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ORIGINAL ARTICLE

The relationship between precocious puberty and the COVID-19 pandemic

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Abstract

Precocious puberty is a phenomenon that occurs when secondary sexual characteristics appear before the age of eight in girls and before the age of nine in boys. The diagnosis is made after observing the appearance of pubertal signs and carrying out additional tests to confirm the type of precocious puberty. The treatment of central precocious puberty is done with GnRH analogues, aiming to block pubertal progression. Data provided by the Regional Department of Health (DRS) before and during the COVID-19 pandemic were analyzed, and it was possible to observe an increase in cases of precocious puberty, indicating a possible relationship between the COVID-19 pandemic and the increase in cases. Factors such as stress, changes in daily routine and exposure to the virus may have influenced the onset of puberty. Studies show that other aspects, such as nutrition, exposure to chemicals and use of electronic devices, can also contribute to the early onset of puberty. In other countries, an increase in the incidence of precocious puberty was also found during the pandemic. All of these factors highlight the importance of continuing to study and monitor the incidence of precocious puberty and its impact on different populations.

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INTRODUCTION

Puberty is a process of biological maturation that leads to the appearance of secondary sexual characteristics, an acceleration of growth rate, and the acquisition of reproductive capacity. When secondary sexual characteristics appear before the age of eight in girls and before the age of nine in boys, the condition is defined as precocious puberty.[1]

The clinical suspicion of precocious puberty arises when thelarche—the development of glandular breast tissue—occurs before age eight in girls, or when testicular enlargement (testicular volume ≥ 4 mL) occurs before age nine in boys.[2]

The onset of puberty may be influenced by genetic, environmental, nutritional, and socioeconomic factors. There is a higher prevalence of precocious puberty among girls. A review showed that among 104 children analyzed, 87% were female. There are two main types of precocious puberty: central precocious puberty (CPP), which is the most common and is associated with early activation of the "gonadostat," leading to the secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus, followed by the secretion of pituitary gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In female patients, CPP is commonly idiopathic. Other etiologies include genetic mutations and malformations of the central nervous system (CNS), such as hamartomas and other tumors.

There is also peripheral precocious puberty (PPP), in which gonadal stimulation does not originate from the hypothalamic-pituitary axis. Causes of PPP include adrenal tumors, ovarian tumors, testicular tumors, McCune-Albright syndrome, and testotoxicosis. In some cases of PPP, exposure to sex steroids may induce maturation of the hypothalamic-pituitary-gonadal (HPG) axis, leading secondarily to central precocious puberty.[3]

The diagnosis of precocious puberty is primarily clinical. Once clinical suspicion arises, complementary tests help determine whether the condition is central or peripheral. Hormone assays for gonadotropins, assessment of bone maturation, and, in girls, pelvic ultrasound are performed. An LH level greater than 0.3 IU/L by electrochemiluminescence (ICMA) confirms the diagnosis of central precocious puberty.[2]

In cases where basal LH levels are inconclusive but there is suspicion of CPP, a GnRH stimulation test may be required. A GnRH analogue, such as triptorelin or leuprolide, is administered, and LH is measured after one to two hours. The test is considered positive when LH exceeds 5.0 IU/L by electrochemiluminescence (ICMA).[2]

Imaging exams are also important in evaluating patients with suspected CPP. A hand and wrist radiograph showing bone age one to two standard deviations above chronological age, and a pelvic ultrasound demonstrating uterine volume greater than 3 cm^3, support the diagnosis of precocious puberty in girls. In boys, testicular examination replaces pelvic ultrasound. Brain MRI should be performed to detect CNS tumors or malformations when clinical and laboratory findings confirm central precocious puberty.[2]

Treatment consists of GnRH analogues, aimed at halting pubertal progression, reducing growth velocity, and slowing bone age advancement. The treatment duration is determined according to the appropriate chronological age for pubertal development, taking into account bone age, height age, predicted final height, and psychosocial aspects.[2]

A study demonstrated that cases of central precocious puberty increased approximately threefold during the COVID-19 pandemic period. Precocious puberty can directly affect adult height, cause psychological issues, and increase the risk of cardiovascular events, breast cancer, and other conditions.[4]

Critical stages of human development—including fetal and neonatal life, as well as the onset of puberty—are characterized by their ability to respond to nutritional and environmental factors through epigenetic programming. Some risk factors for the onset of precocious puberty include being small for gestational age, maternal obesity, and maternal hyperglycemia during pregnancy. These associations have been observed in girls but not in boys.[4,5]

Studies suggest that infection by SARS-CoV-2, the virus responsible for COVID-19, may have a direct effect on the onset of puberty. The virus reaches the CNS through the olfactory bulb, and it has been shown that the olfactory nerve shares the same embryonic origin as the neurons responsible for the production of GnRH in the hypothalamus, which may have contributed to the increased number of precocious puberty cases. MRI studies in girls have revealed a strong correlation between olfactory bulb enlargement and precocious puberty. Furthermore, the olfactory bulb contains GABAergic neurons involved in regulating the onset of puberty.[6]

SARS-CoV-2 can also activate N-Methyl-D-aspartate (NMDA) receptors, and previous animal studies have demonstrated that activation of these hypothalamic receptors may promote pulsatile GnRH secretion and the initiation of puberty.[7]

The investigation of central precocious puberty cases from 2018 to 2023 was conducted by analyzing data on the dispensing of Leuprolide and Triptorelin (table 1).

Leuprolide acetate and Triptorelin are agonists of gonadotropin-releasing hormone (GnRH). They act on GnRH receptors in the pituitary gland, causing suppression of luteinizing hormone (LH) secretion after a brief initial stimulatory phase.[8,9]

OBJECTIVES

This report aims to analyze whether there was an increase in prescriptions of the medications Leuprolide and Triptorelin in order to infer whether cases of precocious puberty increased during the confinement period caused by the COVID-19 pandemic.

Table 1. Use of medications for precocious puberty from 2018 to 2023.

	Leuprorelin 3.75 mg	Leuprorelin 11.25 mg	Triptorelin 3.75 mg	Triptorelin 11.25 mg
2018	20.55 units	73.97 units	0.00 units	00.00 units
2019	22.62 units	71.27 units	0.00 units	0.00 units
2020	32.72 units	71.27 units	1.15 units	1.23 units
2021	22.49 units	162.41 units	3.21 units	12.09 units
2022	27.49 units	74.50 units	11.38 units	97.55 units
2023	28.47 units	36.69 units	5.60 units	127.54 units

METHODS

This is a retrospective cross-sectional study evaluating the dispensing of medications used for the treatment of central precocious puberty between the years 2018 and 2023.

Data were collected from the archives of the State Health Department (*Secretaria Estadual de Saúde*), specifically from the Regional Health Department (DRS) located in the interior region of the state of São Paulo. Therefore, submission to a Research Ethics Committee (CEP) was not required, as justified by the Public Archives Law (Law 8.159/91), which establishes the national policy for public archives and allows data consultation by individuals or legal entities, provided it occurs under the conditions established by law.

The effective dose of each medication was calculated based on the pharmaceutical form and duration of effect. Prescription patterns before and during the COVID-19 pandemic were analyzed.

Eligibility criteria for group selection were: use of the GnRH analogues Leuprolide or Triptorelin distributed by the State Health Department through the Regional Health Department (DRS) in the interior region of São Paulo. Patients who used GnRH analogues for other purposes were not included.

The annual effective dose for each medication was calculated based on daily dosage as follows:

- **Leuprolide 3.75 mg:** Annual effective dose = Number of units × (30/365)
- **Leuprolide 11.25 mg:** Annual effective dose = Number of units × (90/365)
- **Triptorelin 3.75 mg:**Annual effective dose = Number of units × (30/365)
- **Triptorelin 11.25 mg:** Annual effective dose = Nu

RESULTS

According to the data collected from the Regional Health Department (DRS) of the State Health Secretariat, located in the interior region of the state of São Paulo, it was possible to obtain the following information regarding the annual effective dose of the medications:

Graph 1 shows the annual effective dose of the medications over the years. It is possible to see a very significant increase in the prescription of these medications, which allows us to infer a rise in cases of precocious puberty. Several factors may have contributed to this outcome, such as inadequate diet, excessive use of electronic devices, and stress.[10]

In the pre-pandemic period (2018–2019), the use of GnRH analogues remained relatively stable. However, during the pandemic period (2020–2023), a notable increase in these medications was observed, suggesting a rise in cases of precocious puberty or changes in prescribing practices during and after the lockdown.

COVID-19 created the sudden need for changes in social behavior and home isolation. During this period, children's routines underwent numerous changes with a significant emotional stress load. The pandemic also impacted the development of obesity due to sedentary behavior and changes in eating habits. All these factors may have contributed to the increase in precocious puberty observed in the graph above.[11]

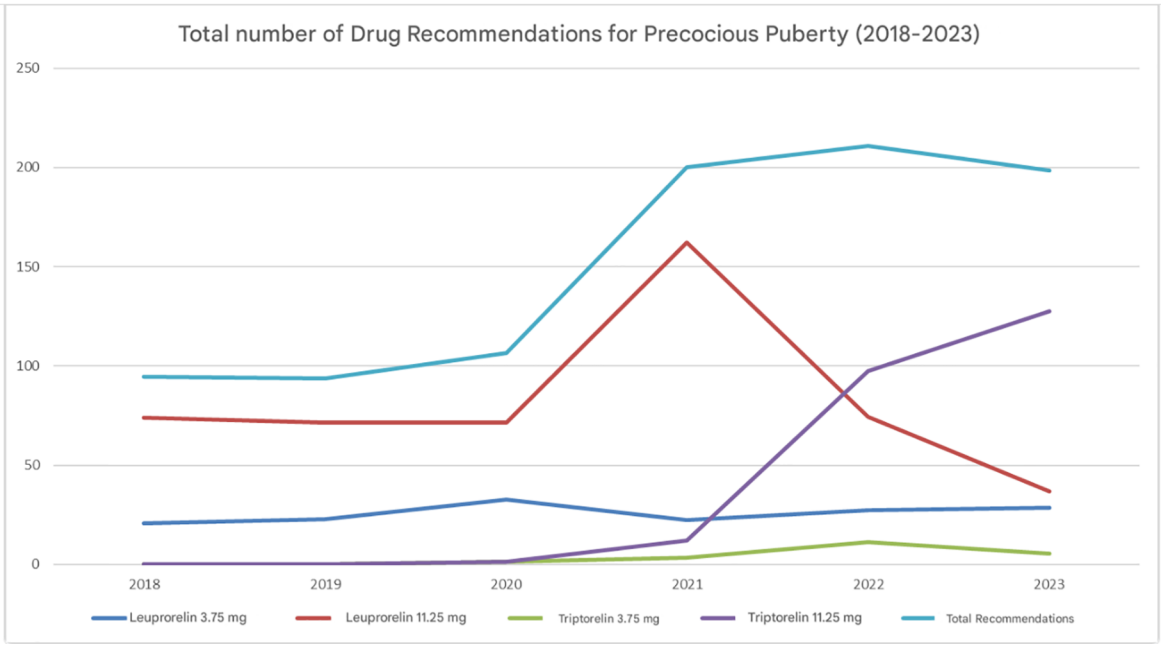
DISCUSSION

The analyzed data suggest that there was an increase in treatments for precocious puberty during and after the lockdown period. Numerous national and international studies describe several factors that likely contributed to the rise in precocious puberty during the analyzed period; however, these potential causes were not evaluated in the present study.

In 2020, an increase in consultations for suspected precocious puberty was observed when compared to the pre-pandemic period, corroborating the findings of this study. The authors attributed the rise in cases to deep lifestyle changes experienced during the lockdown.[12]

Previous studies have demonstrated associations between precocious puberty and environmental, nutritional, and genetic factors, as well as changes in melatonin, serotonin, leptin, and kisspeptin levels during the pandemic. Increased levels of kisspeptin and leptin may have resulted from dietary changes during home confinement, reduced outdoor activities, and higher body mass index (BMI).[13]

Risk factors for precocious puberty include prolonged electronic device use, reduced physical activity, increased BMI, maternal early menarche, use of cosmetics, consumption of instant and processed foods, exposure to tobacco smoke, and lower parental education.[14]



Graph 1. Total number of medication recommendations for Precocious Puberty (2018–2023).

Light emitted by electronic devices suppresses the secretion of melatonin, a hormone regulating the sleep–wake cycle. Melatonin receptors are expressed in the hypothalamus, pituitary gland, and ovaries, and melatonin plays a regulatory role in the hypothalamic–pituitary–ovarian axis. Melatonin binds to hypothalamic receptors and inhibits GnRH secretion, thereby suppressing gonadal activation.[14]

Furthermore, animal studies have shown that reduced melatonin levels can accelerate pubertal development and that melatonin administration can suppress GnRH secretion. Additionally, animals exposed to LED screen light exhibited earlier pubertal maturation, and exposure to electromagnetic fields was associated with decreased melatonin production. Altogether, these findings indicate that electronic device use reduces melatonin levels and induces endocrine changes that trigger earlier pubertal onset.[13]

An analysis conducted at a tertiary endocrinology center identified an increase in girls referred for precocious puberty between 2019 and 2021 during the SARS-CoV-2 pandemic lockdown. A comparison between the pre- and post-pandemic groups showed a significant increase in BMI in the post-lockdown period.[15]

In absolute numbers, Turkey reported that diagnoses of central precocious puberty tripled during the pandemic (2020–2021) compared to the pre-pandemic period (2019–2020). Similarly, the endocrinology clinic at the University of Campania Luigi Vanvitelli also documented a rise in CPP incidence—2.5 times higher in 2020–2021 compared to 2017–2020.[15]

Among several environmental factors, hyperinsulinemia has been described as contributing to precocious puberty. Insulin resistance can increase the bioavailability of sex hormones by reducing sex hormone–binding proteins. This results in higher levels of free sex hormones, which may lead to early pubertal onset.[15]

Early development of secondary sexual characteristics has been associated with increased risk of breast cancer, endometrial cancer, obesity, type 2 diabetes mellitus, cardiovascular disease, impaired bone health, reduced final height, and behavioral disorders. Therefore, health professionals must establish the most appropriate treatment approach.[3]

Psychological factors such as fear and anxiety may also have contributed to the surge in precocious puberty cases by stimulating N-methyl-D-aspartate (NMDA) receptors, which promote pulsatile GnRH secretion via neurotransmitters such as glutamate. Increased anxiety levels may trigger activation of GABA A receptors, which are involved in pathways that initiate puberty.[15]

At an endocrinology outpatient clinic in Turkey, 66 patients with CPP were diagnosed between 2017 and 2020 (22 per year), whereas from April 2020 to March 2021, 58 patients were diagnosed—more than doubling the incidence after the pandemic began. In Japan, CPP diagnoses nearly doubled in a pediatric endocrinology hospital, rising from 7.3% to 14.3%.[6]

Thus, factors such as sedentary behavior, increased screen time, sleep disturbances, and stress may have contributed to the increased incidence of precocious puberty. In the present study, however, there are insufficient data to determine which specific factors explain the higher incidence observed.

CONCLUSION

The analyzed data indicate an increase in the consumption of medications during and after the COVID-19 pandemic, suggesting a possible rise in the number of CPP cases. This phenomenon may be related to a combination of environmental and psychological factors associated with the lockdown period—such as stress, sedentary behavior, and changes in diet—which may have influenced early hormonal activation. We recommend conducting longitudinal studies and in-depth analyses to investigate how these factors interact and impact the premature onset of puberty, since the present study did not assess the actual cause-and-effect relationship of the factors mentioned.

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