The Reason of Increasing Puberty Precocious Cases During the Pandemic Period: Obesity or Not?

Pandemi Döneminde Artan Puberte Prekoks Vakalarının Nedeni: Obezite mi Değil mi?

Seçil ÇAKIR GÜNDOĞAN[1]*, Aylin KILINÇ UĞURLU[1]*, Fatih GÜRBÜZ[2], Gönül BÜYÜKYILMAZ[1],

Gönül YARDIMCI[1], Abdurrahman BITKAY[1], Emre ÖZER[1], Keziban TOKSOY ADIGÜZEL[1], Emregül IŞIK[1],

Pınar KOCAAY[1], Derya TEPE[1], Mehmet BOYRAZ[2]

[1]Department of Paediatric Endocrinology, Ankara Bilkent City Hospital, Ankara, Turkey
[2]Department of Paediatric Endocrinology, Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Ankara, Turkey

ABSTRACT

Objective: Publications have shown increased rate of precocious puberty and rapidly progressing puberty during the pandemic period. During the pandemic period, obesity has become widespread in children due to sedentary life, an increase in the time spent at home, and prolonged use of mobile devices. Obesity is a significant contributor to early puberty in females.We aimed to investigate whether obesity is a factor in the increase of puberty precocious cases during the pandemic.

Material and Methods: In the study, female patients diagnosed with Puberty precocious /Rapidly Progressive Puberty in our clinic were divided into three groups August 2019-February 2020 before the pandemic (Group1-G1), August 2020-February 2021 during the pandemic (online education - Group2-G2), August 2021-February 2022 during the pandemic (face-to-face education -Group3-G3). The groups were retrospectively compared in terms of clinical, laboratory, and imaging findings.

Results: A total of 495 female patients were included in the study. There was no difference between the groups in terms of age at the presentation. The most common complaint at presentation in the three groups was thelarche. Also, presentation with combination of thelarche and pubarche was more common in G3, and presentation due to menarche was more common in G2 (p=0.011). No difference was found between the groups regarding body weight SDS, and height SDS. The BMI SDS was 0.69±1 SD for all patients, 0.78±0.94 SD for G1, 0.67±1 SD for G2, and 0.67±1 for G3, and the BMI SDS of the groups were comparable (p=0.630). The majority of patients at the presentation were Breast Tanner stage 3. G2 (9%) and G3 (9%) were presented with Breast Tanner stage 4 at a higher frequency compared to G1 (2%). There was no difference between the groups' FSH, LH, estradiol, LHRH test peak FSH, peak LH, and LH/FSH values. There was no difference between the bone ages of the groups at the presentation. The uterus size, right and left ovary volumes of G2 and G3 were significantly bigger than those of G1 (p=0.001). No difference was found between the groups in the rates of precocious puberty and rapidly progressing puberty cases.

Conclusion: In our study, the age at presentation and BMI were similar pre-pandemic group G1 and during the pandemic, online education (G2) and pandemic face-to-face education (G3). We determined that obesity may not be one of the factors triggering precocious puberty cases during the pandemic period.

Key Words: Covid -19 Pandemic, Obesity, Ovarian size, Puberty precocious, Uterus size

ÖZ

Amaç: Pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik olgularında artış olduğunu gösteren yayınlar mevcuttur. Pandemi döneminde sedanter yaşam, evde kalınan sürede artış ve mobil cihaz kullanım sürelerinin uzaması nedeni ile obezite çocuklarda yaygınlaşmıştır. Obezite, kızlarda ergenliği öne çeken önemli bir faktördür. Bu çalışmada pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik vakalarının artışında obezitenin bir faktör olup olmadığını araştırılması amaçlanmıştır.

Pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik olgularında artış olduğunu gösteren yayınlar mevcuttur. Pandemi döneminde sedanter yaşam, evde kalınan sürede artış ve mobil cihaz kullanım sürelerinin uzaması nedeni ile obezite çocuklarda yaygınlaşmıştır. Obezite, kızlarda ergenliği öne çeken önemli bir faktördür. Bu çalışmada pandemi döneminde puberte prekoks ve hızlı ilerleyen ergenlik vakalarının artışında obezitenin bir faktör olup olmadığını araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada kliniğimizde Puberte Prekoks/Hızlı ilerleyen ergenlik tanısı alan kız olgular pandemi öncesi Ağustos 2019-Şubat 2020 (Grup1-G1), pandemi dönemi Ağustos 2020-Şubat 2021 (çevirimiçi eğitim- Grup2-G2), pandemi dönemi Ağustos 2021-Şubat 2022 (yüzyüze eğitim-Grup3-G3) olarak üç gruba ayrıldı. Gruplar klinik, laboratuvar ve radyolojik bulguları açısından retrospektif olarak karşılaştırıldı.

Bulgular: Toplam 495 kız hasta çalışmaya alındı. Gruplar arasında başvuru yaşı açısından fark saptanmadı. Üç grubun başvuru şikayetleri en sık telarş iken (n:76) iken, telarş ve pubarş birlikteliği ile başvuru Grup 3' te, menarş nedeni ile başvuru Grup 2' de diğer gruplara göre daha fazla saptandı (p=0.011). Gruplar arasında vücut ağırlığı, boy ve vücut kitle indeksi SD açısından fark saptanmadı. Başvuru esnasındaki meme tanner evrelemesi en sık evre üçtü. Grup 2 ve Grup 3' te meme evre 4 ile başvuru Grup1'e göre daha sık gözlendi. Grupların FSH, LH, östrodiol, LHRH testi pik FSH ve pik LH, LH/FSH değerleri arasında fark saptanmadı. Grupların başvurudaki kemik yaşları arasında fark saptanmadı. Grup 2 ve Grup 3'ün uterus boyutu, sağ ve sol over hacimleri Grup 1'e göre daha büyüktü (p=0.001). Gruplar arasında puberte prekoks ve hızlı ilerleyen ergenlik olgularının oranları arasında fark saptanmadı.

Sonuç: Pandemi döneminde tanı alan puberte prekoks ve hızlı ilerleyen ergenlik olgularında artıştan obezite ve mobil cihaz maruziyeti ön planda bahsedilmektedir Çalışmamızda pandemi öncesi Grup 1, pandemi dönemi (çevirimiçi eğitim) Grup 2 ve (yüzyüze eğitim) Grup 3' ün başvuru yaşı ve VKİ benzerdi. Pandemi döneminde obezitenin erken ergenlik vakalarını tetikleyen faktörlerden biri olmayabilir

Anahtar Sözcükler: COVİD-19 pandemi, Obezite, Over boyut, Puberte prekoks, Uterus boyut

INTRODUCTION

Puberty is a crucial and multifaceted phase that involves significant physiological maturation and variance. The timing of puberty and the rate of development are complicated processes influenced by interactions between genetic, dietary, and environmental factors (1,2). Obesity is one of the factor of precocious puberty in females (3). Home quarantine has significantly impacted people's daily lives because of the global coronavirus disease 2019 (COVID-19) pandemic, including dietary changes, exercise patterns, work and rest routines, and medical care access. Schools around our country were closed between March and June (4). Children were kept out of school during the lockdown, and their daily physical routines were severely restricted. Studies have reported an increase in puberty precocious and rapidly progressing puberty during the pandemic period, which is associated with a sedentary life, increased obesity with an increase in the time spent at home, and prolonged use of mobile devices (5,6). While obesity is generally highlighted as the risk factor with the most potential to disrupt the physiology of puberty, research has shown that physical inactivity, excessive screen time, altered sleep patterns, and psychological issues may also directly contribute to the issue (6,7)compared to subjects observed in the same period of the previous year. Design: The study population (490 children.

In this study, we evaluated the pre-pandemic and pandemic periods of the patients diagnosed with puberty precocious in our clinic, clinical features, laboratory findings, and whether obesity is a factor.

MATERIALS and METHODS

In the study, female patients diagnosed with Puberty precocious / Rapidly Progressive Puberty in our clinic were divided into three groups August 2019-February 2020 before the pandemic (Group 1), August 2020-February 2021 during the pandemic (Group 2), August 2021-February 2022 during the pandemic (Group 3).

Among the study groups, Group 1 (G1) covers the pre-pandemic period, Group 2 (G2) covers the whole closure period during the pandemic period, and Group 3 (G3) covers the face-to-face education period with partial closure during the pandemic period. The groups were retrospectively compared in terms of clinical, laboratory, and radiologic findings.

The study was conducted as a single-center retrospective case-based study. Two pediatric endocrinology specialists recorded demographic information, physical examination findings, hormone tests, and radiological imaging information from the

files of these patients diagnosed with puberty precocious.

Precocious puberty is defined as puberty stage 2 and above according to Marshall and Tanner staging, pubertal gonadotropin levels (basal LH > 0.3 IU/L, stimulated LH > 5 IU/L, and LH/FSH > 0.6), advanced bone age and pubertal findings on pelvic imaging (uterus > 35 mm, ovary > 2cc) before the age of 8 years. Progressive precocious puberty is defined as pubertal stage advancement from one stage to another in 3-6 Months or Growth velocity Accelerated >6 cm/year or bone age, typically advanced, variable, at least two years, predicted adult height, below target height or decreasing on serial determinations (8). Patients with peripheral puberty precocity and organic pathology on cranial MRI were excluded from the study.

Height and weight were measured, body mass index (BMI) was calculated using the standard formula [weight in kg/(height in m), and the respective standard deviation score (SDS) was calculated based on Turkish reference data (9). Obesity was defined percentile for age z-score 1.64, equivalent to 95 th percentile. Bone age (x-ray of the left hand) was assessed according to the method of Greulich and Pyle. FSH, LH, and estradiol (ATELLİCA System, Siemens) concentrations were measured using immunochemiluminometric assay (ICMA). The Ethics Committee of Ankara City Hospital approved this study. (27.05.2022/E2-22-1926).

SPSS 26 program was used for statistical analysis. Descriptive statistics were used to evaluate demographic and clinical characteristics. Data were described as a percentage and mean ± standard deviation (SD) or median (minimum-maximum) and categorical data. ANOVA, Kruskal-Wallis test and χ^2 tests were used according to data distribution. The "Kruskal-Wallis" test was used when comparing the medians of three independent groups in the data that did not fit the normal distribution, and the "Mann-Whitney U" test was used when comparing the medians of two independent groups. All data are given as mean ± SD Bonferroni correction was used in post hoc tests. Statistically, $p<0.050$ was considered significant.

RESULT

A total of 495 patients diagnosed with precocious puberty and rapidly progressive puberty were included in the study. The patients in the groups were as follows: n: 98 in G1, n: 194 in G2, n: 203 in G3. The median (min-max) age at presentation

was 8.3 (5.4-9.8) years in G1, 8.4 (5-9.9) years in G2, 8.3 (5.6-10) years in G3 and the age at presentation was similar in the groups (p=0.160) (Table I). The most common complaint at presentation in the three groups was thelarche, and presentation with combination of thelarche and pubarche were more common in G3 than in the other groups (p>0.050) (Figure 1). In comparison to the other groups, G2 had a significantly higher incidence of menarche (p=0.011) (Figure 1).

No difference was found between the groups regarding body weight SD and height SD (p>0.05). The BMI SD was 0.69±1 SD for all patients, 0.78±0.94 SD for G1, 0.67±1 SD for G2, and 0.67±1for G3, and the BMI SDS of the groups were comparable (p=0.630) (Table I).

In the physical examination findings at the presentation, the most common breast staging was Tanner stage 3. Breast Tanner stage 4 was detected more frequently in G2 and G3 than in G1 (p=0.057). In pubis Tanner staging, stage 1 and stage 2 were at the same rate in G1 (36.7%); the most common presentation was with Tanner stage 2 (38.7%) in G2; and the most prevalent manifestation was with Tanner stage 1 (38.4%) in G3 (Figure 2).

No difference was found between the groups' FSH, LH, estradiol, LHRH test peak FSH, peak LH, and LH/FSH values (p> 0.050) (Table II). There was no difference between the bone ages of the groups at presentation (p> 0.050). The uterine size, right and left ovarian volumes and endometrium thickness of G2 and G3 were larger than G1 (p=0.001) (Table II).

Ratio of puberty precocious to rapid progressive puberty cases 1:1.9 in G1, 1:2.2 in G2, 1:2.9 in G3. There was an increase in the incidence of rapid progressive puberty compared to puberty precocious during the pandemic, but no difference was found between the groups in the rates of puberty precocious and rapid progressive puberty cases (p = 0.239) (Table III).

DISCUSSION

Many publications have been shared about the increase in puberty precocious cases from different continents of the world during the pandemic (5,10–13). This increase during the pandemic is associated with increased obesity and screen exposure due to closure and sedentary life (10). Our study

Table I: Age and Anthropometric Findings of the Patients					
	Total n:495	G1 n:98	G2 n: 194	G3 n:203	p
Age at application (years)	8.3 (5-10)	8.3 (5.4-9.8)	8.4 (5-9.9)	8.3 (5.6-10)	0.160
Age at treatment (years)	8.6 (5-10)	8.5 (5.4-9.8)	8.6 (5-10)	8.6 (6-10)	0.430
Weight (sds)	0.99±1.08*	1±1.1*	0.9±1.1*	1±1*	0.560
Height (sds)	0.96±1.1*	0.92±1.1*	0.88±1.1*	1±1*	0.300
BMI (sds)	0.69±1*	0.78±0.94*	0.67±1*	0.67±1*	0.630

Values represent median (minimum-maximum), **Values represent mean ± SD*

Table II: Laboratory Results, Bone Age, and Pelvic Ultrasonography Findings of the Groups

	Total	G1	G2	G3	p
FSH (U/L)	5 (0.7-19)	5.3 (0.7-17)	5.1 (1.3-19)	4.9 (0.7-11.8)	0.770
LH (U/L)	0.9 (0.05-49)	0.8 (0.1-7.3)	1 (0.1-49)	0.9 (0.05-6.1)	0.280
Estradiol (pmol/l)	30 (8.2-345)	29.5 (12-345)	31 (8.2-257)	29 (12-91)	0.460
LHRH test					
Peak FSH (U/L)	15 (1.8-48)	14.8 (5.4-30)	15.5 (7.5-48)	14 (1.8-41)	0.210
Peak LH (U/L)	10.5 (3.2-93)	9.9 (4.4-47)	10.4 (4.8-78)	10.6 (3.28-93)	0.750
LH/FSH	0.8 (0.1-5.9)	0.8 (0.3-1.9)	0.7 (0.3-3.6)	0.9 (0.1-5.9)	0.56
Imaging findings					
Bone Age (years)	10.2 (5-13)	10 (5.4-12.5)	10 (5-13)	12.5 (6.8-13)	0.720
Uterine size (mm)	33 (13-67)	26 (15-59)	35 (15-67)	34.5 (13-66)	**0.001**
Right ovary (cc)	2.7 (0.5-24)	2.39 (0.5-19.7)	2.5 (0.5-24)	3 (0.9-10.5)	**0.001**
Left ovary (cc)	2.5 (0.5-20.2)	2.2 (0.5-6.5)	2.45 (0.5-20.2)	2.9 (0.9-8.4)	**0.038**
Endometrial thickness (mm)	0 (0-17)	0 (0-6.5)	0 (0-17)	0 (0-12)	**0.041**

Values represent median (minimum-maximum)

Table III: Distribution of puberty precocious and rapidly progressive puberty diagnoses in the groups

	Puberty Precocious n (%)	Rapidly Progressive Puberty n (%)	Total n (%)
G1	33 (33.7)	65 (66.3)	98 (100)
G2	60 (30.9)	134 (69.1)	194 (100)
G3	51 (25.1)	152 (74.9)	203 (100)
Total	144 (29.1)	351 (70.9)	495 (100)

showed that the BMI SD of the cases with puberty precocious who presented during the pandemic did not differ from those who presented before the pandemic. With this study, we have determined that obesity is not a factor of puberty precocious during the pandemic.

Nutrition is an accepted factor in sexual maturation (14). Although BMI has frequently increased during the epidemic due to decreased physical activity, this increase is often not noteworthy (5,15). Therefore, it is questionable whether a slight rise in BMI alone may account for the reported increase in the prevalence of precocious puberty in clinics. When we analyzed our patients in terms of obesity, which is defined as an essential factor in the increase in the frequency of cases in this period, the BMI SDS of the groups were similar. The balance of leptin and ghrelin is essential for eating, obesity, and puberty. Puberty is indicated by increased leptin and lower ghrelin levels in obese individuals (16). Chen et al. (3) found no difference in leptin levels between pandemic and pre-pandemic cases while finding similar BMI SD in pre-pandemic and pandemic. However, they found that ghrelin levels were lower in cases during the pandemic period. Since a positive correlation was discovered between serum ghrelin and serum MKRN3 concentrations, the researchers hypothesize that the lower concentrations of ghrelin may have downregulated the concentrations of MKRN3 and subsequently upregulated the pulsatile secretion of GnRH to promote the onset of puberty. In addition to psychological distress, dietary changes, and pandemic-related food changes, it is also required to incorporate alterations in microbiota, the microRNA network, and DNA methylation in the previously

described (17). And all of these factors may affect the mediators and signaling pathways involved in the onset of puberty. At this point, rather than obesity itself being a factor, the foods prefered, like antioxidant foods which used to protect from Sars-Covid19-B may also be a factor. Glutathione peroxidase, one of the enzymatic antioxidants, plays a role in cell differentiation and proliferation in gametes and those are related to the onset of puberty (18).

Screen exposure, which is mentioned as an important reason for the increase in the incidence of precocious puberty, may be explained by the suppression of melatonin and the elimination of the inhibitory effect of melatonin on GnRH. In our study, the screen exposure of the cases was not questioned individually, but G2 group in the study reflects the period when children were most exposed to the screen due to online education. In the literature, screen exposure time increased in children during the pandemic. Some studies questioned daily screen exposure before sleeping and daily screen exposure in puberty precocious cases and have shown increase in both parameters (5,19).

In our study, the ages at the presentation of the patients who presented before and during the pandemic period were similar to each other. In studies in the literature, studies are showing that the ages of the cases admitted during the pandemic period were younger (11,12,20).

While the most common complaint at presentation was thelarche, an especially increased number of patients in the G2
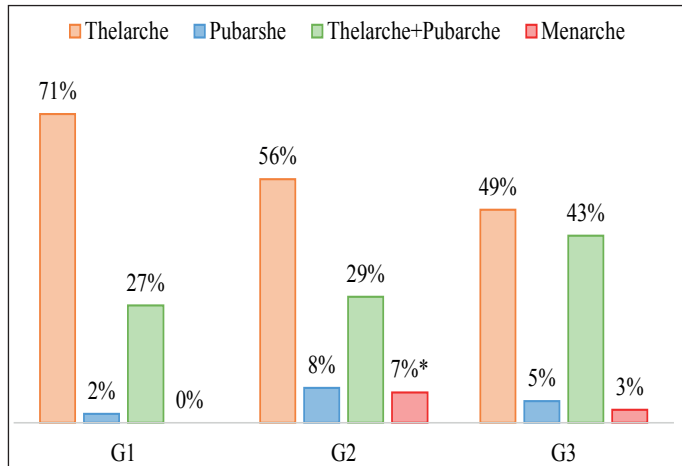
Figure 1: Application Complaints of Groups.
***Menarche was detected more in Group 2 compared to other groups (p=0.011)

BREAST TANNER STAGE

	G1	G2	G3	Total
Stage 5		1%		
Stage 4	2%	9%	9%	8%
Stage 3	61%	58%	67%	62%
Stage 2	37%	33%	24%	30%

PUBIS TANNER STAGE

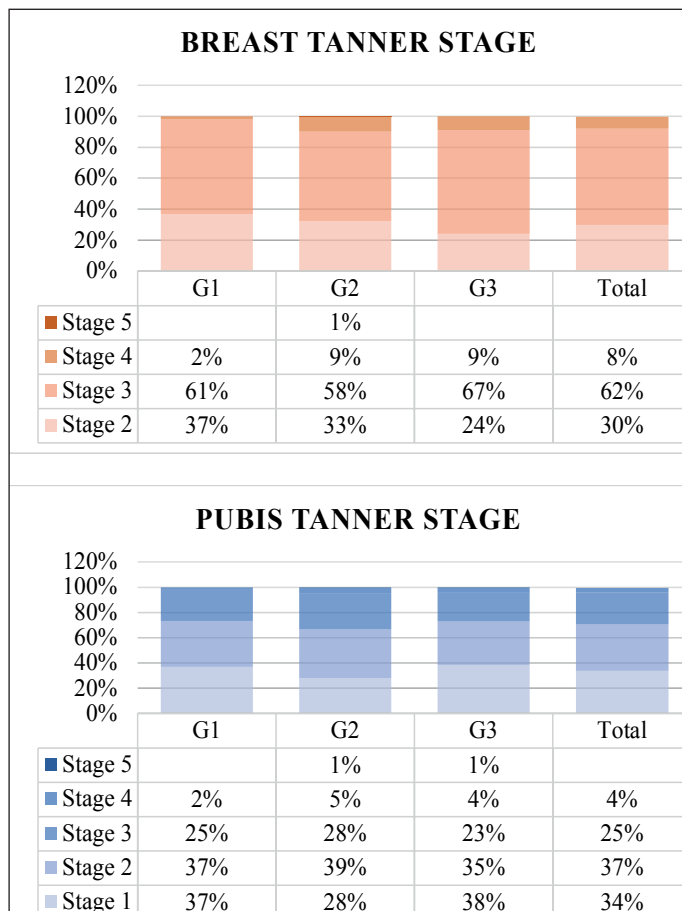|	G1	G2	G3	Total
Stage 5		1%	1%	
Stage 4	2%	5%	4%	4%
Stage 3	25%	28%	23%	25%
Stage 2	37%	39%	35%	37%
Stage 1	37%	28%	38%	34%

Figure 2: Pubertal Examination Tanner Staging of the Group.

group and G3 group, who were admitted with menarche after the complete closure period, were observed. This was thougth to be the effect of closures, fear of virus and late admission to hospital for puberty concerns. In addition, the increase in the G2 group was also statistically significant. In support of these cases, in the physical examination findings, a high percentage of patients presenting with breast tanner stage 4 and an increase

in uterine size and ovarian volumes in pelvic ultrasonography were detected in the pandemic period groups compared to the pre-pandemic period. The emergence of the first findings of the G2 and G3 pandemic period groups may have occurred earlier, or the puberty tempo may have progressed faster. Although there was no difference between the LH and Estradiol concentrations of the cases.

The strengths of our study are that the groups defined as the pandemic period in the groups taken in the literature's reflections cover the pandemic's initial period. Puberty development is a process, and the cases in that period reflect the pre-pandemic period. However, G2, one of our study groups, reflects the period in which we saw the effects of full closure; G3 reflects the period in which we saw the impact of the partial closure - face-to-face education continued process in which the pandemic effect.

In our study, we aimed to investigate whether obesity was a factor rather than an increase in the number of cases during the pandemic. In addition, we did not make a subjective evaluation in our study to learn the screen time of the instances one-to-one. However, it includes the period when the online education process and the time spent in front of the screen increased significantly in our country's G2 group of prepubertal children. Still, in the G3 group, out-of-home and in-school activities increased with a partial closure but were more limited compared to the pre-pandemic period.

In conclusion, obesity, increased screen exposure time, and immobility are shown as factors for the increase of puberty precocious during the pandemic. In our study, the BMI of pandemic groups (G2-G3) was similar before the pandemic group(G1). Our study showed that obesity was not a factor in precocious puberty during the pandemic.

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