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ORIGINAL RESEARCH

Pelvic Ultrasound Parameters of Long-Acting Depot Formulation of Leuprorelin in the Treatment of Idiopathic Central Precocious Puberty in Girls

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Objective: The present study was designed to compare the changes in ovarian and uterine parameters in girls with idiopathic central precocious puberty (ICPP) before and after gonadotropin-releasing hormone analogues (GnRHa) treatment to determine which sensitive indexes effectively reflect the therapeutic effect.

Methods: Sixty girls diagnosed with ICPP were enrolled in the present study. Relevant data were recorded before treatment. Leuprorelin acetate microspheres were injected at a dose of 30–180 μg/(kg four weeks). Relevant parameters were measured and recorded every three months. Changes in each parameter were analyzed to evaluate the clinical effect of leuprorelin in the treatment of girls with ICPP.

Results: 1) The height grew at a constant rate. 2) The breasts retracted. 3) Changes in pelvic parameters: the volume of the ovary and uterus and major axes of the ovary, uterus, and cervix were reduced; there were no significant changes in vaginal thickness or the uterine fundal–cervical ratio (FCR). 4) Body mass index (BMI) increased.

Conclusion: Pelvic ultrasound is helpful in evaluating the efficacy of GnRHA treatment. The changes of ovarian volume and the major axes of the ovary, uterus, cervix can be used as sensitive observation indexes.

Keywords: leuprorelin microspheres, idiopathic central precocious puberty in girls, pelvic ultrasound, sensitive indicators

Introduction

Central precocious puberty (CPP) refers to premature activation of the hypothalamic–pituitary–gonadal (HPG) axis, resulting in the early development of secondary sexual characteristics.[1] It can cause the premature development of gonadal tissue (eg, ovarian enlargement, uterine enlargement), advanced menarche in girls, the premature closure of epiphysis which leading to impairment of final height and may bring psychological problems and behavioral abnormalities.[1,2] At present, the development of secondary sexual characteristics before the age of 8 years old or menarche before the age of 10 years old is defined as precocious puberty in China,[1] and precocious puberty without organic lesions is defined as Idiopathic central precocious puberty (ICPP). ICPP is a common disease in pediatrics, and its incidence has increased in recent years.[2] GnRHa is the first-choice treatment for

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ICPP.[1,2] Leuprorelin microspheres are GnRHa that can inhibit or delay gonadal development and delay puberty development.[1,3]

In the present study, the short-term effect of leuprorelin microspheres in the treatment of ICPP in girls was observed, and changes in ultrasound parameters were analyzed to identify the sensitive ultrasound indicators for evaluating short-term efficacy to serve in clinical work.

Information and Methods

Basic Information

A total of 60 girls diagnosed with ICPP in the outpatient department of Health Care and Endocrinology of Baoding Children's Hospital from 2016 to 2020 were enrolled in the present study. The age of onset was 8.12 ± 0.32 years old. The youngest participant was 6.5 years old, and the oldest was 10 years old. The inclusion criteria were as follows: 1) Secondary sexual characteristics appeared in advance (second sexual development in girls before eight years old, with breast nodules as the first manifestation), and menstruation occurred before 10 years old. 2) Linear growth acceleration: the annual growth rate was higher than that of normal children of the same age. 3) Advanced bone age: the bone age was one year or more than one year older than the actual age. 4) Enlarged gonad: increased volume of the uterus and ovary shown by pelvic ultrasound, with numerous follicles with a diameter of more than 4 mm in the ovary. 5) The function of HPGA was activated, and the serum gonadotropins and sex hormones reached puberty level (chemiluminescence): luteinizing hormone (LH) peak value ≥ 5.0 U/L; GnRHa provocative test: LH peak/follicle-stimulating hormone (FSH) peak value >0.6, and LH peak value ≥5.0 U/L. 6) Central organic lesions were excluded. 7) Consent to LA treatment.

All the 60 girls had menstruation. Of these girls, 33 had menstruation and 13 had pubic hair.

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by the Ethics Committee of the Baoding Children's Hospital. The guardians of all the included girls were informed and provided signed informed consent.

Experimental Methods

The following indexes of all girls were measured and recorded before treatment: height, weight, the major axes of the ovary and uterus, ovarian volume (length * width * thickness * 0.523), uterine volume (length * width * thickness * 0.523), uterine fundal–cervical ratio (FCR, anteroposterior diameter of the uterus/anterior and posterior cervical diameter), and the major axis of the cervix and bilateral vaginal wall thickness by color Doppler ultrasound.

The leuprorelin acetate microspheres used in this study were the 1-month depot formulation. Leuprorelin acetate microspheres were injected at a dose of 30–180 μg/(kg four weeks).[1] In this study, leuprorelin microspheres were injected subcutaneously at the first dose of 3.75mg. For girls with bodyweight < 30kg, the conventional treatment dose was 1.875 mg/4 weeks. For girls with bodyweight ≥30kg, the conventional treatment dose was 3.75mg/4 weeks. For the girls who have menstruation, the first dose of injection is followed by an intensive injection (dosage is the same as the conventional treatment amount).

Height, weight, hormone level, and pelvic ultrasound parameters were measured every three months. During the follow-up period of half a year, changes in ultrasound-related parameters, height, and body mass index (BMI) were assessed.

Statistical Methods

After accurately recording and inputting data, SPSS21.0 software was used to analyze the data. All indexes were expressed as mean ± standard deviation (X ± SD). Height, weight, ovarian length, uterine length, FCR, BMI, ovarian volume, and other normally distributed indexes with homogeneous variance were evaluated using a *t*-test, while ovarian volume was evaluated using Wilcoxon rank-sum test. $P<0.05$ was considered statistically significant.

Results

Data collected before treatment and at three and six months after treatment were set as Time 1, Time 2, and Time 3 to facilitate the statistical analysis.

Height Change

Height growth was recorded in the first three months and second three months of treatment, respectively. The girl's height increased by 3.36±0.438cm during the first three months, and 2.565±0.343cm during the second three months. The height growth parameters were analyzed by statistical analysis of variance, and the difference was not statistically significant ($P>0.05$). The height of the girls increased uniformly within six months of initial treatment.

Change in Secondary Sexual Characteristics

Secondary sexual characteristics were reduced to varying degrees after three and six months of treatment. The reduction was significant within six months of treatment compared with before treatment. After six months of treatment, the breast gland mass was soft and small, and the breast retracted in 60 girls. Of the 33 girls with menstruation, 29 girls did not menstruate again after treatment, and 4 girls still had menstruation, but the amount and frequency of menstruation were lower than before treatment. The pubic hair in four of 13 girls remained unchanged after six months of treatment and decreased compared with before treatment in the remaining girls.

Pelvic Ultrasound

Changes in the Ovary

Before treatment, the left ovarian volume was 2.8 ±0.98cm^3 and the right ovarian volume was 3.6 ±1.16 cm^3. A Wilcoxon test was performed on both sides of the ovarian volume, and the difference was statistically significant ($P < 0.05$).

Ovarian volume: Bilateral ovarian volume was decreased at Time 2 and Time 3 compared with Time 1 (P<0.05, Table 1). There was no significant difference in ovarian volume at Time 2 compared with Time 3 (P>0.05, Table 1).

Ovarian major axes: Both sides of the ovarian major axes were decreased at Time 2 and Time 3 compared with Time 1 (P<0.05, Table 1). There was no significant difference in ovarian major axes at Time 2 compared with Time 3 (P>0.05, Table 1).

Changes of the Uterus

The major axes of the uterus: Compared with Time 1, the major axes of the uterus were decreased at Time 2 and Time 3 (P<0.05, Table 2). There was no significant difference between Time 2 and Time 3 (P>0.05, Table 2).

Uterine volume: Uterine volume was decreased at Time 3, and the difference was statistically significant (P<0.05, Table 3). Although this parameter was decreased at Time 2, there was no statistical difference (P>0.05, Table 3).

FCR of the uterus: The FCR of the uterus did not change significantly at Time 2 and Time 3 compared with Time 1 (P>0.05, Table 2).

The major axis of the cervix: The major axis of the cervix was decreased at Time 2 and Time 3 compared with Time 1 (P<0.05, Table 2).

Thickness of Both Sides of the Vaginal Wall

Compared with Time 1, there was no significant change in the thickness of both sides of vaginal wall at Time 2 and Time 3 (P>0.05, Table 2).

BMI Changes

BMI increased at Time 3 compared to Time 1 (P<0.05, Table 1), but there was no significant change at Time 2 (P>0.05, Table 1).

Discussion

Pelvic ultrasound is a simple and reliable method for diagnosing ICPP in girls. The therapeutic effect of ICPP can be evaluated by dynamic observation of the internal genital morphology.[4] Pelvic ultrasound examination can be used as an auxiliary means to distinguish normal women and women with varying degrees of precocious puberty.[5] The combination of basic luteinizing hormone (LH) measurement and pelvic ultrasound can improve the diagnostic accuracy of ICPP.[6–8]

GnRHa is the preferred drug for the treatment of ICPP domestic and overseas and has been used clinically for

Table 1 Comparison of Parameters Among the Three Groups (x±s)

		BMI	Left Ovarian Volume (cm^3)	Right Ovarian Volume (cm^3)	Left Ovarian Major Axis (cm)	Right Ovarian Major Axis (cm)
Time 1		18.1±1.13	2.8±0.98	3.6±1.16	2.28±0.195	2.32±0.195
Time 2		18.2±1.03	1.7±0.88	2.1±1.44	1.89±0.193	2.00±0.255
Time 3		18.9±2.55	1.6±0.89	1.8±1.43	1.84±0.183	1.83±0.176
p-value	Time 2:Time 1	>0.05	<0.05	<0.05	<0.05	<0.05
	Time 3:Time 1	<0.05	<0.05	<0.05	<0.05	<0.05
	Time 3:Time 2	<0.05	>0.05	>0.05	>0.05	>0.05

Table 2 Comparison of Parameters Among the Three Groups (x±s)

		The Major Axis of the Uterus (cm)	The Major Axis of the Cervix (cm)	FCR of the Uterus	Thickness of Vaginal Wall (cm)
Time 1		2.40±0.351	1.83±0.237	1.30±0.137	0.24±0.04
Time 2		2.02±0.259	1.55±0.224	1.30±0.186	0.26±0.115
Time 3		1.98±0.190	1.52±0.144	1.26±0.140	0.21±0.03
p-value	Time 2:Time 1	<0.05	<0.05	>0.05	>0.05
	Time 3:Time 1	<0.05	<0.05	>0.05	>0.05
	Time 3:Time 2	>0.05	>0.05	>0.05	>0.05

more than 40 years. The secretion of sex hormones is regulated by the hypothalamic–pituitary–gonad axis system. Gonadotropin-releasing hormone (GnRH) is a kind of decapeptide hormone secreted in pulsed form by hypothalamic arcuate nucleus nerve cells through the pituitary portal system. GnRH binds to the GnRH receptor (GnRHR) on the surface of the pituitary gonadotropin cell membrane to form ligand-receptor complex and enter the cell. Then, the pituitary periodically secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH stimulate the ovary to secrete sex hormones, which constitute the hypothalamic-pituitary -ovary regulation system. Indications for GnRHA treatment in children with ICPP: 1) Fast-progressing type; 2) Predicted adult height impaired; 3) Psychological and behavioral problems directly related to sexual precocity.[1] Drug therapy is not recommended for patients with relatively slow sexual development and no significant impairment of predicted adult height. The therapeutic drug used in this study was leuprorelin microspheres. By replacing the sixth and tenth amino acids of GnRH, leuprorelin extended the half-life and increased the affinity with G-protein coupled receptor (GnRHR) on the membrane surface. GnRHA and GnRH combine competitively with GnRHR. Since the affinity between GnRHA and GnRHR is much higher than that of GnRH, the pituitary gland is no longer sensitive to GnRH produced by the body itself, thus inhibiting gonadal development.

Table 3 Comparison of Parameters Among the Three Groups (x ±s)

		Uterine Volume (cm^3)
Time 1		5.80±2.19
Time 2		3.62±1.46
Time 3		3.03±0.96
p-value	Time 2:Time 1	>0.05
	Time 3:Time 1	<0.05

In the present study, there was no significant increase in height between the first and second 3 months of treatment. This suggests that the height of treated girls may increase at a constant rate. Before treatment, all the girls had varying degrees of breast development; some had induration, some had menarche and vaginal secretion, and some had body hair development. After six months of treatment, the breast gland mass was soft and small and the breast retracted in all girls. Menstruation and vaginal discharge disappeared, body hair development stagnated, the development of secondary sexual characteristics was inhibited or delayed in most girls.

Ultrasound can intuitively reflect the development of the gonads by dynamically monitoring the volume change of the uterus and ovaries after treatment.[9] Analysis and comparison revealed no significant change in the thickness of both sides of the vaginal wall and FCR of the uterus after three and six months of treatment; therefore, they cannot be used as an effective index to evaluate the therapeutic effect. It has been reported that ovarian volume, uterine major axis, and other indicators have the highest conformance with age.[10] In the present study, the volume of both sides of the ovaries, the major axes of both sides of the ovaries, the volume and major axis of the uterus, and the major axis of the cervix were significantly reduced after treatment. After three months of treatment, the volume and major axes of both sides of the ovaries, the major axis of the uterus, and the thickness of the cervix decreased significantly compared

with those before treatment. The uterine volume decreased significantly after six months of treatment, and changes in the other parameters were not significant. The changes of bilateral ovary volume and long axis, the major axis of uterus and the thickness of cervix appear earlier than the changes of uterine volume, which can be used as more sensitive indexes for clinical treatment.

In the present study, changes in BMI were statistically analyzed, and the results revealed no significant change in BMI after three months of treatment. However, BMI increased significantly after six months of treatment. Therefore, BMI was not affected in the first three months of treatment, but increased significantly after six months of treatment; this result could be due to the side effects of leuprorelin microspheres. Some researchers have pointed out that treating ICCP with GnRHa can increase BMI.[11] However, Sorensen et al revealed that the BMI value of adolescent children is related to their development stage,[12] and an increase in BMI in girls may be related to abnormal endocrine metabolism, as regulated by the KiSS-1/GPR54 system.[11] The increase in the secretion of growth hormone during puberty leads to the increase of insulin-like growth factor (IGF-1) in the blood circulation; further, transient insulin resistance may occur in the early and middle stages of puberty, and there can be an increase in adipose tissue content and BMI.[11]

There is a need to pay attention to the changes in uterine and ovarian parameters in girls detected by pelvic ultrasound before and after GnRHa treatment; further, changes in BMI before and after treatment must be studied with large samples.

Conclusion

In summary, the treatment of ICPP patients with GnRHa should be individualized. Monitoring changes in pelvic ultrasound parameters is helpful to evaluate the therapeutic effect of GnRHa and assist in adjusting the treatment plan. After 3 months of treatment, the ovarian volume and the major axes of the ovary, uterus, cervix decreased significantly, which could be used as sensitive observation indexes. Leuprorelin microsphere may cause an increase in BMI in children.

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Disclosure

The authors declare that they have no competing interests.

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