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Precocious Puberty Diagnoses Spike, COVID-19 Pandemic, and Body Mass Index: Findings From a 4-year Study

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Abstract

Context: Since the COVID-19 outbreak, the number of girls with suspected precocious puberty has increased.

Objective: To compare the incidence of idiopathic central precocious puberty (ICPP) during COVID-19 with that of the previous 4 years.

Methods: Anthropometric, biochemical, and radiological parameters were collected between January 2016 and June 2021 from 133 girls who met the Rapidly Progressive ICPP criteria (RP-ICPP).

Results: We found a higher incidence of RP-ICPP between March 2020 and June 2021 (group 2) compared with January 2016 through March 2020 (group 1) (53.5% vs 41.1%); 2021 showed the highest annual incidence ($P < .05$). Group 1 and group 2 differed in age at diagnosis (7.96 ± 0.71 vs 7.61 ± 0.94; $P < .05$), mean Tanner stage (2.86 ± 0.51 vs 2.64 ± 0; $P < .05$), and in the time between the appearance of thelarche and diagnosis (0.93 ± 0.75 vs 0.71 ± 0.62 years, $P < .05$). There was an increase in the number of girls aged <8 years in group 2 and a significantly higher number of girls aged >8 years was found in group 1 (42 in group 1 vs 20 in group 2, $P < 0.05$). Overall body mass index SD score showed higher values in group 2 (1.01 ± 1.23 vs 0.69 ± 1.15; $P = .18$), which spent an average of 1.94 ± 1.81 hours per day using electronic devices; 88.5% of this group stopped any physical activity.

Conclusions: A spike in new diagnoses of idiopathic (1.79-fold higher) and RP-CPP coincided with the COVID-19 pandemic. The incidence of RP-ICPP was 1.3-fold higher during COVID-19 with a trend toward an increase in body mass index SD score. The expanding use of digital devices and the reduction of daily physical activity represent possible risk factors.

Key Words: precocious puberty, rapidly progressive idiopathic central precocious puberty (RP-ICPP), COVID-19, BMI-body mass index, screen exposure

Abbreviations: BA, bone age; BMI, body mass index; E2, 17-beta estradiol; GnRHa, GnRH analog; H, height; HDL, high-density lipoprotein; HV, height velocity; ICPP, idiopathic central precocious puberty; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; PP, precocious puberty; RP ICPP, Rapidly Progressive idiopathic central precocious puberty; SDS, SD score; TH, target height; V1, visit 1; V2, visit 2; W, weight.

Over the past 2 years, the number of girls referred to pediatric endocrinologists for suspected precocious puberty (PP) increased significantly; this phenomenon was reported by many centers from different countries [1-11]. Since early December 2019, COVID-19 has spread rapidly worldwide [12], and Italy was the first European country hit by the SARS-CoV-2 virus in the early months of 2020 [12]. The growing number of hospitalizations and deaths prompted the Council of Ministers to approve emergency measures for containment and prevention [13]. From March to May 2020, the entire country underwent a total lockdown, resulting in a radical change in habits and family lifestyles, with serious impacts on children's lives. After the total lockdown, government measures continued, with closure of parks and gyms, until May 2021, leading to reduced social interaction and physical activities over a long period. Furthermore, distance learning and forced home breaks have had a significant impact on mental health [14] and have promoted the adoption of inappropriate habits such as increased screen time, impaired sleep, and unhealthy food consumption [15, 16].

The aim of the study is to evaluate the incidence of idiopathic central precocious puberty (ICPP) before and after the

COVID 19 pandemic in Italy compared with the incidence of PP assessed over the previous 4 years and of a possible relationship between COVID-19 and pandemic-related lifestyle changes. We analyzed the anthropometric, biochemical, and radiological characteristics of girls diagnosed with rapidly progressive idiopathic precocious puberty during the COVID-19 pandemic compared with those who were diagnosed before the COVID-19 pandemic.

Materials and Methods

We retrospectively assessed the health records of girls referred to a tertiary-level academic center (Pediatric Endocrine Unit, IRCCS Istituto Giannina Gaslini, University of Genova, Genova, Italy) for suspected precocious puberty from January 2016 to June 2021.

We included patients diagnosed with ICPP who had criteria to be classified as rapidly progressive idiopathic central precocious puberty (RP-ICPP)[17]: girls with breast development Tanner stage ≥ 2 before 8 years of age, as reported by parents, and 1 or more of the following criteria: height velocity (HV) >6 cm/years, advanced bone age by at least 1 year [18], basal serum LH >0.3 U/L, peak LH >5 U/L after LH releasing hormone test [19, 20], and negative brain magnetic resonance imaging (MRI). Patients who did not meet the criteria for RP-ICPP at first evaluation (visit 1 [V1]) were defined as slowly progressive ICPP and were followed up with a second clinical assessment (visit 2 [V2]); those who demonstrated signs of pubertal progression at V2 were included in the RP-ICPP group. The girls diagnosed with RP-ICPP between January 2016 and February 2020, before the COVID-19 pandemic (total, 50 months) belonged to group 1 and those diagnosed with RP-IPPC between March 2020 and the end of June 2021, during the COVID-19 pandemic (total, 16 months) were included in group 2. For each year (2016-2021), we analyzed the periods of January-June and July-December; the girls were classified based on chronological age at GnRH analogue (GnRHa) start (aged <6; 6-6.99; 7-7.99; >8 years).

Girls with premature thelarche, those with a genetic syndrome, brain tumor, or other preexisting condition, and those with peripheral precocious puberty or with isolated premature thelarche referred before 2 years of age were excluded from the study.

The study was approved by the local ethical committee (Protocol Number 13777/21; CER, Genova, Italy), and written informed consent was obtained from parents or the caregiver of patients after the received a full explanation of the study according to the Declaration of Helsinki.

Data Collection

We collected anamnestic data, including age at thelarche, family history for PP, ethnicity (European vs non-European), sport activity, COVID-19 infection in patients or parents in the previous months, changes in eating habits and screen viewing history (these last 3 pieces of data were collected retrospectively for girls in group 2 by means of a telephone interview), anthropometric/clinical data (weight, height [H], H SD score [SDS], body mass index [BMI] SDS, target height [TH], delta TH-H SDS, HV, pubertal Tanner stage), biochemical data (basal and peak gonadotropins [FSH, LH] after GnRH test, 17-beta estradiol [E2], metabolic parameters (total cholesterol, low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol, triglycerides, glycated hemoglobin, and insulin basal levels), and radiological data (bone age [BA], uterine length and transverse diameter, ovarian volumes, and neuroradiological imaging).

Family history for PP was considered as the appearance of menarche before the age of 10.25 years in a patient's mother, sister, or grandmother [21].

Our study includes only females in whom the first sign of pubertal development was the appearance of breast buds before age 8 years. We also excluded those in whom parents reported the appearance of pubic or axillary hair as the first sign of pubertal development. We also excluded cases associated with hypothalamic-pituitary abnormalities on MRI performed after the diagnosis of PP; we also collected biochemical data of all patients included.

Clinical Data

Pubertal maturation was determined through breast inspection and palpation and classified according to Tanner stage [22]. Height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) were measured by using a calibrated Harpenden stadiometer and an electronic scale. TH was calculated according to the formula: (father's height + mother's height − 13 cm)/2 [23] by measuring parents' height with calibrated Harpenden stadiometer whenever possible (not for adopted girls). SD scores of the children's height and TH were computed according to Tanner Whitehouse (1976) reference charts [24]. H-TH SDS was considered as the difference between H SDS and TH SDS.

BMI SDS was calculated by using the LMS method presented in the 2006 World Health Organization chart [25]. According to consensus position statement of the Italian Society for Pediatric Endocrinology and Diabetology and the Italian Society of Pediatrics [26], we defined overweight as BMI between the 85th and 97th percentile and obesity as BMI > 97th percentile of the 2007 World Health Organization charts [27].

Endocrine and Metabolic Data

FSH, LH, and E2 were measured after venous blood sampling between 8.00 and 9.00 AM with the electrochemiluminescence method by using a Roche Elecsys Kit (Roche Diagnostics GmbH, Mannheim, Germany).

Total cholesterol, cholesterol LDL/HDL, and triglycerides were measured with a colorimetric enzyme immunoassay; insulin basal level was determined with chemiluminescence; and hemoglobin was measured with immunoturbidimetry.

The GnRH test was performed by administering IV Lutrelef (Ferring) at the dose of 100 μg/m^2 (maximum dose: 100 μg) IV. Blood samples were taken at 0, 15, 30, and 60 minutes for the determination of LH and FSH.

Radiological Data

Bone age was determined based on radiography of the left hand and wrist according to Greulich and Pyle [28] with the BoneXpert software[29] or by 2 experts (D.F., C.P.). Delta BA was considered as the difference between BA and chronological age. Pelvic transabdominal ultrasonography was performed with a curvilinear 2- to 7-MHz probe by 2 skilled gynecologists (R.A. and V.T.) working at our center. Uterine length, transverse uterine diameter, and the height, width, and length of the ovaries were measured; the volume of each
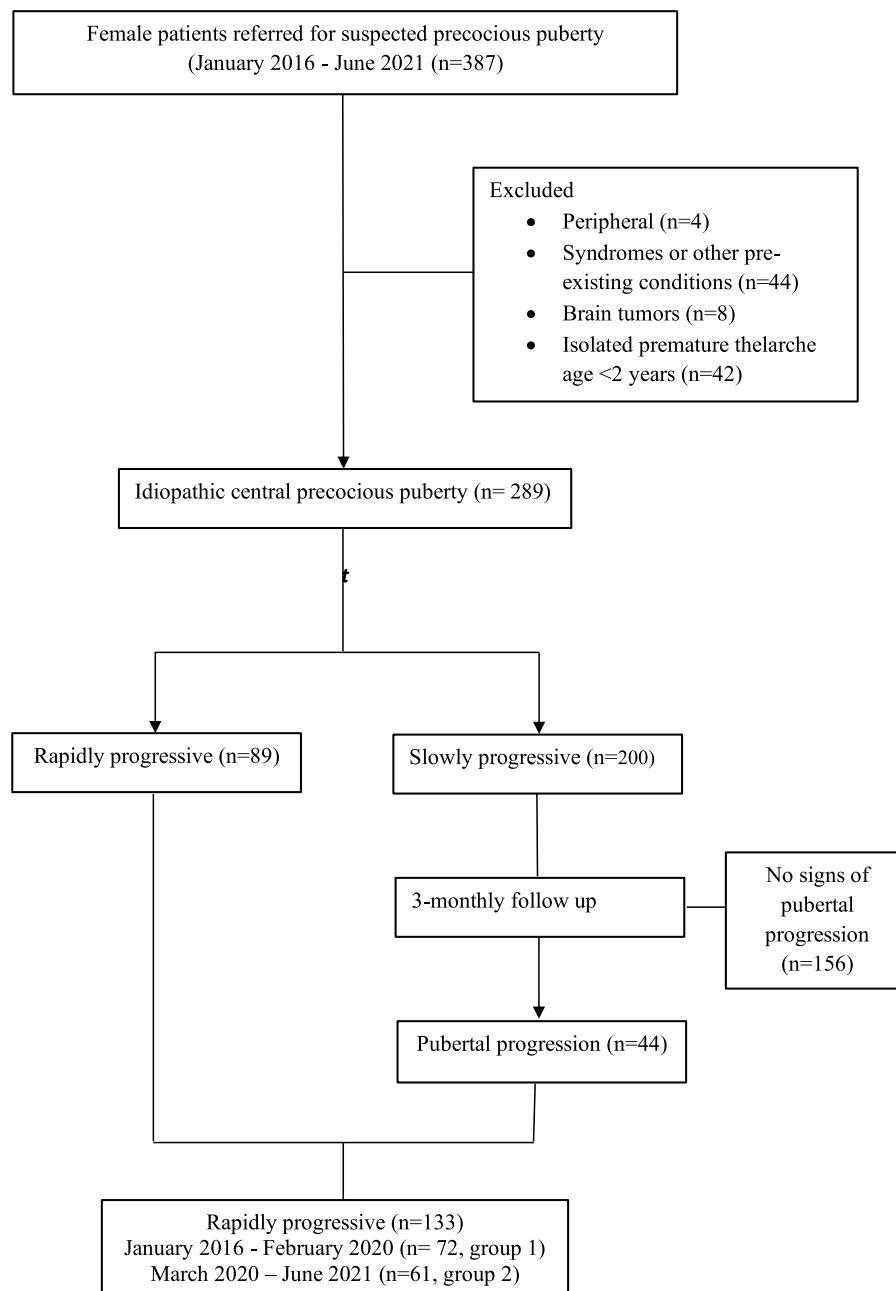
Figure 1. Flowchart for selection of girls with central precocious puberty based on the adopted criteria for the study.

ovary was calculated according to the ellipse formula (length × transverse diameter × fundal anteroposterior diameter × 0.5233).

Neuroimaging Data

All girls with RP-ICPP underwent brain MRI. MRI scans were performed with a 1.5-T MR system (InteraAchieva 2.6; Philips, Best, the Netherlands) using an 8-channel parallel imaging head coil. Standard evaluation of the sellar region included spin-echo T1- and turbo/fast spin-echo T2-weighted images on sagittal and coronal planes, acquired with a slice thickness of 3 mm. Additionally, a T2-weighted Driven Equilibrium (DRIVE) sequence (a high-resolution, heavily T2-weighted sequence acquired with a slice thickness 0.6 mm [25 slices] and a scan time of 2 minutes and

32 seconds, using a 3-dimensional technique with isotropic voxels ($0.6 \times 0.6 \times 0.6$ mm) was acquired on the sagittal plane as part of our routine sellar protocol.

Statistical analysis

Descriptive statistics were generated for the whole cohort. Data were expressed as mean and SD for continuous variables and as absolute or relative frequencies for categorical variables. The distribution of the data was analyzed using the Kolmogorov–Smirnov test. Nonparametric statistics were considered as appropriate. Differences between groups were evaluated using the Mann–Whitney U test for continuous variables and the χ^2 or Fisher exact test for categorical variables. A P value <.05 was considered statistically significant; all P values were based on 2-tailed tests. Statistical analysis was
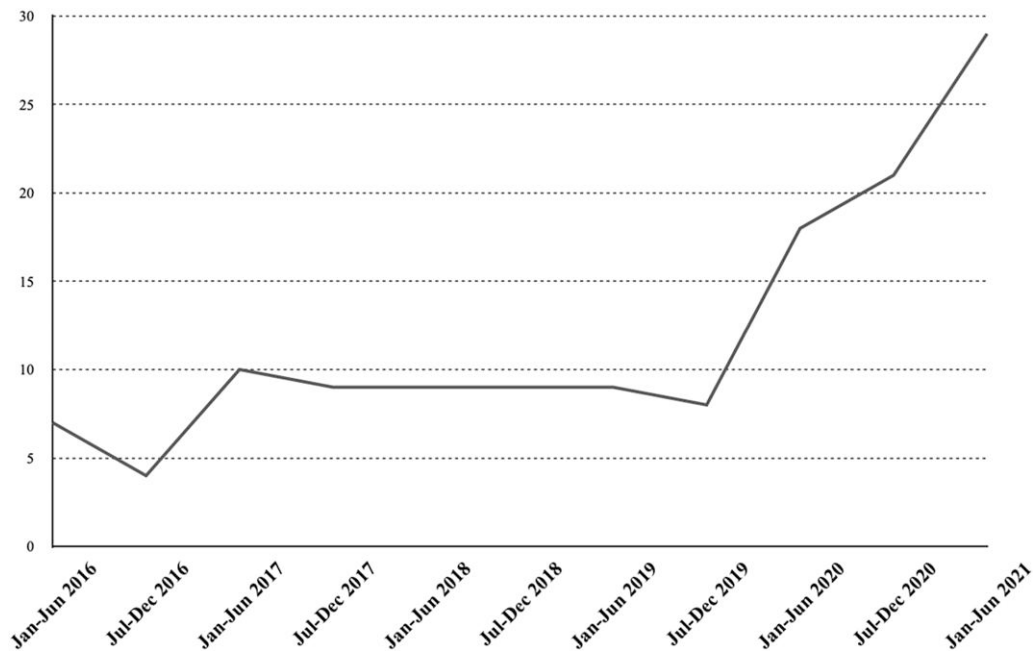
Figure 2. Number of cases of rapidly progressive idiopathic central precocious puberty divided by semesters and years of diagnosis.

Group 1 diagnosed between January 2016 and March 2020
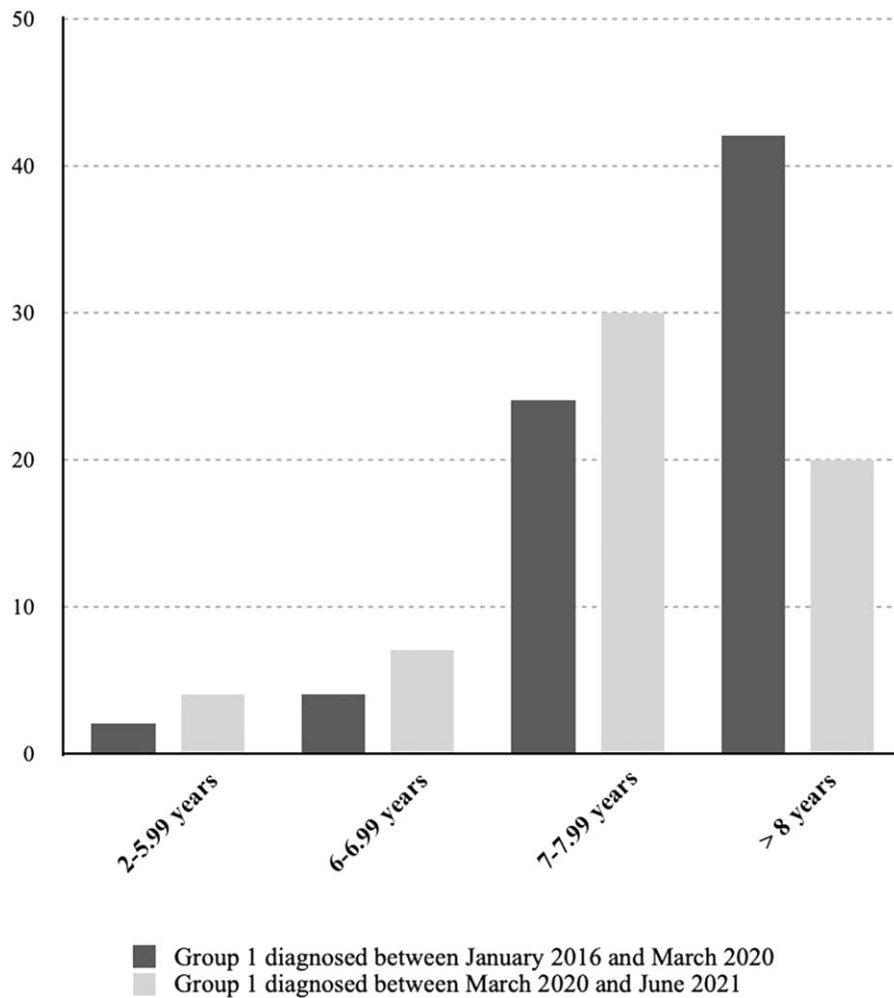Group 1 diagnosed between March 2020 and June 2021

Figure 3. Number of cases of rapidly progressive idiopathic central precocious puberty divided by age at diagnosis.

Table 1. Demographic and anthropometric data of 133 girls diagnosed with rapidly progressive idiopathic central precocious puberty

	Group 1 n = 72	Group 2 n = 61	*P* value
Clinical/anamnestic data (mean ± SD)			
Age at puberty onset (y)	7.03 ± 0.99	6.89 ± 0.99	.25
Age at GnRHa start (y)	7.96 ± 0.71	7.61 ± 0.94	**.005**
Delta age GnRHa start-puberty onset	0.93 ± 0.75	0.71 ± 0.62	**.03**
Height SDS	1.65 ± 1.15	1.37 ± 1.18	.21
BMI SDS	0.69 ± 1.15	1.01 ± 1.23	.18
Target height SDS	−0.20 ± 0.95	−0.26 ± 0.85	.74
Delta H-TH SDS	1.88 ± 0.99	1.67 ± 1.09	.26
Tanner stage	2.86 ± 0.51	2.64 ± 0.61	**.02**
Age at BA evaluation	7.94 ± 0.82	7.55 ± 0.96	**.004**
Bone age (BA)	9.75 ± 1.29	9.25 ± 1.48	.06
Delta CA-BA	1.80 ± 0.88	1.70 ± 1.02	.46
Age at V1[a]	7.46 ± 0.74	7.33 ± 0.63	.29
BMI SDS at V1[a]	0.62 ± 1.04	0.77 ± 1.49	.65
Delta BMI SDS (V2-V1)[a]	−0.13 ± 0.51	0.12 ± 0.45	.15
Screen time (hours/day)	NA	1.94 ± 1.81	
Familial history for CPP (number of patients)	16	12	
Endocrine data (mean ± SD)			
Baseline LH (U/L)	1.75 ± 2.24	1.26 ± 1.40	.56
LH peak (U/L)	16.22 ± 12.31	16.80 ± 13.17	.10
Baseline FSH (U/L)	4.36 ± 2.43	3.69 ± 2.00	.15
FSH peak (U/L)	11.99 ± 3.69	11.63 ± 3.82	.52
E2 (pg/mL)	19.49 ± 20.06	20.97 ± 22.54	.82
Metabolic data (mean ± SD)			
Glycated hemoglobin (%)	5.02 ± 0.27	5.07 ± 0.27	.60
Baseline insulin (uU/mL)	13.34 ± 8.06	17.35 ± 14.22	.22
Triglycerides(mg/dL)	65.85 ± 36.96	67.43 ± 35.33	.61
Total cholesterol(mg/dL)	146.85 ± 24.36	150.62 ± 18.90	.40
HDL cholesterol (mg/dL)	54.91 ± 12.87	61.56 ± 12.21	**.03**
LDL cholesterol (mg/dL)	80.09 ± 18.10	84.78 ± 18.54	.15
Ultrasound data (mean ± SD)			
Uterus length (mm)	37.09 ± 7.50	39.70 ± 8.62	.06
Uterus anteroposterior diameter (mm)	12.45 ± 3.38	11.59 ± 4.42	.08
Right ovary (cm^3)	2.51 ± 1.67	2.20 ± 1.48	.25
Left ovary (cm^3)	2.44 ± 1.36	2.47 ± 1.66	.69

Group 1: girls diagnosed between January 2016 and March 2020, before the COVID-19 pandemic; group 2: girls diagnosed between March 2020 and the end of June 2021, during the COVID-19 pandemic.
Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; E2, 17-beta estradiol; GnRHa, GnRH analog; HDL, high-density lipoprotein; H-TH, height-target height; LDL, low-density lipoprotein; NA, not available; SDS, SD score; V1, visit 1; V2, visit 2.
[a]Girls diagnosed with slowly progressive idiopathic central precocious puberty at V1 (n = 27/72, 37.5% [group 1] vs n = 17/61, 27.9% [group 2]). All statistically significative *P*-values (<0.05) have been boldfaced.

performed using the Statistical Package for the Social Sciences for Windows (SPSS Inc. Chicago, IL).

Results

A total of 387 girls with breast development presenting before the age of 8 years were evaluated for suspected PP between January 2016 and the end of June 2021. Their clinical data and laboratory characteristics were analyzed, and 289 girls were included (175 girls in group 1 and 114 girls in group 2; Fig. 1). The total number of RP-ICPP patients diagnosed was 133, 72 positive cases over 50 months (1.44 cases per month) in group 1 vs 61 cases over 16 months (3.8 cases per month) in group 2. Patients who met the

criteria for RP-ICPP at first evaluation were 89 (45 girls in group 1 and 44 girls in group 2) and girls diagnosed with slowly progressive ICCP at V1 who progressed to RP-ICPP at V2 were 44 (27 girls in group 1 and 17 girls in group 2). A total of 121 girls were treated with GnRHa and the parents of 12 girls chose not to treat their daughters with GnRHa.

A higher incidence of RP-ICPP was found in group 2 than in group 1 (n = 61/114 (53.5%) vs n = 72/175 (41.1%); the annual RP-ICPP incidence was the highest in 2021 even though the study ended in June 2021 and incidence was thus calculated for only 6 months (*P* < .05) (Fig. 2).

A progressive increase in the number of group 2 girls diagnosed with RP-ICPP was observed in every age group <8 years

Table 2. Mean BMI-SDS at GnRHa start according to chronological age and Tanner stage

Age at GNRHa start	N	BMI SDS (mean ± SD)	N		P value
		Group 1		Group 2	
<6 y	n = 2	−0.05 ± 0.78	n = 4	−0.21 ± 0.36	NA
6-6.99 y	n = 4	0.77 ± 1.33	n = 7	1.88 ± 0.95	.11
7-7.99 y	n = 24	0.65 ± 1.17	n = 30	1.03 ± 1.22	.22
>8 y	n = 42	0.75 ± 1.15	n = 20	0.93 ± 1.27	.68
Tanner stage		BMI SDS (mean ± SD)			
	N	Group 1	N	Group 2	P value
2	n = 15	0.44 ± 1.04	n = 26	0.85 ± 1.23	.38
3	n = 52	0.81 ± 1.16	n = 31	1.01 ± 1.19	.41
4	n = 5	0.25 ± 1.26	n = 4	2.07 ± 1.33	.06

Group 1: girls diagnosed between January 2016 and March 2020, before the COVID-19 pandemic; group 2: girls diagnosed between March 2020 and the end of June 2021, during the COVID-19 pandemic.
Abbreviations: BMI, body mass index; GnRHa, GnRH analog; SDS, SD score.

(<6 years, n = 4 vs n = 2 in group 1; 6-6.99 years, n = 7 vs n = 4; 7-7.99 years, n = 30 vs n = 24), but the number of girls aged >8 years diagnosed with RP-ICPP was significantly higher in group 1(n = 42 vs n = 20 group 2, $P < .05$) (Fig. 3). A family history of early menarche was reported in 28 of 133 girls (21%), 16 in group 1 (22%) and 12 in group 2 (19%).

Among 133 RP-ICPP girls, 20% (n = 27/133) had non-European origin, 16.6% (n = 12/72) in group 1 and 24.5% (n = 15/61) in group 2.

No significant difference was found in mean age at pubertal onset (aged 7.03 ± 0.99 vs 6.89 ± 0.99 years; $P = .25$) between group 1 and group 2 RP-ICPP (Table 1), though girls in group 1 were older at RP-ICPP diagnosis (aged 7.61 ± 0.94 years vs 7.96 ± 0.71 years; $P < .05$). The mean time between pubertal onset and RP-ICPP diagnosis was aged 0.93 ± 0.75 years in group 1 vs aged 0.71 ± 0.62 years in group 2 ($P < .05$). The mean Tanner stage observed at RP-ICPP diagnosis was 2.86 ± 0.51 in group 1 vs 2.64 ± 0.61 in group 2 ($P < .05$)

There were no differences between these 2 groups concerning the anthropometric and radiological parameters analyzed (W, H, H SDS, HV, HV SDS, TH, Delta H-TH, BA, Delta BA, pelvic ultrasound data). BMI SDS did not show significant difference, but we observed higher values in group 2 (1.01 ± 1.23 vs 0.69 ± 1.15 in group 1; $P = .18$), which were confirmed when we compared all chronological age categories (Table 2), except for those younger than aged 6 years, in which group 1 girls had a higher BMI. Furthermore, BMI SDS was higher in all girls in group 2 when considered according to Tanner stage at diagnosis (stage 2, 3, or 4) (Table 2).

Comparing V2 data of girls diagnosed SP-ICPP at V1, no significant differences were found in Delta BMI SDS V2-V1 (−0.13 ± 0.51 in group 1 vs 0.12 ± 0.45 in group 2; $P = .15$).

There were no differences in sex hormones values between group 1 and group 2 (LH and FSH levels, both at baseline and peak after GnRH test, and E2 basal levels). No differences were found in the values of triglycerides, total and LDL cholesterol, basal insulin, and glycated hemoglobin levels, whereas cholesterol HDL levels were higher in group 2 (61.56 ± 12.21 vs 54.91 ± 12.87 in group 1, $P < .05$).

Group 2 girls showed a medium of 2 or more daily hours spent using electronic devices (1.946 ± 1.813 hours/day), and 54 girls (88,5%) of this group stopped the scheduled physical activity they had been doing prepandemic. No girls had COVID-19 before the diagnosis of RP-ICPP; whereas only 1 had a mother hospitalized because of a severe SARS-CoV-2 infection. No one reported changes in eating habits during COVID-19 pandemic.

Regarding European girls (n = 106; n = 60 in group 1; n = 46 in group 2; Table 3), significant differences in mean age (7.97 ± 0.74 in group 1 vs 7.60 ± 1.00 in group 2, $P < .05$) and mean clinical Tanner stage (2.85 ± 0.48 in group 1 vs 2.63 ± 0.61 in group 2, $P < .05$) at RP-ICPP diagnosis were found. The biochemical data confirmed higher HDL cholesterol levels in group 2 (62.40 ± 12.53 vs 53.26 ± 12.22 in group 1, $P < .05$), and showed increased basal insulin levels in the same girls (19.34 ± 15.73 vs 12.55 ± 7.87 in group 1, $P < .05$).

No significant differences emerged between non-European girls (n = 27; n = 12 in group 1; n = 15 in group 2) in terms of clinical, biochemical, and radiological data (Table 4).

Discussion

A growing body of evidence suggests a possible increased incidence of PP in girls during the COVID-19 pandemic because of multiple potential causes [1, 2, 11, 3-10]. Children, adolescents, and adults became less physically active and rates of overweight and obesity, as well as stress, increased during the pandemic [15, 16].

Our data confirm the increased number of patients referred for suspected PP during COVID-19 pandemic, and the increased incidence of RP-ICPP over the same time interval (1.3 times higher in group 2 than group 1). Unlike other Italian studies, we analyzed our data taking into consideration a longer interval, in particular the period between March 2020 and June 2021, during which Italy underwent a total —then partial—lockdown and reduction of activities (school closure, disruption in daily physical activities routine—especially noncompetitive ones) compared with annual cohort data of the previous 4 years. A significant increase in those newly diagnosed with CPP in the first total lockdown (March–July 2020), compared with the same period in previous years (March–July 2015-2019; 37 vs 89) were reported by Stagi et al [1], as well as by Barberi et al [6], who found a

Table 3. Demographic and anthropometric data of 106 European girls diagnosed with rapidly progressive idiopathic central precocious puberty

	Group 1 n = 60	Group 2 n = 46	P value
Clinical data (mean ± SD)			
Age at puberty onset (y)	7.04 ± 1.06	6.93 ± 1.03	.38
Age at GnRHa start (y)	7.97 ± 0.74	7.60 ± 1.00	**.01**
Delta age GnRHa-puberty onset	0.93 ± 0.79	0.67 ± 0.50	**.06**
Height SDS	1.34 ± 0.08	1.31 ± 0.10	.27
Tanner stage	2.85 ± 0.48	2.63 ± 0.61	**.03**
Age at BA evaluation	7.95 ± 0.85	7.56 ± 1.04	**.02**
BMI SDS	0.61 ± 1.17	0.92 ± 1.20	.28
Target height SDS	−0.18 ± 0.88	−0.17 ± 0.76	.97
Delta H-TH SDS	1.77 ± 0.99	1.63 ± 0.95	.42
BA	9.70 ± 1.31	9.21 ± 1.60	.09
Delta CA-BA	1.76 ± 0.86	1.65 ± 1	.50
Age at V1[a]	7.52 ± 0.74	7.27 ± 0.51	.06
BMI SDS at V1[a]	0.62 ± 1.03	0.88 ± 1.61	.36
Delta BMI SDS (V2-V1)[a]	−0.14 ± 0.55	0.07 ± 0.38	.29
Endocrine data (mean ± SD)			
Baseline LH (U/L)	1.76 ± 2.16	1.28 ± 1.43	.53
LH peak (U/L)	16.28 ± 12.35	16.80 ± 11.24	.76
Baseline FSH (U/L)	4.33 ± 2.42	3.82 ± 2.10	.31
FSH peak (U/L)	11.99 ± 3.93	11.73 ± 3.86	.70
E2 (pg/mL)	20.38 ± 20.21	22.11 ± 24.05	.90
Metabolic data (mean ± SD)			
Glycated hemoglobin (%)	5.01 ± 0.28	5.04 ± 0.29	.79
Baseline insulin (uU/mL)	12.55 ± 7.87	19.34 ± 15.73	**.03**
Triglycerides (mg/dL)	65.16 ± 39.03	66.70 ± 36.29	.70
Total cholesterol (mg/dL)	143.10 ± 24.56	149.50 ± 19.69	.16
HDL cholesterol (mg/dL)	53.26 ± 12.22	62.40 ± 12.53	**.01**
LDL cholesterol (mg/dL)	76.88 ± 17.26	83.16 ± 19.55	.08
Ultrasound data (mean ± SD)			
Uterus length (mm)	37.22 ± 7.62	39.40 ± 9.18	.20
Uterus anteroposterior diameter (mm)	12.56 ± 3.52	11.55 ± 4.61	.09
Right ovary (cm^3)	2.63 ± 1.76	2.29 ± 1.56	.31
Left ovary (cm^3)	2.48 ± 1.32	2.50 ± 1.56	.75

Group 1: Girls diagnosed between January 2016 and March 2020, before Covid-19 pandemic; Group 2: Girls diagnosed between March 2020 and the end of June 2021, during Covid-19 pandemic;
Abbreviations: BA, bone age; BMI, body mass index; E2, 17-beta estradiol; GnRHa, GnRH analog; HDL, high-density lipoprotein; H-TH, height-target height; LDL, low-density lipoprotein; SDS, SD score; V1, visit 1; V2, visit 2.
[a]Girls diagnosed as SP-ICPP at V1 (n = 26/60, 43,3% (Group1) vs n = 32/46, 69,6% (Group2)). All statistically significative P-values (<0.05) have been boldfaced.

significant increase of CPP diagnosed between March 2020 and April 2021 compared with the previous 13 months. Other authors [2, 4, 5] reported either a total increase of 108% of girls diagnosed between March and September 2020 compared with the same period of the previous year (246 vs 118) or a 2.5-fold higher incidence rate of CPP diagnosed in 12 months (April 2020–April 2021), compared with the 3 previous years (35 vs 34). Chioma et al [7], in turn, confirmed a 1.57-fold increase in the incidence of PP, together with a general change in daily habits during COVID-19, including a reduction of physical activity, an overall greater use of electronic devices, and behavioral changes.

A similar pattern of CPP increase was also observed in other countries, including India [8], where the authors reported 155 children referred for PP during COVID-19 against 59 in pre-COVID-19 period with a total of 136 and 44 diagnosed ICPP, respectively, during and before COVID-19; and Turkey [30], where Acar et al reported a double number of girls diagnosed with ICPP in the 1-year study period during the pandemic compared with the previous 3 years (58 girls, vs 19 in 2017, 22 in 2018, and 25 in 2019).

Although the age of thelarche has declined by an average of nearly 3 months per decade as reported previously [31], we cannot rule out a role, direct and not, of COVID-19 as an additional environmental trigger for hypothalamic-pituitary reproductive axis [32]. Eckert-Lind et al [31], in a recent meta-analysis, found different mean ages at thelarche in girls of different ethnicity, with a geographical variation that showed the earliest onsets in the United States (aged

Table 4. Demographic and anthropometric data of 27 extra-European girls diagnosed with rapidly progressive idiopathic central precocious puberty

	Group 1 n = 12	Group 2 n = 15	*P* value
Clinical data (mean ± SD)			
Age at puberty onset (y)	7.00 ± 0.66	6.78 ± 0.85	.65
Age at GnRHa start (y)	7.95 ± 0.58	7.63 ± 0.73	.35
Delta age GnRHa-puberty onset	0.95 ± 0.60	0.85 ± 0.92	.28
Height SDS	1.79 ± 1.35	1.19 ± 1.70	.43
Tanner stage	2.92 ± 0.67	2.67 ± 0.62	.40
Age at BA evaluation	7.92 ± 0.67	7.51 ± 0.70	.08
BMI SDS	1.11 ± 0.95	1.28 ± 1.31	.40
Target height SDS	−0.35 ± 1.36	−0.56 ± 1.07	1
Delta H-TH SDS	2.51 ± 0.74	1.80 ± 1.52	.55
Bone age (BA)	9.83 ± 1.05	9.55 ± 1.24	.87
Delta CA-BA	1.88 ± 0.83	1.91 ± 1.14	.65
Age at V1[a]	7.26 ± 0.76	7.52 ± 0.96	.56
BMI SDS at V1[a]	0.63 ± 1.18	0.44 ± 1.21	.73
Delta BMI SDS (V2-V1)[a]	−0.07 ± 0.37	0.27 ± 0.67	.56
Endocrine data (mean ± SD)			
Baseline LH (U/L)	1.70 ± 2.72	1.20 ± 1.34	1
LH peak (U/L)	15.95 ± 12.77	16.81 ± 18.62	.48
Baseline FSH (U/L)	4.52 ± 2.61	3.31 ± 1.76	.24
FSH peak (U/L)	12.00 ± 2.53	11.32 ± 3.89	.63
E2 (pg/mL)	15.00 ± 19.47	17.21 ± 16.85	.63
Metabolic data (mean ± SD)			
Glycated hemoglobin (%)	5.08 ± 0.21	5.13 ± 0.20	.78
Baseline insulin (uU/mL)	16.42 ± 8.50	11.37 ± 5.13	.16
Triglycerides (mg/dL)	69.00 ± 27.69	70.11 ± 33.45	.84
Total cholesterol (mg/dL)	164.71 ± 13.77	154.67 ± 16.04	.30
HDL cholesterol (mg/dL)	61.29 ± 14.29	58.67 ± 11.20	.92
LDL cholesterol (mg/dL)	92.00 ± 17.21	90.56 ± 13.78	.76
Ultrasound data (mean ± SD)			
Uterus length (mm)	36.42 ± 7.18	40.64 ± 6.71	.14
Uterus anteroposterior diameter (mm)	11.91 ± 2.66	11.71 ± 3.91	.61
Right ovary (cm^3)	1.94 ± 1.09	1.91 ± 1.25	.70
Left ovary (cm^3)	2.23 ± 1.58	2.39 ± 2.00	.98

Group 1: girls diagnosed between January 2016 and March 2020, before the COVID-19 pandemic; group 2: girls diagnosed between March 2020 and the end of June 2021, during the COVID-19 pandemic.
Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; E2, 17-beta estradiol; GnRHa, GnRH analog; HDL, high-density lipoprotein; H-TH, height-target height; LDL, low-density lipoprotein; SDS, SD score; V1, visit 1; V2, visit 2.
[a]Girls diagnosed with slowly progressive idiopathic central precocious puberty at V1 (n = 5/12, 41.6% [group 1] vs n = 4/15, 26.6% [group 2]).

8.8-10.3 years) and the latest ones in Africa (aged 10.1-13.2). Large population studies have already shown a secular decrease in the median age of pubertal onset, clearer in Hispanic and Black girls [33, 34]. Indeed, further studies are needed to confirm that COVID-19 pandemic may have exacerbated this trend.

According to other Italian studies [2, 5, 6], we found no significant differences in the anthropometric parameters studied. Although not statistically significant, we detected higher BMI SDS in group 2, both considering the entire group and the subgroups based on chronological age and Tanner stage. These data are in line with the positive worldwide trend in weight gain reported before and during COVID-19 pandemic, and the data reported by others who found a significant increase in BMI during lockdown in Italian girls diagnosed with CPP during COVID-19 pandemic [1, 35-38]. Obesity and overweight are positively correlated with early puberty [39, 40], although the possible mechanisms implicated remain to be elucidated. The rapid increase in body weight is associated with advanced pubertal development [41], and an increase in body fat mass, especially central, seems to have an important role [42]. In line with this concept, the change in everyday habits could have modified body composition in term of fat distribution, without causing a significant increase in BMI SDS. Finally, other possible mechanisms linking adiposity with pubertal timing include leptin, adipocytokines, gut peptides, endocrine disrupting chemicals, and sexual hormones [41, 43-48].

Despite data reporting significantly higher levels of FSH, LH, and 17-beta estradiol or increased ovarian volume and uterus length in girls diagnosed during the COVID 19 pandemic by others [1, 5], our results did not confirm these findings. The higher cholesterol HDL levels found in group 2 RP-ICPP, and the higher serum insulin levels observed in European RP-ICPP group 2 girls, could suggest that the containment measures adopted during the pandemic have had a greater metabolic impact on some girls than others. Hyperinsulinemia, alone or in conjunction with adiposity, has already been described as a trigger for precocious puberty; it increases the bioavailability of sex hormones by reducing the levels of sex hormone binding proteins [49]. And puberty itself, on the contrary, cause insulin resistance with consequent hyperinsulinemia [50].

Excessive screen exposure is a risk factor for obesity and pubertal timing in youth, though the role of specific types of screen viewing is not fully understood [1, 7, 48]. According to other authors [6, 7], we observed, during the COVID-19 lockdown, a prolonged use of electronic devices and a reduced scheduled physical activity, factors that could have influenced pubertal timing through direct and indirect factors. Several studies, furthermore, have also investigated the effect of electromagnetic fields on sexual development [51]. Whether the greater amount of time spent by the parents with their children during lockdown could have favored the recognition of early signs of pubertal onset cannot be ruled out; this aspect could have contributed to the higher amount of referral of ICPP, as reported by Cemeroglu et al [52]. In addition, the role of psychological distress, high parental conflict, economic status, and the endocrine disruptors along with the increased use of hand sanitizers and surface disinfectants, represent potential further interesting hypotheses [5, 53-56].

In our study, the percentage of non-European RP-ICPP was almost the same during COVID-19 compared with prepandemic period (around 20% in both groups, one-fifth of the total RP-ICPP); although not significant, data coming from this group support the results obtained in all 133 RP-ICPP in terms of BMI SDS. Conversely, European girls confirmed, also, a lower age at diagnosis with less developed Tanner stage, higher HDL cholesterol levels, and, not found in the total group, a higher basal insulin level.

Inherent limitations of our data are related to the retrospective and observational nature of the study that cannot address cause and effect; furthermore, some data could be inaccurate, in particular those recorded by the mean of a phone call. Finally, the absence of data suggesting a decrease in new diagnoses over time suggests that the results do not imply a causal relationship.

Conclusion

A sharp spike in new diagnoses of idiopathic and rapidly progressive PP coincided with the COVID-19 pandemic. Although our results seem to suggest a correlation between the COVID-19 pandemic and PP based on the observed changes in daily family habits, the main conclusion from this analysis is that the relationship between COVID-19 pandemic and lifestyle changes requires careful consideration, and further studies are needed on this subject. Whether PP may have been detected because of a greater attention of families to the appearance of the first pubertal signs that may be linked to some genetic, cultural, and environmental factors and life

stress specific to some countries during COVID-19, or to an increased interaction of the patient with health care providers after the lockdown cannot be ruled out.

During the COVID-19 pandemic, the number of girls with suspected PP resulted 1.79-fold increased, with a 1.3-times higher incidence of RP-ICPP. Although obesity is most frequently proposed as being the greatest risk factor in terms of affecting the physiology of puberty, there are also findings that suggest that other factors contribute directly to early pubertal activation. Further studies are needed to investigate how the increasing use of digital devices, the reduction of daily physical activity and changes in sleep patterns impact on body composition and fat distribution, and how this influences children's pubertal development. Assessment of the causal relationships between the COVID-19 pandemic and early/rapidly progressive puberty requires short-term and long-term rigorous epidemiologic and mechanistic studies.

Author Contributions

All listed authors contributed substantially to this study, in accordance with the *Journal of the Endocrine Society* authorship guidelines and reviewed and approved the final version of the manuscript. They agree to be accountable for all aspects of this work and are prepared to take public responsibility of it. This manuscript is original and has not been already published or preprint in any language or format and has not been submitted elsewhere for print or electronic publication consideration.

Disclosures

The authors report no competing interests.

Data Availability

All datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. Raw data were generated at Giannina Gaslini Institute. Individual patient data will be made available on request in agreement with data privacy statement signed by all patients.

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