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Evaluation of the efficiency of treatment in girls with central precocious puberty/rapidly progressive puberty via ultrasonography

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ABSTRACT

Introduction: Central precocious puberty (CPP) is defined as the development of secondary sexual characteristics in girls before the age of 8 years due to the activation of the hypothalamus-pituitary-gonadal (HPG) axis, and long-acting GnRH analogues (GnRHa) are used in its standard treatment. The gold standard method for evaluating the efficiency of treatment is to demonstrate the suppression of the LH response with the GnRH stimulation test. Pelvic ultrasonography (US) is an easily accessible, safe, free of ionizing radiation and non-invasive imaging method, which is used for the evaluation of internal genital organs, monitoring of sexual development, and excluding ovarian mass. This study aimed to evaluate the effect of GnRHa treatment on internal genital organs and to determine the role of pelvic ultrasonography in treatment follow-up.

Material and Method: Between January 2017 and May 2021, 50 girls who were started on GnRHa treatment due to the diagnosis of CPP or rapidly progressing puberty were followed up, and who underwent pelvic US imaging at the beginning of treatment and in the 1st year of treatment were included in the study. The clinical and sonographic findings were compared before and after the treatment.

Results: Of the 50 patients in the study, 52% (n=26) were being followed up with CPP, and 48% (n=24) with rapidly progressive puberty. In the first year of GnRHa treatment, while the suppression of the HPG axis was detected in 82% (n=41) of the cases with the GnRHa test, there was no suppression in 18% (n=9). A decrease in ovarian volume was observed in 73.2% (n=30) of 41 patients with suppression of the HPG axis, a decrease in uterine volume in 65.9% (n=27), and a decrease in uterine anterior-posterior size in 61% (n=25). While endometrial thickness could be measured in 64% (n=32) of the cases before treatment, measurable endometrial thickness was detected in only 6% (n=3) of the cases in the 1st year of treatment.

Conclusion: We detected in this study that GnRHa treatment in girls with a diagnosis of CPP/rapid puberty caused a significant regression in ovarian and uterus dimensions and endometrial echo selectability. Our results, in line with the literature, support that pelvic ultrasonography is an appropriate modality for monitoring the suppression of the HPG axis during CPP treatment and may reduce the need for repeated GnRH stimulation tests.

Keywords: Central precocious puberty, ultrasonography, GnRHa therapy, uterine diamater, ovarian volume

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INTRODUCTION

Central precocious puberty (CPP) is defined as the development of secondary sexual characteristics due to the activation of the hypothalamus-pituitary-gonad (HPG) axis before the age of 8 years in girls and 9 years in boys (1). The maturation of reproductive functions is dependent on the stimulation of increased pulsatile Gonadotropin-releasing hormone (GnRH) release into the pituitary portal circulation and, accordingly, pulsatile luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release into the peripheral circulation (2). FSH released from anterior pituitary gonadotroph cells with GnRH stimulation causes the growth of ovarian follicles and production of estrogen from androgens in girls (3). Estrogen levels fluctuate, but are usually measured in excess of 12 pg/ml.

Pelvic ultrasonography (US) is an easily accessible, safe, free of ionizing radiation and non-invasive imaging method for the evaluation of internal genital organs and

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gonads, monitoring sexual development, and excluding ovarian mass in girls (4,5). In prepubertal girls, uterine length should be less than 35 mm; over long diameter should not exceed 20 mm. Bilaterally large ovaries is one of the important criteria of CPP. An increase in uterine length (≥ 35 mm) and tubular shape of the uterus changing to pear-like appearance are determinative findings. The ovaries showing homogeneous or microcystic features before puberty acquire a multicystic or macrocystic/follicular structure. Endometrial echo may thicken and become selectability. Menarche usually begins when the endometrium thickness reaches 5 mm (6). Diagnosis is made by history, clinical findings, hormonal and radiological evaluation.

The aim of treatment in CPP is to suppress pulsatile gonadotropin release, to keep accelerated sexual maturation under control until normal pubertal age, to regress or stop sexual characteristics, to prevent premature closure of epiphyses, and to achieve adult target height. Long-acting GnRH analogues (GnRHa) have been used in the standard treatment of CPP since the 1980s. Puberty stages and growth of patients with CPP treated with GnRHa are evaluated every 3-6 months, and bone age is monitored periodically (7,8). Discontinuance or regression in the development of secondary sex characteristics, decreased growth rate to the prepubertal level, slowing of rapid progression in bone age (the ratio of bone age progression to chronological age progression<1.2) are clinical indicators of response to treatment (9). However, today, the gold standard in evaluating the efficiency of treatment is the GnRH stimulation test, and it is determined by showing the suppression of the LH response (10). However, the GnRH test is a laborious and invasive procedure that requires multiple blood sampling (11,12). This has led to the investigation of different methods to evaluate the HPG axis and response to treatment.

There are limited studies in the literature in which pelvic US is used to monitor GnRHa therapy in girls with CPP (12-16). Moreover, controversial results have been obtained about which pelvic US parameters are best in the evaluation of HPG axis suppression (12,14,16). This study aimed to evaluate the effect of GnRHa treatment on internal genital organs and to determine the role of pelvic ultrasonography in treatment follow-up.

MATERIAL AND METHOD

This study was approved by the Hitit University Faculty of Medicine, Non-interventional Researches Ethics Committee (Date: 26.05.2021, Decision No:2021-467). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 65 female patients who admitted to the Pediatric Endocrinology Polyclinic of our hospital with the complaint of early puberty and were diagnosed with CPP or rapidly progressive puberty (RPP) according to the following criteria and were treated with GnRHa.

- Secondary sex characters developed before the age of 8 years (CPP).
- RPP was diagnosed according to the appearance of breast buds between the ages of 8 and 10 years, accompanied by the presence of pubic or axillary hair and/or accelerated growth rate or bone age greater than 2 SD above chronological age (17).
- Increased levels of gonadotropins accepted in the pubertal interval (basal LH level of ≥0.3 mIU/mL or a peak LH response of ≥5 mIU/mL in standard intravenous GnRH tests).
- The following sonographic characteristics were considered as evidence of puberty: Ovarian volume > 2 mL, uterine length > 35 mm and pubertal configuration of uterus with a thickened endometrial echo > 2 mm (6).

GnRHa treatment was started when baseline LH or peak LH met the criteria given for CPP patients. In patients aged between 8 and 10 years (RPP group), GnRHa treatment was started in the presence of pubertal laboratory findings with rapid progression of pubertal findings. A rapid progression of pubertal findings was considered to be a one-stage progression of breast stage within 3–6 months and emergence of uterine length over 35 mm in pelvic US (18).

Initially, 65 female patients who were diagnosed with CPP or RPP in the Pediatric Endocrinology outpatient clinic between January 2017 and May 2021 and were started on GnRHa treatment (leuprolide acetate or triptorelin acetate, intramuscular or subcutaneous injection 3.75mg every 28 days) were included in the study. Fifteen of these patients were excluded from the study because they were receiving GnRHa therapy for less than 12 months or who had missing anthropometric measurements, physical examination or laboratory/radiological findings before or during treatment, or had irregular treatment and follow-up. Thus, 50 patients who had received GnRHa treatment for at least 12 months, who came for regular follow-ups, and who had anthropometric measurements, physical examination, and laboratory findings, as well as pelvic US and left wrist X-ray data before treatment and at the first year of treatment were included in the study. Patients with peripheral precocious puberty, organic CPP, chronic disease, and patients who were treated in another center before applying to our outpatient clinic were excluded.

The patients' chronological age (years), bone age (years), puberty stage, peak luteinizing hormone level in basal and GnRHa test, estradiol (E2) level , uterus transverse

and anterior-posterior (AP) diameter, uterus length, endometrial thickness, and bilateral ovarian 3 dimension determined by pelvic US were recorded retrospectively in the hospital information system. Uterine and ovarian volumes were calculated. The clinical and sonographic findings were compared before and after the treatment.

Clinical Follow-up

Children with basal LH levels above 0.3 mIU/mL, who also met the above criteria were accepted to have CPP/RPP if no GnRH stimulation test was performed. The GnRH stimulation test was performed after the intravenous administration of 0.1 mg of Gonadorelin acetate (gonadorelin acetate, Ferring®). LH and FSH levels were measured at 15, 30, 45, 60 and 90 minutes after injection (13,14,16). For patients diagnosed with CPP/RPP, treatment was started with GnRH analogue (3.75 mg as intramuscular or subcutaneous injection every 28 days). Physical examinations were made prior to and during the course of treatment at each follow-up visit once every 3 months, and staging of puberty was determined according to the criteria by Marshall and Tanner (19). The bone age was estimated by same pediatric endocrinologists (HNPK) using the Greulich and Pyle Atlas (20).

In order to evaluate the efficiency of the treatment, suppression of HPG axis was monitored with GnRHa tests at intervals of 3 months. Blood samples were collected for the measurements of basal LH, FSH, and E2 levels prior to intramuscular GnRHa injections and serum LH levels at 30 and 60 minutes following the injections. A peak LH response of <3 mIU/mL was accepted as the diagnostic criteria for suppressed HPG axis (21). Patients with peak LH levels of ≥3 mIU/mL were suspected to have nonsuppressed HPG axis, and, thus, the HPG axis of these patients was reassessed with standard intravenous GnRH tests 3 weeks after the GnRHa injection. The criterion for a suppressed HPG axis was a peak LH level of <2 mIU/mL in this test (22,23), and GnRHa doses for patients with a peak LH level of ≥2 mIU/mL were increased up to 7.5 mg every 28 days.

Hormone Analysis

Basal FSH, LH, and E2 levels were analyzed in blood samples collected between 8:00 and 8:30 a.m. The immunochemiluminometric assay (ICMA) method using commercial kits (ADVIA Centaur analyzer system, Bayer Diagnostics, USA) was used to measure FSH and LH levels.

Sonographic Evaluation

Transabdominal pelvic ultrasonography examination was performed by a single radiologist (NF) with 10 years of experience in the field, blind to clinical findings, when the cases had sufficient bladder fullness following 1 liter oral fluid intake 1-2 hours ago. Affiniti 70 ultrasound system (Philips Healthcare; Bothell, WA, USA), 3.5-5 Mhz frequency convex, and 9-12 Mhz frequency superficial probe were used. The width and AP dimension of the uterus was measured in the transverse plane, and the length of the uterus including the cervix in the longitudinal plane was measured in millimeters (**Figure 1**). Endometrial thickness and 3 dimensions of both ovaries were measured and recorded in both planes (**Figures 1-3**). The volume of the uterus and both ovaries was calculated using the ellipsoid formula (width × anterior-posterior dimension × length × 0.523).

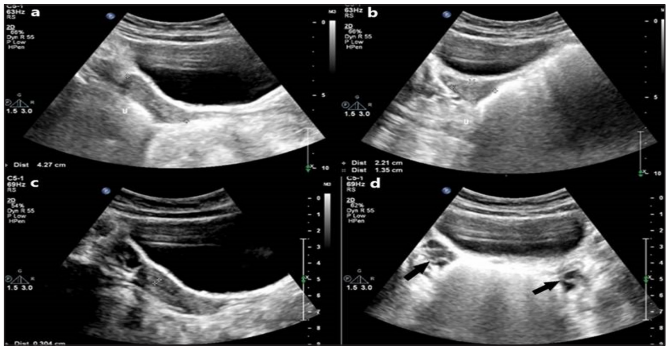

Figure 1. Transabdominal pelvic US imaging of internal genital organs in a 9-year-old girl a) Measurement of the length of the uterus including the cervix b) Measurement of the transverse and anterior-posterior size of the uterus c) Endometrial thickness measurement d) Imaging of the ovaries in the right and left posterolateral adjacent of the bladder (arrows).

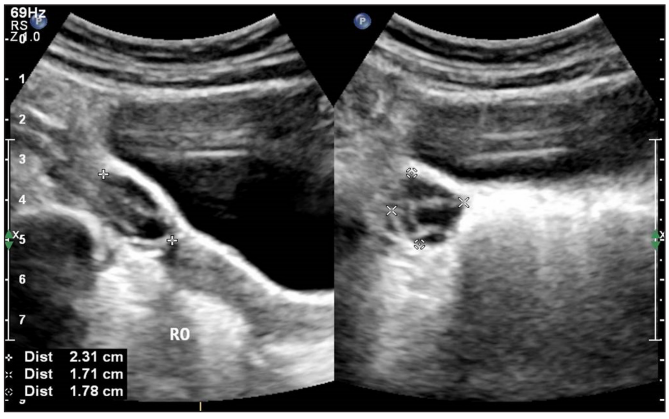

Figure 2. Sonographic measurement of right ovary 3 dimension of the same case

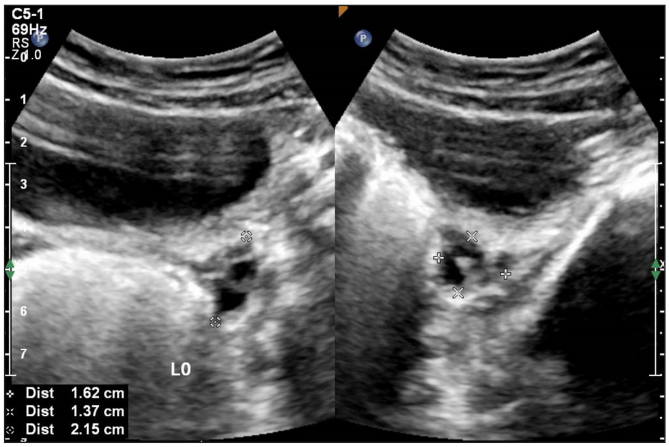

Figure 3. Sonographic measurement of left ovary 3 dimension of the same case

Statistical Analysis

Statistical analyses in our study were performed using the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normality distribution of the retrospective data was evaluated with the Kolmogorov–Smirnov test. Descriptive statistics for continuous variables were presented as mean ± standard deviation (SD) in normally distributed data, median (min-max) in non-normally distributed data, and categorical data as numbers and percentages (%). Student's t-test, Mann-Whitney U test were used to compare groups, and Fisher's chi-square test was used to compare group ratios. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 50 patients included in the study, 52% (n=26) were being followed up with the diagnosis of CPP, and 48% (n=24) with RPP. The clinical and laboratory findings of the cases are presented in **Table 1**.

It was determined that the uterine and ovarian volumes, uterine transverse, and AP size decreased statistically in the 1st year of the treatment compared to the beginning of the treatment (p<0.05) (**Table 2**). While endometrial thickness could be measured in 64% (n=32) of the cases before treatment, measurable endometrial thickness was detected in only 6% (n=3) of the cases in the 1st year of treatment. In the 1st year of GnRHa treatment, while the suppression of the HPG axis was detected in 82% (n=41) of the cases with the GnRHa test (the treatment was effective), there was no suppression in 18% (n=9). A decrease in ovarian volume in 73.2% (n=30) of 41 patients with suppression of the HPG axis, a decrease in uterine volume in 65.9% (n=27) of patients, a decrease in uterine AP size in 61% (n=25) of patients, a decrease in uterine transverse size in 56% (n=23) of patients and a decrease in uterine length in 48.7% (n=20) of the patients were observed. It was found that the most significant change in the internal genital organs was the decrease in the ovarian volume in the patients in whom the treatment was effective. The change in uterine dimensions was found to be more prominent in the AP dimension. There was no difference between the cases with and without suppression of the HPG axis in terms of age, pre-and post-treatment pubertal stage, bone age, estradiol level, and sonographic parameters (p>0.05).

Table 1. Clinical and laboratory findings of the cases before treatment and in the 1st year of treatment

	Pre-treatment (mean±SD) (min-max)	1st year of treatment (mean±SD) (min-max)	p
Chronological age (years)	7.99±1.36 (3.90-10.16)	8.99±1.36 (4.90-11.16)	<0.001
Bone age (years)	9.24±1.62 (3.50-13.50)	10.09±1.70 (4.00-14.00)	<0.001
Puberty stage	3* (2-5)	2* (1-5)	<0.001
Estradiol (pg/ml)	28.93±23.59 (5.00-89.00)	8.02±5.32 (5.00-25.10)	<0.001

*is the median value

Table 2. Pelvic US findings of the cases before treatment and in the 1st year of treatment

	Pre-treatment (mean ± SD) (min-max)	Post-treatment (mean ± SD) (min-max)	p
Uterus length (mm)	38.60±9.90 (17.00-55.00)	36.31±7.71 (14.0-50.0)	0.078
Uterine transverse size (mm)	18.25±6.71 (8.00-35.0)	15.43±4.83 (9.00-28.00)	0.001
Uterine AP size* (mm)	12.48±4.53 (7.00-25.00)	10.04±3.40 (5.00-22.00)	<0.001
Uterine volume (mm^3)	5245.32± 4328.38 (689.00-20625.00)	3126.90±2282.54 (504.00-10560.00)	<0.001
Right ovarian volume (mm^3)	2643.16±1582.47 (378.00-7744.00)	1827.48±1046.52 (31500-5049.00)	<0.001
Left ovarian volume (mm^3)	2582.40±1592.49 (308.00-6732.00)	1801.58±944.66 (315.00-4896.00)	<0.001
Total ovarian volume ** (mm^3)	2612.78±1534.55 (343.00-6167.00)	1814.53±966.98 (409.50-4972.50)	<0.001

*Uterine AP size: anterior posterior length measured from the uterine fundus section, **Total ovarian volume: Calculated as right ovarian volume+left ovarian volume/2.

DISCUSSION

In this study, we found regression in pubertal stages, decrease in E2 levels, uterus and ovarian volumes, more prominent in ovarian size and endometrial selectivity in the 1st year of GnRHa treatment in our CPP and RPP cases. It was noteworthy that the change in uterine dimensions was more pronounced in the AP dimension. GnRHa are known to be effective in the treatment of CPP. Post-treatment follow-up is important in order to provide parameters such as adherence to treatment, adequate dose, and to monitor adequate suppression. In the last few decades, a number of studies have been conducted to address the sonographic changes that occur in girls receiving GnRHa therapy (12,15,16,24). In the study of Jensen et al. (15) in which they examined 33 girls with idiopathic CPP treated with GnRHa, it was reported that the uterus and ovaries were larger than normal in 50% of the cases at the time of diagnosis and significantly regressed to age-appropriate normal values at the 3rd month after treatment. Yu et al. (16) evaluated 119 girls diagnosed with CPP and reported that pelvic US is a suitable and objective modality for monitoring the suppression of the HPG axis during CPP treatment and can reduce the need for repeat GnRH stimulation tests.

deVries et al. (12) concluded that pelvic US is an appropriate and objective method to monitor the suppression of the HPG axis during CPP treatment. In their study, they stated that the case in which GnRHa treatment was not effective and therefore the absence of sonographic

findings of these cases was the weakness of their study. In our study, although 18% of our patients did not have HPG axis suppression, we did not find any difference in terms of age, pre-and post-treatment puberty stage, bone age, E2 level, and sonographic parameters between the cases with and without suppression of the HPG axis. In addition, although the HPG axis was found to be suppressed by the GnRHa test, no decrease was found in the ovary volume in 11 patients and in the uterus volume in 14 patients. Ersen et al. (25) defined uterus and ovarian volumes in healthy Turkish girls according to age, and reported ovarian volume>1.58 cm3 (73% sensitivity and 48% specificity), uterine volume>2.57 cm3 (80% sensitivity and 50% specificity) as the threshold value for the onset of puberty. When the data of our patients were evaluated according to these threshold values, we had 9 cases with uterine and ovarian volumes in the normal range for age before treatment, and 14 cases with uterus or ovarian volumes within the normal range. After the treatment, the calculated volumes were within the normal range for age in 5 of 9 cases with both ovarian and uterine volumes in the normal range, in 11 of 14 cases with uterine volumes in the normal range, and in 10 of 14 cases with ovarian volumes in the normal range. We think that our results in the patient group who did not have a significant/apparent regression in uterus and ovary dimensions with treatment may be due to this occasion.

The time course of hormone-gonadal interaction in the diagnosis and treatment of CPP and the morphological changes that will occur in this process are important factors to consider when evaluating these patients. Ambrosino et al. (14) reported that a 3-month interval is required for the morphological changes to occur after GnRH treatment, the most significant improvement occurs after the 6th month, and the decrease in ovarian volume is the fastest morphological response. They noted that changes in the uterine size and configuration occur more slowly, with a later response, and reflect the general long-term trend. It was emphasized in another study that the ovarian changes were faster, the decrease in the uterine volume started after the 3rd month and continued at the 12th month (15).

On the other hand, there is some debate about which pelvic US is the best parameter to evaluate suppression of the HPG axis. Yu et al. found in their study that all parameters related to uterus/ovarian size and volumes were significantly decreased compared to pre-treatment measurements, and they reported uterine body volume as the best sonographic parameter to distinguish patients with CPP from normal girls (sensitivity 91%, specificity 68%)(16). In the same study, the other parameters with the highest sensitivity were found to be the uterus AP size and the ovarian volume (89%). Wen et al. (26) reported that the best parameter to distinguish the cases with CPP from normal girls in the 8-10 age group is the endometrial thickness, and they said that the cut-off value of 2.6 mm has a sensitivity of 76% and a specificity of 100%. deVries et al. (12) reported that the most important response to treatment is the uterine parameters and absence of endometrial echo, and they are better indicators than ovarian parameters. They suggested that each patient started the treatment with a different size of uterus, ovary, and different Tanner stage, and that there were individual differences, and to compare the pre-treatment and post-treatment sonographic parameters of the same patient., not the healthy control group. In our study, the most significant decreasing parameters in the follow-up of treatment efficiency were ovarian volume, uterine volume, and endometrial selectivity. Among the uterine size parameters, the AP size is the parameter with the most significant decrease, and we did not detect a significant decrease in the measured uterine length, including the cervix. In line with these data, we believe that it is necessary to combine multiple ultrasound parameters with clinical symptoms and sexual hormone levels in the diagnosis and treatment follow-up of CPP.

The limitations of our study are its retrospective design, small sample size, and lack of a control group consisting of healthy volunteers. Prospective studies involving longer-term ultrasonography results in girls diagnosed with CPP/RPP and treated with GnRHa are needed.

CONCLUSION

We found in this study that GnRHa treatment in girls with CPP or RPP caused a significant regression in ovarian and uterus dimensions and endometrial echo selectivity. Our results, in line with the literature, support the view that pelvic ultrasonography is a suitable modality for monitoring the suppression of the HPG axis in the evaluation of the efficiency of GnRHa therapy and may reduce the need for repeated GnRH stimulation tests.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Hitit University Faculty of Medicine, Non-interventional Researches Ethics Committee (Date: 26.05.2021, Decision No:2021-467).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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