https://doi.org/10.17816/PED10445-50

EXPERIENCE OF TREATMENT PRECOCIOUS PUBERTY BY GONADOTROPIN-RELEASING HORMONE AGONISTS OF PROLONGED ACTION

© O.V. Lagno [1], M.E. Turkunova [1], E.B. Bashnina [2]

[1] St. Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Russia;
[2] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

For citation: Lagno OV, Turkunova ME, Bashnina EB. Experience of treatment precocious puberty by gonadotropin-releasing hormone agonists of prolonged action. *Pediatrician (St. Petersburg)*. 2019;10(4):45-50. https://doi.org/10.17816/PED10445-50

Received: 11.06.2019 Revised: 15.07.2019 Accepted: 19.08.2019

Central precocious puberty (CPP) occupies an important place in the practice of pediatric endocrinologist. In the treatment of all forms of CPP, there are used drugs of GnRH (gonadotropin-releasing hormone) agonists group, whose pharmacological effect of is based on desensitization of the pituitary gland to the stimulating effect of GnRH. Therapy with agonist of gonadotropin-releasing hormone allows to stop the progression of sexual development, reduce the rate of bone maturation and, thereby, increase the final growth of the child. The article demonstrates the structure of the dispensary group of patients with CPP who were treated with the agonists GnRH of prolonged action. There has been conducted the analysis of the observation results of patients with idiopathic CPP who received 3.75 mg Triptorelin therapy in the standard regimen once every 28 days and transferred to Tryptorelin 11.25 mg once every 3 months, as well as patients with different forms of CPP with a newly established diagnosis. The presented results of treatment with 11.25 mg Triptorelin drugs by intramuscular injection in a regimen of 1 time in 3 months in comparison with the results of treatment with 3.75 mg of Triptorelin patients in the regimen of intramuscular injections once every 28 days in patients with CPP showed their effectiveness. Preparations of the agonists GnRH group of prolonged action inhibit the development of secondary sexual characteristics, lead to a decrease in the size of the internal genitalia in female and external genitalia in male and reduce the progression of bone age. It was also noted that reducing the frequency of injections of drugs of this group from 1 time in 28 days to 1 time in 3 months positively affects the emotional state of children receiving this treatment for a long period (3-6 years).

Keywords: gonadotropin dependent precocious puberty; idiopathic central precocious puberty; GnRH agonist treatment; Triptorelin.

ОПЫТ ЛЕЧЕНИЯ ПРЕЖДЕВРЕМЕННОГО ПОЛОВОГО СОЗРЕВАНИЯ АГОНИСТАМИ ГОНАДОТРОПИН-РИЛИЗИНГ-ГОРМОНА ДЛИТЕЛЬНОГО ДЕЙСТВИЯ

© О.В. Лагно [1], М.Е. Туркунова [1], Е.Б. Башнина [2]

[1] ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России;
[2] ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И. И. Мечникова» Минздрава России

Для цитирования: Лагно О.В., Туркунова М.Е., Башнина Е.Б. Опыт лечения преждевременного полового созревания агонистами гонадотропин-рилизинг-гормона длительного действия // Педиатр. – 2019. – Т. 10. – № 4. – С. 45–50. https://doi.org/10.17816/PED10445-50

Поступила: 11.06.2019 Одобрена: 15.07.2019 Принята к печати: 19.08.2019

Центральное преждевременное половое созревание (ЦППС) занимает важное место в практике детского эндокринолога. В лечении всех форм ЦППС используют препараты группы агонистов гонадотропин-рилизинг-гормона, фармакологическое действие которых основано на десенсибилизации гипофиза к стимулирующему воздействию гонадотропин-рилизинг-гормона. Терапия агонистами гонадотропин-рилизинг-гормона позволяет остановить прогрессирование полового развития, снизить темпы костного созревания и тем самым увеличить конечный рост ребенка. В статье продемонстрирована структура диспансерной группы пациентов с ЦППС, которым был назначен препарат группы агонистов гонадотропин-рилизинг-гормона пролонгированного действия. Проанализированы результаты наблюдения пациентов с идиопатическим ЦППС, получавших терапию Трипторелином 3,75 мг в стандартном режиме 1 раз в 28 дней и переведенных на Трипторелин 11,25 мг 1 раз в 3 мес., а также пациентов с разными формами ЦППС с впервые установленным диагнозом. Представленные результаты лечения препаратами Трипторелина 11,25 мг путем внутримышечных инъекций в режиме 1 раз в 3 мес. в сравнении с результатами лечения пациентов Трипторелином 3,75 мг в режиме внутримышечных инъекций 1 раз в 28 дней у пациентов с ЦППС показали свою эффективность. Препараты группы агонистов гонадотропин-рилизинг-гормона пролонгированного действия тормозят развитие вторичных половых признаков, приводят к уменьшению размеров внутренних

гениталий у лиц женского пола и наружных гениталий у лиц мужского пола, снижают прогрессирование костного возраста. Отмечено также, что сокращение частоты инъекций препаратов данной группы с 1 раза в 28 дней до 1 раза в 3 мес. позитивно влияет на эмоциональное состояние детей, получающих в течение длительного периода (3–6 лет) данное лечение.

Ключевые слова: гонадотропин-зависимое преждевременное половое развитие; идиопатическое центральное преждевременное половое развитие; лечение агонистами гонадотропин-рилизинг-гормона; Трипторелин.

BACKGROUND

Premature sexual development is characterized by the appearance of secondary sexual characteristics up to the age of 8 years in girls and up to 9 years in boys. Clinically, central precocious puberty (CPP) is manifested by the acceleration of physical development, premature appearance of secondary sexual characteristics, early closure of growth zones, and short stature in adulthood [3, 4].

Gonadotropin-releasing hormone (GnRH) agonist therapy with prolonged action has been performed for more than 20 years to suppress the progression of sexual development and increase the final height. Triptorelin 3.75 mg suppresses effectively the secretion of gonadotropins and sex steroid hormones, which, in turn, leads to failure of secondary sexual characteristic development and regression in some patients, and helps to regulate patient behavior [1, 7, 10].

The conditions for the treatment of long-acting GnRH agonists include therapy continuity, calendar management, and injection regimen compliance. Regular administration of long-acting GnRH agonist preparations causes its constant increased concentration in the blood, which helps to suppress the secretion of gonadotropic hormones, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). The reduction of secretion of gonadotropic pituitary hormones leads to a decrease in the sex hormone production in ovaries or testicles. Long-term therapy with triptorelin allows effective bone age (BA) adjustment and ensures optimal growth in children with CPP [5, 11, 12].

The reversibility of the effects of this group of drugs has been proved. Normal puberty occurs 6–12 months after discontinuation of therapy. A review of recent scientific publications confirms the effectiveness of triptorelin in CPP children [2, 9, 12].

In pediatric practice, a decrease in the number of injections is critical to improving patient adherence. Because of the emergence of new pharmacological forms of long-acting GnRH agonists, such as triptorelin 11.25 mg (triptorelin pamoate, in terms of triptorelin 11.25 mg), and their use in pediatric practice, the principles of treatment and the efficacy of CPP therapy are discussed [7–9].

This study aimed to evaluate the efficacy and tolerability of triptorelin 11.25 mg in CPP children when switched from triptorelin 3.75 mg and started with triptorelin 11.25 mg therapy.

The criteria for the efficacy of therapy with long-acting GnRH agonists include the following:

- decrease in growth rate to the age norm,
- lack of progression of sexual development or regression of secondary sexual characteristics,
- increase in BA by no more than 1 year during the current year, and
- basal levels of LH and estradiol (E2) for girls and testosterone for boys can be criteria for effectiveness in the case of initially increased levels of these hormones.

After 3–6 months from the start of therapy, in doubtful cases, a test with GnRH is performed (the absence of LH release during the test is more than 4 U/L) [3].

In St. Petersburg, the treatment of CPP with GnRH agonists has been performed since 2002 [1], with patients receiving triptorelin 3.75 mg. Meanwhile, triptorelin 11.25 mg therapy was started in 2016.

PATIENTS AND METHODS

In St. Petersburg, 56 patients with CPP are currently included in the registry of orphan diseases; all of them are receiving 11.25 mg of triptorelin.

The dispensary group structure of CPP patients is presented in Figure 1.

In 50% of cases, an idiopathic variant of CPP is registered. Pediatric patients with residual organic lesions of the central nervous system (CNS) make up 23% of patients. CNS tumors (gliomas and astrocytomas of the chiasmosellar region and the floor of the ventricle III) account for 7% of all CPP cases. Of cases, 16% has hypothalamic hamartoma, which is represented by ectopia of hypothalamic tissue caused by the migration of neurons in the embryonic period and secretion of GnRH. Patients who have developed CPP syndrome during simple virilizing and nonclassical forms of congenital adrenal cortical hyperplasia make up 4%.

To analyze the efficiency of triptorelin 11.25 mg, the outpatient record data of CPP patients for the 12-month follow-up period were obtained, which included physical examination with assessment of physical and sexual development, hormonal exami-

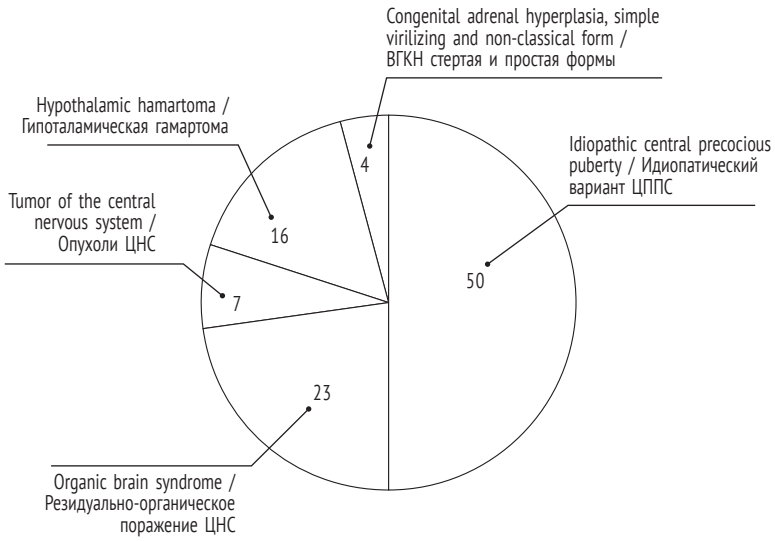

Fig. 1. The structure of the dispensary group of patients with CPP in St. Petersburg (%)

Рис. 1. Структура диспансерной группы пациентов с центральным преждевременным половым созреванием в Санкт-Петербурге (%): ЦППС — центральное преждевременное половое созревание; ЦНС — центральная нервная система; ВГКН — врожденная гиперплазия коры надпочечников

nation (basal levels of FSH, LH, E2, and testosterone 1–3 days before the planned injection), ultrasound (US) examination results of the pelvic organs in girls, and X-rays of hands with BA assessment.

An analysis was done to monitor the results of 10 girls with idiopathic CPP, who received triptorelin 3.75 mg therapy as a standard dose once every 28 days and switched to triptorelin 11.25 mg once every 3 months, and 10 patients with a newly diagnosed CPP (eight girls and two boys who received triptorelin 11.25 mg once every 3 months).

RESULTS AND DISCUSSION

Group 1 included patients with idiopathic CPP. The age of the therapy initiation with triptorelin 3.75 mg in patients averaged 6.5 years (±1 year and 1 month), whereas the age when they were examined while receiving triptorelin 3.75 mg was 7 years and 8 months (±1 year). After switching to triptorelin 11.25 mg in 6–12 months, they were examined repeatedly. There were no clinical signs of puberty progression in the patients. Most girls had a stable mood. Parents of two patients noted an increase in emotional lability 2–3 days before the next injection of triptorelin 11.25 mg. Meanwhile, the parents of three patients noted improvement in the psychoemotional state after they were switched to triptorelin 11.25 mg. All patients felt more comfortable with the injection regimen once every 3 months, as they expressed less anxiety before the next injection, and went to the clinic more calmly.

The average (M) basal levels of LH, FSH, and E2 in treatment with both triptorelin 3.75 mg and triptorelin 11.25 mg were comparable ($p \leq 0.001$):

M ($LH_{3.75\ mg}$) = 0.92 (±0.79) mIU/mL,
M ($LH_{11.25\ mg}$) = 0.44 (±0.47) mIU/mL,
M ($FSH_{3.75mg}$) = 1.62 (±1.28) mIU/mL,
M ($FSH_{11.25\ mg}$) = 1.91 (±0.95) mIU/mL,
M ($E2_{3.75\ mg}$) = 13.2 (±12.2) pg/mL, and
M ($E2_{11.25\ mg}$) = 13.6 (±12.8) pg/mL.

In 80% of patients in Groups 1 and 2, the E2 level did not exceed 20 pg/mL in both 3.75 and 11.25 mg doses (Figure 2).

In Group 1 (patients with idiopathic CPP), the length of the uterine body with the triptorelin 3.75 mg therapy averaged 28 ± 7.7 mm, and 6–12 months after the treatment with triptorelin 11.25 mg, the uterine body length indicators were within 33.9 ± 5.1 mm. According to the US of the pelvic organs, two patients had an increase in the uterine length by 12 and 9 mm, although the average uterine length in the study group did not exceed 34 mm, which indicates the absence of hormonal stimulation [6].

Group 2 consisted of patients whose therapy started with triptorelin 11.25 mg: four pediatric patients had idiopathic CPP, three with a residual organic lesion of the CNS, and one had gray tuber hamartoma. The presented cohort of patients represents the structure of CPP. The follow-up period was 6–12 months.

Clinically, there was no progression of secondary sexual characteristics. In female patients with idiopathic CPP, changes in behavioral reactions occurred

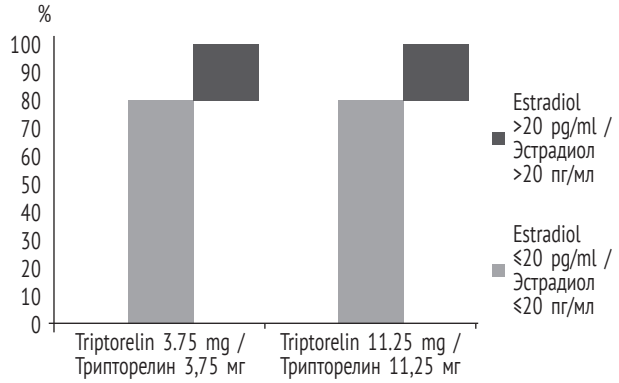

Fig. 2. The number of patients (%) whose basal estradiol levels of did not exceed 20 pg / ml when treated with 3.75 mg and 11.25 mg of Triptorelin

Рис. 2. Количество пациенток (%), у которых уровни базального эстрадиола не превышали 20 пг/мл при лечении Трипторелином 3,75 мг и 11,25 мг

after 2 months, as episodes of mood swings occurred less often, and the children became calmer.

Growth rates before treatment with drugs of the GnRH antagonist group and during therapy with triptorelin 11.25 mg are illustrative (11.2 ± 3.6 and 5.75 ± 1.5 cm/year, respectively), which meets the efficiency criterion for reducing the growth rate to the age norm.

In most pediatric patients in Group 1, noticeable changes in the growth rate during the switch from triptorelin 3.75 mg to triptorelin 11.25 mg therapy were not noted, as presented in Figure 3.

The changes in BA have been estimated. According to the criteria of the efficacy of GnRH agonist therapy, BA progression is acceptable for no more than 1 year of treatment. In Group 1, 8 out of 10 patients showed no pathological progression of BA. In the group of patients starting with triptorelin 11.25 mg, the BA indicators stabilized in 7 out of 10 pediatric patients over a year of follow-up.

Basal levels of LH 1–3 days before the injection of triptorelin 11.25 mg in most patients of Group 2 were within 0.47 ± 0.38 mIU/mL. In six out of eight patients, the E2 level was initially increased (39.4 ± 17.2 pg/mL). During the course of triptorelin 11.25 mg therapy, a significant decrease in the basal level of E2 was established (6.05 ± 2.85 pg/mL; $p \leq 0.001$).

In one patient with an initially normal indicator of E2, the LH level was increased (7.49 mIU/mL), and after 6 months of therapy, the basal levels of LH and E2 were 0.8 mIU/mL and 4.2 pg/mL, respectively.

In another patient with initially normal levels of LH (0.58 mIU/mL) and E2 (5 pg/mL), the stimulated LH level was 25 mIU/L. During the course of therapy, a regression of secondary sexual characteristics occurred. After 6 months of treatment, the E2 and LH levels were less than 5 pg/mL and 0.28 mIU/mL, respectively.

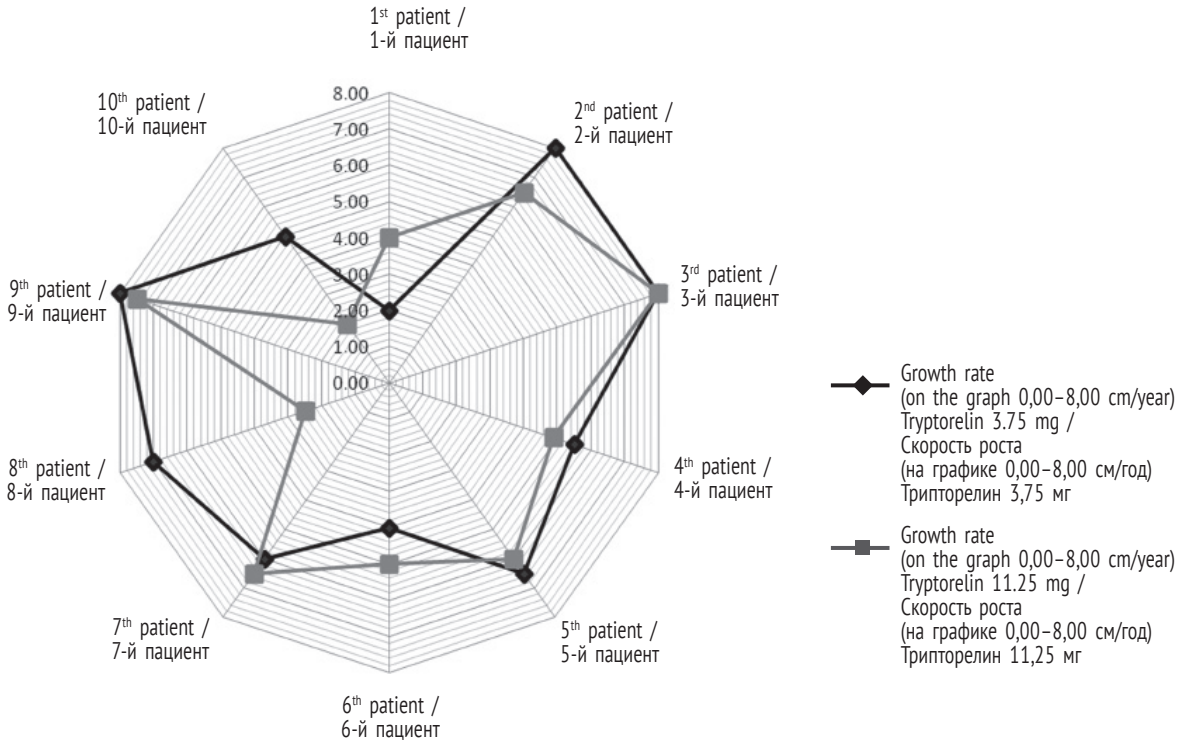

Fig. 3. Growth rate (cm/year) in the treatment of Tryptorelin at a dose of 3.75 mg and 11.25 mg

Рис. 3. Скорость роста (см/год) при лечении Трипторелином в дозе 3,75 и 11,25 мг

According to the literature, a basal LH level of less than 0.3 mIU/mL indicates the efficacy of therapy with prolonged-acting GnRH agonist drugs [6].

Since there was no progression of BA and the size of the uterus decreased with the intake of triptorelin 11.25 mg therapy, there was no need for a second stimulation test.

A significant decrease was noted in the testosterone levels of two boys from 5.14 to 0.025 ng/mL and from 86.9 to 0.5 ng/mL after 6 months of treatment with triptorelin 11.25 mg.

A reduction in testicle size in boys from 12 to 8 cm^3 and a decrease in uterus length in girls from 39.9 ± 6.2 to 34.2 ± 4.4 mm after 12 months of therapy with triptorelin 11.25 mg should be noted.

In Group 1 (patients with idiopathic CPP), the length of the uterus during the triptorelin 3.75 mg therapy averaged 28 ± 7.7 mm, and after 6–12 months of treatment with triptorelin 11.25 mg, the uterine body length indicators were within 33.9 ± 5.1 mm. According to the US of the pelvic organs, two girls had an increase in uterine length by 12 and 9 mm, although the average uterine length in the study group did not exceed 34 mm, which indicated the absence of hormonal stimulation [6].

In case of puberty progression, despite the therapy performed, international guidelines recommend transfer to injections of GnRH agonist drugs at a dose of 3.75 mg once a month and, in the absence of a therapeutic effect, increase in the dose by two times to 7.5 mg [6]. In the Russian clinical guidelines, in case of insufficient suppression of the secretion of gonadotropins, the possibility of an increase in the dose of the drug by two times or reduction in the interval between injections to 21 days is indicated [3].

CONCLUSIONS

Triptorelin 11.25 mg suppresses effectively the secretion of gonadotropin and sex steroid hormones, levels the accelerated skeleton maturation, and determines the prevention of short stature in the long-term prognosis.

Monitoring the follow-up of CPP patients revealed comparable efficacy of treatment with 3.75 and 11.25 mg long-acting GnRH agonists. Moreover, the decrease in the number of injections when using the drug with a duration of action of 3 months has a beneficial effect on the mental and emotional state of a child and can be recommended if rarer injections are required.

REFERENCES

1. Башнина Е.Б., Корытко Т.Е. Отдаленные результаты лечения гонадотропинзависимого преждевременного полового развития аналогами люлиберина // Лечащий врач. – 2013. – № 11. – С. 40–42. [Bashnina EB, Korytko TE. Long-term effects of luteinizing hormone-releasing hormone analogues treatment in patients with gonadotrophin-dependent precocious puberty. *Practitioner*. 2013;(11):40-42. (In Russ.)]
2. Болмасова А.В., Карева М.А., Орлова Е.М. Особенности течения, диагностики и терапии детей с преждевременным половым развитием при гипоталамической гамартоме и идиопатической форме // Проблемы эндокринологии. – 2012. – Т. 58. – № 1. – С. 17–22. [Bolmasova AV, Kareva MA, Orlova EM. Peculiarities of the clinical course, diagnostics, and therapy of premature sexual development in the children presenting with its idiopathic form and with hypothalamic hamartoma. *Problems of endocrinology*. 2012;58(1):17-22. (In Russ.)]
3. Федеральные клинические рекомендации (протоколы) по ведению детей Ф32 с эндокринными заболеваниями [интернет] / под ред. И.И. Дедова, В.А. Петерковой. – М.: Практика, 2014. – С. 277–294. [Federal clinical guidelines (protocols) for the management of children with endocrine diseases [internet]. Ed. by I.I. Dedov, V.A. Peterkova. Moscow: Practica; 2014. P. 277–294. (In Russ.)]. Доступно по: http://nauka.x-pdf.ru/17raznoe/41649-11-federalnie-klinicheskie-rekomendacii-protokoli-vedeniyu-detey-f32-endokrinnimi-zabolevaniyami-pod-red-dedova-peterko.php. Ссылка активна на 12.08.2019.
4. Эндокринные заболевания у детей и подростков: руководство для врачей / под ред. Е.Б. Башниной. – М.: ГЭОТАР-Медиа, 2017. – 411 с. [Endocrine diseases in children and adolescents: a guide for doctors. Ed. by E.B. Bashnina. Moscow: GEOTAR-Media; 2017. 411 p. (In Russ.)]
5. Arrigo T, Cisternino M, Galluzzi F, et al. Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. *Eur J Endocrinol*. 1999;141(2):140-144. https://doi.org/10.1530/eje.0.1410140.
6. Brito VN, Spinola-Castro AM, Kochi C, et al. Central precocious puberty: revisiting the diagnosis and therapeutic management. *Arch Endocrinol Metab*. 2016;60(2):163-172. https://doi.org/10.1590/2359-3997000000144.
7. Carel JC, Blumberg J, Symour C, et al. Three-month sustained release triptorelin (11.25mg) in the treatment of central precocious puberty. *Eur J Endocrinol*. 2006;154(1):199-124. https://doi.org/10.1530/eje.1.02056.
8. Chiocca E, Dati E, Baroncelli GI, et al. Central precocious puberty: treatment with triptorelin 11.25 mg. *Scientific World Journal*. 2012;2012:583751. https://doi.org/10.1100/2012/583751.

9. Durand A, Tauber M, Patel B, Dutailly P. Meta-analysis of paediatric patients with central precocious puberty treated with intramuscular triptorelin 11.25 mg 3-month prolonged-release formulation. *Horm Res Paediatr*. 2017;87(4):224-232. https://doi.org/10.1159/000456545.
10. Harrington J, Palmert MR, Hamilton J. Use of local data to enhance uptake of published recommendations: an example from the diagnostic evaluation of precocious puberty. *Arch Dis Child*. 2014;99(1):15-20. https://doi.org/10.1136/archdischild-2013-304414.
11. Swaenepoel C, Chaussain JL, Roger M. Long-term results of long-acting luteinizing-hormone-releasing hormone agonist in central precocious puberty. *Horm Res*. 1991;36(3-4):126-130. https://doi.org/10.1159/000182145.
12. Zenaty D, Blumberg J, Liyanage N, et al. A 6-month trial of the efficacy and safety of triptorelin pamoate (11.25 mg) every 3 months in children with precocious puberty: a retrospective comparison with triptorelin acetate. *Horm Res Paediatr*. 2016;86(3):188-195. https://doi.org/10.1159/000448840.

◆ Information about the authors

Olga V. Lagno — MD, PhD, Associate Professor, Department of Propaedeutics Childhood Diseases with a Course of General Care. St. Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: olga1526@yandex.ru.

Mariia E. Turkunova — Postgraduate Student, Department of Pediatrics, Endocrinology and Abilitologii AF and DPO. St. Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: 89650505452@mail.ru.

Elena B. Bashnina — MD, PhD, Dr Med Sci, Professor, Department of Endocrinology named after V.G. Baranov. North-Western State Medical University named after I.I. Mechnikov, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: bashnina@mail.ru.

◆ Информация об авторах

Ольга Васильевна Лагно — канд. мед. наук, доцент, кафедра пропедевтики детских болезней с курсом общего ухода за детьми. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: olga1526@yandex.ru.

Мария Евгеньевна Туркунова — аспирант, кафедра педиатрии, эндокринологии и абилитологии ФП и ДПО. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: 89650505452@mail.ru.

Елена Борисовна Башнина — д-р мед. наук, профессор, кафедра эндокринологии им. акад. В.Г. Баранова. ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Минздрава России, Санкт-Петербург. E-mail: bashnina@mail.ru.