



Increase of prevalence of Idiopathic Precocious Puberty in Girls, during the Covid-19 Pandemic: What are the possible causes? A systematic Review.

Konstantina Toutoudaki, George Paltoglou, Eleni Paschalidou, Olga Triantafyllidou, Emmanouil Kalampokas, Panagiotis Christopoulos

Division of Pediatric - Adolescent Gynecology and Congenital Anomalies, 2nd Dept Ob/Gyn, "Aretaieion" Hospital, Medical School, National and Kapodistrian University of Athens, Greece

ABSTRACT

Background: The COVID-19 pandemic changed everyday life dramatically. Lockdowns, imposed to prevent viral transmission have been investigated as possible contributors to negative health outcomes for all ages, as well as disruptors of normal children's development. In this setting, an increase in consults for precocious puberty has been observed.

Aim: To investigate the possible effects of the pandemic and lockdowns on the timing of puberty, along with the mechanisms interfering with pubertal onset.

Methods: The study was conducted, according to the PRISMA guidelines, using the Advanced Search tools of the PubMed and Google Scholar platform. Only the articles that were considered relevant were included.

Results: The review included ten studies, recruiting a total of 1904 individuals who had been referred for possible CPP or diagnosed with CPP, in 5 different countries (Spain, Italy, Turkey, China, Brazil), before and during lockdown. An increased incidence of precocious puberty was reported, upon comparison of data with the pre-lockdown era, while an attempt to highlight the possible causes of this trend was performed.

Conclusions: The most popular factors that could have an influence in pubertal timing were BMI increase, overuse of electronic devices and psychological stress.

Key Words: COVID-19, Lockdown, Idiopathic Precocious Puberty, Adolescence

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) is the responsible coronavirus for the Coronavirus Disease 19 (COVID-19) pandemic. The virus was identified in late 2019 in the city of Wuhan in China, after a notable increase in the number of lower respiratory tract infections of unknown origin (1,2). By March 2020, COVID-19 had escalated to a pandemic (1,2). According to the official website of the World Health Organisation (WHO), 468.202.755 cases of Sars-Cov-2 infection and 6.074.058 deaths related to COVID-19 had been recorded until March 20th, 2022 (3).

Many governments implemented measures of social distancing, with the goal of restraining viral transmission and protecting national healthcare systems from excessive work overload. Among measures taken, national lockdowns were the strictest (4). The effect of the pandemic and lockdowns on children and adolescents has been enlightened by studies, examining different aspects of various populations' health, both physical and psychological (5, 6).

Pubertal onset comes as a result of the GnRH axis reactivation, that provokes pulsatile secretion of LH and FSH in the pituitary, and, in turn, sex steroid production by the gonads. The hallmark of these events is the appearance of secondary sexual characteristics. In girls, the main indicative sign of puberty is the increase of breast size, known as thelarche (7). Precocious puberty is defined as the appearance of thelarche, at an age younger than 8 years for girls of Caucasian origin (8). The tendency of earlier incidence of puberty during the last decades constitutes common ground among many specialized centers, but the exact reasons for this afflux of cases remain unknown. In general, abnormalities in pubertal development can be detrimental for both physical and psychological health (8,9,10).

The aim of the present study was to assess the possible effects of the Covid-19 pandemic on the timing of puberty, by comparing the findings of current literature. Multiple centers, globally, have reported an increase in new diagnoses of pubertal precocity during the last two years of the pandemic. The evaluation of these hypotheses, as well as the identification of potential causes for this phenomenon were the primary endpoints of our study.

Methods

The study was designed according to PRISMA guidelines for systematic reviews. For the purposes of the study, the databases of Pubmed and Google Scholar were used in two independent searches by two reviewers. Data were compared and discussed, and no significant disagreements arose. Firstly, a thorough examination of publications until the 6th of March was conducted on Pubmed platform, using the following terms: [(pubertal disorders) OR (precocious puberty) OR (delayed puberty)) AND (covid 19)]. Fifteen (15) articles appeared as results of this initial search. After reading the abstracts of all results, only five (5) were included as relevant to the study topic. Later, a new search with the same terms was performed on the 25th of May on Pubmed and Google Scholar. On Pubmed, 20 articles appeared during the second search. Additional research on the Google Scholar Platform did not reveal any additional articles, during the same dates. Only original studies examining incidence of precocious puberty and possible causative factors for that were included. The process followed for study selection is shown in Table 1.

Results:

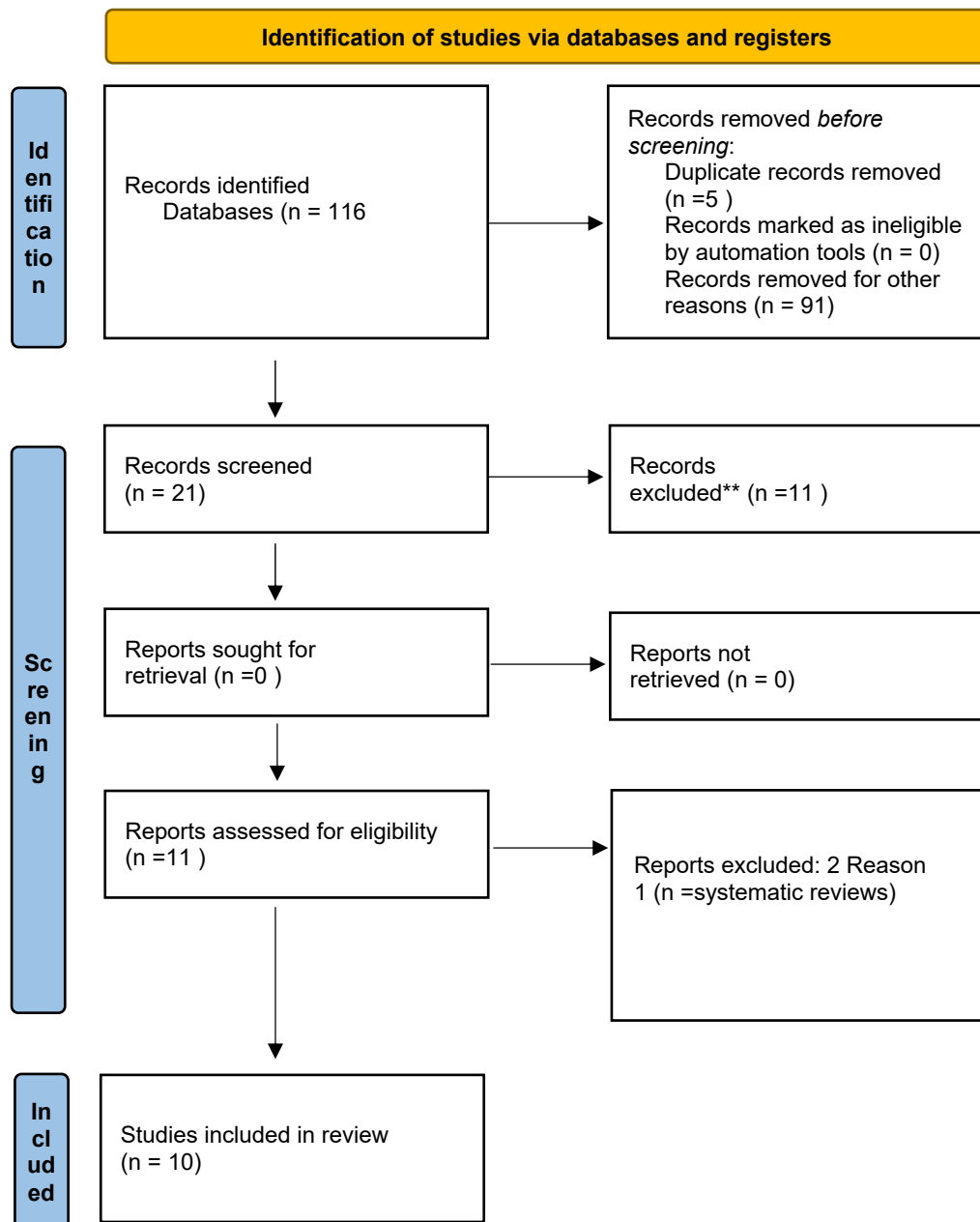
Epidemiologic data:

The systematic search concluded to ten studies. In total, data of 1904 subjects were estimated. Among them, 826 and 1066 were females with probable or confirmed CPP before (2015-2020) and during the COVID-19 pandemic (2020-2021), accordingly. 57 subjects were followed up for disease progression. Subjects enrolled came from countries such as Italy (6 studies), Spain (1 study), Turkey (1 study), China (1 study), and Brazil (1 study).

During most of the studies, researchers attempted to compare the number of referrals or confirmed cases of CPP in girls before and during the pandemic. Their results indicated a clear increase in the number of CPP cases. Also, in some of the studies anthropometric and hormonal values were estimated, while lifestyle parameters were recorded in an effort of highlighting possible etiologic factors of the trend of CPP incidence increase. All the studies reported an increase in the yearly diagnoses or referrals for CPP in girls.

The subjective experience of significant increase in the cases of pubertal precocity was confirmed by Ariza Jime-

Table 1. Study selection process.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71 For more information, visit: <http://www.prisma-statement.org/>

-nez et al., who indicated a statistically significant increase in cases of precocious puberty during the Spanish lockdown ($p=0.0092$) in a tertiary hospital, during the pandemic (11). The time points under investigation were March to December of 2019 and 2020, and the subjects included were all patients younger than 14 years old visiting the pediatric endocrinology department for the first time. During 2019, a homogenous distribution of cases was noted, followed by a significantly greater incidence during the last 3 months of 2020 (11).

A total increase of 108% from March to September 2020, compared to the same time period of 2019 (246 new cases in 2020, while 118 cases were recorded on 2019) was indicated by Verzani et al. (12). However, body measurements, such as height, weight, and BMI were not significantly affected (12).

Another study examined the changes in the incidence of precocious puberty among female subjects during the Italian lockdown, in comparison to those diagnosed during the previous 5 years, after excluding secondary cases (13). Stagi et al. not only reported a statistically significant increase, in novel cases of precocious puberty ($p < 0.0005$), but also an acceleration of already diagnosed slow progressing cases (13). Interestingly, the hormonal (peak LH, after LHRH stimulation test, LH and E2 for the accelerated puberty group) and anatomical (uterine length, ovarian volume) indexes of disease progression were also statistically affected in both groups (13).

In their retrospective study during the Italian lockdown, Chioma et al. discovered a significant increase in consults for precocious puberty, while the percentage of CPP diagnoses to consults also raised up to 122%, during lockdown period of 2020, compared to 2019 (14). No significant differences in body weight and other anthropometric and biochemical parameters were noticed among patients recorded in 2019 or 2020 (14). After distributing questionnaires among patients, the researchers reported an increase in hunger and stress related psychological aggravations (14).

In the study by Umano et al. a comparison of the incidence of CPP among girls visiting a tertiary unit of pediatric endocrinology in Italy between April 2020- April 2021 and the previous 3 years (2017-2020) indicated, not only a 2.5-fold increase in the incidence of CPP in girls (35 during lockdown to 34 during the previous 3 years), but also an exacerbation of sleep disturbances and postponing of bedtime in this patient group during lockdown in comparison to controls (15).

A study by Acar et al. calculated the novel cases of CPP during a one-year period and compared them to the ones of the last 3 years (2017-2019) (16). Fifty-eight new cases were detected among girls during the first wave of the Covid 19 pandemic in Turkey (April 2020- March 2021), which was double the number of cases, during the same time periods of each of the previous 3 years (2017- 2019) (16). However, there were no significant differences in biometric parameters, such as BMI, height, bone age, bone age/ chronological age and Tanner stage in the

CPP patients diagnosed between different years (16).

An increase in the number of monthly visits and incidence rate of CPP cases in girls during 2020 was ascertained by Chen et al. (17). Interestingly, GnRH levels were higher among the patient group of 2020 and the levels of MKRN3 and ghrelin were significantly lower in patients diagnoses in 2020 (17). Similarly, LHRH stimulation tests increased together with new diagnoses of CPP among girls in a tertiary center in Italy (18).

A brief review of the studies included is shown in Table 2.

Lifestyle parameters:

In these studies, most investigators attempted to assess the role of multiple parameters that could contribute to earlier pubertal onset. BMI, use of electronic devices and psychosocial stressors were the main factors that were examined.

Results concerning BMI were controversial. Internationally, sedentary lifestyle and repeated consumption of food of low nutritional value were common characteristics of everyday life during lockdowns (11,12,14). One study reported higher Z score of weight among girls diagnosed with CPP during the pandemic (19). Even though some studies revealed a statistically significant increase in BMI (13), indicating a possible causative role in the appearance of CPP, others did not confirm this change (14, 16, 18).

The use of electronic devices was undoubtedly increased during the lockdown both for scholar and extracurricular purposes, as shown by most studies. (12,13,14). This increase was especially evident in girls during 2020, compared to the previous year (14). The study by Stagi et al. exhibited a 2.5-fold increase in the use of these devices by children, during lockdown (13).

These changes came with sleep disturbances among many patients diagnosed with CPP, as noted in the study by Umano et al. Excessive somnolence, sleep breathing disorders, sleep-wake transition disorders, along with delay in bedtime were the most increased among girls with CPP (15). The COVID-19 pandemic came bearing aggravating effects on psychological and social parameters (20,21). In an effort to reveal the possible influence in behavioural and psychological outcomes, Chioma et al. distributed questionnaires among participants. The answers revealed a clear increase of behavioural and psychologic disturbances.

Table 2. Overview of articles included in our study.

Researchers (Year of Publication)	Country	Population in comparison	Outcome	Possible causes
Jimenez et al. (2021)	Spain	All children under 14 years old visiting the local pediatric endocrinology department from March to December of 2019 and 2020	Increase in new cases of precocious puberty during lockdown (87) versus 2019 (45) (p=0.0092)	Decrease in physical activity, dietary deviations, use of electronic devices, psychological stress
Verzani et al. (2021)	Italy	All consultations in Endocrinology Unit of Bambino Gesù Children's Hospital from March to September of 2019 and 2020	108% increase in the number of precocious puberty cases in 2020 compared to 2019 (246 to 118)	Increase in low quality food consumption, excessive use of electronic devices, psychological stress
Stagi et al. (2020)	Italy	Patients with new diagnosis of CPP, untreated patients with slow-progressing CPP during March- July 2020 and similar groups during March- July 2015-2019	Significant increase (p<0.0005) in yearly count of new cases of precocious puberty (37 during 2020 versus 89 during 2015- 2019) and acceleration of slowly proceeding precocious puberty (p < 0.0005), affected hormonal and rapid development of anatomic characteristics (uterine length, ovarian volume) and Tanner staging	Significantly increased use of electronic devices (p < 0.0005), according to parents' answers in questionnaires distributed
Chioma et al. (2022)	Italy	Children examined for precocious puberty in five Italian centers during March-September 2019 and 2020	122% more referrals for precocious puberty investigation (152 versus 338 in 2019 versus 2020), increased percentage of CPP diagnoses (41%/26%) among females in 2020, compared to 2019	No deviation in hormonal and anthropometric profile, while on-screen time was increased
Acar et al. (2021)	Turkey	Girls diagnosed with CPP in a three year period before lockdown April 2017 to March 2020, and girls diagnosed from April 2020 to March 2021	Clear increase in CPP cases during April 2020–March 2021(58), compared to cases from April 2017 to March 2020 (66)	No significant increase in BMI. No possible causative factors investigated due to retrospective type of the study
Umano et al. (2022)	Italy	Girls with CPP visiting a tertiary pediatric endocrinology Unit from April 2020 to April 2021, and girls with CPP from 2017-2020	2.5-fold increase in CPP cases during April 2020-2021 (35), compared to yearly cases during 2017-2020 (34). Higher levels of oestradiol, LH and FSH in CPP cases after lockdown, compared to patients before lockdown	Later bedtime in CPP subjects compared to controls during lockdown, increase in sleep disturbances (total rate, excessive somnolence, sleep breathing disorders, sleep-wake transition disorders) no change in total hours of sleep, no significant change in use of electronic devices
Chen et al. (2022)	China	Girls diagnosed with CPP during March- August 2020 (n=191) and inpatient CPP girls during March-August 2016-2019 (n=209) in Shanghai Children's Medical Center	Increase in monthly visits and incidence rate of CPP in girls during March-August 2020 (2020), compared to March- August 2016-2019 (2016-2019).	Higher levels of GnRH among 2020 CPP girls, lower MKRN3 and ghrelin levels in the 2020 CPP girls
Oliveira Neto et al. (2022)	Brasil	22 girls diagnosed with CPP during July 2020 to June 2021 and 33 girls diagnosed from March 2019 to February 2020	-	Wider association of CPP with higher Z-score of weight, lower ovarian volume and shorter interval between thelarche observation and CPP diagnosis
Peinkhofer et al. (2022)	Italy	Girls undergoing LHRH stimulation testing in a tertiary centre during 2019 and 2020	+22% increase of LHRH stimulation tests (38 versus 45 in 2019 versus 2020) and +38% increase in diagnoses of CPP in 2020 compared to 2019 (26 versus 16 accordingly)	Lower BMI SDS among girls with CPP in 2020 (median 0.11 [IQR -0.52;0.72]) than girls diagnosed in 2019 (median 0.93 [IQR 0.38;1.10]) (p =0.01).
Turriziani Colonna et al. (2022) (from abstract)	Italy	26 referrals for suspected CPP during the COVID-19 pandemic and 64 during the previous 3 years	Increase in CPP diagnoses during the pandemic (11 (39.3%) children during pandemic, versus 15 (24.2%) in the previous 3 years). Accelerated rate of pubertal progression in 22/45 (48.9%) patients, more children in stages T3 and T4-5.	Hypothetically, due to weight - BMI increase, or psychological burden of the pandemic.

Discussion:

The results of the above-mentioned studies confirm the international subjective view of an increase in new diagnoses of CPP, among female subjects. However, a definite answer, concerning the factors responsible for this phenomenon has not been acknowledged yet. It is certain that during the pandemic, major changes in everyday life were introduced, acting as possible contributors to idiopathic precocious puberty. These alterations along with the possible effects of the disease are estimated to be contributors to long-term negative health outcomes, even during the 22nd century (20). The three most studied parameters that were affected during lockdown and were hypothesised to participate in early onset of puberty were obesity- increase in BMI, use of electronic devices, and psychosocial stress.

Lockdowns were accompanied by an increase in the risk of obesity among children, adolescents, and young adults. This was partially attributed to changes in alimentary habits. Not only the amount of food intake was increased, but also the nutritional value of meals was severely deteriorated (22). Simultaneously, there were variable changes in physical activity. In Germany, for example, even though organised sports were halted, habitual exercise was increased, leading to an augmentation in the amount of daily physical activity among children and adolescents (23). However, many studies revealed a substantial decrease in physical activity during quarantine, internationally, due to restricted access to physical activity (24,25).

The correlation between obesity and probability of CPP has been extensively studied (26). Some hypotheses include fatty acid-mediated hypothalamic inflammation and subsequent activation of microglia, which, in turn, stimulates GnRH producing neurons. Another suggestion involves the neuropeptide phoenixin, that could be activated by fatty acid consumption. Phoenixin enhances GnRH expression, contributing to the initiation of the hypothalamic- pituitary- gonadal axis function, that is responsible for pubertal onset (27). Leptin, a hormone produced in adipose tissue, is also suggested as a regulator in pubertal onset, by giving the hypothalamus 'feedback' on the amounts of total body adipose tissue, allowing initiation of puberty. However, the implication of adipocyte-produced hormones does not end there. Insulin resistance, that often accompanies obesity, comes with hyperinsulinemia, along with sex-hormone-binding globulin (SHBG) alterations. Aromatase overproduction by adipocytes could increase estrogenic exposure among

girls, during prepubertal years (26). Even though studies were inconclusive concerning BMI changes in the course of lockdowns, among children and adolescents, a potential contribution to early puberty has not been excluded.

A definite increase in the use of electronic devices during lockdowns was recorded, internationally. Devices were no longer used exclusively for entertainment, but also for scholar purposes, thus increasing on-screen-time. Stagi et al. referred to findings of studies, that indicated a possible provocation of CPP by melatonin disruption from electromagnetic fields (13). The exact role of melatonin in CPP is not known, even though abnormal melatonin values are a common finding in HPG axis disorders (28). While some studies indicated a fall of melatonin levels during the dawn of puberty, others failed to establish such a correlation (29,30). Despite the conflicting results of studies, there might be a proportional correlation among levels of melatonin and age of pubertal onset, meaning that lower levels of melatonin come with greater sexual maturation (29,30,31).

During lockdowns, populations are, by definition, obliged to stay in isolation for extensive periods of time. Social gatherings and activities are suspended, which creates a stressful familial environment. Studies that examined the psychosocial effects among Italian families during lockdown indicated that behavioural and psychological problems of children derived from parents' difficulty facing the stressful events of lockdown (22). Internalization of anxiety in girls has been correlated with precocious puberty. (32). According to Chioma et al. stress could intensify GnRH secretion in predisposed females (14).

Finally, a common characteristic among articles reviewed was that the increase in novel diagnoses of precocious puberty during lockdown was significantly more prominent among girls (12,14). The reasons for what might be an indication of sexual dimorphism remain unknown (14).

Despite the large number of patients included in these studies, the risk of bias could not be excluded, upon study selection. The increase in the incidence of CPP could potentially be partially attributed to more prompt actions by parents. Closer monitoring of children development during the pandemic, aided by the rise of hours spent at home, might have contributed to the increase of referrals for

CPP.

The major strength of the present review is the potent number of subjects included, as well as the diversity of their ethnic backgrounds. Most of the studies included in this review are of European origin (Italy (6), Spain (1), Turkey (1)), where similar lifestyle and weather conditions apply. Also, a thorough research of possible causative factors was performed. As far as limitations are concerned, no clear etiologic relation among risk factors and CPP could be established. Moreover, the extent of available articles covering this topic are not yet adequate for safe conclusions. It is definite that the number of studies that have been published, concerning the increasing incidence of CPP during lockdowns is limited. Results from a greater number of specialized centers, all over the World, are still expected, in order to have a more elaborate overview of a possible trend.

Conclusion:

Lockdowns constituted a widely used tool in the hands of governments for the confrontation of the pandemic. Data arising from current literature report a substantial increase in new cases of precocious puberty, especially among females. This finding has started to become evident in studies conducted in different countries under lockdown. The factors that have led to this phenomenon are still under investigation, but obesity, due to malnutrition and sedentary lifestyle, overuse of electronic devices, and psychological stress are the most frequent explanations. More in-depth analysis of this trend and its possible etiologic factors seems to be needed, to investigate the causes and dimensions of an arising epidemic, the one of pubertal precocity.

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