İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2024;24(4):215-218
DOI: 10.26650/jchild.2024.1595906

RESEARCH ARTICLE

The Effects of the COVID-19 Pandemic on Pubertal Development in Girls: A Retrospective Evaluation of Girls Presenting with Precocious Puberty Before and During the Pandemic

Esin Karakılıç Özturan[1,3], Aslı Berru Arslan Özden[2], Tuğçe Kandemir[3], Şükran Poyrazoğlu[3], Firdevs Baş[3], Feyza Darendeliler[3]

[1]Kartal Dr. Lütfi Kirdar City Hospital, Istanbul, Türkiye
[2]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Türkiye
[3]Istanbul University, Istanbul Faculty of Medicine, Pediatric Endocrinology Division, Istanbul, Türkiye

ORCID ID: E.K.O. 0000-0002-8842-1752; A.B.A.O. 0000-0002-8531-6893; T.K. 0000-0003-1561-2862; S.P. 0000-0001-6806-9678; F.B. 0000-0001-9689-4464; F.D. 0000-0003-4786-0780

Citation: Karakılıç Özturan E, Arslan Özden AB, Kandemir T, Poyrazoğlu Ş, Baş F, Darendeliler F. The Effects of the COVID-19 Pandemic on Pubertal Development in Girls: A Retrospective Evaluation of Girls Presenting with Precocious Puberty Before and During the Pandemic. Çocuk Dergisi - Journal of Child 2024;24(4):215-218. https://doi.org/10.26650/jchild.2024.1595906

ABSTRACT

Objective: The timing of pubertal onset is a complex biological process influenced by various factors, many of which remain poorly understood. A notable increase in early puberty cases was observed during the COVID-19 pandemic. This study evaluated girls presenting with early or precocious puberty both during and in the five years before the pandemic.

Methods: Thirty-six girls (Group 1) with suspected early puberty during the COVID-19 pandemic (March 2020–July 2021) and forty girls (Group 2) diagnosed with central precocious puberty between 2015 and 2019 were included. Retrospective data on demographic, anthropometric, clinical, and laboratory findings were analyzed.

Results: The median (IQR) age at presentation was 8.07 (1.37) years in Group 1 and 7.89 (1.35) years in Group 2 (p=0.038). No significant differences were observed between the groups regarding height SDS, BMI-SDS, bone age, or Δ target height–predicted adult height SDS.

Conclusions: Despite a common association between obesity and early puberty, no differences in BMI were identified in this cohort. Environmental factors related to the pandemic conditions may have influenced the timing of puberty. Larger studies with broader populations are needed for definitive conclusions.

Keywords: COVID-19 pandemic, pubertal development, precocious puberty, girls

INTRODUCTION

Central precocious puberty (CPP) is characterized by the early activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in breast development in girls younger than 8 years and testicular enlargement in boys younger than 9 years (1). Pubertal development is a multifaceted process influenced by hormonal, genetic, environmental, ethnic, nutritional, and socioeconomic factors, with genetic contributions accounting for approximately 50-80% (2,3).

The Coronavirus disease 2019 (COVID-19) pandemic, one of the most significant global health crises of recent times, highlighted the critical role of environmental factors in pubertal timing (4-6). During this period, restrictions on outdoor activities, increased sedentary behaviors, overnutrition, and excessive screen time were common, all of which have been implicated in early pubertal onset (4-7). Observations and studies during the pandemic lockdown reported a threefold increase in precocious puberty cases compared to prior years (7).

In this study, we aimed to evaluate girls presenting with early or precocious puberty during COVID-19 pandemic and to compare their clinical features with those of girls diagnosed with CPP in the five years before the pandemic.

MATERIALS AND METHODS

This retrospective study included 36 girls (Group 1) presenting with suspected early puberty during the COVID-19 pandemic

Corresponding Author: Esin Karakilic Ozturan **E-mail:** karakilic.esin@gmail.com

Submitted: 04.12.2024 • **Revision Requested:** 12.12.2024 • **Last Revision Received:** 15.12.2024 • **Accepted:** 18.01.2025

(March 2020 – July 2021) and 40 girls (Group 2) diagnosed with idiopathic CPP between 2015 and 2019. Demographic, anthropometric, clinical, and laboratory data were obtained retrospectively from the patients' medical records. The local ethics committee approved the study.

Patients with MRI abnormalities of the brain and/or pituitary gland as well as other endocrine diseases or chronic conditions were excluded. The pubertal stages were classified according to the Tanner scale (8). Central precocious puberty in girls was defined by a combination of clinical signs of puberty, including the onset of breast development before the age of 8 years, increased growth velocity, accelerated bone maturation, increased uterine and ovarian volumes, a pubertal basal LH level, and a peak LH level above 5 IU/L following a GnRH stimulation test. The target height was calculated using the formula: [(Father's height in cm - 13) + Mother's height in cm] / 2. Standard deviation scores (SDS) were calculated according to age- and sex-specific national standards (9,10). The Greuclih-Pyle method was used for bone age assessment (11). Birth weight according to gestational age were classified as follows: small for gestational age (SGA) if the birth weight and/or birth length is below -2 SDS, large for gestational age (LGA) if the birth weight and/or birth length was above 2 SDS and appropriate for gestational age (AGA) if within -2 and 2 SDS.

Statistical analyses were conducted using the SPSS statistical software, version 22. Due to non-normal distribution, continuous variables are presented as medians and interquartile ranges (IQR) to indicate central tendency and variability, while categorical variables are summarized as counts and percentages. The non-parametric Mann–Whitney U test was applied to compare the medians, considering the non-normal distribution of the covariates. The chi-square test was conducted to determine whether there was a difference between two or more groups. All tests were performed as two-tailed, with statistical significance established at $p \leq 0.05$.

RESULTS

In Group 1, 22.2% (n=8) of patients presented in 2020, while 77.8% (n=28) of them presented in 2021. The median age of breast budding onset was 7.7 years (IQR: 1.0, range 5.6–8.5) in Group 1 and 7.4 years (IQR: 1.0, range 4.0–8.0) in Group 2, with a statistically significant difference ($p < 0.001$). Breast development stages were comparable between the groups. In Group 1, 26 patients (72.2%) presented with breast development stage 2, 8 (22.2%) with stage 3, and 2 (5.5%) with stage 4. In Group 2, 21 patients (52.5%) presented with stage 2, 17 (42.5%) with stage 3, and 2 (5%) with stage 4. No significant differences were found between Group 1 and Group 2 regarding the puberty stages (p=0.077).

Among Group 1 patients, four girls, one of them was adopted, presented with menarche (ages between 9.0-10.5 years). In Group 2, four cases presented with menarche (ages between 7.6-9.2 years).

In both Group 1 and Group 2, there was one patient who was born from an In vitro fertilization (IVF) pregnancy. In Group 1, the patient was born as a preterm twin and was AGA, while the patient in Group 2 was born at term but was SGA. In Group 1, 88.9% of the cases (n=32) were born at term, while 11.1% (n=4) were preterm. Among the girls in this group, 86.1% (n=31) were born AGA, 5.6% (n=2) were SGA, and 8.4% (n=3) were LGA. In Group 2, 95% (n=38) of the cases were term, while 5% (n=2) were preterm. The birth weights of the girls in this group were 77.5% (n=31) AGA, 17.5% (n=7) SGA, and 5% (n=2) LGA.

Family history of early puberty among relatives was 13.8% (n=5) in Group 1, while in Group 2, this rate was 5% (n=2). In Group 1, the median maternal age at menarche was 13 years (IQR: 1.38; range: 9.0–15), whereas in Group 2, it was 12 years (IQR: 1.0; range: 10.5–15). The median target height was 161.1 cm (IQR: 8.85; range: 147.6–172) in Group 1, while it was 160.1 cm (IQR: 4.78; range: 152.1–169.7) in Group 2. No statistical difference was found between the groups (p=0.550).

While the demographic details of the groups and their comparison are provided in **Table 1**, the laboratory findings of the groups and the comparison of these findings are shown in **Table 2.** While the basal E2 level was significantly higher in Group 1 (p=0.042), the peak LH and FSH levels during the GnRH stimulation test were significantly higher in Group 2 (p=0.003 and p=0.002, respectively) **(Table 2).**

Table 1. Demographic data of the groups and their comparison between groups

	Group 1 Median (IQR) (Range)	Group 2 Median (IQR) (Range)	p
CA (years)	8.07 (1.37) (6.04;11.7)	7.89 (1.35) (4.2;9.3)	0.038
Height (cm)	132.7 (14.3) (115.3;157.1)	131 (16.8) (103.2;145.1)	0.250
Height (SDS)	1.12 (1.68) (-1.64; 3.6)	1.1 (1.82) (-1.6;5.2)	0.441
BMI (kg/m^2)	18.0 (4.6) (12.2;28)	17.9 (4.45) (13.7;27.5)	0.835
BMI (SDS)	0.94 (1.76) (-2.8;2.5)	0.85 (1.41) (-1.4;2.9)	0.473
TH (cm)	161.1 (8.85) (147.6;172)	160.1 (4.77) (152.1;169.7)	0.555
TH (SDS)	-0.34 (1.51) (-2.64;1.52)	-0.51 (0.75) (-1.87;1.12)	0.636
BA (years)	8.83 (2.2) (5.0;12.5)	8.83 (2.4) (3.5;12.00)	0.952
PAH (cm)	158.9 (9.2) (147;173.8)	157.7 (7.95) (140.2;174.8)	0.122
PAH (SDS)	-0.72 (1.56) (-2.74;1.82)	0.93 (1.35) (-3.9;2.0)	0.122
ΔTH-PAH (SDS)	0.1 (1.4) (-2.3;2.1)	0.4 (2.0) (-2.4;3.0)	0.640

IQR: Interquartile range, CA: Chronological age, SDS: Standard deviation score, BMI: Body mass index, TH: Target height, BA: Bone age, PAH: Predicted adult height

Table 2. Labatory findings of the groups and their comparison between groups

		Group 1 Median (IQR) (Range)	Group 2 Median (IQR) Range	p
Basal LH (mIU/mL)		0.47 (1.82) (0.1; 15.3)	0.70 (2.0) (0.1; 10.2)	0.181
Basal FSH (mIU/mL)		3.6 (2.3) (1.0; 11.66)	2.2 (2.55) (0.67;9.7)	0.241
Basal E2 (pg/mL)		19.2 (33.8) (1.97; 254)	5.0 (21.4) (5.0;88.8)	0.042
Basal DHEAS (mcg/dL)		84.6 (70.4) (5.47; 364)	76.0 (64.8) (8.9; 160.4)	0.710
LHRH test	**LH peak (mIU/mL)**	5.38 (4.52) (2.43; 13.7)	10.7 (15.4) (2.29; 66.4)	0.003
	FSH peak (mIU/mL)	8.9 (4.52) (5.0; 13.4)	13.2 (5.15) (5.6; 23.7)	0.002
	LH/FSH	0.68 (0.27) (0.2; 1.5)	0.96 (1.01) (0.2; 3.8)	0.068
Uterus volume (mm^3)		3.3 (2.78) (0.9; 32.6)	4.9 (5.75) (1.6; 43.4)	0.019
R over volume (mm^3)		2.5 (1.3) (0.9; 12.9)	2.4 (2.1) (0.5; 11.2)	1.000
L over volume (mm^3)		2.5 (1.4) (0.8; 9.1)	2.7 (2.0) (0.3; 10.7)	0.760

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, E2: Estradiole, DHEAS: Dehydroepiandrosterone sulfate, LH-RH: Luteinising Hormone Releasing Hormone, R: Right, L: Left

DISCUSSION

In this study, we evaluated the clinical findings of girls presenting with pubertal complaints, such as breast budding, at a pediatric endocrinology clinic during the COVID-19 pandemic in Türkiye. Additionally, we compared these girls, using both clinical and laboratory findings, to girls who were diagnosed with precocious puberty before the pandemic.

Especially in the preliminary data from Italy, it has been reported that the incidence of precocious puberty increased threefold during the lockdown period compared to the previous year (5). Additionally, according to the experiences of the same team during the COVID-19 pandemic phases (2019-2022), they evaluated consultations for suspected precocious or early puberty in girls and reported a significant increase in the rates of central precocious puberty (7).

In our series, the number of cases presenting between 2020 and 2021 was approximately similar to the total number of patients in the five years before the pandemic. Therefore, we can conclude that there was an increase in the prevalence of CPP during the pandemic period in our cohort. However, cases with conditions that could contribute to CPP, such as cranial pathology, neuromotor delay, and epilepsy, were excluded from Group 2. Only cases that fully met the definition of CPP were included in this group. Thus, the number of cases from previous years was relatively low.

Although Verzani et al. indicated that the consumption of hypercaloric foods and overnutrition could be contributing factors to precocious puberty, no statistical difference in BMI SDS was observed between the groups (5). In another study, from Italy, cases of early puberty during the COVID-19 lockdown and the previous five years were compared, and no difference was observed in the BMI SDS (11). As in previous studies, Oliveira Neto et al. also did not find a statistically significant difference between groups, although they reported that obesity was more common (36.4% versus 18.2%); however, the group sizes were different in their study (12). In our cohort, we also did not find a statistically significant difference in BMI-SDS when comparing cases from the pandemic period with those from the pre-pandemic period.

In our cohort, we found that the median serum E2 levels of patients presenting during the pandemic (Group 1) were higher than those who presented before the pandemic (Group 2) (p=0.042). We observed that the high median estrogen level in Group 1 was related to markedly elevated E2 levels in two cases of patients who presented with menarche at age 9. In previous studies, no significant difference was reported between serum E2 levels (7,12,13).

Interestingly, in our cohort, despite the higher median serum E2 level in Group 1, the median uterine volume was statistically significantly greater in Group 2 (p=0.019). Although no statistical difference was found between the groups, the number of girls with a pubertal stage above stage 2 was higher in Group 2. Moreover, the median LH peak was also higher in Group 2. The advanced pubertal stage and high peak LH levels may be attributed to the higher uterine volumes observed in Group 2.

While Oliveira Neto et al. reported that the mean ovarian volumes were larger in girls who presented before the pandemic (12), we observed no significant difference in the ovarian volumes between the groups (p=1.000 and p=0.760). This discrepancy may be attributed to the small sample size and heterogeneity within the groups in all the studies.

During the pandemic, being forced to stay at home and consequently spending excessive time on electronic devices, whether for educational or recreational activities, may have decreased melatonin levels among children (14). Melatonin secretion is known to be stimulated by darkness and inhibits gonadotropin release (15). Although there was no objective data on screen times for the girls in our cohort during the pandemic, it is reasonable to consider that restrictions during the lockdown period may have contributed to this.

Additionally, the activation of the genes *KISS1* and *KISS1R*, which encode kisspeptin and its receptor, respectively, along with the inactivation of the makorin ring finger 3 (*MKRN3*) gene, play significant roles in the activation of GnRH secretion, leading to the onset of puberty (16-18). Chen et al. reported that when comparing girls who presented during the pandemic with those who presented before the pandemic, MKRN3 levels were lower, and kisspeptin levels were higher in those seen during the pandemic (13). In our study, neither the MKNR3 nor kisspeptin levels of patients who presented during the pandemic period or before the pandemic were available. However, psychological stress, dietary changes, and alterations

in melatonin secretion due to excessive exposure to electronic devices during the pandemic may have led to a decrease in MKRN3 levels and an increase in kisspeptin levels through epigenetic regulation. However, several cohorts are needed to obtain sufficient evidence to explore this topic further.

In conclusion, we present a cohort of girls who presented with central precocious puberty (CPP) during the COVID-19 pandemic and in the 5 years before COVID-19. The number of patients was similar in both groups, however, we observed increasement in CPP presentations during the pandemic. Although high BMI is often cited as a contributing factor, it was not different in our cohort. Additionally, although we lack objective data in this cohort, it is suggested that environmental factors related to pandemic conditions—such as prolonged use of electronic devices and reduced physical activity—may have contributed to epigenetic reprogramming associated with puberty timing, potentially shifting the onset of puberty to an earlier age. However, studies with larger patient populations are needed for more conclusive data.

Ethics Committee Approval: This study was approved by the ethics committee of Istanbul Faculty of Medicine Clinical Research Ethics Committee (29/11/2024 - 23)

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.K.Ö., Ş.P., F..B, F.D.; Data Acquisition- E.K.Ö., A.B.A.Ö., T.K.; Data Analysis/Interpretation- E.K.Ö., A.B.A.Ö., T.K. Ş.P., F.B., F.D.; Drafting Manuscript- E.K.Ö., A.B.A.Ö., T.K.;; Critical Revision of Manuscript- E.K.Ö., Ş.P., F.B., F.D.; Final Approval and Accountability- E.K.Ö., A.B.A.Ö., T.K. Ş.P., F.B., F.D.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

REFERENCES

1. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol 2016;4(3):265-74. doi: 10.1016/S2213-8587(15)00380-0.
2. A Canton APM, Seraphim CE, Brito VN, Latronico AC. Pioneering studies on monogenic central precocious puberty. Arch Endocrinol Metab 2019 22;63(4):438-44. doi: 10.20945/2359-3997000000164.
3. Zhu J, Kusa TO, Chan YM. Genetics of pubertal timing. Curr Opin Pediatr 2018;30(4):532-40. doi: 10.1097/MOP.0000000000000642.
4. Leong A, Vasanwala RF. Early Puberty Trends during the COVID-19 Pandemic in Singapore: A Retrospective Review in a Single Tertiary Center. J ASEAN Fed Endocr Soc 2024;39(1):6-11. doi: 10.15605/jafes.039.01.12.
5. Verzani M, Bizzarri C, Chioma L, Bottaro G, Pedicelli S, Cappa M. Impact of COVID-19 pandemic lockdown on the early onset of puberty: experience of an Italian tertiary center". Ital J Pediatr 2021;47(1):52. doi: 10.1186/s13052-021-01015-6.
6. Goffredo M, Pilotta A, Parissenti I, Forino C, Tomasi C, Goffredo P, et al. Early onset of puberty during COVID-19 pandemic lockdown: experience from two Pediatric Endocrinology Italian Centers. Pediatr Endocrinol Metab 2023;36(3):290-98. doi: 10.1515/jpem-2022-0492
7. Chioma L, Chiarito M, Bottaro G, et al. COVID-19 pandemic phases and female precocious puberty: The experience of the past 4 years (2019 through 2022) in an Italian tertiary center. Front Endocrinol (Lausanne) 2023;14:1132769. doi: 10.3389/fendo.2023.1132769.
8. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Dis Child 1969;44(235):291-303. https://doi.org/10.1136/adc.44.235.291.
9. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F et al. Reference Values for Weight, Height, Head Circumference, and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015;7(4):280-93.
10. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, Calif.: Stanford University Press; 1959.
11. Stagi S, De Masi S, Bencini E, Losi S, Paci S, Parpagnoli M et al. Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic. Ital J Pediatr 2020;46(1):165. doi: 10.1186/s13052-020-00931-3.
12. Oliveira Neto CP, Azulay RSS, Almeida AGFP, Tavares MDGR, Vaz LHG, Leal IRL et al. Differences in the Puberty of Girls before and during the COVID-19 Pandemic. Int J Environ Res Public Health 2022; 19(8):4733. doi: 10.3390/ijerph19084733.
13. Chen Y, Chen J, Tang Y, Zhang Q, Wang Y, Li Q et al. Differences in Precocious Puberty Between Before and During the COVID-19 Pandemic: A Cross-Sectional Study Among Shanghai School-Aged Girls. Front Endocrinol (Lausanne) 2022; 13:839895. doi: 10.3389/fendo.2022.839895.
14. Stagi S, Ferrari M, Paiusco G, Moriondo M, Azzari C. Possible Role of Melatonin in Precocious and Accelerated Puberty in Females during the COVID-19 Pandemic. Ital J Pediatrics 2021, preprint. doi.org/10.21203/rs.3.rs-855928/v1
15. Lockley SW, Skene DJ, Arendt J, Tabandeh H, Bird AC, Defrance R. Relationship between melatonin rhythms and visual loss in the blind. J Clin Endocrinol Metab. 1997;82(11):3763-70. doi: 10.1210/jcem.82.11.4355.
16. Teles MG, Bianco SD, Brito VN, Trarbach EB, Kuohung W, Xu S et al. A GPR54-activating mutation in a patient with central precocious puberty. N Engl J Med. 2008;358(7):709-15. doi: 10.1056/NEJMoa073443.
17. Silveira LG, Noel SD, Silveira-Neto AP, Abreu AP, Brito VN, Santos MG, et al. Mutations of the KISS1 gene in disorders of puberty. J Clin Endocrinol Metab 2010; 95: 2276–80. doi: 10.1210/jc.2009-2421.
18. Abreu AP, Dauber A, Macedo DB, Noel SD, Brito VN, Gill JC, et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. N Engl J Med 2013; 368: 2467–75. doi: 10.1056/NEJMoa1302160.