endocrine disruptors, sleep, stress, and bone maturation (2,3).

With the Coronavirus disease-2019 (COVID-19) epidemic in our country, primary school education was kept closed from March 2020 to June 2021, and unlike many other countries, children under the age of 18 were isolated at home for most of this period (4). During this period, what appeared



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to be a dramatic increase in the cases of central precocious puberty (CPP) and rapidly progressive early puberty (RPEP) were observed in our clinic. The aim of this study was to assess the frequency of admission, risk factors, clinical, and demographic characteristics of such cases before and after the COVID-19 pandemic.

## Methods

### Patients

Female patients diagnosed with CPP and RPEP who presented to our clinic with complaints of precocious puberty before and after the COVID-19 pandemic [15 months' period before and 15 months' period after the start of COVID-19 pandemic lockdown (01 January 2019-30 March 2020 / 01 April 2020-30 June 2021)] were retrospectively assessed. Patients with central or RPEP were included in the study. CPP was defined when breast development was evident before the age of 8 years with a baseline luteinizing hormone (LH) value of  $>0.3$  mIU/mL and/or a stimulated LH value of  $>5$  mIU/mL (5,6). RPEP is defined as: (a) when girls developed breasts after 8 years of age which reached Tanner stage 3 or 4 within 3-6 months; (b) when girls before the age of nine have breast development at Tanner stage 3 or 4; (c) if menarche occurred before the age of ten; or (d) if their predicted adult height was below target height and there was a decline in predicted adult height during follow-up (5,7,8).

Cases with peripheral precocious puberty, premature thelarche, premature adrenarche, and male patients were not included.

### Methods

Clinical records of the patients before and after/during the COVID-19 pandemic period were retrospectively collected. The data collected regarding anthropometric characteristics included: age (years); height (measured with a sensitivity of 0.1 cm, using a Harpenden stadiometer for those who could stand); weight [measured using a scale with a sensitivity of 0.1 kg (Seca, Hamburg, Germany) with light clothing, (kg)]; body mass index (BMI) ( $\text{kg}/\text{m}^2$ ); the respective standard deviation (SD) scores (calculated with an online calculator for pediatric endocrinology according to Turkish standards) (9); and pubertal staging evaluated according to the Tanner method (5). Overweight and obesity was defined when the BMI was  $\geq 85^{\text{th}}$ - $< 95^{\text{th}}$  percentile and  $\geq 95^{\text{th}}$  percentile for age and gender, respectively. Bone ages were determined using the Greulich-Pyle radiographic atlas (10). Serum levels of LH (mIU/mL), follicle-stimulating hormone (FSH) (mIU/mL), and estradiol ( $\text{pg}/\text{mL}$ ) were measured by

immunochemiluminescence (ICMA, ADVIA Centaur XPT, Siemens, USA) immunoassay system. Samples for FSH and LH during GnRH stimulation were obtained 20, 40, and 60 minutes after intravenous administration of  $100 \mu\text{g}/\text{m}^2$  (maximum  $100 \mu\text{g}$ ) LHRH (LHRH Ferring ampule) when basal FSH and LH levels were not conclusive. In this study, all girls with CPP under the age of eight and girls with RPEP over the age of eight with neurological complaints were evaluated with magnetic resonance imaging (MRI).

### Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences application for Windows, version 21.0 (IBM Inc., Armonk, NY, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests revealed that the data did not comply with normal distribution. Descriptive results are presented as median (interquartile range). Comparisons among groups before pandemic and during the pandemic lockdown were made using the Mann-Whitney U test for numeric variables and  $\chi^2$ -test for the categorical variables. A p value of  $<0.05$  was considered statistically significant.

Institutional approval was granted by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (ethics approval number: 2021/21-05). When applicable, both patients and parents signed the informed consent form to participate in the study.

## Results

A total of 89 cases were included, of which 28 had CPP and 61 had RPEP. Of the 28 cases with CPP, six (21%) were diagnosed during the pre-pandemic period and 22 (79%) were diagnosed during the pandemic period. Of the 61 cases with RPEP, 16 (26%) were diagnosed before the pandemic, while 45 (74%) were diagnosed during the COVID-19 pandemic period. CPP and RPEP female cases in total were approximately three times higher during the COVID-19 pandemic period. Among 15 RPEP cases presenting with early menarche, 13 patients (87%) were diagnosed during the pandemic period.

In total, 20 with CPP and 40 with RPEP were treated with GnRH analogs. Treatment was initiated in 85% (17/20) of the cases diagnosed with CPP, and in 67% (27/40) of cases diagnosed with RPEP during the pandemic period. The height, weight, and BMI SD score values and BMI percentile of CPP and RPEP cases were similar in the prepandemic and pandemic periods (Table 1). Twenty-five percent (7/28) of the cases diagnosed with CPP and 42% (26/61) of the cases diagnosed with RPEP were obese or overweight. Two

of the three obese patients with CPP and 10 of the 13 obese patients with RPP were diagnosed during the pandemic period (Table 2).

In patients with CPP 79% (n=22) exhibited breast development at Tanner stage 2 and in 21% (n=6) it was Tanner stage 3. Pubic hair was detected in 42% (n=12) of the cases diagnosed with CPP. In patients with RPEP 47% (n=29) exhibited Tanner stage 2 breast development, 40% (n=24) were at stage 3, and 13% (n=8) were at Tanner stage 4. GnRH stimulation test was performed in 13 of the CPP patients, 12 of whom were during the pandemic period, and the mean peak LH/FSH average 0.9 (± 0.5) and the mean peak LH was 13 (± 10.6) IU/L.

In total 27 (30%) girls underwent brain MRI. Of these 27 patients, 21 (77%) exhibited no alterations in the hypothalamus-pituitary area of the brain, four (13%) had incidental findings with hypothalamus-pituitary lesions, including two non-functioning pituitary microadenomas and two pineal gland cysts. None of the participants exhibited other hormonal abnormalities. All patients with brain lesions continue to be followed up regularly.

## Discussion

In this study, the frequency of cases with CPP and RPEP increased approximately three times in the pandemic

lockdown period compared with the same duration pre-pandemic. Reports from different centers have shown that the incidence of precocious puberty, early menarche, and RPEP in girls has increased after the COVID-19 pandemic (11,12). The exact mechanism of the increase in precocious puberty after restrictions imposed during the pandemic is unknown, and several possible mechanisms have been suggested. One of the mechanisms that may be related to increase in frequency of CPP and RPEP cases during COVID-19 pandemic is the presence of angiotensin-converting enzyme-2 receptor, to which Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) virus binds in the cranial nerves system especially around the olfactory bulb, and the concentration of GnRH neurons and GABAergic neurons in this region. An increased volume of the olfactory bulb has been strongly associated with precocious puberty (13). SARS-CoV-2 may have initiated puberty by disrupting the blood-brain barrier or by direct interaction with neural pathways. In addition, N-methyl-D-aspartate (NMDA) receptors stimulated by inflammatory cytokines may be responsible for increasing GnRH secretion (14,15). However, our patients did not have any sign or history of SARS-CoV-2 virus infection. It should be remembered that, since COVID-19 infection in children is generally considered asymptomatic, patients may not have recognized the related symptoms (16).

**Table 1. Clinical and demographic characteristics of cases diagnosed with early puberty before and after the COVID-19 pandemic**

	Central puberty precocious (n = 28)			Rapidly progressive puberty (n = 61)		
	Before pandemic (n = 6)	After pandemic (n = 22)	p	Before pandemic (n = 16)	After pandemic (n = 45)	p
Age (years)	7.5 (1.0)	7.5 (0.9)	0.53	8.7 (1.2)	8.9 (1.1)	0.58
Bone age	8.2 (1.6)	8.8 (1.6)	0.71	11 (1.5)	10.5 (2.1)	0.74
Bone age to chronological age ratio	1.2 (0.3)	1.1 (0.2)	0.93	1.1 (0.2)	1.1 (0.1)	0.51
Weight SD score	0.7 (1.7)	0.9 (1.2)	0.51	1.2 (2.0)	1.0 (1.5)	0.96
Height SD score	1.5 (2.4)	1.2 (1.2)	0.86	0.9 (1.8)	1.4 (1.9)	0.74
BMI SD score	0.5 (1.9)	0.5 (0.8)	0.88	1 (1.8)	0.7 (1.2)	0.73
FSH (mIU/mL)	3.3 (3.5)	3.7 (3.2)	0.53	4 (4.1)	4.5 (3.3)	0.95
LH (mIU/mL)	0.7 (0.7)	0.5 (0.9)	0.84	0.9 (1.4)	0.6 (1.9)	0.61
Estradiol (pg/mL)	19 (48)	18 (24)	0.82	27.5 (30)	24 (24)	0.73

\*Data are presented as median (IQR).

IQR: interquartile range, SD: standard deviation, FSH: follicle-stimulating hormone, LH: luteinizing hormone, BMI: body mass index, COVID-19: Coronavirus disease-2019

**Table 2. Frequency of cases**

	Before pandemic	After pandemic	p
Central puberty precocious, n (%)	6 (21)	22 (79)	0.02
Rapidly progressive early puberty, n (%)	16 (26)	45 (74)	<0.001
CPP and RPEP cases, n (%)	22 (25)	67 (75)	<0.001
GnRH treatment, n (%)	16 (26)	44 (74)	<0.001
Obesity and overweight, n (%)	10 (31)	23 (69)	0.024

GnRH: gonadotropin-releasing hormone, CPP: central precocious puberty, RPEP: rapidly progressive early puberty

COVID-19 lockdown has created chronic and prolonged stress, due to fear of infection and prolonged home quarantine (17). This stress could have increased the release of GnRH through some neurotransmitters and neurons. Studies have shown that prolonged stress accelerates puberty through NMDA, GRF1, CRF, and GABA A receptors in a rat model, and increased cortisol and catecholamines in the mouse model, indirectly (11,12). However, to the best of our knowledge, these mechanisms have not been accepted for humans to date and thus this mechanism remains hypothetical. Another study of the frequency of early puberty in the use of methylphenidate showed that dopamine and norepinephrine may trigger puberty, through transporter blockage, as their concentrations in synaptic gaps increase (18).

We did not include any assessment of patient stress levels during the COVID-19 outbreak and the number of quarantine days. However, several reports have documented both increased parental stress and children's psychological problems during the pandemic, using measurable parameters (19,20). However, at present the evidence for this is very limited.

In the present study, it was found that 28% of CPP and 69% of RPEP cases were either obese or overweight and who were diagnosed during the pandemic period. Nutrition is the most important determinant of pubertal maturation. It is well-known that puberty may be triggered by nutritional correction in malnourished, adopted children (21,22). It has been shown that the prevalence of obesity increased during the COVID-19 pandemic in the USA, especially between the ages of 5-9 years (23). Furthermore, overnutrition in low-birth-weight girls may lead to accelerated puberty, ovarian dysfunction, and polycystic ovary syndrome in the future, by various factors and mechanisms, including DNA methylation, microRNAs, and microbiota (22). There were no low-birth-weight cases among our patients.

It is also well established that vigorous physical activity delays the onset of puberty (24). There is no study investigating the mechanisms by which limited physical activity may affect pubertal timing or sedentary lifestyles will likely accelerate the onset of puberty. In epidemiological studies of adolescent girls in India and Ethiopia, the age of menarche was earlier in sedentary urban girls compared to girls in rural areas with increased daily physical activity (25,26).

In many studies evaluating the relationship between exposure to endocrine disruptors and the timing of puberty in girls, many endocrine disruptor chemicals have been associated with early pubertal changes, although the effects vary according to exposure time, period, and the gender of

the patient (27,28). We suggest that exposure to endocrine disruptors probably increased through more intensive use of disinfectants and the use of immune-boosting supplements in the COVID-19 pandemic.

Distance education and the use of electronic devices and screen exposure have increased in Turkey during the COVID-19 pandemic. A study by Stagi et al. (11) showed that the total screen time children were exposed to has increased 2.5 times during the COVID-19 pandemic. High melatonin levels detected at night in prepubertal children were found to decrease with puberty (29). Salti et al. (30) showed a decrease in urinary melatonin concentration was associated with children's television screen exposure. It is thought that increased use of electronic devices may lead to a decrease in melatonin levels, causing the onset of pubertal development. The study of Tsai et al. (31) showed that internet use in adolescents was positively correlated with early puberty frequency. These authors estimated that increased use of electronic devices increased obesity and increased BMI may induce early puberty (31). Given these findings, we also suggest that prolonged exposure of children to the screen of electronic devices, such as televisions and computers, may also be a factor in the increase in the frequency of cases with CPP and RPEP during the COVID-19 pandemic.

### Study Limitations

COVID-19 infection and endocrine effects have not been explored previously. Our study is one of the first studies to examine this, with regard to the interaction between the lockdown period and the endocrine system. We also believe that our study may provide further information about the specific mechanisms initiating puberty. The main limitation of this study was the short follow-up period of our patients, due to the closure of the outpatient clinics in lockdown period for a long time, during which only emergent cases were examined. The other limitation of this study was that, although there are a number of hypothetical factors which may be associated with the increased frequency of CPP and RPEP, in this study evidence of past SARS-CoV-2 infection, patient screen time, sleep time, physical activity time, dietary changes, and additional stress factors were not investigated.

### Conclusion

In conclusion, the frequency and number of CPP and RPEP cases increased during the COVID-19 pandemic compared with the same 15 month period prior to the pandemic. Several factors which have increased during the restrictions imposed in an attempt to control infections rates, such as changes in dietary habits, greater use of technology

products, decrease in physical activity, and increase in sedentary lifestyle because of distance education and quarantine, could precipitate an increase in numbers of cases of precocious puberty. Further larger studies are needed to investigate the possible causes of the association between the COVID-19 pandemic and precocious puberty.

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### Ethics

**Ethics Committee Approval:** Approval was granted by the Ethics Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2021/21-05, date: 14.07.2021).

**Informed Consent:** All participants provided informed consent.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci, Korcan Demir, Ayhan Abacı, Ece Böber, Concept: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci, Korcan Demir, Ayhan Abacı, Ece Böber, Design: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci, Korcan Demir, Ayhan Abacı, Ece Böber, Data Collection or Processing: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci, Analysis or Interpretation: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci, Literature Search: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci, Writing: Kübra Yüksek Acinikli, İbrahim Mert Erbaş, Özge Besci.

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