


Etiology of Increased Referrals for Evaluation of Early Puberty in a Tertiary Care Center in Turkey: True Precocious Puberty, Obesity, or Parental Anxiety and Lack of Knowledge?

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Abstract

There has been a global increase in pediatric endocrinology referrals for the concerns of early puberty. The objective of this study was to determine the reasons behind this increase. A retrospective cross-sectional study was designed to analyze the clinical characteristics of patients seen for the concerns of early puberty in pediatric endocrinology clinic of a tertiary care center (Study A). Additionally, a prospective questionnaire study was designed to assess the knowledge and concerns of the mothers regarding the timing of puberty in girls (Study B). In study A, of the 305 girls, 42.9% were overweight/obese, 68.5% either had normal pubertal development for age or were prepubertal, 1 had non-classic congenital adrenal hyperplasia, and 2 had central precocious puberty. Of the 36 boys, 56% were overweight/obese, 64% either had normal pubertal development for age or were prepubertal, and 1 had non-classic congenital adrenal hyperplasia. In study B, 95% of the participants thought the girls have been developing earlier, over 10% considered the first sign of puberty to be normal after the age 14 years and 12.4% considered menarche to be normal after age 14 years. The common sources of anxiety for the participants regarding the earlier timing of puberty were psychosocial issues and short final height. In conclusion, many parents had wrong beliefs/information about the normal timing of puberty and were concerned about precocious puberty in girls. Education of parents about the normal timing of puberty may help avoiding unnecessary referrals, parental anxiety, and financial burden to the society.

Keywords

obesity, precocious puberty, education

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Introduction

The first sign of puberty in girls is considered normal when it occurs between the ages of 8 and 13.5 years, based on the data published by Marshall and Tanner.¹ However, the timing of puberty may vary according to the nutritional status of the child.²⁻⁴ There has been an increased number of pediatric endocrinology referrals of girls for the concerns of early puberty in most medical centers all over the world,⁵ paralleling the increase in childhood obesity in the past 2 decades.⁶ However, the

reasons behind the increased referrals for the concerns of early puberty is not clear and has not been well studied. The aim of this study was to assess the reasons

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behind this increase and whether this is due to a true increase in the incidence of precocious puberty or increased referrals are due to parental anxiety and misconception about the normal pubertal timing in girls.

Methods

This study was a combination of 2 sub-studies as described below:

- 1) *Study A*: In this retrospective cross-sectional study, the clinical characteristics of the patients seen for the concerns of early puberty in the pediatric endocrinology clinic of Baskent University Hospital in Turkey between January 1, 2017 and January 1, 2018, were analyzed. All the patients included in this study were seen by a single pediatric endocrinologist (APC). The data were obtained from the electronic medical records of the patients by screening for the chief complaint of possible early puberty, by reviewing every single chart of the patients seen in pediatric endocrine clinic for various reasons (a total of 1700 in 12 months' period). For each patient included in the study, a data collection form was filled out for the information needed for this study and then the data were transferred to an excel file by APC.
- 2) *Study B*: This was a prospective questionnaire study. All the mothers of the children seen in pediatric outpatient clinics of Baskent University Hospital between September 1, 2017 and February 1, 2018 were offered to fill about a questionnaire (Supplemental Material 1) during their routine visit, only if at least 1 of their children were female. The questionnaire consisted of several demographic questions as well as questions about the normal timing of puberty and menarche and the mothers' concerns about the causes and complications of early puberty in their daughters. A total of 220 participants accepted to fill out the questionnaire within the 4 months' period. and 16 were excluded because the answers to the questions were incomplete. After completion of the questionnaire, all the data from each questionnaire were transferred to an excel file for data analysis.

Ethical Approval and Informed Consent

The study A (IRB number: KA17/204) and B (IRB number: KA17/372) were both approved by the Institutional Review Board of the Baskent University School of Medicine. Informed consent was waived for study A

since it was a retrospective study and a verbal informed consent was obtained from the participants in study B (questionnaire study). All the data collected were kept in locked cabinets and no patient identifier information were put on the data collection tools. For patient confidentiality, a separate list of patient names for the corresponding case number was constructed and kept in a separate folder for future reference.

Statistical Analysis

The nominal values are expressed as percentages. The quantitative data are reported as mean \pm standard deviation (SD) and median.

Results

Study A

A total of 1700 new patients were seen by a single pediatric endocrinologist (APC) between January 1, 2017 and January 1, 2018 over a 12-month period.

Clinical characteristics of the patients in study A. Of the 1700 patients, 341 (20%) were for the concerns of early puberty with a predominance of girls (89.4% female vs 10.6% male). The mean age of girls was 8.23 ± 1.96 years and of boys was 9.94 ± 1.27 years. The mean age of menarche for mothers of boys and girls were similar. The history of early puberty (10.5% in girls vs 5.6% in boys) or delayed puberty (14.4% in girls vs 5.6% in boys) in the family were higher in girls compared to boys (Table 1).

Diagnostic work-up of the patients in study A. Typically, work-up ordered for early breast development in girls included Luteinizing Hormone (LH), Follicle stimulating Hormone (FSH), and estradiol and for early testicular enlargement in boys included LH, FSH, and total testosterone concentrations. For early pubic or axillary hair growth for both sexes, total testosterone, 17-hydroxyprogesterone, and Dehydroepiandrosterone-sulphate (DHEA-S) concentrations were ordered. Further work-up including gonadotropin releasing hormone (GnRH) stimulation test for possible central precocious puberty and adrenocorticotrophic hormone (ACTH) stimulation test for possible non-classic congenital adrenal hyperplasia (CAH) were performed when needed (Table 2).

Final diagnoses in patients seen for concerns of early puberty. Majority of patients did not have precocious puberty. In girls, 209 (68.5%) either had normal pubertal development for age or had no signs of puberty. Of these

Table 1. Study A. The Clinical Characteristics of the Patients and Parents of the Patients Seen in Pediatric Endocrinology Clinic of Baskent University for the Concerns of Early Onset of Puberty Over a Period of 12-months.

Parameters	Girls	Boys
Number (% of total number)	305 (89.4)	36 (10.6)
Age patients (years) (mean \pm SD, median, and range)	8.23 \pm 1.96, 8.58, 0.8-11.9	9.94 \pm 1.27, 10, 6.9-12.8
Age of menarche of mothers (years) (mean \pm SD, median, and range)	12.8 \pm 1.3, 13, 9-17	12.8 \pm 1.2, 13, 11-16
*History of early puberty in the family: N (%)	32 (10.5)	2 (5.6)
**History of delayed in the family: N (%)	44 (14.4)	2 (5.6)

*First signs of puberty before age 8 years for girls and 9 years for boys or menarche before the age of 10 years.

**Linear growth through college or menarche after age 14 years.

Table 2. Study A. Diagnostic Work-Up Performed for the Patients Seen in Pediatric Endocrinology Clinic of Baskent University for the Concerns of Early Onset of Puberty Over a Period of 12-months.

Diagnostic work-up	Girls: N (%)	Boys: N (%)
None	56 (18.4)	5 (14)
Bone age only (without blood work)	24 (7.9)	1 (2.7)
Bone age with or without blood work	192 (62.9)	26 (72)
Blood work only (without bone age)	54 (17.7)	1 (2.7)
Blood work with or without bone age	203 (66.5)	31 (86)
GnRH stimulation test	9 (2.9)	1 (2.7)
MRI of the brain/pituitary	1 (0.4)	None
ACTH stimulation test	None	1 (2.7)
Pelvic USG	2	—

209 girls, 131 (42.9%) were overweight or obese. Benign premature adrenarche (BPA) was defined as presence of pubic or axillary hair before the age of 8 years for girls and before the age of 9 years for boys with no other signs of puberty, and with or without an isolated increase in DHEA-S level. BPA was the final diagnosis in 25.2% of girls. Over 50% of girls with BPA were obese. Only 2 girls (0.66%) had central precocious puberty requiring treatment with GnRH (gonadotropin releasing hormone) analog and 1 girl had non-classic CAH (congenital adrenal hyperplasia) and was started on glucocorticoid treatment due to advanced bone age. Benign premature thelarche (BPT) was the final diagnosis in 16 girls (5.2%) with a mean age of 3.5 ± 2.8 (range 0.9-7.7) years. Two of the girls with BPT had a single ovarian cyst on pelvic ultrasound. In all girls with BPT, the findings resolved within the next 3 to 6 months. In boys, 23 (63.9%) had either normal pubertal findings for age or were prepubertal. Of these 23 boys, over 50% were obese and 33.3% had BPA. Over 50% of the boys with BPA were obese. None of the boys had central precocious puberty and only 1 (age 3.5 years) was diagnosed with non-classic CAH (Table 3).

Frequency of obesity in patients seen for concerns of early puberty. Obesity with or without other diagnoses was

noted in 42.9% of girls and 55.6% of boys. The mean age of obesity was 8.2 ± 1.4 (median: 8.3, range: 4.8-12) years for girls and 9.8 ± 1.3 (median: 9.8, range: 6.9-11.8) years for boys. The mean body mass index (BMI) percentile was 94.2 ± 3.9 for girls and 92.5 ± 2.1 for boys. Out of 131 obese girls, 31.3% and out of 20 obese boys, 30% had BPA. Among all the referrals for early puberty, obesity was the sole diagnosis in 28.2% of the girls and 33.3% of the boys (Table 4).

Study B

A total of 204 mothers were included in this study. The mean age of participant mothers was 38.5 ± 5.6 years and the mean age of menarche was 12.7 ± 1.3 years (Table 5).

The earliest age that was considered normal by participants for the first sign of puberty and for menarche differed widely. The mean youngest age for the first signs of puberty considered to be normal by participant mothers was 11.7 ± 1.5 (range: 8-15, median: 12 years). The mean youngest age for menarche considered to be normal by participant mothers was 12.1 ± 1.4 (range: 8-16, median: 12 years). Only 2.9% of the participants thought the earliest age for the first sign of puberty that should be considered normal was 8 years and only 8.3%

Table 3. Study A. The Final Diagnoses of Girls and Boys Seen in Pediatric Endocrinology Clinic of Baskent University for the Concerns of Early Onset of Puberty Over a Period of 12-months.

Final diagnosis	Girls: N (%)	Boys: N (%)
Normal pubertal findings (normal for age or prepubertal) with or without obesity	209 (68.5)	23 (63.9)
Normal pubertal findings (normal for age or prepubertal) excluding overweight and obese patients	123 (40.3)	11 (30.6)
Prepubertal patients	45 (14.8)	4 (11.1)
Overweight and obese prepubertal patients	26 (8.5)	1 (2.8)
BPA excluding overweight and obese patients	36 (11.8)	5 (13.9)
BPA including overweight and obese patients	41 (13.4)	7 (19.4)
BPA with or without other diagnoses	77 (25.2)	12 (33.3)
Obese and overweight patients only (without other diagnoses)	86 (28.2)	12 (33.3)
Obese and overweight patients with or without other diagnoses	131 (42.9)	20 (55.6)
Non-classic CAH	1 (0.33)	1 (2.8)
Central precocious puberty	2 (0.66)	None
BPT	16 (5.2)*	—

*Two had a single ovarian cyst diagnosed on ultrasound. In all patients with BPT, findings resolved within 3 to 6 months.

Table 4. Study A. The Clinical Characteristics of Obese Girls and Boys Seen in Pediatric Endocrinology Clinic of Baskent University for the Concerns of Early Onset of Puberty Over a 12-month Period.

Parameter	Girls	Boys
Mean age (years) \pm SD, median, and range (years)	8.2 \pm 1.4, 8.3, 4.8-12	9.8 \pm 1.3, 9.9, 6.9-11.8
BMI percentage (mean \pm SD, median, and range)	94.2 \pm 3.9, 95, 85.8-99.7	92.5 \pm 2.1, 92.5, 88.5-99.3
Obesity, total number* (%)	131 (42.9)	20 (55.6)
**Mild obesity (overweight) number* (%)	64 (20.9)	9 (25)
***Obesity number* (%)	27 (8.9)	5 (13.9)
****Severe obesity number* (%)	40 (13.1)	6 (16.7)

*Of all female referrals for girls and of all male referrals for boys.

**BMI > 85th to 94th percentile.

***BMI 95th to 97th percentile.

****BMI > 97th percentile.

Table 5. Study B. The Clinical Characteristics of the Participant Mothers and Their Daughters.

Questionnaire questions	Mean \pm SD	Median	Range
Participant mothers' age (years)	38.5 \pm 5.6	38	21-56
Menarche of participant mothers (years)	12.7 \pm 1.3	13	8-17
Age of daughters of participant mothers (years)	10.1 \pm 4.9	9.5	0.5-23
Age of first signs of puberty of daughter(s) of participant mothers (years)	9.7 \pm 2.0	9.5	4.5-14

thought the earliest age for menarche that should be considered normal was 10 years. Over 10% of the participants thought the first sign of puberty was normal only if it occurred after the age 14 years and 12.4% thought menarche would not be considered early only if it occurred at age 14 years or later (Table 6).

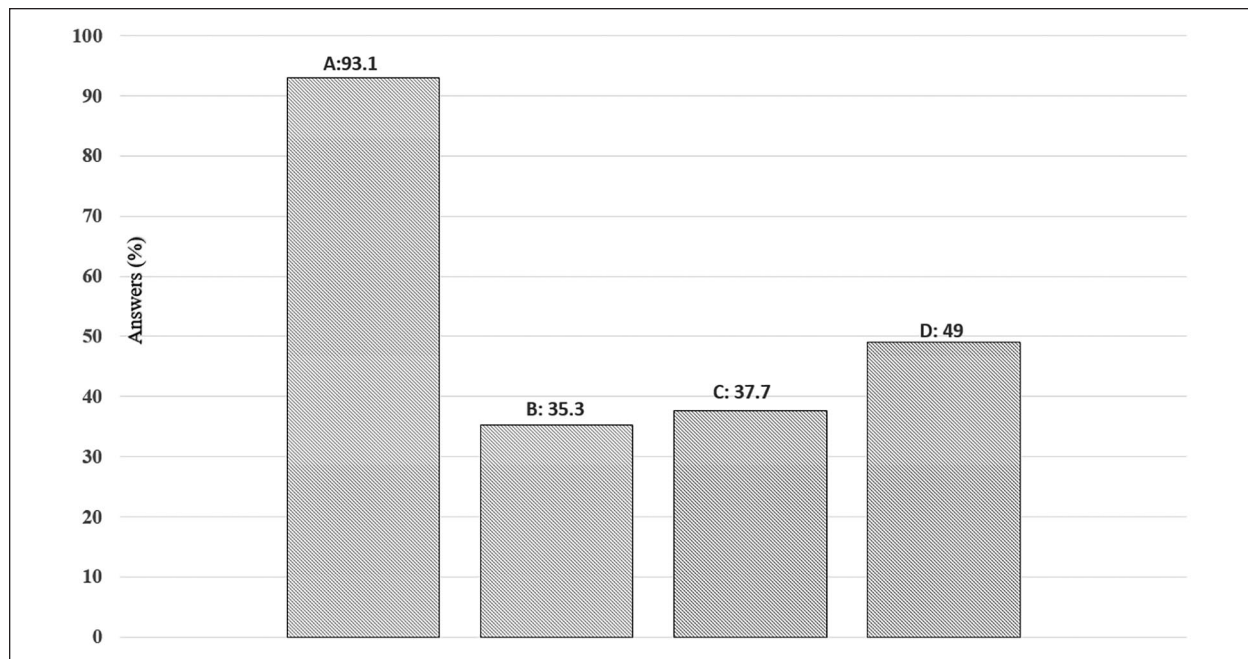
About 95% of participants thought, the timing of pubertal development in girls has been getting earlier in recent years. The most reason blamed for earlier onset of

puberty in girls were hormones and additives in foods consumed (93.1%), followed by obesity (49%), computers, TV, and electronic media (37.7%), and environmental pollution (35.3%) (Figure 1).

The most common concerns regarding earlier onset of puberty were that the child may experience psychosocial issues (77.9%) and may end up being a short adult (73.5%). The least concerns of the participant mothers regarding earlier onset of puberty of their

Table 6. Study B. The Questionnaire Responses of the Participant Mothers Regarding the Normal Timing of Normal Pubertal Maturation and the Normal Age of Menarche.

The youngest age considered to be normal (years)	Number of participants and (%)	
	For the first signs of puberty	For menarche
8	6 (2.9)	3 (1.5)
9	7 (3.4)	3 (1.5)
10	31 (15.2)	17 (8.3)
11	42 (20.6)	35 (17.2)
12	62 (30.4)	80 (39.2)
13	35 (17.2)	41 (20.1)
14	10 (4.9)	16 (7.8)
15	11 (5.4)	6 (2.9)
16	None	3 (1.5)

**Figure 1.** Study B. The participant mothers were asked to mark the factor or factors that they believe might be causing earlier onset of pubertal maturation in girls using the questionnaire (Supplemental Material 1).

The columns were marked as A: Hormones and additives in foods consumed, B: Environmental pollution, C: Computers, TV, and electronic media, and D: Obesity. The responses are depicted in percentages for each factor marked.

daughters were that, they may not enjoy their childhood (42.6%), and they may have an underlying illness (39.7%) (Figure 2).

Discussion

There has been an increased number of referrals to pediatric endocrinology clinics for the concerns of early puberty in girls in the past 2 decades. In our retrospective study, of the 1700 of new patients seen in Baskent University pediatric endocrinology clinic, 20% had the

chief complaint of early puberty. However, of the 305 girls, 68% and of the 36 boys about 65% had either normal pubertal staging for age or was prepubertal. Based on a longitudinal study done over a period of 2 decades between the years 1948 and 1960s by James Tanner, a British pediatric, the first sign of puberty is considered precocious when it occurs before the age 8 years for girls and 9 years of Marshall and Tanner.¹ Since then, his data for normal timing and staging of pubertal maturation have been used by the pediatric endocrinologists all over the world. However, the nutritional status of children

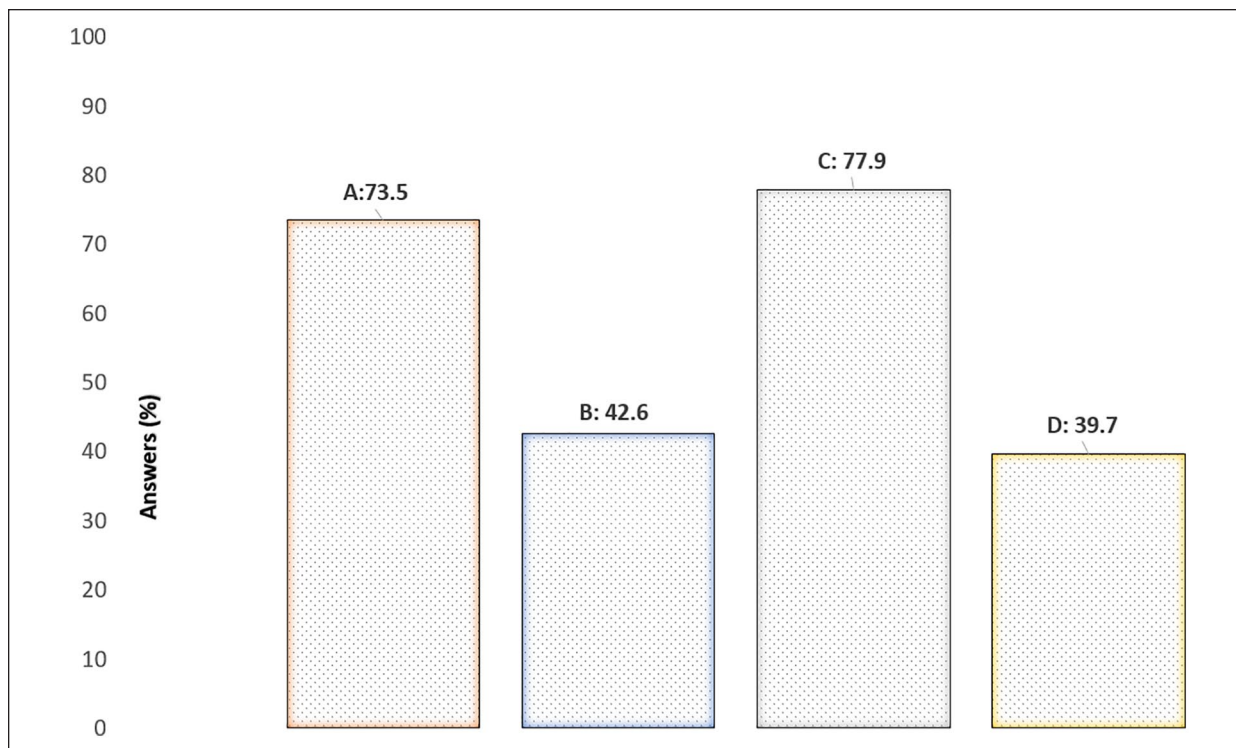


Figure 2. Study B. The participants were asked to mark the reason or reasons for their concerns about the early onset of puberty in girl using the questionnaire (Supplemental Material 1).

The columns were marked as A: may end up being a short adult, B: may not enjoy her childhood, C: may experience psychosocial issues, and D: may have an underlying illness. The responses are depicted in percentages for each reason marked.

has improved in the last 2 decades, compared to the children at the time when the study was done by Tanner. It is now well known that nutrition has a significant effect on the timing of pubertal maturation. While undernourished children tend to go through puberty much later than their peers, obesity in girls has been recognized as a major contributing factor for earlier pubertal maturation.⁷ Overweight boys also mature earlier but moderate to severe obesity may cause delayed puberty in boys.⁸ The data about the relationship between obesity and timing of puberty in boys is not as clear as in girls mainly because there is no clear objective information for puberty in boys that can be obtained by retrospective questioning as menarche in girls. Therefore, large scale studies are harder to perform on boys.⁷ In our retrospective study, about 43% of girls and 55.6% of boys were obese or overweight and in 28% of girls and 33% of boys, the sole final diagnosis was obesity. Childhood obesity has now become a worldwide public health problem⁶ and may be a major contributing factor for the earlier pubertal maturation encountered in the children included in our retrospective study. Therefore, the increase in pediatric endocrinology referrals for the concerns of early puberty could be due to a true increase of early bloomers due to childhood obesity. Increased

caloric intake causes faster linear growth, accelerated bone age maturation, and earlier onset of puberty.²⁻⁴ The earlier onset of puberty due to obesity does not cause problems that we commonly encounter in true precocious puberty. Usually, these girls do not menstruate before the age of 10 years and the final height stays within the target height since they are typically taller for their age.^{7,9} Despite the benign course of early bloomers, most parents are still concerned and seek medical advice. In our retrospective study, most of the patients (68.5% of girls and 63.9% of boys) seen for the concerns of early puberty in pediatric endocrinology clinic did not have early signs of puberty, similar to the findings of the study by Kaplowitz.¹⁰ It may not always be easy even for physicians to differentiate between normal and abnormal pubertal findings. Especially lipomastia in obese girls may also cause the false impression of breast development. Even an experienced pediatric endocrinologist may not be able to determine whether the palpable tissue represents a true pubertal onset or is just a fat tissue. Therefore, the physicians may have to order some laboratory work-up in these questionable cases. Furthermore, sometimes it is the parents' pressure or extreme anxiety that may push the physician to order a mini-work up. That was the case in the study reported

here, where the number of work-up ordered was much higher than the number of patients with early pubertal findings for age. Trying to convince an overanxious parent that their child has normal pubertal maturation for age and trying to avoid unnecessary work up may often be unsuccessful and may result in parents seeking medical advice from multiple other physicians. Unfortunately, this issue results in increased financial burden for both the families who have a copay for the medical expenses and for the society. However, an interesting finding in our retrospective study was that, about 6% of girls and 8% of boys were both normal weight and prepubertal. Some of these patients were referred by primary care physicians because primary care physicians were unable to convince the parents that he or she did not have precocious puberty. Others were seen without referral since these had a private insurance that allowed self-referrals.

Another interesting finding of our retrospective study was that, history of early puberty or delayed puberty were higher in the family of girls compared to boys seen for the concerns of early puberty. It could be speculated that the mothers' experience of their own pubertal timing may be causing a bias and leading to concerns of about the pubertal timing of their own daughters.

Pediatric endocrine society (PES) has revisited the normal timing of pubertal maturation in girls in 1995, based on a study by Herman-Giddens et al¹¹ PES suggested that the youngest age for the first sign of puberty in girls that is considered normal should be changed from 8 to 7 years in Caucasian and to 6 years in African-American girls and treatment with GnRH analogs should be reserved for girls with the onset of puberty before the age of 7 years.¹²⁻¹⁴ Despite this recommendation statement by PES, most pediatric endocrinologists still prefer to use the age cut off of 8 years for the diagnosis of precocious puberty in girls to avoid missing the rare cases of early puberty with an underlying pathology between the ages 6 and 8 years. However, most girls with the onset of puberty between the ages of 6 and 8 years are normal variants and do not need any intervention. Treatment with GnRH analogs for pubertal onset after the age 8 years in girls has not been proven to be beneficial for the final height except for certain circumstances such as girls born as SGA (small for gestational age) or girls with rapid pace of pubertal maturation.¹⁵ Although the lower and upper age limits of normal pubertal maturation in girls did not change, the mean age for the first sign of puberty has been declining from of 11.5 years as described in 1960s to 9.9 years in recent years,¹⁶ paralleling the increase in childhood obesity. Similarly, a study has shown that testicular volumes of ≥ 4 mL were achieved at ages 11.5 years in white, 11.8 years in African American, and 11.3 years in Hispanic boys, 2 years earlier than reported in the past.¹⁷ In boys, the

onset of puberty before the age of 9 years is rare and is still considered precocious and needs to be investigated thoroughly since an underlying pathology is more commonly encountered compared to girls.¹⁸ In our retrospective study, only 10.5% of the patients referred for early puberty were boys and none had central precocious puberty. The most common final diagnosis was BPA in 33.3% of the boys and 25% of the girls. Over 50% of these patients with BPA were overweight/obese in both sexes which is consistent with the other studies.¹⁹⁻²¹ BPA is considered to be a benign variant of puberty and most children reach their expected target height.^{20,21} However, studies have shown that girls with BPA develop metabolic syndrome or polycystic ovarian syndrome in adulthood more frequently.^{22,23}

Our questionnaire study revealed that, most parents had false beliefs/knowledge and unnecessary anxiety about normal pubertal maturation, possibly due to over-emphasis of the electronic media about the earlier timing of pubertal maturation in recent years. According to our questionnaire study, mothers' opinion for the normal age of onset of puberty in girls varied widely, and most considered 8 years of age as precocious. Over 10% of the participants thought that the first sign of puberty was considered normal only after the age 14 years and 12.4% considered menarche to be normal if it occurred at age 14 years or later. This might be a reason for over-anxious parents to seek medical advice from a pediatric endocrinologist for their children even with normal pubertal maturation.

The most common reasons blamed by the participant mothers as a cause of earlier onset of puberty in girls were exposure to food additives and hormones in the foods consumed. This may be a result of misinformation about the environmental chemicals or food additives in electronic media. Some endocrine disruptors as a cause of earlier onset of puberty have been well studied and reported in the literature.²⁴ However, there are also some speculative information with no scientific proofs. Some parents take these remarks very seriously and avoid many nutrients even milk or chicken or prefer consuming only "organic" foods, causing extra financial burden. The most common concerns and sources of anxiety for parents were either the risk of short final height and psychosocial issues their daughters might face. Of note, an underlying illness for the earlier onset of puberty was not the primary concern of most parents, an interesting finding suggesting that most parents did not really believe that their children had a serious medical issue.

Conclusions

Most of the girls seen in pediatric endocrinology outpatient clinics in a tertiary care center for the concerns of

precocious puberty were overweight/obese and either had no signs of puberty or had normal pubertal findings for age. Parents were over-anxious about precocious puberty, even if their children had no signs of puberty, resulting in increased pediatric endocrinology referrals. Education of primary care providers and parents about the normal timing of puberty and about prevention of obesity may be provided through school conferences given by pediatric endocrinologists, pamphlets distributed at schools or offices of health care providers, seminars given to local primary care physicians and parents, to avoid unnecessary referrals, parental anxiety, and financial burden to the society.

Author Contributions

All the authors have read and approved the manuscript. APC has contributed to the conception, design of the work, interpretation of data; contributed to the acquisition and analysis of the study and drafted the manuscript and substantively revised and approved the submitted version of the manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. OO and DK have contributed to the acquisition and analysis of the study and have approved the submitted version of the manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

The study A and B were both approved by the Hospital Institutional Review Board of the Baskent University Faculty of Medicine. Study A was a retrospective study from the electronic medical records and therefore consent was waived by Hospital Institutional Review Board of the Baskent University Faculty of Medicine. For study B, verbal consent to participate was obtained from the participants for study B. A written consent was waived and a verbal consent was approved by Hospital Institutional Review Board of the Baskent University Faculty of Medicine in study B because this was a questionnaire study and had risk for the participants and no personal data were requested or stored.

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Supplemental Material

Supplemental material for this article is available online.

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