

# Growth, bone maturation and ovarian size in girls with early and fast puberty (EFP) and effects of three years treatment with GnRH analogue (GnRHa)

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**Abstract.** *Introduction:* Early puberty (EP) in girls is defined as the onset of thelarche that begins after 6 years and before 8 years and/or acceleration in the tempo of pubertal development. The stage of puberty and the ovarian volume at presentation and the effect of treatment with GnRH analogue (GnRHa) on final adult height are still debated. *Patients and methods:* We analyzed the data of 22 girls, who presented early and fast puberty (FEP). The clinical stage of puberty, hormonal levels, and ovarian volume (OV) (measured by ovarian ultra-sonography) at presentation were studied. We recorded the effects of 3 years of treatment with GnRHa on their growth in relation to their mid parental height, pubertal progression, and bone maturation. *Results:* At presentation, the mean age of girls was  $7.7 \pm 0.7$  yr, Ht-SDS was  $0.8 \pm 0.9$ , and growth velocity (GV) was  $8.7 \pm 1.4$  cm. Bone age was advanced by  $1.9 \pm 1$  yr compared to their chronological age. The difference between their standing height (Z-Score: Ht-SDS) and their mid-parental Ht-SDS (MPht-SDS) was  $1.4 \pm 0.7$ . Their predicted final adult height (FA-Ht) was  $155 \pm 8$ cm. After 3 years of using GnRHa (Triptorelin: 3.75 mg I.M. monthly), their mean Ht-SDS was  $0.5 \pm 1.5$ , associated with reduced growth velocity (GV:  $5 \pm 1.5$  cm/yr) and deceleration of bone age ( $0.7 \pm 0.8$  yr compared to their chronological age). The difference between their Ht-SDS and their MPht-SDS was  $1.2 \pm 1$  and their predicted FA-Ht improved to  $159 \pm 9$ cm. Their average MPht was  $159 \pm 4$  cm. There was no change in breast development during the 3 years of therapy. The BMI-SDS significantly increased from  $1.3 \pm 0.7$  before treatment to  $1.7 \pm 0.8$  after 3 years of treatment ( $P = 0.001$ ). At presentation, the mean OV was  $2.3 \pm 1.2$ mL. The OV correlated significantly with breast and pubic hair Tanner stages ( $r = 0.34$ , and  $0.56$ , respectively;  $P < 0.05$ ). There was also a significant correlation between OV and the hormonal profile (LH, FSH,  $17\beta$ -estradiol and IGF-1 levels;  $r = 0.80$ ,  $0.54$ ,  $0.485$  and  $0.40$ , respectively;  $P < 0.05$ ). There was no correlation between OV and bone age. Larger OV at presentation was associated with reduced Ht-SDS after 3 years of GnRHa treatment ( $r = 0.42$ ,  $P < 0.01$ ) and negatively with the difference between Ht-SDS and MPH-SDS at the end of treatment (lower potential for growth;  $r = 0.47$ ,  $P < 0.01$ ). *Conclusion:* GnRHa therapy decreased the fast progress of puberty, skeletal maturation, and GV/year. It was successful in increasing the predicted final adult height comparable to or surpassing their mid-parental height. A larger OV at presentation was associated with reduced Ht-SDS after 3 years of GnRHa treatment. Clearly, a definitive evaluation of the efficacy of GnRHa as a treatment for EFP in girls will require expanded and concerted studies. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Early and fast puberty (FEP), growth, bone maturation, ovarian size, GnRH analogue treatment

## Introduction

Pubertal timing is influenced by complex interactions among genetic, nutritional, environmental, and socioeconomic factors. Early activation of the hypothalamic-pituitary-gonadal axis (HPG) results in gonadotropin-dependent precocious puberty, also known as central precocious puberty (CPP). The diagnosis of CPP is based on clinical evaluation (pubertal development before the age of 8 years in girls), advanced bone age, and laboratory values. The maximal growth rate occurs 1 year after the onset of breast budding and precedes menarche. The average interval from normal breast development to menarche is 2 to 2.5 years. Although in clinical practice, gonadotropin-releasing hormone (GnRH) stimulation test is frequently still used, results confirm the diagnostic utility of basal LH levels in the diagnosis of CPP (1).

Early puberty (EP) is not a rare condition; nevertheless, there is no single age range that defines this period. Several studies have reported age ranges of 6-8 years (1), 8-10 years (2,3), 7.5-8.5 years (4), and 8-9 years (5), and most physicians agree that the occurrence of pubertal changes before the age of 8 years in a girl or 9 years in a boy warrants at least a clinical and bone age evaluation. In girls, the onset of puberty at the lower physiological age range (8-9 yr) (2-5) is sometimes defined as being early but not precocious and is considered to be normal. However, it is also apparent that some girls with EP have a fast progressive form (EFP), so the rate at which puberty and growth acceleration advance is another important variable that can affect the level of concern (6).

The early activation and maturation of the HPG axis leads to hormonal changes, physical signs of puberty, acceleration of linear growth, and may also lead to compromised final adult height, especially in girls born from short parents (2,7). Moreover, EP has been related to various consequences in the medium and long term such as behavioral problems, breast cancer, obesity, and metabolic comorbidities (8,9). Consequently, the clinical strategy of choice for girls with CPP below the age of 6 years is to administer gonadotropin-releasing hormone analogs (GnRHa), which down-regulate and desensitize pituitary GnRH receptors, inhibiting the HPG axis, thereby slowing the

onset of puberty. This, in turn, reduces the GV, giving the long bones more time to lengthen before the growth plates fuse, thus maximizing the adult height that the child obtains (7, 9). However, the effectiveness of treatment in the EP and EFP is still controversial because the improvement in final height is equivocal and there is a concern about gaining excess weight during therapy. Most of the controlled studies showed that attained height in treated and untreated groups was almost the same, with no statistically significant differences among the groups (average = 153-155 cm) (2-6). Remarkably few studies have not evaluated the behavioral and psychological outcomes of precocious/early puberty, in contrast to early normal maturation.

Furthermore, there is a discrepancy in the literature regarding the cut-off values for ovarian volume versus age and pubertal stage. Haber et al. (10) found that girls with CPP (Tanner stages PH 1, B 2-3;  $n = 11$ ) had an ovarian volume  $2.2 \pm 1.3 \text{ ml}^3$  vs  $0.6 \pm 0.2 \text{ ml}^3$  for controls ( $P < 0.01$ ). Salardi et al. (11) found that girls with breast Tanner stage 2 and 3 had an ovarian volume of  $2.5 \pm 1 \text{ ml}^3$ . Ovarian volume was correlated well with pubertal progression as evidenced by breast Tanner staging ( $r = 0.57$ ,  $P < 0.0001$ ) (12).

In Badouraki et al. report (13) the best parameter for identifying patients with CPP puberty was a cut-off of  $3.04 \text{ ml}^3$  (sensitivity of 100% and a specificity of 97.1%) for age interval 0-6 years, a cut-off of  $3.35 \text{ ml}^3$  (sensitivity of 100% and a specificity of 89.5%) for age interval  $> 6-8$  years, and a cut-off of  $4.46 \text{ ml}^3$  (sensitivity of 80.8% and a specificity of 88.5%) for age interval  $> 8-10$  years).

Magnetic resonance imaging (MRI) of the hypothalamic-hypophyseal area is recommended in girls with CPP before the age of 6 years to exclude central nervous system (CNS) abnormalities. In a meta-analysis, the prevalence of MRI intracranial lesions was reported in 25% of girls with CPP started  $< 6$  years and in 3% of girls aged 6-8 yr (14). In another study, the proportion of intracranial lesions, requiring intervention in girls with EP, was equal to or below 2 % (15).

The aim of the present study was to investigate the growth pattern, bone maturation, and ovarian volume in girls with EFP and the effects of three years of treatment with GnRHa on linear growth, in

relation to mid-parental height, weight gain, and bone maturation.

## Patients and methods

Thirty-five female children were referred for early puberty ( $> 6$  years and  $< 8$  years of age).

Our present study included 22 girls with EFP, in the absence of thyroid pathology, growth hormone deficiency, adrenal or gonadal pathology. Cases with dysmorphic syndrome, skeletal dysplasia, chronic illness, cerebral palsy, and hydrocephalus were excluded.

According to auxological and pubertal parameters, acceleration of GV, assessment of bone age, predicted adult height, mid-parenteral height, and hormonal evaluation the girls were treated with GnRHa and were followed every 6 months for 3 years.

Their clinical assessment included: pubertal status (Tanner staging), anthropometric measurement [standing height (Z-Score) (Ht-SDS)], weight, and body mass index (BMI,  $\text{Kg}/\text{m}^2$ ), BMI-SDS (Z-score). Target height was defined as mid parental height adjusted for female gender and expressed as mid-parenteral height SDS (MPht-SDS).

The bone age was assessed using the atlas of Greulich and Pyle, and the predicted height was calculated by the method of Bayley and Pinneau (which has been found to be the most accurate method for patients with precocious puberty).

The hormonal evaluation included: basal levels of LH and FSH, and basal levels of  $17 \beta$ -estradiol (E2), and insulin growth factor-1 (IGF-1). All hormonal examinations were performed by standard techniques in the endocrine laboratory of our hospital, using ultrasensitive commercial immunoassays for the gonadotropins.

An MRI of the hypophyseal–hypothalamic area was requested to exclude central nervous system abnormalities.

Skeletal maturation for bone age, brain MRI scanning, and pelvic Doppler ultrasound imaging, at presentation, were reviewed and findings recorded by two experienced radiologists.

GnRHa therapy (Triptorelin:3.75 mg I.M. monthly) was given in all girls with EFP.

The study was approved by the Ethics Committee of the Hamad General Hospital of Doha (Qatar), and parental informed consent was obtained from all participants.

## Statistical analysis

The data presented as mean  $\pm$  SD. Paired student t-test was used to compare the anthropometric results when the data were normally distributed and Wilcoxon test when they were not normally distributed. A linear regression equation was used to investigate the correlation between different variables. P-value  $< 0.05$  was accepted as significant. Statistical analyses were performed using Excel 10 statistical package.

## Results

The mean age, at presentation, of our 22 girls with EFP was  $7.7 \pm 0.7$  yr, Ht-SDS was  $0.8 \pm 0.9$ , and annual growth velocity was  $8.7 \text{ cm} \pm 1.4 \text{ cm}$ .

At first examination, the bone age was advanced by  $1.9 \pm 1$  yr, compared to their chronological age. The difference between their Ht-SDS and their MPht-SDS was  $1.4 \pm 0.7$ . Furthermore, their predicted final adult Ht (FA-Ht) was  $155 \pm 8 \text{ cm}$ .

After 3 years of treatment with GnRHa, their mean Ht-SDS was  $0.5 \pm 1.5$ , associated with a slow progression of bone maturation ( $0.7 \pm 0.8$  yr. compared to chronological age), and annual growth velocity (from  $8.7 \text{ cm} \pm 1.4 \text{ cm}$  to  $5 \pm 1.5 \text{ cm}$ ). The difference between their Ht-SDS and their MPht-SDS was  $1.2 \pm 1$ , and their mean predicted FA-Ht improved to  $159.7 \pm 9.7 \text{ cm}$ . Their average MP-ht was  $159 \pm 4 \text{ cm}$  (Table 1).

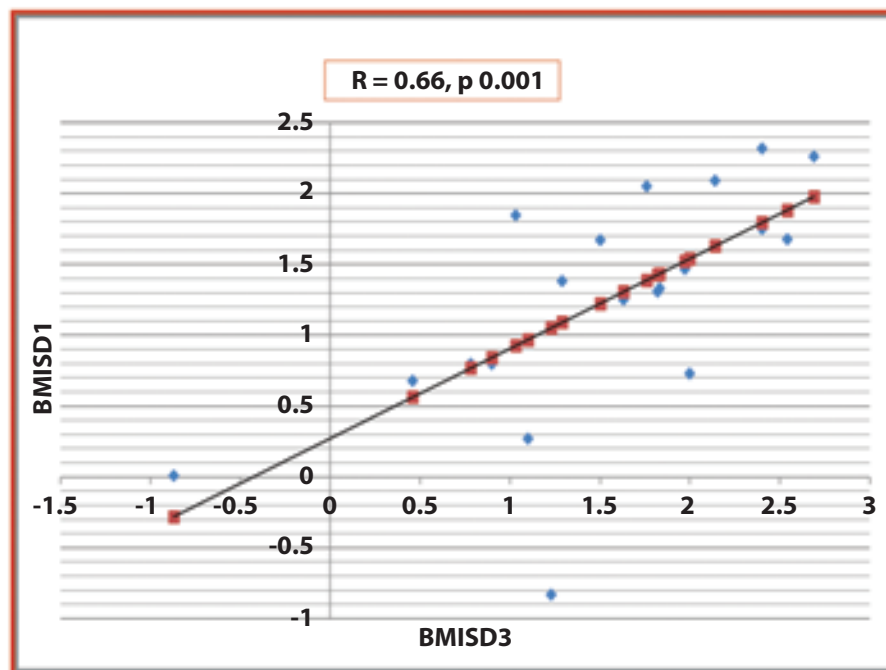
During the treatment, there was no clinical evidence of breast progression, assessed by Tanner staging, during the treatment, but a significant increase in BMI-SDS (from  $1.3 \pm 0.7$  before treatment to  $1.7 \pm 0.8$  after the treatment;  $P = 0.001$ ) was observed. BMI-SDS, after treatment, correlated significantly with BMI-SDS before treatment (Figure 1).

Transabdominal pelvic ultrasound scans, at presentation, were furtherly reviewed in 13 girls with EFP.

**Table 1.** Auxologic data, at presentation and 3 years after GnRHa therapy, in girls with EFP

	At presentation	After 3 years
Age (years)	7.7 ± 0.7	10.7 ± 1
Ht-SDS	0.8 ± 0.9	0.5 ± 1.3
Growth velocity (cm/yr)	8.7 ± 1.4	5 ± 1.5
Ht-SDS minus MPHSD	1.4 ± 0.7	1.2 ± 1
MP-Ht (cm)	159 ± 4	159 ± 4
Predicted FA-Ht (cm)	155 ± 8	159 ± 9
BA - CA	1.9 ± 1	0.7 ± 0.8
BMI-SD	1.3 ± 0.7	1.7 ± 0.8*

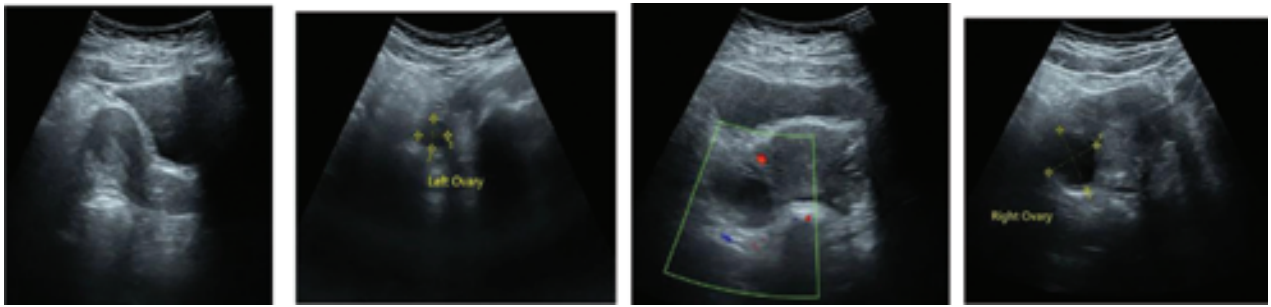
Legend: BMI-SD = body mass index Z score, MP-Ht = mid parental height, BA= bone age, CA = chronological age, FA-Ht = final adult height - \*P<0.05



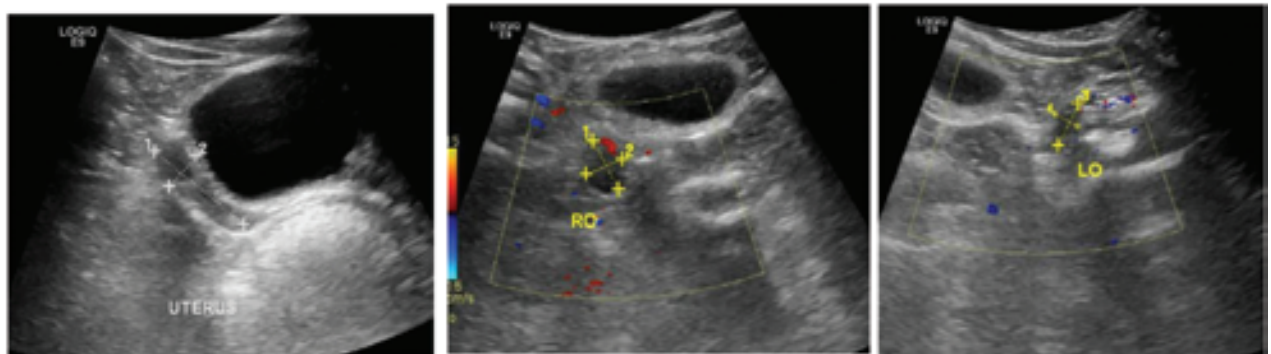
**Figure 1.** Correlation between BMI-SD at presentation (BMI-D1) versus 3 years treatment with GnRHa (BMI-D3).

Their mean ovarian volume (OV) was  $2.3 \pm 1.2$  mL. A variability in ovarian volume was noticed, despite the presence of pubertal changes (Figures 2 and 3). Two girls had an OV < 1.2 mL on both sides. Two other girls had OV from >1.2 to <2 mL, and the rest of the girls had an OV > 2 mL. Asymmetrically enlarged ovaries were found in 8 patients. Significant correlations were found between OV and hormonal profile (LH,

FSH, 17  $\beta$ -estradiol, and IGF-1 ( $r = 0.80, 0.54, 0.485$  and  $0.40$ , respectively;  $P < 0.05$ ). The OV was correlated significantly with breast and pubic hair Tanner stage ( $r = 0.34$ , and  $0.56$ , respectively;  $P < 0.05$ ). A larger OV, at presentation, was negatively correlated with the difference between Ht-SDS and MPH-SDS at the end of treatment (lower potential for growth;  $r = 0.47$ ), and was negatively correlated with the Ht-SDS after 3 years of



**Figure 2.** Pelvic US of uterus and ovaries in a 9 years old girl (Breast Tanner's stage 3) showing uterine size about 5.8 x 1.8 cm with an endometrial thickness of 6mm (advanced pubertal normal-sized uterus). The right ovary (volume 4.6 ml) showed a solitary large follicular cyst (20x18 mm) while the left ovary volume (1.2 ml) with no identifiable follicles.



**Figure 3.** Pelvic US in a 7 years old girl (Breast Tanner's stage 2) showing small infantile uterus (3.2 x 1cm) with a poorly identified endometrial interface, small ovaries (right ovarian volume about 1.1ml and left ovarian volume about 0.9 ml) with no identifiable follicles.

GnRHa treatment (Figure 4). There was no significant correlation between OV and bone age, at presentation.

An MRI of the hypophyseal– hypothalamic area was done in 22 girls with EFP to exclude central nervous system abnormality. None showed structural abnormalities or tumors. Three had a small increase of pituitary size that was attributed to EFP. The gland was graded according to the concavity or convexity of the upper surface, and the signal intensity of the gland was assessed visually.

Apart from local pain after the injection, no significant adverse side effect was noted that necessitated stopping the treatment.

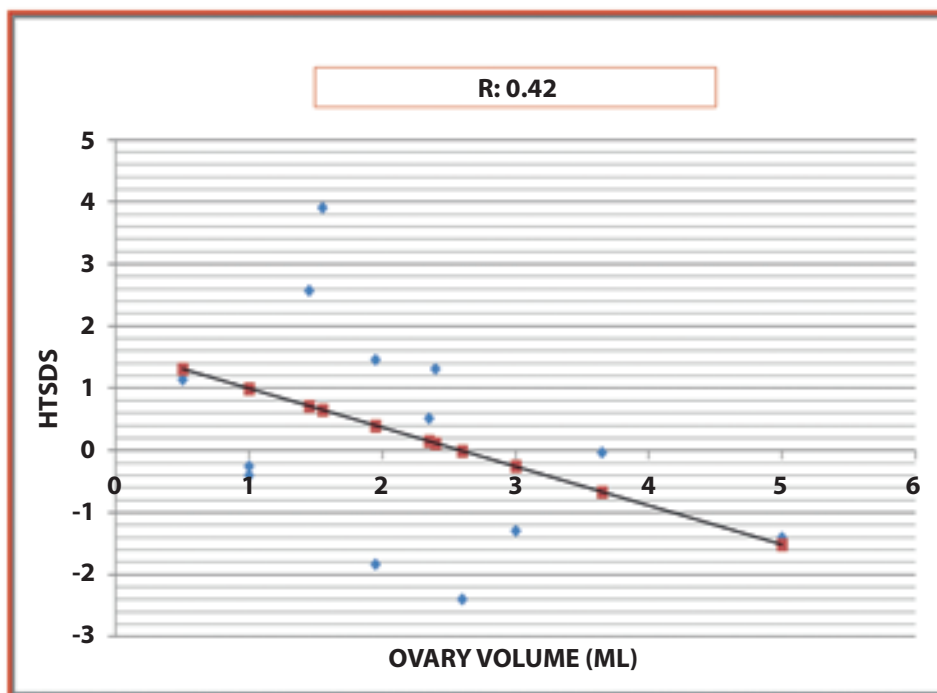
## Discussion

A normal but EP may exert a negative effect on final height (16,17). It has been shown that suppressive therapy with GnRHa improves final height in girls

with CPP. However, conflicting results there are on the effectiveness of treatment on final adult height of girls with EFP (2,6,18). Nevertheless, Lazar et al. (6) suggested that girls with EFP may benefit from postponing their pubertal development if the predicted height, based on bone age, is less than 5 feet (152 cm) and when early puberty causes emotional psychosocial embarrassment. Moreover, none of the reported studies have calculated the difference between the predicted FA-Ht and MP-HT, as criteria for treatment.

We studied the effects of 3 years of GnRHa therapy, in girls who presented EFP, on Ht-SDS in relation to their MPht-SDS.

At presentation, our patients were experiencing an acceleration in growth velocity (GV:  $8.7 \pm 1.4$  cm/year). The treatment reduced their linear growth velocity ( $5 \pm 1.5$  cm/year) and the advancement of bone age. After 3 years of GnRHa therapy, there was an increase in the predicted FA-Ht corresponding to or surpassing their MPht-SDS.



**Figure 4.** Correlation between ovarian volume (ml), at presentation, and predicted final height (Ht-SDS) after 3 years of treatment with GnRHa.

In a study on 80 girls with idiopathic CPP and bone age  $\geq 10$  years, Wang et al. (19) reported that GnRHa plus rhGH and GnRHa alone improved their near-final height. Therefore, it has been suggested that rhGH should be added to GnRHa therapy to increase FAH in specific cases. Three meta-analyses have been conducted in this area in the last 10 years. The overall analysis of the data fails to indicate any benefit of combined therapy, while the individual reports suggest that in specific instances combined therapy may be beneficial in preserving or reclaiming growth potential and improving adult height (20).

Previous studies suggested that the improvement of adult height was greater in those with pubertal onset before 7 years of age (6,14,18). The age of our girls with EFP was negatively correlated with the gain in the final adult height SDS ( $r = -0.47$ ;  $P < 0.01$ ).

On the other hand, another controlled study reported absence of significant effect of GnRHa therapy (neither negative nor positive) on final adult height, despite its effect on the pace of pubertal changes. The authors explained their findings on the assumption

that the evolution potential of the growth plate at each pubertal stage is probably predetermined. Therefore, the bone growth for each pubertal stage is genetically inherent and is not affected by the pubertal pace (6,21).

In early puberty, there is an increase in body fat and body mass index (BMI). The effect of GnRHa therapy on BMI and body fatness in patients with CPP is still controversial. Some reports suggested an increase in BMI during GnRHa therapy and an increase in total body fat, trunk fat mass, and insulin resistance (22-24). On the contrary, other studies did not find a significant effect of GnRHa therapy on weight gain in patients with CPP and suggested a reduction of BMI during gonadotropin-suppressive therapy (25).

In our study, a slight but significant increase in BMI-SDS was noted (from  $1.3 \pm 0.7$  before treatment to  $1.7 \pm 0.8$  after 3 years of therapy;  $P: 0.04$ ).

In some studies, the changes of BMI-SDS, during GnRHa treatment, were correlated to baseline BMI status. Before treatment, 4 of our girls were obese ( $\text{BMI-SD} > 2$ ) and, after 3 years of GnRHa therapy, 8 girls resulted obese. These findings support the

observation of Wolters et al. (26) and Yang et al. (27) who found an increase of BMI-SDS during GnRHa treatment only in normal-weight children but not in overweight children. In addition, in our study, the BMI-SD before treatment was correlated significantly with the BMI-SDS after 6 months and 3 years of therapy ( $r = 0.85$  and  $0.66$ , respectively;  $P: < 0.001$ ).

The measurement of ovarian volume has been found to be useful in a wide range of disorders in children and young females. Measurement of ovarian volume may be used as a supplementary tool for diagnosing early puberty. However, there is still debate about the ovarian size that corresponds to early puberty. Different studies have suggested different OV as an indicator of early initiation of puberty (OV:  $> 1.7 \text{ ml}^3$  (28),  $3.3 \text{ ml}^3$  (13),  $2.2 \pm 1.3 \text{ ml}^3$  (10);  $2.4 \text{ ml}^3$  (11), and  $1.2 \text{ ml}^3$  (29).

Our patients with EFP had an OV ranging from 1 to 4.6 ml, with a mean OV of  $2.3 \pm 1.2 \text{ ml}$ . In 8/11 girls with EFP, the OV was  $> 1.2 \text{ ml}$ . Furthermore, we found a positive correlation between ovarian volume, Tanner staging, and hormonal profile. In addition, we found that larger OV at presentation was associated with lower HT-SDS, after 3 years of GnRHa therapy.

The psychological stress of EFP (emotionally immature) is another suggested indication for GnRHa treatment. However, there is a paucity of published studies on the psychological consequences that accompany EFP as well as the effect of pubertal suppression with GnRHa (18,30,31).

Mensah et al. (32) found that girls who entered puberty early (age 8-9 years) experienced a poorer psychosocial behavior that persisted to the age of 10-11 years. In Cavanagh et al. study (33), girls who went through early puberty had more difficult transitions into high schools and had more problematic journeys through high school. In a recent cohort study by Roberts et al. (34), early pubertal timing was significantly associated with self-harm by the age of 16 years. Therefore, these potential psychosocial negative effects related to EFP should be additionally considered in the decision of using GnRHa therapy to arrest the pubertal progression in girls with EFP.

In our study, brain MRI imaging did not show any structural abnormality or tumor affecting the hypothalamic-pituitary region. Considering the very low

frequency of structural abnormality or tumor which require intervention in 6-8 year old girls with EP and the absence of CNS-related symptoms, Kaplowitz (15) has proposed that "brain imaging should not be ordered routinely but discussed with the family after explaining both the benefits and risks.

Our study has several limitations. The main limitation was the lack of untreated controls with EFP because of ethical issues or healthy age-matched controls. Furthermore, we only evaluated growth parameters after 3 years of GnRHa therapy. We failed to include girls with CPP before 6 years of age in this study.

In conclusion, we suggest that treatment with GnRHa should be considered in girls diagnosed with EFP between ages 6 and 8. It was successful in achieving a predicted adult height comparable to or surpassing mid-parental height. An OV of 1.2 ml or above suggested the beginning of puberty. A larger OV at presentation was associated with reduced HT-SDS after 3 years of GnRHa treatment. Clearly, a definitive evaluation of the efficacy of GnRHa as a treatment for EFP in girls will require expanded and concerted studies.

**Conflicts of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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