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Original Article

The Clinical Effects of GnRHa in Treating Idiopathic Central Precocious Puberty in Girls

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Abstract ***Purpose:*** This study will explore the clinical effects of the gonadotropin-releasing hormone analogue (GnRHa) to treat girls with idiopathic central precocious puberty (ICPP). ***Methods:*** Fifty-four ICPP girls were treated with triptorelin acetate. To evaluate the clinical effects of GnRHa, measurements were taken of the girls' height, weight, ovaries, and uterus before treatment and at 6 and 12 months after treatment. ***Findings:*** During the one-year treatment period, the height growth rate slowed in the second half of the year, and the secondary sexual characteristics retracted to varying degrees. Intracavitary ultrasound showed a decrease in the ovary and uterus volumes and in the ovaries' longitudinal diameter, transverse diameter, and anteroposterior diameter and the uterus's transverse diameter. ***Conclusions:*** GnRHa can inhibit the development of the gonads and secondary sexual characteristics and induce significant changes in the volume of the ovaries and uterus, longitudinal ovarian diameter, transverse ovarian diameter, anteroposterior ovarian diameter, and transverse uterine diameter.

Key words *BMI; GnRHa; Idiopathic central precocious puberty in girls; Pelvic ultrasound; Secondary sexual characteristics*

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Introduction

Developing secondary sexual characteristics before the age of eight or menarche before the age of ten is defined as precocious puberty.[1] In recent years, with increasing social and economic growth, the rate of central precocious puberty among girls has increased every year. Idiopathic central precocious puberty (ICPP) refers to precocious puberty without organic lesions. ICPP is caused by the release of the gonadotropin-releasing hormone (GnRH) after early activation of the hypothalamic-pituitary-gonadal axis (HPGA) function. The pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to an increase in ovarian and uterine volumes.

Girls with precocious puberty have higher levels of criminal activity, substance abuse, social isolation, early sexual behaviour, and mental health problems.[2] Precocious girls with a history of adolescent behaviour disorder have more depressive tendencies compared to their peers.[2]

The gonadotropin-releasing hormone analogue (GnRHa), including triptorelin, is the first choice for treating ICPP.[3] GnRHa can act as a hypothalamic analogue to competitively inhibit the GnRH secreted by the hypothalamus and reduce the secretion of pituitary gonadotropin, inhibiting or delaying gonadal development and delaying puberty.[1] GnRHa treatment can effectively delay the development of gonads and sexual characteristics and improve adult height, with few side effects.[4]

To develop a therapeutic model and evaluate the clinical effects of triptorelin in ICPP treatment, this study analyzed and compared the changes in height and weight, uterus and ovaries, and other key parameters.

Methods

Subjects

Fifty-four girls diagnosed with ICPP were enrolled in this study. The age range was six to ten years old, with an average age of 8.62±1.15 years old. The study was approved by the hospital's ethics committee. The study protocol was outlined to the girls' guardians, and they signed informed consent.

Inclusion criteria: (1) secondary sexual characteristics developed before the age of eight and menarche or breast development before the age of 10, (2) linear growth acceleration with an annual growth rate higher than that of normal children, (3) bone age at least one year older than the actual age, (4) a pelvic ultrasound showing an increased volume of the uterus and ovaries and multiple ovarian follicles with diameters greater than 4 mm, and (5) activated HPGA with serum gonadotropins and sex hormones at puberty levels. The immunochemiluminometric assay (ICMA) showed that the LH peak value was ≥5 U/l; the GnRHa stimulation test showed that the LH peak FSH peak was >0.6.[1]

Treatment of GnRHa

All the girls were treated with triptorelin acetate intramuscularly every 4 weeks, the starting dose was 60-160 μG/kg. We adjust the dose of triptorelin according to the gonadal suppression and the weight changes of the children. The maximum single dose was 3.75 mg.

Detection of height, weight, and body mass index (BMI) The girls' height and weight were measured and recorded before treatment and at 6 and 12 months after treatment. Height growth rate = height after treatment - the height before treatment; BMI = weight (kg)/square of height (m).

Ultrasound Detection

The girls were examined by transrectal ultrasonography before treatment and at 6 and 12 months after treatment, and the parameters of the uterus and ovaries were recorded. No girl had significant differences between the parameters of the left and right ovaries. The ovaries' longitudinal diameter, anteroposterior diameter, and transverse diameter were defined as the mean values of the parameters of the right and left ovaries. Ovarian volume (ml) = (longitudinal diameter × anteroposterior diameter × transverse diameter) × 0.523. The volumes of the two ovaries and the mean volume were calculated. The uterus volume (ml) = (longitudinal diameter × anteroposterior diameter × transverse diameter) × 0.523. The fundal-cervical ratio (FCR) of the (uterus = anteroposterior diameter of the uterus/ anteroposterior diameter of the cervix).

Statistical Analysis

After the data had been collected, they were statistically analysed using the software SPSS 16.0. The measurement data were expressed as mean ± standard deviation (x ± SD). In the present study, single-factor, least significant difference analysis was used to compare normally distributed data with homogeneous variance. Non-normally distributed data, such as volumes of the uterus and ovaries, were compared using a nonparametric *U*-test. $P<0.05$ was considered statistically significant.

Results

Secondary Sexual Characteristics

After treatment, the secondary sexual characteristics retracted by varying degrees: the breast glands became softer and smaller in 37 of 54 girls; menstruation disappeared in 24 of 33 girls; and vaginal secretion decreased or disappeared after treatment in 21 girls.

Changes in Height and BMI

In the first six months of treatment, the height growth rate was greater compared to the rate at 6 to 12 months after treatment, and the difference was statistically significant ($P<0.05$) (Table 1).

There was no significant change in BMI before and after treatment, and the difference was not statistically significant ($P>0.05$).

Pelvic Ultrasound

To facilitate the statistical analysis, the data before

treatment and at 6 and 12 months after treatment began, respectively, were designated as group 1, group 2, and group 3.

Changes in the Ovaries

The longitudinal ovarian diameter, transverse ovarian diameter, and anteroposterior ovarian diameter decreased after treatment began ($P<0.05$) (Tables 2 and 3), when compared to the measurements before treatment; the reduction in the first six months of treatment was significant ($P<0.05$) (Table 4 and Figure 1). The volume of the ovaries shrank during treatment, and this was most obvious in the first six months of treatment ($P<0.05$).

Changes in the Uterus

The transverse diameter of the uterus decreased during treatment ($P<0.05$), and the reduction was most pronounced during the first six months ($P<0.05$) (Tables 3 and 5). The results showed no significant changes in the longitudinal uterine diameter, anteroposterior uterine diameter, and uterine FCR before and after treatment ($P>0.05$). The results showed that the volume of the uterus decreased during treatment, and this was most obvious during the first six months ($P<0.05$) (Table 4 and Figure 2). The results showed that there was no significant difference in the anteroposterior diameter and transverse diameter of the cervix before and after treatment ($P>0.05$) (Table 1).

Vaginal Wall Thickness

There was no significant change in the thickness of the vaginal wall before and after treatment ($P>0.05$) (Table 6).

Discussion

The incidence of ICPP is correlated to race, heredity, environment, and other factors. For example, Jayasena et al reported that the overactivation of the kisspeptin (KISS) gene, which produces a hypothalamic neuropeptide, can lead to precocious puberty in children.[5] Therefore, KISS gene polymorphism was associated with ICPP.[6] A scholar also reported that ICPP is correlated with the mutation of the *mkrn3* gene.[6] In addition, genetic factors, obesity, and environmental factors may be involved in the occurrence and development of ICPP. The widespread presence of endocrine disorder chemicals is suspected of contributing to the trend of the pathogenesis of early puberty.[7]

Table 1 Changes in height and BMI before and after treatment (x±SD)

	Anterior-posterior diameter of the cervix (cm)	Transverse diameter of the cervix (cm)	BMI (kg/m^2)	Growth value of height (cm/6 months)
Before treatment	1.78±0.43	1.17±0.26	17.88±2.80	
Six months after treatment	1.62±0.42	1.01±0.24	18.50±2.16	3.87±0.90
One year after treatment	1.67±0.51	1.07±0.33	18.80±2.67	2.64±1.2
F	0.919	2.253	2.094	-3.36
P	>0.05	>0.05	>0.05	<0.05

BMI: body mass index

Table 2 Changes in the ovary before and after treatment (x±SD)

	Ovary long diameter (cm)	Ovary anterior-posterior diameter (cm)	Ovary transverse diameter (cm)
Before treatment	2.42±0.53	1.46±0.41	1.85±0.46
Six months after treatment	2.02±0.40	1.13±0.23	1.54±0.36
One year after treatment	2.16±0.50	1.27±0.28	1.64±0.53
F	4.790	7.818	3.222
P	<0.05	<0.05	<0.05

Table 3 Comparison of parameters before and after treatment

	Mean difference (95% CI)		
	Before treatment vs. Six months after treatment 1,2	**Before treatment vs. One year after treatment 1,3**	**Six months after treatment vs. One year after treatment 2,3**
Ovary long diameter	0.40056 (0.1395, 0.6616)	0.25722 (-0.0039, 0.5183)	-0.14333 (-0.4044, 0.1177)
P	<0.05	>0.05	>0.05
Ovary anterior-posterior diameter	0.3387 (0.1673, 0.5101)	0.19963 (0.0282, 0.3711)	0.3711 (-0.3105, 0.0324)
P	<0.05	<0.05	>0.05
Ovary transverse diameter	0.307778 (0.06183, 0.55373)	0.205926 (-0.04002, 0.45188)	-0.101852 (-0.3478, 0.1441)
P	<0.05	>0.05	>0.05
Uterus transverse diameter	0.32 (0.063, 0.577)	0.2389 (-0.018, 0.496)	-0.0811 (-0.338, 0.176)
P	<0.05	>0.05	>0.05

CI: confidence interval

Table 4 Changes in the ovarian volume and uterine volume before and after treatment (x±SD)

Time		**Ovarian volume (ml)**	**Uterine volume (ml)**
(1) Before treatment		4.07±3.55	5.64±5.44
(2) Six months after treatment		2.04±1.12	3.16±2.50
(3) One year after treatment		3.94±3.04	4.05±3.91
(1) : (2)	P	<0.05	<0.05
(1) : (3)	P	>0.05	>0.05
(2) : (3)	P	<0.05	<0.05

Table 5 Changes in the uterus before and after treatment (x±SD)

	Uterus long diameter (cm)	**Uterus anterior-posterior diameter (cm)**	**Uterus transverse diameter (cm)**
Before treatment	2.41±0.65	2.30±0.57	1.58±0.58
Six months after treatment	2.08±0.53	1.98±0.51	1.26±1.34
One year after treatment	2.19±0.67	2.09±0.68	1.34±0.47
F	1.913	1.966	3.331
P	>0.05	>0.05	<0.05

Table 6 Changes in the thickness of the vaginal wall (x±SD)

	FCR of the uterus	**Thickness of the vaginal wall (cm)**
Before treatment	1.33±0.30	0.24±0.07
Six months after treatment	1.27±0.32	0.21±0.08
One year after treatment	1.29±0.35	0.22±0.06
F	0.264	0.846
P	>0.05	>0.05

FCR: fundal-cervical ratio

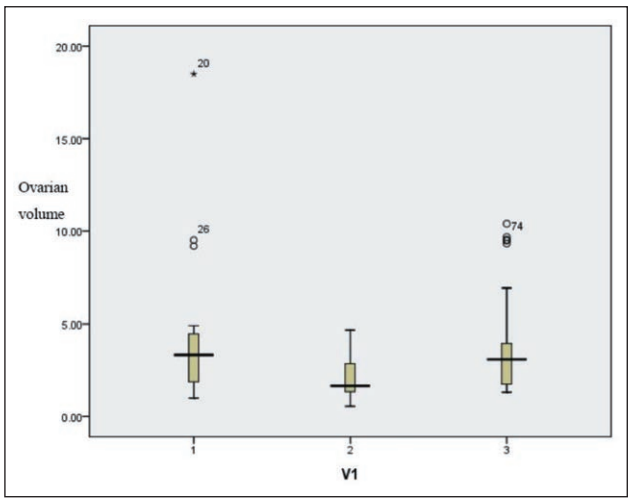

Figure 1 Changes of ovarian volume.

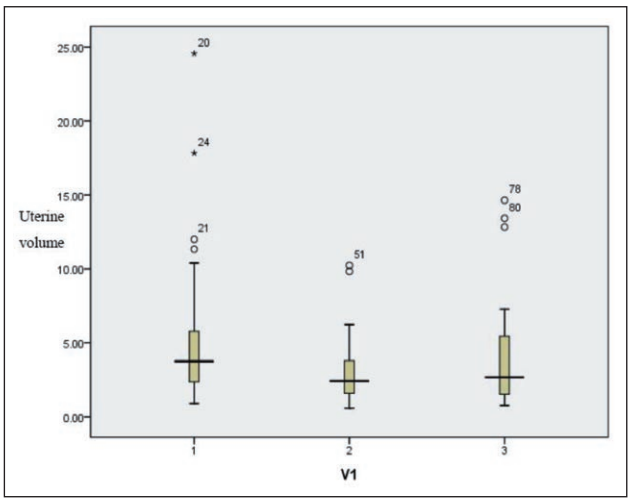

Figure 2 Changes of uterine volume.

Kim et al[8] examined 118 ICPP girls and 91 age-matched healthy girls, and the results showed that the plasma levels of daidzein (P=0.0202), genistein (P=0.0021), and total isoflavones (P=0.0009) were higher in ICPP girls than in healthy girls. This result suggests that the increase in serum isoflavones may be correlated to the risk of ICPP in Korean girls.[7] Zhang et al[9] reported that concentrations of environmental endocrine disruptors (such as diethylhexyl phthalate, octylphenol, and bisphenol A) were important pathogenic factors of precocious puberty.[10] Tassinari et al[11] detected the serum concentration of polybrominated diphenyl ether (PBDEs) in 31 girls with ICPP, and the results showed that the levels were higher than the levels in healthy girls. Girls with higher BMIs had higher serum levels of PBDEs.[8]

GnRHa is the first choice for treating ICPP globally.[1] For patients with typical central precocious puberty, GnRHa treatment can effectively improve adult height and does not cause adverse effects on the body and reproductive functions.[9,11] In addition, Li et al[12] reported that GnRHa could delay the development of secondary sexual characteristics and ovarian maturity with almost no side effects.[13] Therefore, this study evaluated the clinical effect of GnRHa triptorelin on ICPP. Fifty-four girls accurately diagnosed with ICPP were treated with GnRHa triptorelin. After treatment began in this study, the secondary sexual characteristics were retracted to varying degrees in 54 girls. The height growth rate was significantly greater in the first six months than in the second six months.

In 2011, Taşcilar et al[14] reported that treating ICPP with triptorelin could increase the BMI, puberty growth hormone secretion, and insulin-like growth factor in the blood. Transient insulin resistance in early and middle adolescence can also increase the adipose tissue content and BMI. Jaruratanasirikul et al[15] reported that the sexual development of girls was correlated to BMI. The BMI of girls affects the endocrine metabolism regulated by the KISS-1/GPR54 system.[16] In the present study, there was no significant change in BMI before and after treatment, and no increase in BMI was found in ICPP girls treated with GnRHa.

Razzaghy-Azar et al[17-19] reported that uterine and ovarian parameters are significantly correlated with age, height, weight, puberty stage, and puberty development. The parameters of the uterus and ovaries detected by pelvic ultrasound are important for the diagnosis and evaluation of precocious puberty. Ultrasound can directly reflect the development of the gonads by dynamically monitoring the volume change of the uterus and ovaries after treatment.[20-22]

The present study showed that the longitudinal ovarian diameter, transverse ovarian diameter, anteroposterior ovarian diameter, ovarian volume, transverse uterine diameter, and uterine volume decreased after treatment, and this reduction was most significant during the first six months. However, there was no significant difference between the reduction six months after treatment and 12 months after treatment. The inhibition effect was most obvious when the drugs were used for six months. However, there were no significant changes in longitudinal uterine diameter, anteroposterior uterine diameter, uterine FCR, cervix transverse diameter, and thickness of the vaginal walls before and after treatment. Hence, these changes cannot be used as sensitive indexes to evaluate the effect of treatment.

Conclusions

GnRHa triptorelin treatment for girls with ICPP can retract the secondary sexual characteristics and inhibit gonad development. There was no significant change in BMI. The reduction in the volume of the ovaries and uterus, longitudinal ovarian diameter, transverse ovarian diameter, anteroposterior ovarian diameter, and transverse uterine diameter can be an effective and sensitive index for observation.

Conflicts of Interest

The authors declare that they have no competing interests.

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