Short Communication

The Addition of Aromatase Inhibitors to Gonadotropin Releasing Hormone Analogues, Does It Improve Height Prediction in Girls with Low Estimated Adult Height? A Retrospective Study

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Abstract

Background and Objectives: The aim of this study is to investigate if the addition of Aromatase Inhibitors to Gonadotropin releasing analogue can increase the predicted adult height in girls with low predicted adult height. **Materials and Methods:** This is a retrospective cohort study conducted in pediatric endocrine clinics in Dr Jamal Ahmad Rashed Hospital and Mercy Hospital between November 2024 and August 2025. Gonadotropins releasing analogue therapy for at least 1 year due to central precocious puberty, or low predicted adult height, were included in the study. After excluding group 3 because of small sample size, there were 3 groups: (1) Gonadotropin releasing analogue alone, (2) Gonadotropin releasing analogue + growth hormone, (4) Gonadotropin releasing analogue + growth hormone+ Aromatase Inhibitors. The main outcomes were gain in estimated adult height and change in bone age /chronological age ratio Z-score. **Results:** Both Gonadotropin releasing analogue + growth hormone + Aromatase Inhibitors, and Gonadotropin releasing analogue + growth hormone showed higher Gain in estimated adult height than Gonadotropin releasing analogue alone, but the addition of Aromatase Inhibitors to Gonadotropin releasing analogue + growth hormone showed a mild advantage in Gain in Estimate adult height that was not statistically significant. Bone age advancement was significantly less in the group with Aromatase Inhibitors. **Conclusion:** The addition of Aromatase Inhibitors to Gonadotropin releasing analogue and growth hormone is a feasible choice for selected girls in puberty with very low estimated adult height.

Keyword: Gonadotropin releasing hormone analogue, low estimated adult height, short stature, precocious puberty

Introduction

Estrogen is the main hormone that modulates epiphyseal fusion in both males and females, estrogen also promotes growth spurt. The use of Gonadotropin releasing analogue (GNRHA) suppresses puberty hence theoretically prolonging growth period, but it also suppresses the Hight velocity to prepubertal levels in children with precocious puberty. [1], and can significantly lower it bellow prepubertal levels or even below normal childhood growth villosity in pubertal age girls [2] this should be taken into consideration whenever the discission of using this medication arises in short children with normal puberty. Growth promoting treatment are generally more effective when used for longer durations and before puberty, but often is the case that the parents first notice the child's short stature, in midst of puberty or even late puberty, hence the clinician is faced with the difficult situation of a child with short predicted adult height and with very short time left for growth. From this dilemma arose the off-label practice of pubertal suppression in girls with normal puberty

who are short or are predicted to become short adults (-2SD for height or shorter). Aromatase inhibitors (AI) block the enzyme aromatase preventing the formation of estrogen from androgen, lowering estrogen level significantly can cause delay in epiphysial closure, and theoretically improve height prediction [1]. The aim of this study is to examine whether the use of Aromatase inhibitors (AI) with GNRHA has further advantage over the use of GNRHA alone, whether in combination with growth hormone or not. Although in the last few years some research has been done on this topic, still the volume of evidence is not enough; to draw relevant recommendations, the aim is to participate in the evidence pool and contribute to drawing conclusions that later can help in clinical practice.

Materials and Methods

This is a retrospective cohort study. Data were collected from patients' files at the Pediatric Endocrine Clinic of Dr. Jamal Ahmad Rashed Pediatric Teaching Hospital and the Pediatric Endocrine Clinic at Mercy Private Hospital.

Inclusion Criteria

Girls who received GNRHA for one year or more for precocious puberty, or low predicted adult height due to advanced bone age, were included in the study.

Exclusion Criteria

1. Use of GNRHA for less than one year
2. Incomplete or insufficient data in patient files
3. Poor compliance with medication
4. Inadequate suppression of pubertal status

Treatment Groups

Patients were treated under one of the following regimens:

- Group1; GNRHA alone
- Group2; GNRHA with growth hormone (GH)
- Group 3; GNRHA with aromatase inhibitors (AI)
- Group 4; GNRHA +GH+AI

The primary comparison focused on the effect of aromatase inhibitors. Group 3 (GNRH + AI) was later excluded from the analysis, as it contained only three patients.

Bone Age and Height Assessment

Bone age was assessed using the Greulich and Pyle method. Bone age advancement was expressed as a BA/CA Z-score at three time points:

- At the initiation of GNRHA therapy
- Midway through treatment
- At the end of treatment (or at the time of data collection if treatment was ongoing)

Estimated adult height (EAH) was calculated at each time point, and the gain in estimated adult height (GEAH) was recorded.

Additional Analysis

- Age at initiation of each treatment (GNRHA, GH, AI)
- Duration of each therapy
- Mid-parental height (MPH), to assess its potential role as an independent influencing factor.

Statistical Methods

Data entry performed via and statistical analysis SPSS program, version 24.0 (IBM SPSS Statistical Package for the Social Sciences). Compliance of quantitative random variables with the Gaussian curve (normal distribution) was analyzed using the Kolmogorov-Smirnov and Shapiro – Wilk test. The data are presented in tabular form showing the frequency and relative frequency distribution of different variables among all three groups. Chi-square

tests were used to compare the categorical data between these groups of patients with respect to different variables. Variables showed to be normally distributed quantitative continuous variables and described by mean and SD (standard deviation). The statistical significance of difference in mean among these three groups ANCOVA test and the comparison of the data of each group between the start of treatment and at the end of treatment were performed by using paired t test. P values of 0.05 were used as a cut-off point for significance of statistical tests.

Ethical considerations

The study was approved by the ethics committee at the College of Medicine, University of Sulaimani, and conducted according to Helsinki Declaration principles, ensuring confidentiality, anonymity, and voluntary participation. Written informed consent was obtained from all participants.

Results

Total number of participants in this study was 90 girls, after excluding group 3 which included only 3 participants, and the statistical analysis was done for 3 treatment groups: GNRHA alone, GNRHA + GH, and GNRHA + GH + AI. Table 1 show that the main characteristics of the 3 groups were comparable, and there is no statistically significant difference between the groups.

Table 1: Descriptive statistics and comparison of key variables between the 3 treatment groups

Variable	Group 1 (GNRHA) (N=29)	Group 2 GNRHA+GH) (N=32)	Group 4 (GNRHA+AI +GH) (N=29)	P value
Age at Starting GNRH (years)	7.29 ± 1.90	7.76 ± 2.08	8.38 ± 2.52	0.178
Duration on GNRH (months)	25.52 ± 12.48	25.34 ± 15.93	26.90 ± 16.84	0.932
Age at Starting GH (years)	N/A	8.03 ± 2.23	8.38 ± 2.52	0.551
Duration on GH (months)	N/A	26.59 ± 21.71	24.07 ± 13.31	-

Table 2 shows significant increase in estimated adult height and reduction in bone age advancement in all treatment groups when comparing beginning and end point of treatment.

Table 2: change in estimated adult height (EAH) and Bone age/chronological age Z score (BA/ CA ratio Z score) in all groups at beginning and end of treatment using paired t test

Treatment Group	EAH (cm) Baseline	EAH (cm) End	EAH Z-Score (Baseline)	EAH Z-Score (End)	BA/CA Z Score (Baseline)	BA/CA Z Score (End)	P-value
GNRHA	150.73 ± 7.15	155.04 ± 5.28	-1.94 ± 1.15	-1.09 ± 1.03	1.78 ± 1.87	1.18 ± 0.92	0.035
GNRHA + GH	144.51 ± 5.13	152.37 ± 4.92	-2.88 ± 0.78	-1.68 ± 0.75	1.82 ± 0.96	1.36 ± 0.88	< 0.001
GNRHA + AI + GH	145.23 ± 5.37	154.43 ± 7.38	-2.76 ± 0.82	-1.00 ± 2.44	2.4 ± 1.63	1.04 ± 0.72	< 0.001

Table 3 Shows that both group 2 and 4 had significantly more GEAH in comparison to group1 (only on GNRHA), but group4 had only 1.6 cm gain higher than group 2, which was not statistically significant.

Table 3: Gain in Expected Adult Height (GEAH) Across Treatment Groups

GEAH	Mean ± SD			P value
	GNRHA+GH	GNRHA+AI +GH	GNRHA	
	8.88 ± 4.80	9.47 ± 6.49	5.57 ± 6.21	0.027

	-	9.47 ± 6.49	5.57 ± 6.21	0.023
	8.88 ± 4.80	-	5.57 ± 6.21	0.023
	8.88 ± 4.80	9.47 ± 6.49	-	0.69

Tale 4. Shows that both GNRHA and GH therapy shows stronger positive correlations with greater gain in estimated adult height (EAH) and slower bone age advancement (BA SDS). Duration effects were weaker and often not significant. Earlier initiation of AI shows a stronger positive correlation with both greater GEAH and enhanced suppression of bone age progression (BA SDS). Longer AI duration demonstrates weaker but still positive associations.

Table 4: factors affecting GEAH and change in BA/CA z score

Variable	Outcome	r (Pearson)	R^2	P value
Duration of GnRHA	**Gain in EAH**	0.494	0.244	< 0.001 *
Age at starting GnRHA		0.311	0.097	0.003 *
Age at starting GH		0.558	0.311	< 0.001 *
Duration of GH		0.135	0.018	0.303 ns
Duration of AI		0.365	0.134	0.051
Age at starting AI		0.669	0.448	< 0.001 *
Mid-parental Height		0.238	0.06	0.038*
Duration of GnRHA	**Change in BA SDS**	0.541	0.292	< 0.001 *
Age at starting GnRHA		0.374	0.140	< 0.001 *
Age at starting GH		0.338	0.114	0.008 *
Duration of GH		0.127	0.016	0.330 ns
Duration of AI		0.419	0.176	0.024 *
Age at starting AI		0.524	0.248	0.004 *

* Statistically significant correlation ($p < 0.05$); ns = not significant.

Table 5. After adjusting confounding factors and comparing group 2 and group 4, it was found that the group with AI inhibitors had slower bone age progression, but no significant difference in GEAH.

Table 5: ANCOVA Results for Change in BA SDS and Gain in EAH between group 2 and 4

Outcome Measure	Group	Adjusted Mean ± SEa	Mean Difference (95% CI)	P value
Change in BA SDS	GNRHA+GH	-0.54 ± 0.16	0.49 (0.02 to 0.95)	0.043
	GNRHA+AI+GH	-1.03 ± 0.16	-	-
Gain in EAH (cm)	GNRHA+GH	8.17 ± 0.82	1.30 (-1.10 to 3.69)	0.283
	GNRHA+AI+GH	9.47 ± 0.83	-	-

Discussion

GNRH analogs have been used to improve predicted height efficiently in girls at the age of 6 or less, while it seems to not have the same advantage for the predicted height after ages of 7 years [3].The use of Aromatase inhibitors (AI) in girls has been traditionally limited to peripheral precocious puberty as in cases with McCune Albright syndrome. Recently, some studies investigated the use of Aromatase inhibitors in combination with GNRHA in girls with precocious puberty and compromised adult height, in which there has been encouraging results [4,5]. In this current study it was found that all three treatment groups, GNRHA, GNRHA+GH, GNRHA+GH+AI, showed a significant reduction in bone age progression and improvement in GEAH when compared to the pretreatment estimations, indicating improvement in height prediction in all treatment groups. As for the use of GNRHA, most studies have also found some improved height prognosis, though this finding was not consistent. Assessing the current evidence on the use of GNRH

analogue for improving final or predicted adult height. It is well known that using it in girls with precocious puberty at the age of 6 years and below has shown a significant effect in restoring height prediction to genetic potential. While its effect in girls with normal puberty has been at most modest or not effective alone in improving height prognosis, it was also found that for the best height prognosis, GNRHA should be stopped before the bone age of 12 years [6, 7]. A retrospective study done in Korea involving 36 girls with CPP (central precocious puberty) who did not receive GNRHA and another 206 girls who received treatment, found that those not receiving treatment, the final adult height (FAH) was marginally higher 160.7± 4.6, versus 159.3±4.3. This can be due to selection criteria that treatment was mainly given to those with lower height prediction from the start [8]. In the current study, we found that the group treated with GNRHA alone had the lowest gain in EAH (estimated adult height), but still it had a mean of 5.6 cm gain in comparison to previous estimations, though this study did not have a non-treatment group, and most had not yet achieved final adult height. On the other hand, a study in Turkey involving 135 girls with borderline early puberty, age range (7-10 yrs), concluded that GNRHA resulted in increasing the EAH in selected girls with rapidly progressing borderline early puberty [9]. A Meta-analysis involving 10 studies with a sample size of 720 children, concluded that children treated with GNRHA had a significantly better final adult height than the non-treatment group, concluding that GNRHA treatment was safe and effective in treating children over 6 years of age with CPP and normal early or rapidly progressing puberty [10]. The evidence regarding the use of GNRHA alone is conflicting, given the fact that in normal puberty the tempo of puberty, the rapidity with which the bone age advances, and the level of peak height velocity are subjected to high levels of individual variation, making a conclusion on the subject difficult and controversial. On the other hand, this can make room for individual decision-making to be a logical option, though this would need substantial experience. A study comparing children with precocious puberty treated with GNRHA alone or combined with growth hormone and a non-treated control group showed that there was a significant difference in final adult height, with the group on the combination of GNRHA with growth hormone gaining more height than the GNRHA alone. While the non-treatment group was within their mid-parental height [11]. A review investigating growth of pubertal children found that the near final adult height was significantly higher in those treated with GNRHA plus growth hormone in comparison with those treated with growth hormone alone. Still, the review emphasized that this combination should be used only in very short children with a poor height prognosis [12]. In this current study, it was also found that adding GH to GNRHA analogue significantly increased the GEAH. Three studies investigating the benefit of adding aromatase inhibitors to GNRHA have shown superiority of this combination over GNRHA alone regarding gain in estimated adult height, with a gain of 3.85-7.5 cm in the group of combined GNRHA and AI, versus 1.6-1.9 cm in the GNRHA group. Concluding that AI enhances height prognosis and slows bone age progression [13–15]. A study done in Greece showed the gain in adult height was about +9.7 cm when a combination of GNRHA and AI (Anastrozole) was used for 2 years, followed by continuation of anastrozole monotherapy till near final adult height. As opposed to +7.4 cm without the period of

monotherapy with anastrozole and 3.6 cm with GNRHA alone [5].

Conclusion

In the current study, when comparing treatment groups to each other after adjusting for confounding variables such as duration and timing of GNRHA and GH treatment, bone age progression was significantly slower in the group of GNRH+GH+AI. The same group had a significantly higher GEAH in comparison to GNRHA alone, but only modestly higher than the GNRHA+GH, which was statistically insignificant. This disassociation may be due to sample size limitations or the need of more time to show significant difference. The time of initiation of AI and its duration were associated with a significant delay in bone age progression and GEAH. We recommend that further prospective randomized controlled trials be done on this controversial subject.

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