Turkish Archives of Pediatrics

SCIENTIFIC LETTER
DOI: 10.5152/TurkArchPediatr.2023.23104

Early Normal Puberty and Accelerated Puberty in Girls: How Can We Avoid Unnecessary Treatment and Identify Children Who Are Likely to Benefit from Gonadotropin-Releasing Hormone Agonist Treatment?

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Early puberty has been a hot topic in the field of pediatric endocrinology, as well as among parents and in the media, ever since it appeared on the cover of the "Time Magazine" on October 30, 2000, with the question "Precocious puberty: Why girls grow up faster?," that is, for almost a quarter of a century.[1]

Early puberty, medically known as "precocious puberty," has been known for many years and is mostly observed in girls between the ages of 4 and 6, and with the use of medications suspending puberty, short stature can be prevented to a certain extent and the age of menstruation can be postponed. In the last 2 decades, the cases of "precocious puberty" or "normal early puberty" in girls aged 7-9 years have increased all over the world. We know a clear relationship exists between this increase and the severity/speed of obesity. This relationship is even more pronounced during rapid lifestyle changes, such as the recent coronavirus disease 2019 pandemic lockdown.[2,3]

The use of gonadotropin-releasing hormone agonist (GnRHa) treatment has increased, just as the increase in the frequency of upper respiratory tract infection cases triggers an increase in the initiation of antibiotics without throat culture. This trend suggests "the medicalization" of physiological variations, reasonable but unproven assumptions such as psychological stress and the possibility of short stature guide decisions, and difficulties in identifying cases in need of treatment.[2] This trend is very much in line with the new orientation of medicine described in the book *Risky Medicine: Our Quest to Cure Fear and Uncertainty*, which largely parallels the new direction of medicine.[4] The fact that the median age of treatment in the USA is 9 years and 11.6%-15% of the cases in whom treatment is initiated are younger than 8 years and the median age of 770 girls in whom treatment is initiated in a multicenter study in Turkey is 7.9 $\pm$ 1.35 years suggests that the majority of the cases in whom GnRHa treatment is initiated are between 7 and 9 years of age and mostly in the 8-9 age group.[2,5] In addition, recent reports from Turkey and Denmark confirm that the majority of the cases in whom treatment was initiated were in the idiopathic group.[5,6]

Within the framework of the literature and our own clinical experience, we can make the following conclusions about the increase in the use of GnRHa in girls aged 7-9 years.

RESEARCH RESULTS AND OBSERVATIONS

Many Physicians Mostly Treat a Physiological Condition, That Is "Constitutional Early Puberty"

The pre-pubertal height percentiles of a group of children can be advanced compared to their target height (mostly due to increased adipose tissue/excess calorie diet); these children also have advanced bone age (BA) and are more likely to progress into puberty at an earlier stage. These children have constitutional advancement of growth and then present as

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Received: May 17, 2023
Accepted: June 30, 2023
Publication Date: August 9, 2023

Cite this article as: Mutlu GY, Hatun S. Early normal puberty and accelerated puberty in girls: How can we avoid unnecessary treatment and identify children who are likely to benefit from gonadotropin-releasing hormone agonist treatment? *Turk Arch Pediatr.* 2023;58(6):664-667.

cases of constitutional early puberty (CEP); this situation can be considered the opposite of constitutional delayed growth and puberty.[7] In a study based on the annual follow-up of 170 Israeli (60 girls) and 335 Polish (162 girls) children aged 8-18 years, it was shown that children who were in the higher height percentile (positive "height gap") compared to their pre-puberty target heights had earlier puberty and these children subsequently "physiological catch down" to their target height percentiles.[8] Similarly, according to other studies from Denmark and Israel, the growth pattern at 6-12 months and 5-7 years of age affects the onset and pace of puberty, and tall girls enter puberty earlier and short girls later.[9,10] Therefore, it is necessary to consider the height at the onset of puberty instead of the target height and avoid creating false expectations.

Considering all these data, we can use the concept of "CEP" inspired by the concept of "Constitutional delayed puberty" in girls whose puberty begins between the ages of 7 and 9 years, except, for cases with peripheral, genetic precocious puberty, small for gestational age (SGA) and additional central nervous system (CNS) problems, and we may not rush for treatment in these cases.

The Parameters Used in Decision-Making Are Imprecise, and Medication Is Often Initiated to Stay on the Safe Side and with the Perspective of "We Have a Chance, Why Not Try"

Drawing a definite and clear boundary between puberty and prepuberty is not possible; this is because the transition to puberty is gradual. Therefore, it is important to evaluate the process and always consider more than 1 parameter rather than making a judgment based on initial evaluation or cross-sectional findings.[11,12] The mechanism in cases of slowly progressive precocious puberty is unknown. They have pubertal findings, but their gonadotropic axis is not activated. On the other hand, in cases of premature adrenarche, breast development may occur due to the aromatization of weak androgens, and lipomastia can be a confounding factor. Breast size does not always indicate an estrogen effect. Other findings indicating estrogen effects such as uterine findings and accelerated growth should also be carefully assessed. There is no method to predict the time of menstruation in cases of CEP, and it is not correct to assume that growth will stop as soon as menstruation occurs "as if the brakes were applied." The criteria for progressive/non-progressive precocious puberty defined by Carel and Léger[13] in 2008, frequently used in clinics, accept the criteria related to the onset of puberty as progressive central precocious puberty (CPP). However, the vast majority of CEP cases fulfill these criteria and are considered progressive accordingly. In the UpToDate, there is clarity on 2 issues[14]: The criterion for BA progression is advanced (>120%) for height-for-age, meaning that if this is the case, the final height may be negatively affected. Additionally, even if the peak luteinizing hormone (LH) is pubertal in the luteinizing hormone releasing hormone (LHRH) test if the peak LH/Peak follicle-stimulating hormone (FSH) ratio is <0.66, this is considered in favor of non-progressive early puberty. In the 7-9 age group, where GnRHa treatment is most commonly recommended, there may be differences in the evaluation of predicted adult height (PAH) according to the Greulich Pyle atlas (especially when the Sesamoid bone is observed, it is assessed as 11 years of BA). In general, the calculation of PAH according to the "advanced column" in cases of early puberty provides a closer estimate of the final height (although there are also publications showing the opposite). Nevertheless, it should be kept in mind that PAH calculation is based on a mathematical model and the gradual decrease in the estimated adult height in the follow-up should be taken into consideration rather than the initial cross-sectional evaluation.[12]

However, peak LH/FSH ratio is not sufficiently taken into consideration in daily clinical decisions. In cases of pramature telarche between 1-3 years of age, we know that a peak LH level >5 IU/L does not always indicate pubertal activation and that the peak LH/FSH ratio is more discriminative.[15] Therefore, we note that it is useful to use peak LH and peak LH/FSH ratio together.

Studies Showing No Effect of Gonadotropin-Releasing Hormone Agonist Use on Height in Most Early Normal Puberty Cases Are Ignored

Gonadotropin-releasing hormone agonist treatment has 2 main aims: to ensure that final height is not adversely affected by the early puberty process and to postpone the age of menstruation to the normal range. Studies on the favorable effect of GnRHa treatment on final height are largely applicable to cases of precocious puberty diagnosed before the age of 6 years, whereas clinical trials on the effect of treatment on adult height in girls with idiopathic CPP lack a solid evidence base, mainly due to the lack of well-designed randomized controlled trials and our inability to estimate a child's adult height precisely.[11,12] This is particularly true for girls whose age at the onset of puberty is close to the physiological age of puberty and who currently make up the majority of cases treated with GnRHa.[12] Various studies from Turkey have shown that there is no difference in the final height of girls who were treated with GnRHa or not between the ages of 7 and 10.[16-20] In a study, it was shown that GnRHa treatment did not improve final height after the age of 8.3 years, but treatment provided better height in the group with pubertal development of stage 3 and above between the ages of 6.4 and 8.3 years and BA was 2.6 years or more advanced compared to chronological age. Similarly, in a meta-analysis, data from 300 girls who did not receive treatment and 183 girls who were treated with GnRHa were analyzed; no difference was found between spontaneous puberty and reaching the target height and the effect of GnRHa treatment.[21]

Although there are many similar data, we need to think together to what extent our clinical practice is compatible with these data. In general, the main reasons for the lack of a final color effect of GnRHa treatment except in some cases are that we prevent the synergy between estrogen and growth hormone as a result of the suppression caused by GnRHa treatment and that there is no pubertal growth spurt when the treatment is discontinued.[22] In fact, with this treatment, we disrupt the puberty physiology of many children for no reason and we do not get the expected result. Maybe we change the path/speed but we cannot change the destination.

A favorable effect of GnRHa treatment on final height can be expected in a small number of cases of SGA (small for gestation

age) and/or born prematurely, familial cases of precocious puberty (family history of menstruation before the age of 10 years or mutations), neuromotor developmental problems, organic lesions, adopted girls, rapidly progressive puberty (children whose BA is 2.6 years ahead of chronologic age, or breast development consistent with Tanner Stage 3 and above) between 6 and 8.3 years of age. In clinical practice, these cases constitute a smaller group and are already easy to detect. In children born with SGA and/or intrauterine growth retardation, the pace of puberty is known to be rapid and it has been reported that the use of GnRHa treatment with growth hormone at the onset of puberty for up to 2 years may improve final height, especially in cases of Silver Russel Syndrome or SGA with poor final height prognosis.[23] However, a recent article emphasizes that such treatments are off-label, that there is currently no replication of data, and that further studies on efficacy and safety are needed.[24]

Mostly Non-Evidence-Based Concerns Are Emphasized But Side Effects, Concerns About Treatment, and Costs Are Underplayed

In a study from Turkey, 209 girls who presented with early puberty were evaluated; it was shown that the mean age at presentation was 8.2 years, 68.5% had normal puberty findings, and only2 % had CPP; the most important concerns were the risk of short stature and psychosocial problems. The importance of educating families about the normal onset times of puberty was emphasized in this study.[25] Indeed, except for a small number of girls, no sufficient data show that menstruation around the age of 10 causes anxiety (anxiety disorder) in children; observations show that families are more anxious than children.[11]

Menstruation begins 2.4-3 years after breast development, meaning that girls whose breast development begins around 8 years may have periods after the age of 10 years. Similarly, no strong data show that early puberty causes cognitive and psychological problems in children compared to their peers of the same age, and in general, there seems to be no difference in these respects. Data on precocious puberty and adulthood morbidities (cardiovascular disease, breast cancer, etc.) and psycho-social course have serious limitations, and it is more accurate to say that there does not seem to be a significant problem. In recently published comprehensive studies, it has been shown that there is no relation between the age at menopause and breast cancer and the onset of puberty.[26,27]

On the other hand, according to the information obtained from the "Intercontinental Marketing Services Health" database in our country, the frequently used Lucrin Depot 3.75 mg (although not all of them are used in the pediatric age group), which was 62908 boxes in 2018, reached 183377 boxes in 2021, and this increase is 191.5%, and the cost of this drug alone is around 320 million Turkish Liras annually.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, we think that physicians should take the international consensus on the use of GnRHa and evidence-based data[28] summarized in the following into consideration while they are making decisions on precocious puberty management.

1. Apart from the previously mentioned cases of SGA, CNS developmental problems, etc., GnRHa treatment is generally not necessary in cases of CEP whose puberty begins between 7 and 9 years of age. A small number of cases that may benefit from treatment need to be meticulously identified.
2. Avoiding unnecessary treatment should be a priority.
3. If height is above average and BA is not markedly advanced, adult height is likely to be normal and will not be markedly improved by treatment.
4. Psychosocial stress due to early puberty may not occur in all cases, but if it does, GnRHa treatment may not be able to reduce such stress.
5. Puberty may progress slowly, so menses may not occur as early as feared. Observation at 4-6 months will help determine if a child's puberty is progressing rapidly.
6. Treatment is expensive and in addition, the pharmacological intervention, clinic visits, and periodic injections may cause emotional stress in children.
7. Many studies have shown no benefit in terms of height in girls treated after the age of 8 years, and in some girls, the height was even negatively affected as a result of treatment.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.H., G.Y.M.; Design – S.H., G.Y.M.; Supervision – S.H., G.Y.M.; Resources – S.H., G.Y.M.; Materials – S.H., G.Y.M.; Data Collection and/or Processing – S.H., G.Y.M.; Analysis and/or Interpretation – S.H., G.Y.M.; Literature Search – S.H., G.Y.M.; Writing – S.H., G.Y.M.; Critical Review – S.H., G.Y.M.

Declaration of Interests: Professor Şükrü Hatun is a member of the journal's Editorial Board. Gül Yeşiltepe Mutlu has no conflict of interest to declare.

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