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*Original Article*

Factor affecting final adult Height in children with central precocious puberty in Sulaimani governorate

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Abstract

Background and Objectives: Central precocious puberty (CPP) can compromise final adult height (FAH) due to early epiphyseal closure. This study aimed to identify primary factors influencing FAH in children with CPP attending Endocrine department at Dr. Jamal Ahmad Pediatric Teaching Hospital in Sulaimani, Iraq.

Methods: A retrospective, observational cohort study was conducted on 60 children diagnosed with CPP from January 2009 to December 2021. Data were collected from medical records, including demographic, clinical, laboratory, radiological findings, and treatment.

Results: The study included 57 females (95%) and 3 males (5%), with a mean age of at the time of data collection was 14.12 ± 1.74 years, while the mean chronological age at diagnosis of 7.52 ± 1.05 years. The mean height increased significantly from 131.61 ± 7.47 cm before treatment to 152.92 ± 4.62 cm after treatment ($P=0.001$). Bone age increased from 10.61 ± 1.67 to 14.29 ± 0.92 years ($P=0.001$). The factors affecting Final Adult Height, including: Height at diagnosis was a significant factor (OR = 0.448, $P \leq 0.013$, 95% CI: 0.072–0.585). Bone age advancement at diagnosis was also a factor affecting Final Adult Height (OR = 0.556, $P \leq 0.004$, CI 95%: 0.396 – 2.900). The treatment option was another factor affecting Final Adult Height (OR = 0.317, $P \leq 0.036$, 95% CI: 0.181–4.982). While the duration of treatment, BMI, result of investigation, and mid-parenteral height were statistically not significant.

Conclusion: Effective treatment with GnRH agonists, with or without growth hormone and aromatase inhibitors, enables children with CPP to achieve final heights near or above target height. Genetic factors, including family history, significant positive impact on final height, while consanguinity shows a negative effect.

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1. Introduction:

Central precocious puberty (CPP) is defined by the premature activation of the

hypothalamic-pituitary-gonadal (HPG) axis, leading to the early manifestation of secondary sexual features and expedited

linear growth (1). While the precise time boundaries for normal pubertal timing remain debated, widely accepted cutoffs for CPP are 8 years for girls and 9 years for boys (2).

The physiological basis of puberty involves the activation and maturation of the HPG axis. This axis is transiently active in early infancy, a phenomenon known as "mini-puberty," but becomes quiescent until reactivation at the onset of true puberty (3). The pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus activates the anterior pituitary to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thus facilitating gonadal maturation and the synthesis of sex steroids. The activation of this axis underlies the physical and hormonal changes observed during puberty (3).

The most pressing issue in children with CPP is the possible impact on eventual adult height, since early exposure to sex hormones hastens bone maturation and epiphyseal closure, hence restricting growth potential (4). In the last several decades, the management of CPP has improved a lot. GnRH analogs are now considered the best way to stop early puberty and protect height potential (5). The extent of height increase resulting from therapy is significantly diverse and affected by several variables, including age at start, progression in bone age, pretreatment growth velocity, genetic predisposition, and body mass index (1, 6). Even though GnRHa is used a lot, there is still no one-size-fits-all strategy for treating CPP. Instead, treatment choices are generally made depending on the patient's symptoms, family preferences, and available resources (7). In Sulaimani Governorate, there is a lack of evidence about the factors influencing eventual adult height in children with CPP.

Understanding the local epidemiology and treatment outcomes is essential for optimizing care and developing evidence-based protocols tailored to the needs of this population.

This research aims to assess the main determinants affecting ultimate adult height in children with a history of CPP receiving care at Dr. Jamal Ahmad Rashid Pediatric Teaching Hospital in Sulaimani city.

2.1. Patients and Methods

The present research was structured as a retrospective, observational study carried out at the Dr Jamal Ahamed Rashid Pediatric teaching hospital, Endocrinology Department in Sulaimani Governorate, Iraq. The research data collected from those patients were registered and followed up from January 2009 to December 2021, covering a duration of 13 years.

2.2. Participants

The study population comprised children diagnosed with CPP who attended the Pediatric Endocrinology Clinic during the study period. Participants were identified through a review of hospital medical records. All eligible children who met the diagnostic criteria for CPP and had complete clinical, laboratory, and follow-up data were included in the analysis. The final sample consisted of 60 children. Children were included if they met the following criteria:

- (1) diagnosis of CPP based on clinical, hormonal, and radiological findings
- (2) onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys;
- (3) evidence of pubertal activation of the hypothalamic-pituitary-gonadal (HPG) axis, confirmed by a pubertal response to the GnRH stimulation test (peak LH >5 IU/L);
- (4)

availability of baseline and follow-up data, including anthropometric measurements, laboratory results, and imaging studies; and (5) completion of at least 6 months of follow-up after initiation of therapy.

Exclusion criteria included: (1) children with peripheral (gonadotropin-independent) precocious puberty; (2) those with chronic systemic diseases, genetic syndromes, or other endocrine disorders affecting growth or puberty; (3) children with incomplete medical records or missing key data; and (4) those who did not complete the minimum follow-up period.

A consecutive sampling method was employed, whereby all eligible children presenting to the clinic during the study period were included. The sample size was established by the aggregate number of children fulfilling the inclusion criteria during the designated period.

2.3. Data Collection

Data were retrospectively collected from patient medical records. Demographic data included age, sex, ethnicity, residence, consanguinity and family history of precocious puberty. Clinical data encompassed age at onset of puberty, presenting symptoms (thelarche, menarche, adrenarche), and anthropometric measurements (height, weight, BMI percentile, and mid-parental height). Height and weight were measured using a calibrated stadiometer and digital scale, following standard protocols.

Laboratory data included basal and stimulated levels of LH and FSH, measured using chemiluminescent immunoassays (e.g., Roche Elecsys, Roche Diagnostics, Germany). The GnRH stimulation test was performed

using subcutaneous administration of synthetic GnRHa (treptoreline 0.1mg), with blood samples collected at baseline, 30-, and 60-minutes post-injection. The LH/FSH ratio was calculated for diagnostic and analytical purposes .

Radiological data included pelvic ultrasound and dynamic brain MRI with contrast and pituitary protocol, interpreted by experienced qualified radiologists. Treatment data included type and duration of GnRH analogue therapy (short-acting 3.6mg or long-acting 10.8mg formulations), use of adjunctive therapies (GH, aromatase inhibitors (laterazole 2.5mg)), and treatment outcomes. Follow-up data included final height, bone age (assessed by left hand/wrist X-ray using the Greulich and Pyle method)(8), and follow-up every 4-6month .

2.4. Statistical Analysis

Data were inputted and analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to encapsulate demographic and clinical variables. Continuous data were represented as mean \pm standard deviation (SD), whereas categorical variables were denoted as frequencies and percentages. Paired t-tests were used to compare height and bone age before and after therapy. One-way ANOVA was used to compare hormone levels across several time periods. The Pearson and Spearman correlation coefficients were computed to evaluate the correlations between final height and prospective predictors. Backward linear regression analysis was used to ascertain independent variables influencing ultimate height. A p-value of less than 0.05 was deemed statistically significant

Results:

A total of 60 children with CPP were included in the study, with a mean age of 14.12 ± 1.74 years and a mean chronological age at diagnosis of 7.52 ± 1.05 years. The mean height was 131.61 ± 7.47 cm, mean weight was 32.38 ± 8.53 kg, and mean BMI percentile was 65.10 ± 30.92 . The average mid-parental height was 157.39 ± 6.38 cm, and the mean bone age before starting treatment was 10.61

± 1.67 years. Females were 57 (95%) and males were 3 (5%). Consanguinity was present in 22 (36.7%) and absent in 38 (63.3%). A family history of precocious puberty was reported in 24 (40%), while 36 (60%) had no such history. Regarding residence, 31 (51.7%) lived inside the city and 29 (48.3%) lived outside the city. All participants were Kurdish, 60 (100%).

Table 1. Demographic information of children with CPP in Sulaymaniyah.

Variable	Mean \pm SD	Frequency (Percent)
Age	14.124 ± 1.740	
Chronological age	7.523 ± 1.049	
Height (cm)	131.610 ± 7.465	
Weight (kg)	32.378 ± 8.527	
BMI %	65.101 ± 30.920	
Mid-parental heigh	157.386 ± 6.383	
Bone Age before starting treatment	10.605 ± 1.668	
Sex	Male	3 (5%)
	Female	57 (95%)
Consanguinity	Yes	22 (36.7%)
	No	38 (63.3%)
Family history of precocious puberty	Yes	24 (40%)
	No	36 (60%)
Residence	Inside city	31 (51.7%)
	Outside city	29 (48.3%)
Nationality	Kurd	60 (100%)
	Arab	0

Clinical manifestations in children showed that 63.3% (38 children) had symptoms of thelarche, 25% (15 children) had symptoms of menarche, and 11.7% (7 children) had symptoms of adrenarche. (Figure 1).

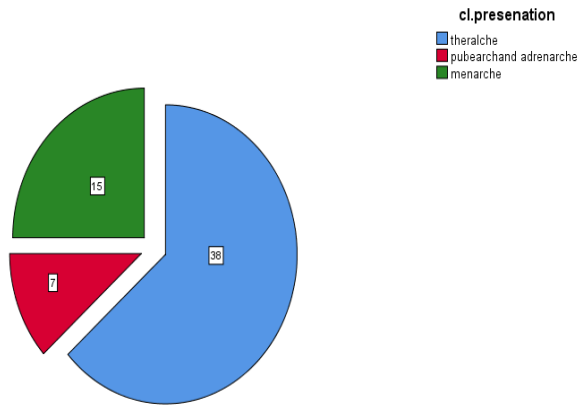


Figure 1. Clinical presentation of children with CPP in Sulaimania.

Table 2 presents the laboratory findings of children with CPP in Sulaimania. The mean basal LH level was 1.86 ± 2.64 mIU/mL, increasing to 12.89 ± 7.49 mIU/mL after 30 minutes and 14.04 ± 8.24 mIU/mL after 60 minutes of stimulation ($P=0.001$). The mean basal FSH level was 4.69 ± 5.56 mIU/mL, rising to 9.94 ± 3.44 mIU/mL after 30 minutes and 10.88 ± 4.21 mIU/mL after 60 minutes ($P=0.001$). The mean LH/FSH ratio was 1.43 ± 0.83 . Regarding the LH/FSH ratio categories, 17 (37.7%) had a ratio <1 , 17 (37.7%) had a ratio between 1 and 2, and 11 (24.6%) had a ratio >2 .

Table 2. Laboratory information of children with CPP in Sulaimania.

Variable	Basal	After 30 minutes	After 60 minutes	P-value*
LH	1.856 ± 2.638	12.886 ± 7.486	14.035 ± 8.239	0.001
FSH	4.688 ± 5.561	9.936 ± 3.440	10.881 ± 4.213	0.001
LH/FSH ratio	1.434 ± 0.830			
LH/FSH ratio Category	< 1	17 (37.7%)		
	1-2	17 (37.7%)		
	> 2	11 (24.6%)		

*P-value based on one -Way ANOVA

Table 3 summarizes the diagnostic information of children with CPP in Sulaimania. On ultrasound, 55 (91.7%) had normal findings, while 4 (6.7%) were abnormal and 1 (1.7%) was not done. Similarly, dynamic brain MRI with contrast and pituitary protocol was normal in 55 (91.7%), abnormal (Microadenoma,

hydrocephalus, anterior pituitary hyperplasia) in 4 (6.7%), and not done in 1 (1.7%).

The most common treatment with GnRH was short-acting in 51 (85%), compared to long-acting in 9 (15%). Regarding treatment options, GnRH alone was used in 29 (48.3%), followed by GnRHA plus GH in 27 (45%), and GnRHA plus GH plus aromatase inhibitor in 4 (6.7%). The most frequent findings in each

category were normal ultrasound and MRI, short-acting GnRH treatment, and GnRH alone as the treatment option.

In 29 children with GnRH alone therapy, the duration of treatment was equal to or less than 2 years in 21 (72.4%) children, and in 8 (27.6%) children, the duration of treatment were more than 2 years. In 27 children with GnRHA+GH therapy, the duration of treatment was equal to or less than 2 years in 18 (69.2%) children, and in 9 (30.3%) children, the duration of treatment were more than 2 years, and all 4 (100%) children with GnRHA+GH+aromatase therapy had a duration of treatment equal to or less than 2 years

Table 3. Diagnostic and treatment information of children with CPP in Sulaymaniyah

Variable		Frequency (Percent)
Ultrasound	Normal	55 (91.7)
	Abnormal	4 (6.7%)
	Not done	1 (1.7%)
Brian MRI	Normal	55 (91.7)
	Abnormal	4 (6.7%)
	Not done	1 (1.7%)
Treatment GNRH	Short acting	51 (85%)
	long acting	9 (15%)
treatment option	GnRH alone	29 (48.3%)
	GnRHA+GH	27 (45%)
	GnRHA+ GH+ aromatase	4 (6.7%)

Table 4. Duration treatment of children with CPP in Sulaymaniyah.

Variable	Patients no.(%) Treatment option		
	GnRH alone	GnRHA+GH	GnRHA+ GH+aromatase
≤ 2	21 (72.4%)	18 (69.2%)	4 (100%)
> 2	8 (27.6%)	9 (30.3%)	0

Table 5 shows the effect of treatment on height and bone age in children with CPP in Sulaymaniyah. The mean height increased significantly from 131.61 ± 7.47 cm before treatment to 152.92 ± 4.62 cm after treatment

($P=0.001$). Similarly, the mean bone age rose from 10.61 ± 1.67 years before treatment to 14.29 ± 0.92 years after treatment ($P=0.001$), indicating significant improvements in both height and bone age following treatment.

Table 5. Effect of treatment on height and bone age of children with CPP in Sulaymaniyah.

Variable	Before treatment	After treatment (Final HT)	P-value*
Height (cm)	131.610 ± 7.465	152.920 ± 4.624	0.001
Bone Age	10.605 ± 1.668	14.288 ± 0.919	0.001

*P-value based on Paired t-test

Table 6 represent the correlation between final height and various demographic, laboratory, and treatment variables in children with CPP. Final height showed a negative correlation with consanguinity ($r = -0.252, P \leq 0.052$) and family history of precocious puberty ($r = -0.278, P \leq 0.03$). A slight positive connection

was seen with baseline LH ($r = 0.126, P \leq 0.336$), basal FSH ($r = 0.001, P \leq 0.997$), LH/FSH ratio ($r = 0.280, P \leq 0.062$), and treatment option ($r = 0.142, P \leq 0.278$). The only statistically significant link was seen with a family history of premature puberty ($P < 0.03$).

Table 6. Correlation between Final HT and demographic, laboratory characteristics, and treatment options of children with CPP in Sulaimania.

Variable	Consanguinity	Family history of precocious puberty	Basal LH	Basal FSH	LH/FSH ratio	Treatment option
Final HT	$r=-0.252$ $p \leq 0.052^*$	$r=-0.278$ $p \leq 0.03$	$r=0.126$ $p \leq 0.336$	$r=0.001$ $p \leq 0.997$	$r=0.280$ $p \leq 0.062$	$r=0.142$ $p \leq 0.278$

*P-value based on Pearson and Spearman correlation

In the present study, factors affecting Final Adult Height included Height at diagnosis, which was a significant factor ($\beta = 0.448, P \leq 0.013, 95\% \text{ CI: } 0.072-0.585$). Bone age advancement at diagnosis was also a factor

affecting Final Adult Height ($\beta = 0.556, P \leq 0.004, \text{ CI } 95\%: 0.396 - 2.900$). The treatment option was another factor affecting Final Adult Height ($\beta = 0.317, P \leq 0.036, 95\% \text{ CI: } 0.181-4.982$) (Table 7).

Table 7. Factors Affecting Final Adult Height

Factor	Coefficient (β)	95% CI	P-value
Age at presentation	0.216	- 0.296 – 1.604	0.172
Height at diagnosis (cm)	0.448	0.072 – 0.585	0.013
Bone age advancement at diagnosis	0.556	0.396 – 2.900	0.004

BMI at diagnosis	0.192	- 0.025 – 0.093	0.253
(mid-parental height)	0.046	- 0.210 – 0.279	0.777
Basal LH (mIU/mL)	0.167	- 0.390 – 1.085	0.346
FSH	0.021	- 0.576 – 0.650	0.903
LH/FSH ratio	0.212	- 0.475 – 3.070	0.147
Duration of treatment	0.168	- 0.502 – 2.031	0.229
Sex (male vs. female)	0.099	- 9.488 – 13.482	0.726
Treatment option	0.317	0.181 – 4.982	0.036
A.GnRH analogue only	0.124	- 0.837 – 2.359	0.345
B.GnRH analogue + GHG	0.332	- 1.009 – 1.411	0.741
C.GnRH analogue + GH +Aromatase inhibitor	- 0.078	- 3.213 – 1.772	0.565

*P-value based on Linear regression, Backward model. Depend variable Final HT

4. Discussion

The CPP is characterized by early activation of the HPG axis, resulting in premature sexual maturation and potential compromise of final adult height (6). The present study aimed to identify factors influencing final adult height in children with CPP in Sulaimania, Iraq. Results demonstrated that appropriate treatment with GnRH agonists, with or without GH and aromatase inhibitors, can result in final heights close to or exceeding target height. Factors affecting Final Adult Height were Height at diagnosis, and Treatment option. Notably, Genetic factors, especially family history, significantly impact final height outcomes while consanguinity showed a negative effect on final adult height.

The predominance of females with CPP in this study is in line with global reports, where most cases in girls are idiopathic and not associated with organic pathology (2). The high rate of

idiopathic cases is expected, given the demographic characteristics of the study population. However, the presence of a small number of abnormal MRI or ultrasound findings underscores the importance of comprehensive imaging in all suspected CPP cases, as recommended by Yuen et al. (9), and Vuralli et al. (10), to rule out rare organic causes.

The mean age at diagnosis in this study aligns with reports from Akın and Özgen in Turkey (11), and Puttawong et al. in Thailand (12), supporting the generalizability of these findings to similar populations.

The observed efficacy of GnRHa-based therapy in improving final height is consistent with previous research, by Seo et al. (13), and Eugster (14), who reported significant height gains following similar interventions. The frequent use of combination therapy with GH in this cohort may have contributed to these favorable outcomes, as Dotremont et al. (15),

and Shi et al. (16), also found that adding GH to GnRHa can further enhance height gain in selected patients.

The pronounced negative correlation between final height and both consanguinity and familial history of precocious puberty underscores the influence of genetic variables on final height in this group, aligning with the results of Turkyilmaz et al. (17), and Bakry et al. (18). The lack of significant associations between final height and other variables, such as laboratory indicators or treatment duration, may be attributed to the sample size and unique characteristics of the studied cohort. This emphasizes the need for further study including larger sample sizes and prolonged follow-up periods to more accurately identify the drivers of final height.

The results of the study revealed that the factors affecting final height were Height at diagnosis, Bone age advancement at diagnosis and Treatment option, meaning that with increasing height at the time of diagnosis and increasing bone age and using GnRHa treatment regimen alone and in combination with other treatment option, they had a direct and significant effect on final adult height and increase it. In line with the results of the present study, in the study of M Demiral et al. (19) in Turkey, it was shown that each of the factors of height at the time of diagnosis, increasing bone age and using GnRHa treatment regimen had a significant increase in final height. In the study of Knific et al. (20) in Slovenia, bone age and treatment regimen were among the factors and factors affecting final height in children, while in the aforementioned study, height at the time of diagnosis did not have a significant effect on final height increase. The reason for this

difference could be the different working methods and sampling methods in the two studies.

However, unlike some studies that identified the LH/FSH ratio or age at treatment initiation as predictors of final height (4, 21), the present results did not show significant associations between final height and these laboratory or clinical parameters. This discrepancy may be due to differences in sample size, genetic background, or treatment protocols. The high prevalence of consanguinity and family history in this cohort is consistent with regional data (22, 23), and highlights the likely genetic contribution to CPP, possibly involving mutations in genes such as MKRN3 or DLK1 (24, 25).

The retrospective design, lack of a control group, and predominance of female participants limit the generalizability and causal inference of these findings. Additionally, the absence of genetic testing and the possibility that some children had not yet reached their true final adult height are notable limitations in addition. The sample size limits the power of the multivariate analysis and may have prevented the detection of other significant factors.

5. Conclusion:

In conclusion, this study shows that efficacious therapy with GnRH agonists, with or without growth hormone and aromatase inhibitors, may assist children with CPP in Sulaymaniyah in attaining final heights that are near or beyond their goal height. The results demonstrate that Genetic factors, particularly a family history of precocious puberty, significantly impact final height outcomes. Consanguinity showed a negative

association, though it did not reach conventional levels

6. Ethical approval:

Ethical committee of College of Medicine, University of Sulaimania approved the study. (Approval No:25 on 23/10/2010) and approved the research protocol. Due to the retrospective nature of the research, informed permission was exempted; yet, patient confidentiality and data privacy were rigorously upheld throughout the investigation.

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9. Conflict of interest: No conflict of interest,

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