

Analysis of the incidence of central precocious puberty treated with gonadotropin-releasing hormone analogs. Impact of the COVID-19 pandemic

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ABSTRACT

Introduction. Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, consultations of girls with idiopathic central precocious puberty (ICPP) increased in several countries, but there were no data from Argentina. This increase may be related to changes in lifestyle and stress levels resulting from the lockdown, which particularly affected the child population.

Objectives. 1) To describe the progression of the incidence of ICPP requiring inhibition of the hypothalamic-pituitary-gonadal (HPG) axis in girls between 2010 and 2021 in a cohort from the Metropolitan Area of Buenos Aires. 2) To compare the characteristics of girls diagnosed with ICPP during the pandemic with those of a control group.

Methods. Interrupted time-series and case-control study.

Results. The annual incidence remained stable between 2010 and 2017. Since 2017, it increased to an average of 59.9% (95% CI: 18.6–115.5) and appears to have accelerated during the pandemic. We found an association between ICPP and requiring inhibitory treatment between June 1st, 2020 and May 31st, 2021 and 2 variables: maternal age at menarche (OR: 0.46, 95% CI: 0.28–0.77) and family history of ICPP (OR: 4.42, 95% CI: 1.16–16.86).

Conclusion. We evidenced a significant increase in the incidence of ICPP with requirement of HPG axis inhibition since 2017. Increased exposure to various environmental triggers during the COVID-19 pandemic may have had a greater influence in girls with some genetic predisposition.

Key words: precocious puberty; pandemics; SARS-CoV-2; lockdown; COVID-19.

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INTRODUCTION

Precocious puberty in girls is defined as the development and progression of pubertal changes before 8 years of age. Assessment and/or treatment is also suggested for girls with rapid progression of pubertal changes, even if they began after 8 years old.^{1,2}

The mechanisms that initiate puberty include a neuroendocrine system that results in an increased pulsatile secretion of gonadotropin-releasing hormone by the hypothalamus. These systems are regulated by genetic and environmental variables.³⁻⁵

In March 2020, the coronavirus disease 2019 (COVID-19) pandemic led different governments to take measures that implied social isolation. Argentina established the closing of in-person school activities, restrictions on recreational activities, and stay-at-home orders between March 20th and November 30th, 2020. In some regions of the country, school activities did not resume in full until July 2021. These measures had an economic, social, and psychological impact on the population in general and on the pediatric population in particular.⁶⁻⁹

In children and adolescents, changes in eating habits, greater screen exposure, sedentary behavior, sleep-wake cycle alterations, and stress-related symptoms were observed.^{10,11}

In the months following the initiation of the lockdown, pediatric endocrinologists noticed an increase in consultations related to early or accelerated pubertal development. Initially, Italian studies reported increases in the incidence of precocious puberty in relation to previous years, and some studies related it to changes in children's habits.^{12,13}

Based on this background, and due to the perception among health care providers from the Department of Pediatric Endocrinology of our hospital,¹⁴ we systematically investigated changes in the incidence of precocious puberty in our setting.

The objective of this study was to describe the incidence of precocious puberty in girls between 2010 and 2021, and the demographic, clinical, and lifestyle characteristics of girls diagnosed with precocious puberty who required treatment with gonadotropin-releasing hormone analogues (GnRHa) during the pandemic, and to compare them with a control group.

METHODS

The design of this study included, on the one

hand, an interrupted time-series with a joinpoint regression analysis to describe changes in the incidence of precocious puberty in girls between 2010 and 2021.

On the other hand, a case-control design was used to compare the demographic and lifestyle characteristics of girls who initiated treatment with GnRHa due to a diagnosis of precocious puberty during the pandemic and those of girls without a diagnosis of precocious puberty during the same period.

Idiopathic central precocious puberty (ICPP) was defined as the onset of thelarche before 8 years of age with an alteration in baseline gonadotropin levels (LH > 0.4 U/L, chemiluminescence) and/or gonadotropin levels stimulated by luteinizing hormone-releasing hormone (LH > 4 U/L or peak LH/FSH ratio > 0.4) and/or ultrasound changes compatible with ICPP diagnosis (uterine length > 39 mm). The decision to initiate treatment with GnRHa was restricted to rapid progression, psycho-emotional impact, or significant impact on adult height prediction.

Girls who were diagnosed with ICPP and started treatment with GnRHa between January 1st, 2010 and December 31st, 2021 were considered incident cases. Girls with neurogenic central precocious puberty or peripheral precocious puberty were excluded.

For the case-control study, girls diagnosed with ICPP and who started treatment with GnRHa between June 1st, 2020 and May 31st, 2021 were considered cases. All girls with associated pathologies, complex comorbidities, and whose parents refused to participate in the study were excluded. From the same cohort, 2 controls of the same age were randomly selected for each case, who were not diagnosed with ICPP during the same period.

The study team validated the classification of each patient as a case or control through a process of electronic medical record review.

The study was carried out in a teaching hospital that mainly caters to patients from the Metropolitan Area of Buenos Aires. It offers health insurance plans, making its patients behave as a semi-captive cohort, and has a pharmacy that provides all expensive drugs (GnRHa).

The following variables were analyzed: age, body mass index (BMI), family history of precocious puberty, maternal age at menarche, father's sexual maturation pattern, use of plastic containers for heating food, use of cosmetics present at home, and daily hours of sleep.

Information was also collected on any changes during the 3 months prior to the initiation of GnRHa (in cases) or during August, September, and October 2020 (in controls) in 4 other variables: changes in diet, parental family climate score as perceived by parents, number of daily hours of screen use, and physical activity.

Source of data collection

Patients diagnosed with ICPP and receiving treatment with GnRHa during the 2010–2021 period were identified through the central pharmacy records of our hospital and the review of medical records.

Data related to the lifestyle of patients included in the case-control study were collected through telephone interviews in January 2022, using a questionnaire designed for the purposes of this study (*Supplementary material*).

Statistical analysis

For the interrupted-time series, the incidence of precocious puberty was calculated by the ratio of new cases (numerator) to the total number of girls aged 6–9 years enrolled in the health insurance register in the middle of each period (denominator). A joinpoint regression analysis¹⁵ was performed to estimate its annual percent change and the potential statistical significance of any change in the slope.

For the case-control study, the association between the development or not of ICPP and potentially related characteristics was assessed by logistic regression (categorical variables) and by comparing the difference between the mean values of both groups (continuous variables).

The sample size for the case-control study was estimated according to the bibliography,¹² assuming a standard deviation of 1.5 hours in screen exposure in both groups. It was estimated that 22 cases and 44 controls (1:2 ratio) would allow a 90% power to detect a difference of, at least, 90 minutes per day in screen exposure between both groups.

According to their distribution, numerical variables were summarized through measures of central tendency (median or mean) and measures of dispersion (interquartile range [IQR] or standard deviation [SD]). Categorical variables were summarized as proportions.

The statistical software STATA 13.0 and the Joinpoint trend analysis software 4.9 were used.

An oral informed consent and/or assent process was implemented. The protocol was

approved by our hospital's Ethics Committee (PRIISA.BA [Platform for Electronical Registration of Health Research in Buenos Aires] file number: 5494; protocol: 6162).

RESULTS

In the analysis of the interrupted-time series, 102 girls who received treatment with GnRHa due to a diagnosis of ICPP were identified. The median age at treatment initiation was 8.5 years (IQR: 7.9–8.8).

The annual incidence (new cases/1000 susceptible girls per year) of precocious puberty with requirement of HPG axis inhibition remained stable between 2010 and 2017, with an annual percent change that averaged 0.2% (95% CI: 11.7–13.7). As of 2017, a sustained increase in ICPP incidence was noticed, with an annual percentage rise that averaged 59.9% (95% CI: 18.6–115.5) (*Table 1* and *Figure 1*).

In the case-control analysis, cases corresponded to 27 girls who initiated treatment with GnRHa during the lockdown. The control group consisted of 56 girls.

A total of 150 families were invited to conduct the telephone interview, and 83 girls agreed to participate (53% response rate) (*Table 2*).

A significant association was observed between the development of ICPP and 2 variables: maternal age at menarche (OR: 0.46, 95% CI: 0.28–0.77; $p = 0.003$) and family history of precocious puberty (OR: 4.42, 95% CI: 1.16–16.86; $p = 0.003$) (*Table 2*). In addition, no differences were observed in BMI, exposure to exogenous agents, physical activity, screen use, sleep hours, or family climate.

DISCUSSION

Our study showed that the annual incidence of precocious puberty with requirement of HPG axis inhibition remained stable until 2017, when it began to increase steadily, with an annual percent rise that averaged 59.9% (95% CI: 18.6–115.5).

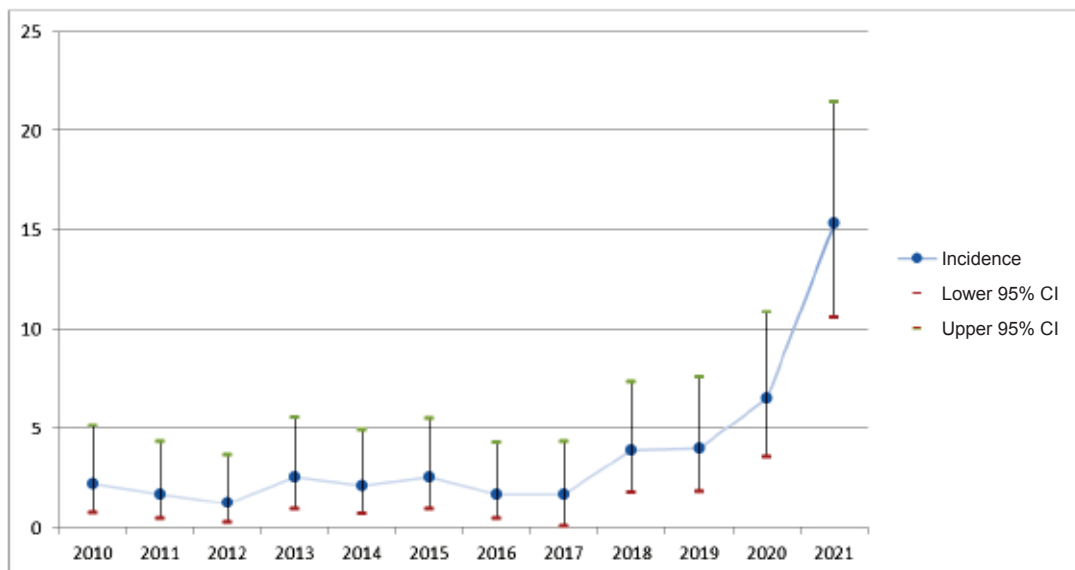
Taking the five-year period prior to the pandemic as a reference, Stagi et al.,¹² reported an increase in the number of ICPP cases as well as in the speed of pubertal progression. In addition, Verzani et al.,¹³ also in a single-center study conducted in Italy, documented a 108% increase in the number of consultations of girls with suspected precocious pubertal development between March 2020 and September 2020, taking the same period of the preceding year as

TABLE 1. Number of annual cases of precocious puberty requiring pharmacological inhibition of the hypothalamic-pituitary-gonadal axis, susceptible population in each period (number of girls aged 6 to 9 years in each period without a diagnosis of precocious puberty) and annual incidence of precocious puberty per 1000 girls

Year	Cases per year	Number of susceptible girls	Annual incidence per 1000 girls aged 6–9 years	95%CI
2010	5	2276	2.2	0.7–5.1
2011	4	2353	1.7	0.5–4.4
2012	3	2400	1.3	0.3–3.7
2013	6	2354	2.6	0.9–5.5
2014	5	2384	2.1	0.7–4.9
2015	6	2377	2.5	0.9–5.5
2016	4	2379	1.7	0.5–4.3
2017	4	2355	1.7	0.1–4.3
2018	9	2319	3.9	1.8–7.4
2019	9	2245	4	1.8–7.6
2020	14	2156	6.5	3.6–10.9
2021	33	2154	15.3	10.6–21.5

CI: confidence interval.

FIGURE 1. Trend in the annual incidence (new cases/1000 susceptible girls) of precocious puberty requiring inhibition of the hypothalamic-pituitary-gonadal axis in a cohort of girls aged 6 to 9 years



CI: confidence interval.

a reference. Using data collected from 5 Italian sites,¹⁶ it was observed that, between 2019 and 2020, there was a 122% increase in the number of cases referred for early pubertal changes and also in that of confirmed precocious puberty; the increase that occurred during the second half of 2020 is noteworthy.

In addition to the initial report, studies have

been recently published in Spain,¹⁷ Turkey,^{18,19} China,²⁰ and Brazil,²¹ which described similar accelerations in pubertal development and an increase in the incidence of ICPP.

Changes in nutrition, body composition, and exposure to endocrine disruptors at home could have triggered hormonal changes amplified by the lockdown. In our case-control study, we did

TABLE 2. Characteristics of patients included in the case-control study. Association between the development of precocious puberty and the requirement of hypothalamic-pituitary-gonadal axis inhibition

Numerical variables (SD)		Cases (n = 27)	Controls (n = 56)	Difference ^c (95% CI)	p
Age (years) ^a		8.1 (1)	8.1 (1.35)	0.01 (-0.56–0.59)	0.96
Body mass index (kg/m ²)		17.8 (2.9)	17.7 (2.6)	-0.09 (-1.37–1.17)	0.88
Maternal menarche (years old)		12.3 (1.1)	13.2 (1.2)	0.92 (0.37–1.48)	< 0.01
Family climate score (0 to 10) ^b		7.6 (0.8)	7.6 (1.3)	0.06 (-0.61–0.49)	0.84
Hours of physical activity		1.2 (0.7)	1.56 (1)	0.36 (-0.09–0.81)	0.11
Daily hours of screen use		5.1 (2.3)	5.1 (1.7)	0.03 (-0.98–0.91)	0.94
Sleep hours	Pre-pandemic	9.5 (0.9)	9.2 (1)	0.27 (-0.77–0.23)	0.29
	Intra-pandemic	9.6 (1)	9.7 (1)	0.13 (-0.36–0.62)	0.6
	Change	0.1 (0.8)	0.51 (1.3)	0.39 (-0.19–0.98)	0.18
Categorical variables (%)		Cases (n = 27)	Controls (n = 56)	Association (OR) (95% CI)	p
Family history of ICPP		7/26 (26.9)	4/52 (7.7)	4.4 (1.2–16.9)	< 0.01
Paternal pubertal development	Early	1/27 (3.7)	1/56 (1.8)	0.5 (0.03–8.5)	0.6
	Average	25/27 (92.6)	49/56 (87.5)	1	
	Late	1/27 (3.7)	6/56 (10.71)	(Reference: average or late development)	
Use of potential endocrine disruptors	Plastic containers	16/27 (59.3)	24/56 (42.9)	1.9 (0.8–4.9)	0.2
	Cosmetics	14/27 (51.9)	18/56 (32.1)	2.3 (0.9–5.8)	0.09
Changes in eating habits		9/27 (33.3)	30/56 (53.6)	0.4 (0.2–1.1)	0.09

SD: standard deviation; OR: odds ratio; CI: confidence interval.

^a The age at the initiation of hypothalamic-pituitary-gonadal axis inhibition was recorded for cases, while the age at mid-period (01/12/2020) was recorded for controls.

^b The family member completing the survey was asked about the family climate during the 3 months prior to diagnosis (cases) and during the lockdown months (controls). The higher the score, the better the family climate.

^c Estimated by means of a t test for independent samples.

^d Estimated by logistic regression analysis.

not observe significant differences in the use of cosmetics by girls with ICPP.

Umano et al.,²² reported that, although the number of sleep hours in girls diagnosed with ICPP during the pandemic did not change, they did evidence a change in the time they went to bed and showed a higher frequency of sleep disturbances, daytime sleepiness, and sleep-related respiratory disorders, which was not documented in our study.

Cacchiarelli et al.,¹⁰ described increased levels of lockdown-related stress. Loss of social relationships, estrangement from extended family members, fear of illness, loss of a loved one, or distress over economic hardships may have increased stress levels in girls. Compared to the previous year, Chioma et al.,¹⁶ documented

behavioral changes and an increase in stress-related symptoms in girls with ICPP, although no differences were observed in healthy controls. Similarly, our survey on family climate showed no differences between cases and controls.

In contrast to Italian studies,^{13,16} in our study we did not document significant differences between cases and controls in terms of screen use on an average day.

In addition to socioeconomic and environmental influences, the age of menarche has a strong heritability component; there is a correlation between the age of girls at menarche and that of their mothers.²³ Chen et al.,²⁰ described that maternal age at menarche was lower in 191 girls diagnosed with ICPP during 2020 compared to 209 girls diagnosed during the

preceding 3 years. In our study population, a younger maternal age at menarche and a higher percentage of family history of precocious puberty were observed in cases compared to controls. Our speculation is that the pandemic and the lockdown may have had an impact on the early activation of the HPG axis in girls with a genetic predisposition. We cannot rule out that some patients have familial forms of precocious puberty or that even a family history of precocious puberty leads to consultation and treatment acceptance to a greater extent.

In our study, during 2020 and 2021, we documented a significant increase in the incidence of ICPP, which could be a consequence of the changes that occurred during lockdown, even though we emphasize that such increase in incidence began gradually since 2017, which is consistent with reports from Denmark²⁴ (remarkable increase between 2006 and 2017) and Korea²⁵ (between 2008 and 2013). The latter report, like our study, estimated incidence based on the population of girls with ICPP who actually received treatment. Calculating the actual incidence based on newly diagnosed cases would require another type of methodological design.

Other influential factors must be considered in determining the increased incidence calculated from the number of patients treated with GnRHa. The parents' refusal to accept treatment for a non-life-threatening condition could be one of these factors. A GnRHa is an expensive drug that has recently been included in the Argentine Mandatory Medical Program, so it could be speculated that this would influence treatment prescription or parental acceptance.²⁶ In any case, the health care plan of our patients has been providing this medication at no cost since 2009. Likewise, the use of more widely spaced preparations may contribute to patient acceptability. Our hospital has used the quarterly indication preparation instead of the monthly preparation since the second half of 2011, which does not strictly coincide with the increased incidence observed since 2017.

One of the strengths of our study is that our hospital offers health insurance that provides care to a patient population that behaves as a semi-captive cohort. In our study population, both clinical assessment and decisions regarding treatment indication are made by the same endocrinology team. Therefore, we have a reliable denominator to estimate changes in the incidence of ICPP.

In addition, there could be potential information biases because the establishment of the lockdown restricted health checkups during that period and the information was collected through telephone interviews with the risk of a recall bias. This limitation itself makes it difficult for us to assess, in some cases, the rate of pubertal progression during the pandemic, in contrast to other authors who suggest an increased rate.^{12,18,21}

In conclusion, during the last 5 years, we have evidenced an increase in the incidence of ICPP, which seems to have accelerated during the COVID-19 pandemic. The increased exposure to environmental triggers during this period may have had a greater influence in girls with certain genetic predisposition. ■

Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/2849_AO_Benedetto_Anexo.pdf

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