Original Article

Preliminary comparison of net gain in final adult height of girls with early menarche treated with or without gonadotropin-releasing hormone agonist

Yingyi Qi, Yao Zhang, Xiaoxiao Liu, Yun Li, Rongxiu Zheng

Department of Pediatrics, Tianjin Medical University General Hospital, Tianjin, China

Contributions: (I) Conception and design: Y Qi, R Zheng; (II) Administrative support: R Zheng; (III) Provision of study materials or patients: Y Qi, R Zheng; (IV) Collection and assembly of data: Y Zhang; (V) Data analysis and interpretation: X Liu, Y Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Rongxiu Zheng, PhD. Department of Pediatrics, Tianjin Medical University General Hospital, 154 Anshan Road, Tianjin 300052, China. Email: rzheng@tmu.edu.cn.

Background: Early menarche is associated with both physical and psychosocial problems. Based on psychological and physical health considerations, for girls with early menarche, some parents and physicians may elect to use gonadotropin-releasing hormone agonists (GnRHa) to delay menstruation. This study aimed to explore the effects of GnRHa treatment on the final height of girls with early menarche and build the models to predict the final adult height (FAH).

Methods: Girls who experienced menarche between the ages of 8 and 10 years and were diagnosed with idiopathic central precocious puberty (ICPP) at Tianjin Medical University General Hospital between July 2017 and August 2023 were included in this study. Participants were divided into two groups based on treatment strategy: GnRHa-treated and GnRHa-untreated groups. Laboratory parameters including growth factors and basal gonadotropins were tested at diagnosis. The heights and weights of the participants were measured every three months. Bone radiographs of the left hand and wrist were assessed by professional appraisers to determine the bone age (BA), which was measured every 6 months after diagnosis.

Results: Clinical data of 176 girls who experienced early menarche were retrospectively analyzed. For participants in the GnRHa-treated group (n=87), growth velocity (GV) showed significant differences between the first 6 months and second 6 months of treatment (P=0.01; 5.82±2.3 *vs.* 4.79±2.31 cm, respectively). The height standard deviation score (SDS) and BA (P<0.001) decreased during treatment. The predicted adult height was higher at the end of treatment, but was not statistically different from that at diagnosis (P=0.73). In the linear regression analysis, no significant relationships were observed between GnRHa treatment and net gain (NG) in final height [Model A, adjusted for BA and chronological age (CA) at baseline: P=0.43; Model B, adjusted for Model A plus HtSDS-BA, HtSDS, and BMISDS: P=0.65; Model C, adjusted for Model B plus LH, FSH, and IGF-1: P=0.82]. The generalized additive model (GAM) for NG in final height in GnRHa-treated participants included three independent risk factors: LH/FSH [estimated degrees of freedom (edf) =5.36, P=0.02], GV (edf =4.11, P=0.007), and the bone maturation ratio (BMR) (edf =4.79, P=0.02). GAM performed better than multivariate linear (stepwise) regression in predicting the FAH in GnRHa-treated girls with early menarche.

Conclusions: For girls who experienced menarche between the ages of 8 and 10 years, GnRHa treatment suppressed GV and skeletal maturity. The GAM provides a theoretical basis for pediatric endocrinologists in deciding whether to apply GnRHa treatment, determining the time to withdraw GnRHa treatment, and predicting the FAH of girls with early menarche.

Keywords: Early menarche; gonadotropin-releasing hormone agonist (GnRHa); final adult height (FAH)

Submitted Sep 05, 2024. Accepted for publication Dec 04, 2024. Published online Dec 27, 2024.
doi: 10.21037/tp-24-348
View this article at: https://dx.doi.org/10.21037/tp-24-348

Introduction

Puberty is a transitional period from childhood to adulthood during which sexual maturation occurs. The onset of puberty in girls is characterized by the appearance of breast buds (1). Menarche is a milestone event in pubertal development in girls and usually occurs 2 or 3 years after breast development. The age at menarche varies across generations, races, and countries. In China, the age at menarche for girls has declined from 14.25 years born before 1976 to 12.60 years born after 2000 (2).

Early menarche is defined as the age at menarche being less than mean ± standard deviation (SD) or before 12 years of age (3). In China, the onset of menarche before the age of 10 years is used as a diagnostic criterion for the diagnosis of central precocious puberty (CPP) (4). Many studies have reported that early menarche is associated with physical and mental illnesses in adolescents. Several studies have reported that girls with early menarche experience higher degree of depressive symptoms and suicidal ideation among adolescents than those with late-onset menarche (5,6). Early menarche may also influence the development of metabolic disorders in adulthood, including obesity, insulin resistance, and hypercholesterolemia (7-9). Furthermore, early menarche is associated with a higher risk of female-specific cancers, such as ovarian, endometrial, and estrogen receptor-positive breast cancer (10,11). Girls with early menarche have a shorter final adult height (FAH) than their potential genetic height because of early fusion of the epiphyseal growth plates.

Physicians and parents often worry about the social and emotional repercussions of a child becoming sexually mature at an early age. Based on psychological and physical health considerations, girls who visit a clinic for early menarche would choose to be treated with gonadotropin-releasing hormone agonist (GnRHa) to delay menstruation. GnRHa plays a therapeutic role in a variety of diseases and is the standard medication for the treatment of CPP (12). GnRHa compounds have a high affinity for the pituitary luteinizing hormone-releasing hormone (LHRH) receptor and are resistant to enzymatic degradation, ultimately resulting in the inhibition of gonadotropin secretion and cessation of pubertal development (13).

It is now generally accepted that final height will benefit from treatment if girls are diagnosed with CPP before the age of 6 years. However, the effects of GnRHa treatment in girls with CPP diagnosed over the age of 6 years, especially older than 8 years old, is unclear. Studies have shown that patients who receive GnRHa treatment at a younger age are most likely to gain more height and achieve a higher adult height (14,15). However, other studies have not shown any correlations between height gain and age at initial treatment (16-18). Additionally, the girls included in previous studies started GnRHa treatment immediately after the appearance of secondary sexual characteristics; therefore, these girls were treated promptly and did not experience menarche the age of 10 years.

Consequently, the girls who visited a clinic because of early menarche may have middle or even late puberty. For these girls, the onset of puberty may start at a very young age and is expected to result a greater loss of height potential. Precise estimation of GnRHa treatment duration and its effect on the final height of girls with early menarche is difficult because of the scarcity and inaccuracy of available data; however, parents and physicians are often concerned about this issue. To the best of our knowledge, the long-term effects of GnRHa alone on the final height

Highlight box

Key findings

- The generalized additive model (GAM) performed well in predicting net gain in final adult height of girls, who experienced early menarche, after gonadotropin-releasing hormone agonist (GnRHa) treatment.

What is known and what is new?

- For girls who experienced menarche between the ages of 8 and 10 years, precise estimation of GnRHa treatment duration and its effect on the final height of girls with early menarche is unclear.
- The GAM explores the effects of GnRHa treatment on the final height of girls with early menarche.

What is the implication, and what should change now?

- The GAM provides a theoretical basis for pediatric endocrinologists in deciding whether to apply GnRHa treatment, determining the time to withdraw GnRHa treatment, and predicting the final height in girls with early menarche.

of girls who experienced early menerche has not yet been performed.

Therefore, we conducted this study to determine the effect of GnRHa treatment alone on FAH in girls with early menarche and constructed regression models associated with net gain (NG) in final height. These results would provide a theoretical basis for the selection of future treatment options and final height predictions in these girls. We present this article in accordance with the TRIPOD reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-348/rc).

Methods

Study design

Study population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Human Research Ethics Committee of Tianjin Medical University General Hospital (No. IRB2024-YX-350-01) and individual consent for this retrospective analysis was waived. We retrospectively analyzed the medical records of girls who experienced menarche between the ages of 8 and 10 years at the Pediatric Endocrinology Clinic of Tianjin Medical University General Hospital between July 2017 and August 2023. All the patients met the following criteria: (I) basal gonadotropins levels up to that of puberty and basal luteinizing hormone (LH) levels up to 0.2 IU/L; (II) ultrasound showing enlargement of both the uterus and ovaries, with multiple follicles >0.4 cm in diameter; and (III) bone age (BA) advanced and >1 year older than chronological age (CA). Patients with peripheral precocious puberty were excluded, such as females receiving exogenous steroids and those diagnosed with tumors or adrenal disorders. Gonadotropin-releasing hormone (GnRH) stimulation tests were not performed because the females attending the clinic were mid-adolescents.

GnRHa-treated and GnRHa-untreated groups

Figure S1 illustrates the population-screening process. In total, 204 patients were recruited for this study. Based on acceptance or refusal of GnRHa treatment, participants were categorized into two groups: GnRHa-treated and GnRHa-untreated groups. Three girls were excluded because they received recombinant human growth hormone (rhGH) treatment after diagnosis.

GnRHa was administered monthly at a dose of at a dose of 3.75 mg subcutaneously and treatment duration was >1 year. Nineteen patients were excluded because they were undergoing treatment and six were excluded because of missing data. Ultimately, 87 patients treated with GnRHa were included in the analysis and 89 girls who did not receive the GnRHa therapy were included as controls.

Evaluation during follow-up

All patients were followed up until they reached the FAH. Of the 87 patients treated with GnRHa, 48 reached FAH; 89 females did not receive GnRHa therapy, of which 21 reached FAH and were recruited as controls. BA was evaluated every 6 months after diagnosis until FAH was reached. FAH was achieved when BA was >14.5 years, and/or when the growth velocity (GV) over the previous year was <1 cm. During the follow-up period, the mean incremental GV was calculated as the ratio of the change in height to the change in CA at approximately 6-month intervals through the follow-up period. For patients who received GnRHa treatment, the bone maturation ratio (BMR) was calculated as ΔBA/ΔCA ratio, which compared the annual change predicted between treatment initiation and withdrawal.

The formula for NG at the final height is as follows. The NG was used to the height benefit for girls in the GnRHa-treated and GnRHa-untreated groups.

$$NG = FAH - PAH \text{ at baseline} \quad [1]$$

Data collection

Anthropometric and BA measurements at baseline

Height and weight were measured for all the girls and their parents. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Targeted height (TH) was calculated using Tanner's formula [(father's height + mother's height – 13)/2] (19).

Bone radiographs of the left hand and wrist were assessed by professional appraisers to determine the BA using Radius, Ulna and Short bone-China 05 (RUS-CHN) method (20). The predictive adult height (PAH) was calculated using the RUS-CHN method.

All measurements were expressed as standard deviation scores (SDS) according to Chinese children and adolescent growth standards, including height SDS (HtSDS), HtSDS-BA, weight SDS (WtSDS), BMI-SDS, and PAH-SDS. The formula was SDS = (individual's measurement – population mean)/SD for the same population.

Laboratory parameters

Growth factors, including insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3), were measured using a two-site radioimmunoassay. They were the key regulators of the actions of growth hormone (GH). Basal gonadotropins, including LH and follicle-stimulating hormone (FSH), were measured using a chemiluminescence immunoassay.

Ultrasound examination

Pelvic ultrasonography was performed at the time of diagnosis in all girls by an experienced pediatric radiologist to evaluate uterine and ovarian development using LOGIQ E9 (GE, Boston, USA). The ovarian volume was calculated as length × width × height × 0.53. Uterine length >3.5 cm and ovarian volume between 1–3 cm^3 were accepted as the inclusion criteria. Pelvic ultrasonography results were assessed in conjunction with other clinical and laboratory parameters.

Statistical analyses

All analyses were performed using R v.3.0 (http://www.r-project.org/). Continuous variables were reported as medians with interquartile ranges (IQRs). Considering the non-normal distribution of variables, continuous variables were compared using a paired two-tailed Mann-Whitney *U* test. Significance was defined as P<0.05 for two-sided tests.

To evaluate the effects of GnRHa treatment on NG in height, linear regression analyses were conducted after adjusting for covariates in three models: Model A was adjusted for BA and CA at baseline; Model B was adjusted for Model A plus HtSDS-BA, HtSDS, and BMISDS; and Model C was adjusted for Model B plus LH, FSH, and IGF-1.

Multiple linear regression (Model 1) and multiple stepwise linear regression (Model 2) were used to predict NG in height in girls with early menarche who were treated with GnRHa. The models were formulated using the "stats" package. The formula is shown below, where β represents regression coefficient, and ε represents intercept.

$$y(NG) = \beta 0 + \beta 1x1 + \beta 2x2 + \ldots + \beta n*xn + \varepsilon \quad [2]$$

However, the incorporation of the polynomial covariate terms is not always accurate. Another linear regression model, the general additive model (GAM) (Model 3), which is a flexible non-linear model, was used to assess the linearity of the relationship between the factors and NG in height using graphical observations. The models were formulated using the "mgcv" package. GAM was indicated as follows: β0 represents the intercept. The non-parametric part of the expression is formed by f(x), which is a smooth function of the influencing factors (21).

$$g(NG) = \beta 0 + f1(X1) + f2(X2) + \ldots + fn(Xn) \quad [3]$$

Results

Baseline characteristics

A total of 176 girls were included in this study. Eighty-seven girls who attained menarche between 8 and 10 years old and were treated with GnRHa were included in the GnRHa-treated group (Figure S1). Among the 87 girls in the GnRHa-treated group, 48 girls had reached the FAH. Eighty-nine girls with early menarche did not receive GnRHa treatment, and 21 girls who reached the FAH were included in the GnRHa-untreated group.

GV were suppressed after 6 months of GnRHa treatment

In the GnRHa-treated group, 67 girls with early menarche were treated for >1 year. The average GV was 5.61±1.44 cm/year in the first year of treatment. The GV showed significant differences between the first and second 6 months of the year (P=0.01) (*Figure 1A*). *Figure 1B* shows the GV transition between the first and second 6 months of the first year. GV was divided into three levels: <4, 4–7, and >7 cm. Among the 67 girls, 47.8% had a significantly reduced GV.

GnRHa suppressed BA and height growth but had no effect on PAH

GnRHa treatment was discontinued in 75 girls who underwent treatment for a mean period of 13.1 months. In detail, GnRHa therapy was discontinued at a mean age of 10.55±0.68 years, with a mean BA of 12.52±0.58 years. The discontinuation time was individualized based on CA, BA, GV, and parent/patient preferences.

The clinical characteristics of the study population at the time of diagnosis and at the end of treatment are shown in *Table 1*. Significant differences were found between the HtSDS, BA/CA, BMI, and BMI-SDS values (P<0.001). HtSDS-BA (P=0.14), WtSDS (P=0.84), BA-CA (P=0.059), and loss in height potential (P=0.40) showed no significant

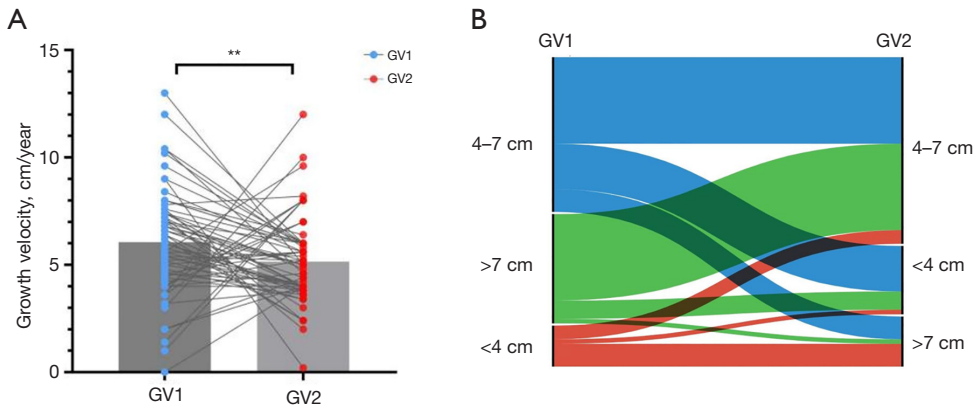

Figure 1 GV were suppressed after 6 months of GnRHa treatment. (A) Comparison of growth velocity in the first and second half of year in the GnRHa-treated group. **, P=0.01. (B) Sankey diagram presents the changes between the first and second half of year. The line represents the GV change between initial and end of treatment. GV1 represents growth velocity in the first half of the year after GnRHa treatment; GV2 represents growth velocity in the second half of the year after GnRHa treatment. GV, growth velocity; GnRHa, gonadotropin-releasing hormone agonist.

Table 1 Comparison of variable between initiation and end of treatment in the GnRHa-treatment group

Variables	Initiation of treatment	End of treatment	Z value	P
HtSDS-BA	−0.64 (−1.11, 0.03)	−0.52 (−0.95, −0.02)	−1.464	0.14
HtSDS	1.52 (0.66, 2.08)	1.17 (0.55, 1.73)	−5.85	<0.001*
PAH (cm)	156.3 (153.9, 160.7)	157.4 (154.6, 160.4)	−0.33	0.73
PAH-SDS	0.21 (−0.37, 0.78)	0.3 (−0.43, 0.73)	−0.96	0.34
BA-CA (years)	2.1 (1.7, 2.5)	2 (1.6, 2.6)	−1.90	0.059
BA/CA (years)	1.22 (1.18, 1.27)	1.19 (1.14, 1.25)	−5.34	<0.001*
WtSDS	1.75 (0.86, 2.5)	1.78 (1.13, 2.33)	−0.21	0.84
BMI (kg/m^2)	19.69 (17.97, 21.57)	21.17 (19.54, 23.19)	−6.10	<0.001*
BMI-SDS	2.15 (1.07, 3.31)	2.35 (1.56, 3.74)	−2.97	<0.001*
Loss in height potential (cm)	−0.59 (−1.19, 0)	−0.61 (−1.19, 0)	−0.84	0.40

Data are presented as median (P25, P75). *, P<0.05. Loss in height potential: (PAH − Tht)/5.4. GnRHa, gonadotropin-releasing hormone agonist; Ht, height; SDS, standard deviation score; PAH, predicted adult height; BA, bone age; CA, chronological age; Wt, weight; BMI, body mass index; Tht, target height.

differences between the start and end of the treatment. Contrary to the expected results, there was no improvement in PAH levels (PAH: P=0.73; PAH-SDS: P=0.34).

GnRHa had no effect on the NG in height compared to the GnRHa-untreated group

All girls who achieved FAH in the GnRHa-treated and untreated groups were included in the analysis. The final height gain from baseline to the end in the GnRHa-treated group was 15.2±6.33 cm compared to 14.1±7.4 cm in the GnRHa-untreated group, with no significant differences between the groups (P=0.75).

NG in height was calculated as the dependent variable. Linear regression analyses were conducted to assess the role of GnRHa treatment and NG in height after adjusting for covariates in the three models (Models A, B, and C). In these models, no significant relationship was observed

Table 2 Multiple GAM of NG in patients with early menarche after GnRHa treatment

Variables	Pre-Model 3			Model 3		
	edf	F	P value	edf	F	P value
HtSDS-BA	1.00	0.43	0.52			
HtSDS	2.15	2.02	0.21			
BA	1.73	1.24	0.31			
BA/CA	3.56	0.31	0.82			
LH/FSH	5.36	3.47	0.02*	5.28	3.41	0.01*
GV	4.11	6.63	0.007*	3.87	5.32	0.001*
BMR	4.79	3.39	0.02*	4.32	2.75	0.04*

*, P<0.05. GAM, generalized additive model; NG, net gain; GnRHa, gonadotropin-releasing hormone agonist; edf, estimated degrees of freedom; Ht, height; SDS, standard deviation score; BA, bone age; CA, chronological age; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GV, growth velocity; BMR, bone maturation rate.

between the GnRHa treatment and NG in height (Model A: P=0.43; Model B: P=0.65; Model C: P=0.82) (Table S1).

Prediction models for NG in height for the GnRHa-treated girls with early menarche

To avoid the influence of collinearity between the variables on the results, we did not use the information of BA and CA at the end of the treatment as variables; however, we used the GV and BMR during the treatment as variables. Thus, HtSDS, HtSDS-BA, and BA represent the information collected at baseline.

We conducted a univariate analysis of the potential predictors of NG (Table S2), and the polynomial curve of significant factors, as shown in Figure S2, were further analyzed using simple multivariate linear regression (Model 1) and multiple stepwise linear regression (Model 2) (Table S3). The formula for Model 2 was Y(NG) = 376.65 – 1.08 × HtSDS – 64.80 × BA + 2.81 × (BA^2).

We constructed a GAM to achieve a better fit for the relationship between the variables and NG. First, we built regression splines for each factor and NG (Table S4). We excluded factors with deviance explained at <1% and incorporated other factors into the GAM to construct pre-model3 (*Table 2*). Pre-Model 3 revealed three independent risk factors: including LH/FSH [estimated degrees of freedom (edf) =5.36, P=0.02], GV (edf =4.11, P=0.007), and BMR (edf =4.79, P=0.02). Model 3 was then constructed after adjusting for BA, BA/CA, HtSDS, and HtSDS-BA (*Table 2*). The independent risk factors in Model 3 were LH/FSH (edf =5.28, P=0.01), GV (edf =3.87, P=0.001) and BMR (edf =4.32, P= 0.04), and the formula for Model 3 is Y(NG) = β0 + s(LH/FSH) + s(GV) + s(BMR) + ε.

Figure 2 shows the smooth curve derived between the independent risk variables in Model 3 and NG in height. The estimated spline of the GAM showed a U-shape for LH/FSH (*Figure 2A*), an inverted U-shape for GV (*Figure 2B*), and a decline, which stabilized with an increasing BMR (*Figure 2C*).

Comparison of prediction performance among three models

The predictive performances, including the adjusted R-squared, Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC) of Models 1, 2, and 3 are shown in Table S5. We further drew the residual dot plots and normal quantile plots from the residual values (Figure S3). The residual plots represent the difference between the actual observed and estimated values (fitted values). A normal plot of the residuals was used to check the normality of the residual distribution.

Compared with Models 1 and 2, the normal probability plot showed a good normal distribution with no residual outliers in the residual versus fitted value plot in Model 3. These results illustrate the superior performance of GAM.

Discussion

Early menarche is associated with reduced adult height, metabolic syndromes, and psychological disorders (10,22-24). Girls with CPP treated promptly at the onset of puberty, which is the early stage of the CPP, can avoid early

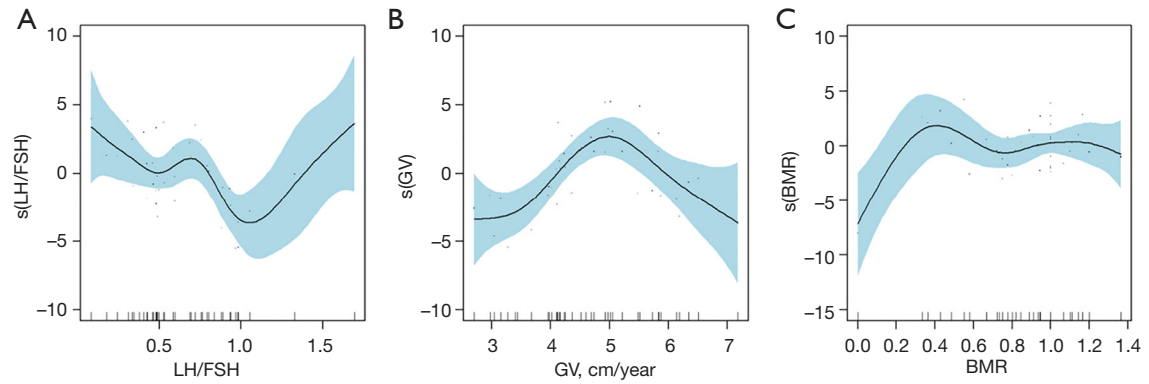

Figure 2 The smooth curve of associations between independent risk variables and NG in height in GnRHa treatment group. (A) LH/FSH; (B) GV; (C) BMR. The x-axis contains the independent risk variables and the y-axis contains NG in height produced by GAM model. This plot takes the fitted values and plots the component smooth functions that make it up on the scale of the linear predictor. Shaded areas are 95% confidence intervals. s, spline; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GV, growth velocity; BMR, bone maturation ratio; GAM, generalized additive model; NG, net gain; GnRHa, gonadotropin-releasing hormone agonist.

menarche. However, many girls were not diagnosed with CPP until the onset of menstruation. In clinical practice, patients whose age at menarche is <10 years are referred to a pediatric endocrinologist and controversy exists regarding how to treat these girls. To the best of our knowledge, this is the first study to evaluate the effectiveness of the GnRHa treatment in Chinese patients with early menarche.

A previous study showed that the decrease in GV was progressive, which was confirmed by our study (25). For girls in the GnRHa-treated group, our retrospective study showed that during the first year of treatment, most girls exhibited a significant reduction in GV in the second 6 months of treatment compared with the first 6 months. During GnRHa treatment, BA and height gain were suppressed; however, contrary to previous reports, no significant difference was observed in PAH levels between the start and end of treatment (26-28). This could be because the participants in this study had reached mid-adolescence and had limited growth potential.

Increase in height after menarche is an important concern for parents and physicians. Thus, we explored the effects of GnRHa treatment on FAH in girls with early menarche. FAH minus PAH at baseline, that is NG, has been widely used to assess potential increases in height (15,29,30). In previous studies, researchers have treated girls diagnosed with CPP before menarche as the object of study, they compared the final heights of treated and untreated groups and reported that FAH or FAH minus PAH was found to vary depending on the characteristics of the patients (e.g., HtSDS, HtSDS-BA, sex hormone levels, etc.). In contrast with previous studies, we examined the effects of GnRHa treatment in girls after menarche. After controlling other related variables, for girls whose age at menarche was <10 years, Although the GnRHa suppressed the growth during treatment and compared with untreated girls, GnRHa treatment had no clear-cut long-standing effect on FAH.

Growth after treatment withdrawal was significantly correlated with CA and BA at the end of treatment and with GV during treatment, indicating that the timing of withdrawal could modify the final result (31-33). Therefore, for physicians, it is important to know which factors can influence FAH so that they can make a better assessment from a height perspective on the necessity of GnRHa treatment, adult height prediction, and finding the best time to withdraw treatment. To this end, we designed three models to predict NG in height: multivariate linear regression, multivariate linear stepwise regression, and GAM. Because of the flexibility of the GAM compared with the traditional parametric modeling tools, it can more accurately characterize the relationship between various variables and NG in height (34).

According to the results of univariate and multivariate GAMs, non-linear functions of LH/FSH at baseline, GV, and BMR during treatment were associated with NG. Since FSH and LH are covariates, the inclusion of both variables would have distorted the predictive model. The participants included in this study did not undergo the GnRHa

stimulation test at diagnosis; thus, it was not possible to determine the ratio of peak LH to FSH. Basal LH/FSH has been shown to be a supporting criterion for diagnosis of CPP; thus, we used basal LH/FSH as a variable in the models (35). The predictive NG was positive when the LH/FSH ratio was <0.5 or >1.5, which is crucial for clinicians to advise patients whether to apply GnRHa therapy based on the predicted FAH. Clinicians should focus on the GV and BMR in females during GnRHa treatment. With increasing GV during GnRHa treatment, the predicted NG first increased and then decreased, and if the GV was between 4 and 6 cm, the patient achieved a positive NG in height. GV is significantly reduced when GnRHa is applied for >6 months, as shown in this study; therefore, clinicians should prevent affecting the FAH by avoiding GV that is too low during treatment. The BMR illustrates the change in BA with CA during treatment. According to the smoothened curve, with an increase in the BMR, the predictive NG first increased until the BMR reached 0.4, and then the NG fluctuated around zero. Similarly, clinicians should pay close attention to changes in the BMR to prevent it from being too low such that it could affect the FAH.

There are some limitations in this study. As this was a single-center retrospective study, a potential center-specific bias could not be excluded. The relatively small sample size, comprising patients primarily of Asian ancestry, restricted the applicability of these results to more diverse populations. Therefore, future research would benefit from a larger multicenter prospective design with a long-term follow-up and a more diverse population.

Conclusions

Our retrospective study showed that for girls whose menarche occurred at age <10 years, GnRHa treatment suppressed the GV and skeletal maturity but had no influence on FAH. Compared with other prediction models, the GAM could predict FAH in these girls post-GnRHa treatment more accurately. This study provides a theoretical basis for pediatric endocrinologists for deciding whether to administer GnRHa treatment, when to withdraw from GnRHa treatment, and predict the FAH of females with early menarche.

Acknowledgments

Funding: This study was supported by a grant from the Tianjin Health Science and Technology Program (grant No. TJWJ2022XK008).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-348/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-348/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-348/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-348/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Human Research Ethics Committee of Tianjin Medical University General Hospital (No. IRB2024-YX-350-01) and individual consent for this retrospective analysis was waived.

References

1. Anderson GM, Hill JW, Kaiser UB, et al. Metabolic control of puberty: 60 years in the footsteps of Kennedy and Mitra's seminal work. Nat Rev Endocrinol 2024;20:111-23.
2. Meng X, Li S, Duan W, et al. Secular Trend of Age at Menarche in Chinese Adolescents Born From 1973 to 2004. Pediatrics 2017;140:e20170085.

3. Chiou JS, Lin YJ, Chang CY, et al. Menarche-a journey into womanhood: age at menarche and health-related outcomes in East Asians. Hum Reprod 2024;39:1336-50.
4. Subspecialty Group of Endocrinologic, Hereditary and Metabolic Diseases, the Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Expert consensus on the diagnosis and treatment of central precocious puberty(2022). Zhonghua Er Ke Za Zhi 2023;61:16-22.
5. Askelund AD, Wootton RE, Torvik FA, et al. Assessing causal links between age at menarche and adolescent mental health: a Mendelian randomisation study. BMC Med 2024;22:155.
6. Silva DAS, Duncan MJ, Kuzik N, et al. Do movement behaviours influence the association between early menarche and depression symptoms among Brazilian adolescents? Appl Physiol Nutr Metab 2024;49:1137-62.
7. Meena D, Huang J, Dib MJ, et al. Body Mass Index and Hypertension as Mediators of the Association Between Age at Menarche and Subclinical Atherosclerosis: A Sex-Specific Mendelian Randomization Analysis. J Am Heart Assoc 2024;13:e032192.
8. Rakic R, Pavlica T, Havrljenko J, et al. Association of Age at Menarche with General and Abdominal Obesity in Young Women. Medicina (Kaunas) 2024;60:1711.
9. Kwan BS, Yang J, Jo HC, et al. Age at Menarche and Its Association With Adult-Onset Metabolic Syndrome and Related Disorders in Women: A Cross-Sectional Study of a Nationally Representative Sample Over 10 Years. Asia Pac J Public Health 2024;36:558-64.
10. Liu M, Kim DW, Zeng H, et al. Make war not love: The neural substrate underlying a state-dependent switch in female social behavior. Neuron 2022;110:841-856.e6.
11. Kumar N, Ehsan S, Banerjee S, et al. The unique risk factor profile of triple-negative breast cancer: a comprehensive meta-analysis. J Natl Cancer Inst 2024;116:1210-9.
12. McKay MJ, Pandey R, Zadeh H, et al. Gonadotropin releasing hormone agonist-related meningioma progression causing abducens nerve palsy: an oncological case report. Precis Cancer Med 2022;5:40.
13. Mauras N, Ross J, Mericq V. Management of Growth Disorders in Puberty: GH, GnRHa, and Aromatase Inhibitors: A Clinical Review. Endocr Rev 2023;44:1-13.
14. Tseng CH, Lee YJ, Huang CY, et al. The effects of gonadotropin-releasing hormone agonist on final adult height among girls with early and fast puberty. Front Endocrinol (Lausanne) 2023;14:1271395.
15. Vuralli D, Gonc NE, Ozon ZA, et al. Which parameters predict the beneficial effect of GnRHa treatment on height in girls with central precocious puberty? Clin Endocrinol (Oxf) 2021;94:804-10.
16. Lin YC, Lin CY, Chee SY, et al. Improved final predicted height with the injection of leuprolide in children with earlier puberty: A retrospective cohort study. PLoS One 2017;12:e0185080.
17. Lerman L, Yackobovitch-Gavan M, Phillip M, et al. Gonadotropin-releasing hormone analogs treatment in girls with central precocious puberty and early fast puberty. Pediatr Res 2024;95:1051-9.
18. Castro C, Espada F, Leite AL, et al. Height benefit of GnRH agonists after age 8 in a Portuguese cohort of central precocious puberty. Clin Endocrinol (Oxf) 2023;98:670-7.
19. Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for heights of parents. Arch Dis Child 1970;45:755-62.
20. Zhang SY, Liu LJ, Han YS, et al. Reference values of differences between TW3-C RUS and TW3-C Carpal bone ages of children from five cities of China. Zhonghua Er Ke Za Zhi 2008;46:851-5.
21. Pedersen EJ, Miller DL, Simpson GL, et al. Hierarchical generalized additive models in ecology: an introduction with mgcv. PeerJ 2019;7:e6876.
22. Lundberg FE, Iliadou AN, Rodriguez-Wallberg K, et al. The risk of breast and gynecological cancer in women with a diagnosis of infertility: a nationwide population-based study. Eur J Epidemiol 2019;34:499-507.
23. Kim SR, Lee S, Chung JH. Association between early menarche and suicidal behaviors in Korean girl adolescents. Medicine (Baltimore) 2021;100:e27301.
24. Lee D, Ahn IY, Park CS, et al. Early menarche as a risk factor for suicidal ideation in girls: The Korea youth risk behavior web-based survey. Psychiatry Res 2020;285:112706.
25. Muratoğlu Şahin N, Uğraş Dikmen A, Çetinkaya S, et al. Subnormal Growth Velocity and Related Factors During GnRH Analog Therapy for Idiopathic Central Precocious Puberty. J Clin Res Pediatr Endocrinol 2018;10:239-46.
26. Głąb E, Wikiera B, Bieniasz J, et al. The Influence of GnRH Analog Therapy on Growth in Central Precocious Puberty. Adv Clin Exp Med 2016;25:27-32.
27. Ying Y, Tang J, Chen W, et al. GnRH agonist treatment for idiopathic central precocious puberty can improve final adult height in Chinese girls. Oncotarget 2017;8:109061-7.

28. Demirkale ZH, Abali ZY, Bas F, et al. Comparison of the Clinical and Anthropometric Features of Treated and Untreated Girls with Borderline Early Puberty. J Pediatr Adolesc Gynecol 2019;32:264-70.
29. Baek JW, Nam HK, Jin D, et al. Age of menarche and near adult height after long-term gonadotropin-releasing hormone agonist treatment in girls with central precocious puberty. Ann Pediatr Endocrinol Metab 2014;19:27-31.
30. Onat PŞ, Erdeve ŞS, Çetinkaya S, et al. Effect of gonadotropin-releasing hormone analog treatment on final height in girls aged 6-10 years with central precocious and early puberty. Turk Pediatri Ars 2020;55:361-9.
31. Borges Mde F, Franciscon Pde M, Cambraia TC, et al. Evaluation of central precocious puberty treatment with GnRH analogue at the Triangulo Mineiro Federal University (UFTM). Arch Endocrinol Metab 2015;59:515-22.
32. Liang Y, Wei H, Li J, et al. Effect of GnRHa 3.75 mg subcutaneously every 6 weeks on adult height in girls with idiopathic central precocious puberty. J Pediatr Endocrinol Metab 2015;28:839-46.
33. Vargas Trujillo M, Dragnic S, Aldridge P, et al. Importance of individualizing treatment decisions in girls with central precocious puberty when initiating treatment after age 7 years or continuing beyond a chronological age of 10 years or a bone age of 12 years. J Pediatr Endocrinol Metab 2021;34:733-9.
34. Bolt MA, MaWhinney S, Pattee JW, et al. Inference following multiple imputation for generalized additive models: an investigation of the median p-value rule with applications to the Pulmonary Hypertension Association Registry and Colorado COVID-19 hospitalization data. BMC Med Res Methodol 2022;22:148.
35. Li Pomi A, Scalini P, De Masi S, et al. Screening for central precocious puberty by single basal Luteinizing Hormone levels. Endocrine 2024;85:955-63.

Cite this article as: Qi Y, Zhang Y, Liu X, Li Y, Zheng R. Preliminary comparison of net gain in final adult height of girls with early menarche treated with or without gonadotropin-releasing hormone agonist. Transl Pediatr 2024;13(12):2204-2213. doi: 10.21037/tp-24-348