Increased Incidence of Precocious Puberty in Girls During COVID-19 Pandemic: Early Indicator of the Upcoming Childhood Metabolic Syndrome Pandemic?

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Abstract
To evaluate retrospectively the incidence of central precocious puberty (CPP) during the COVID 19 lockdown and comparing the data with the corresponding data from the previous 2 years. The study included 23 girls with CPP and 14 patients with early puberty. Nineteen patients were newly diagnosed with CPP compared to 4 patients diagnosed with CPP during the previous 2 years. The number of new patients diagnosed with CPP was significantly higher than the mean during the previous 2 years (P < .001). There were more overweight patients with CPP during and after the lockdown (P < .05). These patients had also increased uterus length (P < .05) and more advanced bone age (P < .05). The increase in the incidence of central precocious puberty during and after the lockdown due to COVID 19 can be considered a serious consequence of the increased fat mass and an early indicator of the worsening of childhood obesity.

Keywords
precocious puberty, early puberty, COVID-19, adiposity, childhood obesity

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Introduction
Puberty is a key stage in a person’s growth and development. A complex series of biological activities leads to a pulsatile rise in gonadotropin secretion.¹,² The age of puberty has a distinct genetic profile.³ Multiple candidate genes and polymorphisms involved in this process have been identified.⁴

The development of secondary sexual features in girls before the age of 8 and in boys before the age of 9 is known as precocious puberty. Gonadotropin-dependent (central/true Precocious Puberty) or gonadotropin-independent (peripheral/pseudo-precocious puberty) puberty can be identified. During both physiological and central precocious puberty, the hypothalamus, pituitary, and gonadal (HPG) axis is active.⁵

In recent decades, several global studies have shown that puberty has become significantly earlier⁶ and the environmental conditions are possibly playing a role.

Early puberty can induce short stature due to early maturation of the growth plate and self-stress due to a different body shape from the peer group, psychological concerns due to discrepancies between physical and chronological age, with long-term behavioral problems including depression and some other chronic diseases like obesity, type 2 diabetes, cardiovascular disease, and cancer.⁷

Puberty is a period associated with significant changes in body composition, including weight gain and elevated body fat; however, it is not clear whether the increase in adiposity precedes puberty or vice versa.⁸

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On the other hand, several studies have found an association between the age of puberty development and body mass index (BMI). Indeed, an increase in childhood adiposity has questioned the change in menarcheal age. The COVID-19 pandemic has had widespread health, social, and economic consequences. Studies have endorsed the theory that these young girls are much less successful in maintaining their healthy lifestyle and preventing weight gain. Increased calories intake and fast food, along with decreased exercise and increased screen time, have been clearly linked to obesity.

Apparently, during and after the lockdown imposed by the authorities during the pandemic, pubertal timing seems to occur at a younger age, reflecting the obesity epidemic and sedentary lifestyle. This research aims to evaluate the incidence of idiopathic central precocious puberty during and after the Lebanese lockdown, to compare it to the previous 2 years, and to study the influence of an eventual increase in the BMI, a reflection of the increase in the body fat, due to some environmental modifications, to understand much better the pathophysiology of precocious puberty.

**Patients and Methods**

We designed a retrospective study where we evaluated the medical records of Lebanese patients referred to pediatric endocrinology clinics in multiple Lebanese regions. In Beirut, data were collected from the Lebanese American University Medical Center Rizk Hospital and in the North of Lebanon, records were obtained from Haykal Hospital.

The patients included were Lebanese girls only, aged between 4 and 9 years old. Patients with hypothalamic pituitary congenital malformations, endocrine impairment requiring prior hormonal treatment, those taking drugs that may interfere with pubertal development, or patients with psychomotor and developmental delay, were excluded from the study.

The study was approved by the Institutional Review Boards. Ethical approval was obtained from the centers where records of outpatients clinics database were recruited.

**Research Design**

Physical examination and auxological evaluation were performed on all patients. Height, weight, body mass index (BMI), and stage of pubertal progression (Tanner scale) were measured. Pubertal development was classified according to the Marshall and Tanner criteria. The age of pubertal onset was defined as the age Tanner B2 stage and confirmed by the auxological, endocrinological, and/or radiological results. All clinical data (family history of major diseases, family history of precocious puberty, mother’s age at menarche) and endocrinological data (follicle-stimulating hormone FSH, luteinizing hormone LH, estradiol E2, 17-hydroxyprogesterone 17-OHP, free thyroxine FT4, thyroid-stimulating hormone TSH) were collected. Pelvic ultrasonography and bone age (BA) assessment using radiographies of the left hand and wrist were performed for all the patients. A LH-releasing hormone (LHRH) stimulation test was performed when needed and possible. Skeletal maturation was evaluated by the bone age and by the difference between the chronological age and the bone age (BA minus CA) in years.

**Auxological Evaluation**

Height was measured using Harpenden’s stadiometer to the nearest 0.1 cm. Weight was determined to the nearest 0.1 kg using a balance scale. BMI was calculated as weight in kilograms divided by height in meters squared.

Weight, height, and BMI were calculated in percentile according to the CDC reference. Overweight patients were defined by their BMI greater or equal to the 85th percentile (CDC).

The familial target height was also calculated as (mother’s height + father’s height)/2 to 6.5 cm. The bone age, assessed via radiographies of the left hand and wrist, was evaluated according to the Atlas of Greulich.

**Pelvic Ultrasonography**

Pelvic ultrasonography was performed by radiologists specialized in pediatric radiology. The prepubertal uterus was determined as a spade shape, with a length of 2.5 to 3.4 cm and thickness that does not exceed 10 mm and no apparent endometrium. The pubertal uterus was defined by uterus length more or equal to 35 mm with an apparent endometrial line.

The ovarian volume was calculated as $V = 0.6 \times \text{length} \times \text{width} \times \text{depth}$.17

**Laboratory Methods**

All laboratory measurements were performed on blood samples collected after overnight fasting.

Plasma FSH and LH, 17OHP, FT4, TSH, and E2 levels were measured using Enzyme Linked Immunosorbent Assay (ELISA) and Chemiluminescence Immunoassay (CLIA).

The LHRH test was carried out by taking blood samples at the 20th, 40th, 60th, and 90th minute after intravenous administration of 100 mg/m² of Luteinizing Hormone Releasing Hormone (LHRH).
Outcome

Precocious puberty was defined as the association between a clinical onset of puberty (Tanner stage 2, breast development isolated or associated with pubic and/or axillary hair with acceleration in the growth velocity) at an age below 8 years, and pubertal hormonal and radiological findings. We considered peak LH values of > 5 IU/L on the LHRH stimulation test and a ratio of stimulated LH to stimulated FSH of > 1.0 or a basal LH value of > 0.1 IU/L. Estradiol > 10 pg/mL with uterus size more than 34 cm were considered as indicators for more evolutive precocious puberty. The patients were assessed individually with a bundle of clinical, endocrinological, and radiological arguments at the same time to confirm the onset of puberty. For each patient who started puberty before 8 years of age, a pituitary MRI was recommended and in the majority of cases performed. The treatment by GnRH analog has been proposed for precocious puberty especially those with rapid evolution or aggressive precocious puberty.

Statistical Analysis

Descriptive analyses were performed to determine means and standard deviations (SD) for continuous variables and frequencies for categorical variables. Cross-tabulation using fisher’s exact test was performed to determine the differences in proportions, while t-tests were used to detect differences in means between those with precocious and early puberty before and after lockdown. Statistical significance was defined as P-value < .05, and STATA 13.0 was used for all analyses.

Results

Nineteen female patients (group 2) received a new diagnosis of precocious puberty after the Lebanese lockdown for the coronavirus between March 2020 and February 2021.

While 4 female patients were diagnosed with central idiopathic precocious puberty during the previous 2 years before the Lebanese Lockdown (4 patients, group 1).

We also compared the patients diagnosed with early puberty (beginning of puberty between 8 and 9 years) during and after the Lebanese Lockdown (6 patients) to the group of patients diagnosed before lockdown (8 patients).

As shown in Table 1, the overall number of new patients diagnosed with central precocious puberty, and their percentage among the total number of new patients referred to the pediatric endocrinology clinics (4.6%) was much higher after the lockdown than the mean number of patients diagnosed with precocious puberty for the 2 previous years and their percentage among the total number of new patients referred to the pediatric endocrinology clinics (0.41%, P < .001).

Tables 2 and 3 showed that the mean age (7.27 ± 0.73 vs 6.66 ± 0.78, P = .15) and the tanner stage (2.00 ± 0.00 vs 2.47 ± 0.51, P = .08) were comparable between the 2 groups. However significantly more patients with CPP were overweight after the lockdown (10/19 patients, P < .05). Likewise, patients with precocious puberty after the lockdown weighed more than those with CPP before lockdown (increased weight mean (28.67 ± 5.46 vs 21.2 ± 1.89, P < .05) and weight percentile (21.2 ± 1.89 vs 74.7 ± 24.01, P < .05). They were also taller regarding the height mean (128.0 ± 5.79 vs 119.6 ± 1.14, P < .05) but the height’s percentile was not significatif between the 2 groups (50.34 ± 28.30 vs 71.86 ± 25.24, P = .14). The mean BMI was higher in the second group but not statistically significatif (17.37 ± 2.39 vs 14.85 ± 1.42, P = .058).

There was also a statistically significant difference in their bone age which was more advanced in the second group (8.52 ± 1.29 vs 6.87 ± 0.75, P < .05) and the uterine length was also greater (36.7 ± 5.26 vs 30.0 ± 4.69, P < .05).

Table 1. Incidence of Precocious and Early Puberty Before and After Lockdown.

|                                      | Before lockdown | Incidence (95% confidence interval) | After lockdown | Incidence (95% confidence interval) | P-value |
|--------------------------------------|-----------------|-------------------------------------|----------------|-------------------------------------|---------|
| Total number of patients referred to the pediatric endocrinology clinics | 964             | 0.41% (0.39-0.43)                    | 416            | 4.6% (4.40-4.70)                    | <.001   |
| Number of patients with precocious puberty (below 8) | 4               | 0.83% (0.82-0.84)                    | 19             | 1.44% (1.39-1.48)                   | .29     |
The LH and the estradiol levels were higher in the second group but not statistically significant (0.93 ± 1.77 vs 0.11 ± 0.04, \( P = .37 \) for the LH, 27.1 ± 15.8 vs 15.0 ± 4.27, \( P = .17 \) for the Estradiol). As expected the number of patients who required treatment was statistically greater than group 1.

All patients showed normal values of TSH, FT4, and 17OHP with no difference between the 2 groups. Pituitary MRI showed a normal pituitary gland without any focal lesions in all patients. No difference was noted for the age of mothers’ menses (12.27 ± 1.66 vs 12.51 ± 1.25, \( P = .76 \)).

Regarding the patients with advanced puberty (between 8 and 9 years old), the number of patients was comparable between the 2 groups and no clinical, biological or radiological significant difference was noted.

### Discussion

Our study showed a significant increase in the incidence of central precocious puberty in Lebanese girls during the lockdown compared to the previous 2 years prior to this pandemic. We found more overweight girls below 8 years who developed CPP during the COVID-19 pandemic. They had significantly higher weight and height, with an increase in their BMI. To the best of our knowledge, this is the first study in Lebanon and the region to examine the incidence of precocious puberty in girls during the lockdown.

Likewise, girls had higher hormone levels (LH, estradiol) and a larger uterus compared to other girls of the same age group. This led us not only to interpret an increase in the numbers of girls with precocious puberty but probably to suppose that they developed more rapid and more aggressive precocious puberty which can explain the higher level of LH and estradiol at the diagnosis. Patients before lockdown seem to have slower precocious puberty when it was idiopathic and required exceptionally a treatment by GnRH analog.

It is generally known that genetic factors, race, and nutrition all impact pubertal timing. Multiple studies showed that mutations in kisspeptin (KISS1), kisspeptin receptor (KISS1R), and makorin RING finger protein 3 (MKRN3) genes are genetic causes of familial CPP.

However, we found that the association of early onset of puberty and environmental factors was also significant.\(^{11,20}\) Girls are now starting puberty earlier where the average age of thelarche has decreased by less than 4 months.\(^{21}\)

It is well known that there is a relationship between childhood obesity and pubertal onset. Girls who developed early puberty and menarche were found to be more obese and having higher visceral adiposity.\(^{10,22}\) On the contrary, chronic malnutrition delays the pubertal onset and its progression.

The worldwide global situation induced by the COVID-19 pandemic impacted the mental health and well-being of children significantly as well.\(^{1,23}\)

Children witnessed unprecedented major lifestyle changes. COVID-19 is causing significant morbidity and mortality, straining health care systems, causing economic downfalls, and closing school districts.\(^{12}\)

Subsequently, the environmental and behavioral determinants were affected dramatically. The closure of schools resulted in decreased organized physical activity, altered sleep patterns, and increased sedentary lifestyle and screen time use which is also found to be associated with poor sleep through several mechanisms,
including nighttime exposure to bright lights, which may suppress melatonin production.\textsuperscript{13,24,25}

All these modifications led to the increase in adiposity, especially visceral adiposity in children who will develop sooner or later overweight or obesity with all the complications of « the fat gaining ».\textsuperscript{11,12,25}

Childhood obesity as well known is associated with hyperinsulinism, insulin resistance, and hyperandrogenism,\textsuperscript{10} both of which may lead to early puberty through altering the hypothalamus-pituitary-gonadal axis\textsuperscript{11} or increasing the bioavailability of sex hormones through insulin’s actions on the liver, adrenals, ovaries, and adipose tissue.

Insulin resistance is a major consequence of obesity and specifically central obesity. It is associated with compensatory hyperinsulinemia which decreases the levels of liver sex hormone binding protein, as a result, increases the free estrogen levels.\textsuperscript{8} On the other hand, insulin resistance affects leptin signaling, a hormone secreted by adipocytes. It stimulates the central pulsatile gonadotropin secretion by binding to their receptors in the GnRH neurons inducing additional weight gain, greater body mass index (BMI), and greater body fat.\textsuperscript{26} Synthesis of androgens is also promoted by the increase of cytokines as an inflammatory reaction due to obesity, participating likewise in early pubertal development.

Other mechanisms could be also implicated. During the COVID-19 pandemic, we have witnessed the excessive use of a hydroalcoholic solution to disinfect hands and this would deserve to make us think about the potential risk of endocrine disruptors in the development of precocious puberty. Also taking into account that these chemical compounds can also be transmitted to the fetus through the placenta or to the baby through breastfeeding, thus affecting the periods of fetal and postnatal development.

In addition, the excessive use of multivitamins in children both during their infection with COVID-19 and as a preventive treatment was also a new element during this pandemic. It is essential to question the potential effect of these vitamins in the modification of the appetite of these children, in the increase of adiposity, or the modification of the distribution of fat in the body. It is strongly recommended to further study the effect of multivitamin use and its association with precocious puberty.\textsuperscript{27,28}

As previously reported, the menses age in mothers of girls with precocious puberty was lower, which would confirm the role of genetic factors in the timing of puberty. While mothers of daughters with central precocious puberty and especially after the COVID pandemic had a normal late menstrual age which confirmed the key role of recent environmental factors involved even without the involvement of genetic factors.

### Study Limitations

One of the main limitations of our study is the small number of the sample. Even though the COVID-19 pandemic did not significantly affect the referrals to our pediatrics endocrinology clinics, it made it more
difficult for the patients to perform all the imaging and lab tests needed due to difficult hospital settings, mainly the LHRH stimulation test, therefore some patients had missing values.

Moreover, data on calories intake, the number of hours spent in physical activity or screen time use, and the velocity of pubertal progression in previously diagnosed girls with slow evolutive precocious puberty were not collected and not available. In addition, data were lacking concerning the BMI evolution, assessment of body fat mass, and a psychological evaluation of these girls. Finally, given the small sample size, multivariable analysis to control for confounding factors could not be performed.

Conclusion
A vicious circle lies between the increasing of the fat percentage in the body and mainly the central or visceral fat inducing an insulin resistance and activating the hypothalamo-pituitary axis and the adrenal glands.

Early recognition and understanding of the importance of this pathophysiology are crucial to prevent metabolic syndrome and precocious puberty in children and mainly in girls.

Curbing the viral spread while protecting population health will remain a top priority until having an effective COVID-19 vaccine. However, it is imperative to address other co-existing problems such as childhood obesity, which if uncontrolled may have long-term profound health and economic consequence of higher eminence than the actual COVID-19 infection.

The prevention and management of childhood obesity should be set as a priority at an individual, community, and population level during this pandemic.

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All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Ethics Committee Approval
The study was approved by Lebanese American University’s Institutional Review Board as Exempt Category D (IRB #: LAUMCRH.AA1.23/Dec/2020).

Informed Consent
Retrospective study.

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