

# Rapidly progressive precocious puberty during the COVID-19 lockdown

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## ABSTRACT

**Introduction.** During the COVID-19 pandemic, an increase in consultations for precocious puberty (PP) was observed. Our objective was to determine the frequency of PP and its progression before and during the pandemic.

**Methods.** Retrospective, observational, analytical study. The medical records of patients who consulted with the Department of Pediatric Endocrinology between April 2018 and March 2021 were assessed. Consultations for suspected PP during the pandemic (period 3) were analyzed and compared to the 2 previous years (periods 1 and 2). Clinical data and ancillary tests done in the initial assessment and PP progression information were collected.

**Results.** Data from 5151 consultations were analyzed. An increase in consultations for suspected PP was observed during period 3 (21% versus 10% and 11%,  $p < 0.001$ ). Patients who consulted for suspected PP during period 3 increased 2.3-fold (80 versus 29 and 31,  $p < 0.001$ ). In total, 95% were female; this was the population analyzed. We included 132 patients with similar age, weight, height, bone age, and hormonal characteristics in the 3 periods. During period 3, a lower body mass index, a higher percentage of Tanner breast stage 3–4, and a greater uterine length were observed. Treatment was indicated upon diagnosis in 26% of the cases. In the rest, their evolution was monitored. During follow-up, a rapidly progressive course was observed more frequently in period 3 (47% versus 8% versus 13%,  $p = 0.02$ ).

**Conclusions.** We observed an increase in PP and a rapidly progressive evolution in girls during the pandemic.

**Key words:** precocious puberty; pandemics; COVID-19.

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## INTRODUCTION

Puberty is an important developmental milestone during which secondary sexual characteristics develop progressively, leading to the attainment of reproductive capacity.<sup>1</sup> The primary event is the activation of the hypothalamic-pituitary-gonadal axis due to the pulsatile secretion of gonadotropin-releasing hormone by the hypothalamus.<sup>2</sup> The mechanisms responsible for the onset of puberty have not been fully explained, but an interaction between genetic and environmental factors, such as nutrition, physical activity, stressful situations, exposure to light, and endocrine disruptors, has been described.<sup>1,3</sup>

Precocious puberty is defined as the onset of progressive pubertal changes at an age of less than 2 standard deviations from the mean for the population; before 8 years of age in girls and before 9 years of age in boys.<sup>1</sup> The timing of normal puberty has changed over the past few centuries; according to historical data, the age of menarche decreased from 17 years in the 19<sup>th</sup> century to 13 years in the mid-20<sup>th</sup> century.<sup>4,5</sup> Over the past 50 years, such trend in the age of menarche has stabilized; however, the age of onset of breast development in girls appears to have decreased over the past two decades,<sup>6-8</sup> which may indicate that the pubertal period has lengthened.<sup>9-11</sup> In relation to boys, the age of onset of genital development has remained around 11.5 years, with no secular trend towards an earlier age of pubertal onset.<sup>12-14</sup>

In 2020, the World Health Organization declared the COVID-19 pandemic. In March 2020, a health emergency was declared in Argentina and a population lockdown was implemented to prevent the infection. During this period, daily activities were affected. The prohibition to circulate, except for essential activities, the impossibility to play sports and attend school in person, etc., resulted in changes in lifestyle, physical activity, and eating habits, in addition to the stressful situation experienced due to the pandemic and the impact of a lockdown that revealed socialization deficiencies.

During this period of time, we have observed an increase in consultations for suspected precocious puberty and rapidly progressive pubertal development. The same situation was reflected in several scientific publications in different countries.<sup>15-20</sup> There is lack of available information about this phenomenon in children in Argentina. The objective was to assess

the frequency of consultations for suspected precocious puberty and its progression in our population during the year of lockdown due to the pandemic, comparing the results with data from previous years.

## METHODS

### Patients

This was a retrospective, observational, and analytical study. We assessed all the consultations made at the Department of Pediatric Endocrinology of Hospital Universitario CEMIC during the months of the COVID-19 pandemic lockdown between April 2020 and March 2021 (period 3) and compared them to the consultations made in the same period in the 2 previous years. (Period 1: April 2018-March 2019. Period 2: April 2019-March 2020).

Patients who consulted for suspected precocious puberty included girls with onset of breast development before 8 years old or between 8 and 9 years old with rapidly progressive puberty (change of pubertal stage in less than 6 months) and boys with increased testicular volume (> 4 mL) before 9 years old, who made a spontaneous consultation or were referred by their pediatrician. Patients who consulted for thelarche younger than 3 years, pubarche, or sweat odor, and patients with a history of neurological diseases, neurosurgical procedures and/or radiotherapy in the central nervous system, cancer, and other endocrine disorders that may interfere with pubertal development were excluded.

The study was conducted in accordance with the Declaration of Helsinki, approved by the Research Ethics Committee of CEMIC, and registered in the Computerized Health Research Registry Platform of Buenos Aires.

### Data collection

Data were collected retrospectively from the medical records. The reasons for consultation were classified and grouped according to the most frequent consultation categories in pediatric endocrinology. For patients who consulted for suspected precocious puberty, their history of adoption, prematurity, intrauterine growth retardation, and other medical history, maternal age at menarche, and mean parental height were recorded.

At the time of the first consultation, sex, age, anthropometric data (weight, height, and body mass index) were recorded, both in units of measurement and standard deviation according

to the Guideline for the Assessment of Physical Growth by the Sociedad Argentina de Pediatría.<sup>21</sup> The pubertal stage was recorded taking into account the Tanner stage of breast development, pubic hair, and male genitals.<sup>22</sup> Testicular volume –as measured using the Prader orchidometer– and the presence of axillary hair were recorded.

The results of the ancillary tests at the time of the initial assessment were recorded. A gynecological ultrasound was done to determine uterine size and ovarian volume; a uterine length > 35 mm and an ovarian volume > 2 cm<sup>3</sup> were considered values indicative of pubertal onset.<sup>23</sup> The bone age was determined by an X-ray of the left hand and wrist and compared to the Greulich and Pyle atlas.<sup>24</sup> Recorded hormonal values, where available, included luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, and testosterone as determined by chemiluminescent immunoassay. A baseline LH determination > 0.3 IU/L was considered pubertal onset.<sup>25</sup>

Upon completion of the initial assessment, in patients with a diagnosis of rapidly progressive precocious puberty, treatment with gonadotropin-releasing hormone (GnRH) analog was indicated, while in patients without evidence of progression, an expectant management was adopted, recording their evolution with clinical, auxological, radiologic, ultrasound, and biochemical parameters. During follow-up, “rapidly progressive puberty” was defined as a change between pubertal stages in a period of less than 6 months, accompanied by growth velocity greater than the 97<sup>th</sup> percentile and ultrasound, radiologic and/or biochemical changes.

### Statistical analysis

The statistical software used was Stata 15.0. Summary statistics for qualitative variables were absolute frequency and proportions, expressed as percentages. In relation to quantitative variables, mean and standard deviation were estimated for those with normal distribution, whereas median and percentile, for those with non-Gaussian distribution.

The association between qualitative variables was assessed with the  $\chi^2$  test and Fisher’s exact test. Quantitative variables were estimated using the Kruskal-Wallis test.

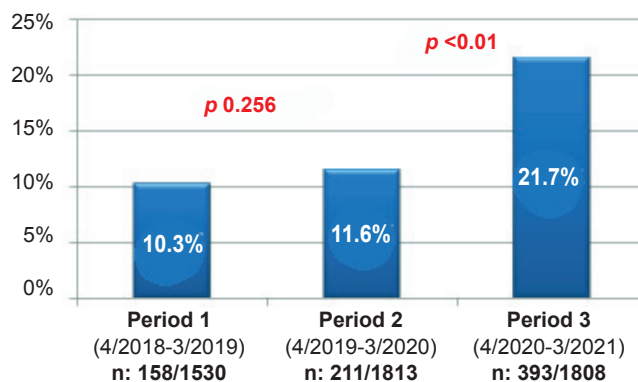
A 95% confidence interval was obtained based on Poisson distribution. The statistical significance was established using a Poisson regression model, considering a  $p$  value < 0.05.

## RESULTS

### Consultations due to suspected precocious puberty

A total of 5151 consultations with the Department of Pediatric Endocrinology were registered: 1530 in period 1 (April 2018-March 2019), 1813 in period 2 (April 2019-March 2020), and 1808 in period 3 (April 2020-March 2021). The analysis of the percentage of consultations for suspected precocious puberty in each period found that 10.3% (158/1530) occurred in period 1; 11.6% (211/1813), in period 2; and 21.7% (393/1808), in period 3. The percentage of consultations for suspected precocious puberty remained constant between periods 1 and 2, whereas it increased significantly in period 3, which was the year of the lockdown (*Figure 1*).

**FIGURE 1. Percentage of consultations due to suspected precocious puberty**



Consultations for suspected precocious puberty corresponded to a total of 140 patients. Twenty-nine patients consulted for the first time in period 1, 31 in period 2, and 80 in period 3. There was a 2.3-fold increase in the number of patients who consulted for the first time for suspected precocious puberty in period 3, compared to the previous periods, during which the number of patients who consulted for the first time for suspected precocious puberty remained stable ( $p < 0.001$ ).

When comparing all the reasons for consultation with Endocrinology during period 3 in relation to the previous year (period 2), a significant increase was observed exclusively in

consultations for suspected precocious puberty (Figure 2).

### Characteristics of the population

The characteristics of the patients who consulted for the first time in the 3 periods were compared. A total of 140 patients consulted for suspected precocious puberty; 1 patient was excluded because of a history of severe head injury. Out of 139 patients, 95% (n: 132) were female and 5%, male (n: 7). Since a significant difference was observed in the increase of consultations exclusively in girls, it was decided to analyze this population. A total of 132 patients were assessed.

FIGURE 2. Consultations with the Department of Pediatric Endocrinology

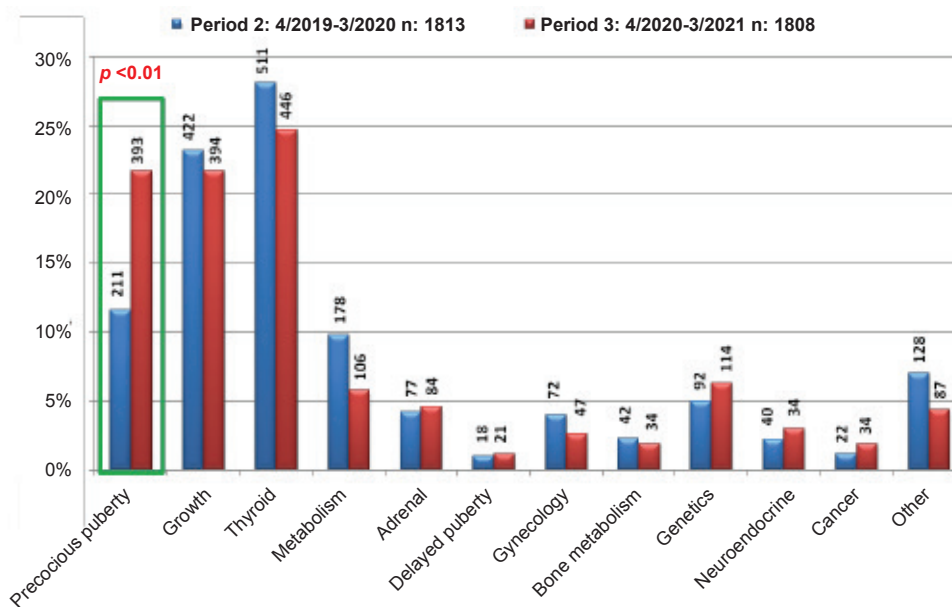


TABLE 1. Initial assessment of patients with suspected precocious puberty

Period	1	2	3	P
n	27	28	77	< 0.01
Age in years, mean and SD	8.09 ± 1	8.2 ± 0.6	8.2 ± 1.2	0.912
Weight: Z-score, mean and SD	1.6 ± 1.4	1.2 ± 1.2	0.9 ± 1.5	0.104
Height: Z-score, mean and SD	1.5 ± 1.2	1.5 ± 1.2	1.2 ± 1	0.308
Δ of GTH-height, mean and SD	0.9 ± 1.3	0.9 ± 1.4	0.8 ± 0.9	0.925
BMI: Z-score, mean and SD	1.3 ± 1	1 ± 0.9	0.7 ± 1.2	0.033
Preterm, %	3.7	0	6.5	0.535
IUGR, %	7.4	3.6	7.8	0.801
Adoption, %	0	7.1	3.9	0.391
Maternal early menarche, %	12.5	13.0	16.4	0.936
Bone age in years, mean and SD	8.9 ± 2	9.5 ± 1.8	9.3 ± 1.7	0.506
Cervical length in mm, mean and SD	29.6 ± 9.9	34.6 ± 6.7	36.2 ± 9.9	0.012
Ovarian volume in cm <sup>3</sup> , mean and SD	2.4 ± 1	2.3 ± 1.4	2.7 ± 2.2	0.560

SD: standard deviation. GTH: genetic target height. BMI: body mass index. IUGR: intrauterine growth restriction.

The characteristics of patients at the time of their initial assessment are described in *Table 1*. The age of the girls at the time of the first consultation was similar in the 3 groups. Anthropometric data were similar in terms of standard deviation scores for weight, height, and the delta of genetic target height-height among the patients in the 3 periods. In the initial assessment of nutritional status, a lower body mass index (BMI) was observed in the group of patients in period 3 compared to those in periods 1 and 2.

The history of risk factors for precocious puberty (prematurity, low birth weight, adoption, and history of maternal early menarche) were assessed and no differences were observed among the groups.

The bone age at diagnosis was similar in the 3 periods, as well as the difference between bone age and chronological age. In the ultrasound assessment, a larger uterine size was observed in the patients of period 3, while ovarian volume was similar across all 3 periods. The basal determinations of FSH, LH, and estradiol of the patients for whom these were available were analyzed (6/27 in period 1, 7/28 in period 2, and 33/77 in period 3) and no significant differences were observed among the 3 groups, although the number of measurements was low to extrapolate conclusions. Nine patients had had the menarche before the first consultation, at an average age of 8.9 years, with no difference among the 3 groups ( $p: 0.290$ ). In relation to the degree of pubertal development at the time of the initial physical

examination, the presence of Tanner breast stage 3–4 was observed in a higher percentage in period 3 (78%) compared to periods 1 and 2 (51% and 64%) ( $p: 0.02$ ). No differences among the 3 groups were observed in the Tanner pubic hair stage ( $p: 0.626$ ).

### Evolution

Of the 132 patients who consulted for suspected precocious puberty, 105 (79.5%) completed the initial assessment (physical examination, anthropometric assessment, bone age, and gynecological ultrasound). At the end of the initial assessment in 28 patients (26%), rapidly progressive precocious puberty was found and treatment with GnRH analog was prescribed; this indication was similar in the 3 periods. In the rest of the patients ( $n: 77$ ), an expectant management was adopted. The evolution of 63 patients (81.8%) was recorded during an average period of 13.5 months. The evolution of 13 patients was recorded during period 1; 23 patients (12 of whom were in follow-up from the previous period), during period 2; and 58 patients (10 in follow-up from period 1 and 9 from period 2), during period 3 (*Figure 3*). During follow-up, a rapidly progressive evolution was observed in 49% of the patients, with a significant difference in the patients followed during period 3 (*Figure 4*). In the patients with rapidly progressive puberty, treatment was indicated to prevent early menarche, except in 6 patients in period 3 who had been receiving follow-up for an average of 13 months since the first consultation.

FIGURE 3. Follow-up

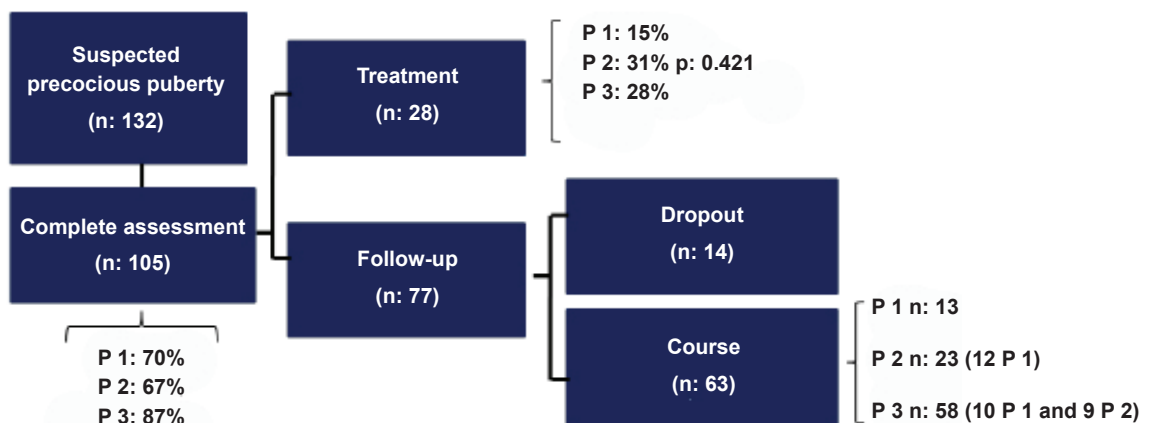
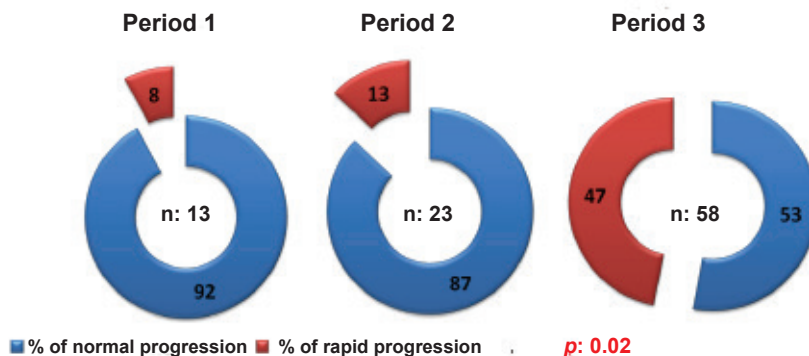


FIGURE 4. Course of patients with suspected precocious puberty



## DISCUSSION

We observed a significant increase in consultations for suspected precocious puberty during the pandemic period; such increase was observed only in girls and is consistent with other studies published in different countries.<sup>15–20</sup> It is probable that there was also an impact on pubertal development in boys that was not reflected in the consultations made during the first year of the pandemic, since the onset of puberty in boys is less evident to parents and many routine pediatric check-ups were postponed during this period. A long-term observation of pubertal development in boys will allow us to note its impact.

The lifestyle changes imposed by the isolation resulting from the pandemic could have affected pubertal maturation. Overweight and obesity are associated with earlier pubertal milestones;<sup>26</sup> however, in our study, we did not observe a negative effect of lockdown on the nutritional status of this group of patients, who had a lower BMI. According to previous publications, no increase was observed in the BMI of patients who consulted during the pandemic, compared to previous years.<sup>15–20</sup> In any case, the restrictions on physical activity could have modified body composition, but this was not assessed in our patients, and could have impacted GnRH neurons through molecules such as ghrelin, as described in the study by Chen et al. in Chinese girls.<sup>20</sup>

Another factor that could be related to the increase in cases of precocious puberty is exposure to electronic devices. During 2020, in Argentina, children exclusively carried out their activities online, with a greater exposure to screens, which is associated with a decrease in melatonin levels in children.<sup>27</sup> During childhood, a physiological decrease in melatonin levels

precedes the onset of puberty<sup>28</sup> and could be a modulating factor of GnRH neuron activity, as shown by animal<sup>29</sup> and *in vitro* studies.<sup>30</sup>

The pandemic and the social isolation had a negative effect on the mental health of many children, with increased symptoms of anxiety and depression.<sup>31</sup> Chronic exposure to stressful situations has been associated with earlier onset of puberty<sup>32</sup> and could be another factor related to the increase in precocious puberty.

The girls who consulted during the year of the pandemic had a greater estrogenic effect, as observed in Tanner breast stage and uterine length, and the girls who received follow-up during this period more frequently showed a rapid progression of pubertal changes compared to the patients assessed in previous periods. Similar data were corroborated by Stagi et al. in their publication.<sup>15</sup>

Long-term studies will allow us to elucidate the mechanisms that led to such increase in precocious puberty during the COVID-19 pandemic, as well as its course.

## CONCLUSIONS

This is the first study in Argentina to assess the frequency of consultations for suspected precocious puberty in a single site, and demonstrated a 2.3-fold increase during the COVID-19 lockdown compared to the 2 previous years. This increase was reflected exclusively in girls. ■

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