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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

CLINICAL CHARACTERISTICS OF GENERAL AND GENITAL INFANTILISM IN GIRLS IN THE EARLY REPRODUCTIVE PERIOD IN BAKU

Speciality:	3215.01 – Obstetrics and gynecology
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GENERAL CHARACTERISTICS OF THE WORK

Relevance and development of research. Protection and maintenance of female reproductive function is one of the actual problems of modern gynecology. It should be noted that among the causes of female reproductive dysfunction along with various gynecological and endocrinological diseases, sexual infantilism, primary and secondary hypogonadism, are comes to the fore. It has great medical and social importance in the increase of infertile marriages[1].

The role of neuroendocrine regulation is important for proper formation of physical and sexual development in girls. It is known that an increase in estradiol secretion is one of the important conditions for the development of the mammary glands, internal and external genital organs, the formation of the body structure in the female type, and the occurrence of cyclical changes in the endometrium. Low quality of life, psychological stress, increased physical and mental overload and unbalanced nutrition, hereditary predisposition are considered the etiological causes for hypothalamic disorder. This leads to hypogonadotropic hypogonadism in adolescent girls[2].

As a result, neuroendocrine disorders are considered the main factor for the emergence of genital infantilism. Studies conducted in recent years emphasize that hypothalamic dysfunction occurs not only during a decrease in body weight, but also due to unbalanced nutrition. The mentioned leads to a violation of neuroendocrine regulation in girls, as a result of which genital infantilism occurs[3].

In the last 10 years, a violation of the synchronous relationship between anthropometric parameters and menarche has been observed

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[1] Axundova N.E. Cinsi yetişkənlik dövründə hiperandrogeniya sindromu olan qızlarda vitamin D və karbohidrat mübadiləsinin dəyişmə xüsusiyyətləri / N.E.Axundova, A.A.Talıblı, E.M.Əliyeva [və b.] // Azərbaycan Tibb Jurnalı, – 2020, №1, – s. 119-123.

[2] Rosenfield R.L., Ehrmann D.A., Littlejohn E.E. Adolescent polycystic ovary syndrome due to functional ovarian hyperandrogenism persists into adulthood // J. Clin. Endocrinol. Metab., – 2015, vol.100, №4, – p.1537-1543.

[3] Пузикова О.З. Влияние умеренной умственной нагрузки на уровень андрогенов крови у девочек-подростков с синдромом гиперандрогении / О.З. Пузикова, А.В. Московкина, В.Ф. Беженарь [и др.] // Ж. Совр. пробл. науки и образования, – 2019, №4, – с. 24-30.

in girls. This is a certain disturbance in the formation of the female organism, as a result of which the required level of somatic development is not observed during the period when the first menstruation occurs. This case is considered one of the causes of reproductive dysfunction, as well as in 75% of cases of infertile marriage.

The basis of hormonal disorders in women in the reproductive period is laid from childhood and adolescence and often begins with the delay of sexual development in 13-18-year-old girls[4].

According to modern studies, the constitutional form of a delay of sexual development has been determined in girls with a delay of physical development. Against the background of regular sexual intercourse in these women, 18% became pregnant at the end of the first year of marriage, 34% without treatment in the second year, and 17% after hormonal treatment. In the anamnesis, spontaneous miscarriages up to 16 weeks were 38%, extrauterine pregnancies was 6%, and medical abortions were 4%[5].

Genital infantilism is complicated by complicated obstetric anamnesis, chronic placental insufficiency, intrauterine hypoxia of the fetus. In these women, the threat of pregnancy deterioration was 54%, the birth of a low body weight fetus was 86%, chronic placental insufficiency was 61%, chronic endometritis was 17%, inflammatory diseases of small pelvic organs were 17%, hypertensive conditions during pregnancy were 56%, anatomical narrow pelvis was found in 48%. All this ultimately determines the risk of perinatal complications[6].

Among women with genital infantilism, premature births were 6%, premature discharge of amniotic fluid was 22%, intrauterine

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[4] Белик С.Н. Место синдрома хронической усталости среди факторов риска нарушения репродуктивного потенциала молодежи / С.Н. Белик, И.В. Подгорный, Ю.В. Можинская [и др.] // Сборник конференции НИЦ Социосфера, – 2016, №23, – с. 44-47.

[5] Саякова А.Т., Бейшенбиева Г.Дж., Исакова Ж.К. Пубертатный период как период становления репродуктивной системы женщины (обзор литературы) // Web of Scolar, – 2018, vol.2, №5 (23), – p. 21-27.

[6] Bozzola M. Delayed puberty versus hypogonadism: a challenge for the pediatrician / M. Bozzola, E. Bozzola, C. Montalbano [et al.] // J.Annals of Pediatric Endocrinology and Metabolism, – 2018, №23, – p. 57-61.

acute hypoxia of the fetus was 42%, anomalies of childbearing activity were 32%, premature partial rupture of the normally located pair was 8%. Apparently, among these women, anomalies of birth activity are 32% birth trauma is 43% more common. Anemia in 42%, endometritis in 14%, and subinvolution of the uterus in 21% are among the pathologies of the menstrual cycle [7].

In modern studies, there is no information on the assessment of reproductive potential in girls with general infantilism, pathologies that can occur during pregnancy, childbirth, especially in women of reproductive age. The problem of infantilism is of great social and medical importance. Until now, there has been no single effective approach to its diagnosis, as well as to the treatment of patients presenting with this problem. The study of infantilism in adolescents can play an important role in solving a number of problems.

Thus, as mentioned, the study of the clinical-diagnostic features of general and genital infantilism in adolescent and young girls in the early reproductive period is of significant scientific-experimental interest and creates the need for more detailed research. Taking into account the relevance of the problem, the goal was set.

The purpose of the research.

The aim of the study was to study the clinical features of general (hypogonadotropic hypogonadism) and genital infantilism (hyper-, normogonadotropic hypogonadism) in girls in the early reproductive period.

Tasks of the study:

1. Determination of the frequency of occurrence of general and genital infantilism in girls in the early reproductive period.

2. Study of the features of physical and sexual development in girls with general and genital infantilism in the early reproductive period.

3. Study of echographic indicators of reproductive organs in girls with general (hypogonadotropic hypogonadism) and genital infantilism (hyper-, normogonadotropic hypogonadism) in the early

[7] Dwyer A.A., Raivio T., Pitteloud N. Management of endocrine disease: Reversible hypogonadotropic hypogonadism // Eur. J. Endocrinol, –2016, №174, – p. 267-274.

reproductive period.

4. Study of characteristics of hormonal changes in girls with general and genital infantilism in the early reproductive period.

5. Features of the change in carbohydrate metabolism in girls with general and genital infantilism in the early reproductive period.

6. Analysis of the results of genetic examination in girls with general and genital infantilism in the early reproductive period.

7. Study of the features of the change of vitamin $D_3 25(OH)_2$ in girls with general and genital infantilism in the early reproductive period.

Research methods.

Clinical, hormonal, biochemical, functional, genetic examinations were performed on girls with general (hypogonadotropic hypogonadism) and genital infantilism (hyper-, normogonadotropic hypogonadism) in the early reproductive period. In the clinical examination, the anthropometric parameters of the young girls included in the main and comparative groups were determined, including height, weight, mass index, chest circumference (CC), the distance of the arms in the unfolded position (AUP), lower limb length (LLL), shoulder width. (SW), external dimensions of the pelvis were measured.

The main provisions defended:

- From the causes of general infantilism (hypogonadotropic hypogonadism) in the early reproductive period, hyperprolactinemia, hypothyroidism, physical tension associated with sport, chronic stress are noted. The normogonadotropic hypogonadism form of genital infantilism reveals itself with high frequency abnormalities of various degrees of uterine development, while the hypergonadotropic hypogonadism form of genital infantilism presents with pure and typical forms of gonad dysgenesis.
- In the early reproductive period, general infantilism (hypogonadotropic hypogonadism) reveals itself with retardation of physical and sexual development, mild hirsutism, a noticeable decrease in the echographic indicators of the uterus and ovaries, a decrease in follicul-stimulating hormone, luteinizing hormone,

estradiol, an increase in prolactin and free thyroxine, with a tendency to insulin resistance, a lack of vitamin D.

- In girls with normogonadotropic hypogonadism form of genital infantilism, it reveals itself with a decrease in the exographic indicators of the length and width of the uterus, with hyperprolactinemia, with an increase in testosterone, with a decrease in the level of estradiol, and with a deficiency of vitamin D.
- Despite the fact that physical development in the form of hypergonadotropic hypogonadism of genital infantilism is suitable for practically healthy girls, it reveals itself with underdevelopment of the mammary glands, with an increase armpit and inguinal hairiness, with medium-severe hirsutism, a statistically honest decrease in the echographic indicators of the uterus and both ovaries, follicul-stimulating hormone, luteinizing hormone, prolactin, thyrostimulating hormone, dehydroepiandrosterone-sulfate, a statistically honest increase in total testosterone, and a decrease in estradiol, a tendency to insulin resistance, and a lack of vitamin D.

Scientific novelty of research work.

As a result of the research, the frequency of occurrence of general and genital infantilism was studied. For the first time, among the causes of general infantilism in the early reproductive period, hyperprolactinemia, hypothyroidism, physical strain associated with sports, and chronic stress were noted. The main cause of genital infantilism (normogonadotropic hypogonadism) is hypoplasia of the uterus of various degrees, and in the form of hypergonadotropic hypogonadism, a pure and typical form of gonadal dysgenesis is noted.

It was determined that general infantilism in the early reproductive period reveals itself with the retardation of physical and sexual development, with the decrease in follicul-stimulating hormone, luteinizing hormone, estradiol, with an increase of prolactin and free thyroxine, with a decrease in the exographic indicators of the uterus and ovaries less than the indicators of practically healthy girls, with a tendency to insulin resistance, reveals with a deficiency of vitamin $D_3 25(OH)_2$. The indicators of physical and sexual

development in girls with genital infantilism (normogonadotropic hypogonadism) in the early reproductive period corresponded to the indicators of practically healthy girls. In the conducted research, in girls with hypergonadotropic hypogonadism form of genital infantilism, despite the fact that the physical development corresponds to the indicators of practically healthy girls, underdevelopment of mammary glands, increase of armpit and inguinal hairiness was observed. This reveals itself with medium-severe hirsutism.

As a result of the conducted research, a tendency to insulin resistance was revealed in girls with general and genital infantilism (hypergonadotropic hypogonadism). This also allows insulin to be absorbed on an empty stomach, reveals itself an increase in the HOMA index, and a decrease in the CARO index. It has been established that in girls with general and genital infantilism, the pathology of the kariotype is found with a frequency of 9.2% and is identified in girls with genital infantilism. It was determined that 90.8% of girls with general and genital infantilism had a normal karyotype, 3.9% had Shershevsky-Turner syndrome (45X0), and 5.3% had Swayer syndrome (46XY). As a result of the conducted research, it was determined that in adolescents and young girls with general and genital infantilism, vitamin $D_3 25(OH)_2$ is noted against the background of deficiency.

Theoretical and practical significance of research work.

As a result of the conducted research, it was determined that the risk factors of general and genital infantilism include retardation of girls development in the womb, premature births, chronic and somatic diseases, chronic inflammatory diseases of the reproductive organs, alimentary nutritional disorders, and chronic stress.

Taking into account the clinical-diagnostic features of general and genital infantilism, the detection, examination and pathogenetic treatment of girls with retardation of physical and sexual development during puberty is appropriate, which will affect the future life indicators of girls.

Approbation and application of research work.

The main provisions of the dissertation was reported in The First International Scientific-Practical Virtual Conference "Clinical

Endocrinology and Endocrine System Disease": Prognosis, Achievement and Challenges. (Izmir, TURKEY 2021) conference.

It was reported at the 10th scientific-practical conference of residents (Baku-2022) dedicated to the 99th anniversary of the birth of the national leader of the Azerbaijani people, Heydar Aliyev. The materials of the dissertation were reported and discussed at the meeting of the Department of I Obstetrics and Gynecology of the Azerbaijan Medical University (27.04.2022, protocol No. 9), and at the scientific seminar of the ED 2.06 Dissertation Council operating under the Azerbaijan Medical University (29.06.22, protocol No. 17).

14 scientific works have been published on the subject of the dissertation. Among them, 11 articles, 3 theses, including 3 articles and 1 thesis were published in a foreign publishing houses.

The results of the research were applied in the educational process of the I Department of Obstetrics and Gynecology of AMU, as well as in the clinical practice of the Educational Surgery Clinic of AMU.

The organization.

Dissertation work was performed at the I Department of Obstetrics and Gynecology of the Azerbaijan Medical University.

The structure and volume of the dissertation.

The dissertation is written on 156 computer pages, consists of an introduction and 3 chapters:

a literature review, material and examination methods, results of a personal research, conclusion, conclusions and practical recommendations.

The dissertation contains 47 tables, 4 charts and 6 images. The list of literature includes 220 sources.

The volume of the dissertation consists of 163217 characters.

MATERIALS AND METHODS OF RESEARCH

According to the purpose, 150 adolescent and young girls with general and genital infantilism were examined. The examination included clinical, functional, hormonal, biochemical, genetic studies (main group).

The comparison group included 30 practically healthy adolescent and young girls in the early reproductive period.

The age of teenagers and young girls included in the main group was 19.56±0.13 (17-22). The mother's age at birth of the examined girls was 28.1±0.33, and the father's age was 32.18±0.36. The weight of young and teenage girls at birth was 3082.4±53.1 (1700-5500) g, and their height was 48.9±0.21 (42-55) cm. 18 out of 150 born girls (12%) were large fetuses (≥4000 g).

Thus, the examined adolescent and young girls had large fetuses at birth. In the anamnesis of the examined girls, it was determined that 38 (25.3%) girls were born prematurely. 16 (10.7%) of them weighed less than 2500 grams, 22 (14.6%) weighed more than 2500 grams. Signs of hypotrophy were determined in 31 (20.7%) of 150 examined girls at birth.

In adolescents and young girls with general and genital infantilism frequency of children's infectious diseases (14.6%), including measles, chicken pox, rubella, infectious mumps, acute respiratory viral infection (10.3%), chronic somatic diseases (18, 7%), anemia (10.4%), neurosis and neurasthenia (6.5%) were assigned.With relatively little frequency, hyperprolactinemia (4.3%), thyroid gland diseases (4.53%), myopia (3.7%), rheumatism (3.4%), vegeto-vascular dystonia (3.5%), obesity (3.2%) were assigned.

Chronic somatic diseases predominate in adolescents and young girls with general and genital infantilism. In the study, the menarche was determined at the age of 15.95±0.12, the duration of the menstrual cycle was 51.66±1.54, and the duration of continuation of the menstrual cycle was 5.24±0.16 days.

In girls with general and genital infantilism in the early reproductive period, amenorrhea with a high frequency was determined 36.8%. Of these, secondary amenorrhea prevails (25.8%). Oligomenorrhoea (25.9%) and algodysmenorrhoea (25.4%) are prescribed with high frequency in the examined girls.

Menstruation and uncomplicated progress of menstrual cycle is noted in 4%. The systolic arterial pressure of teenagers and young girls included in the main group was 109.34±0.91, diastolic BP 75.58±0.58, pulse 78.4±0.34 beats/1 min.

In the conducted research, 30 practically healthy girls in the early reproductive period were examined.

The age of the practically healthy girls examined was 19.64±0.28 (18-21), menarche was 14.73±0.38 years old, menstrual cycle was 30.73±1.33, menstrual period was 5.55±0.31 days..

Clinical examination: Development of mammary glands, hairiness in the armpit and inguinal area was performed according to the Tanner scale.

The Ferriman-Gallway scale was used to find out the degree of hairiness in the examined girls.

During the study, the amount of Folliculstimulating hormone (FSH), luteinizing hormone (LH), thyroostimulating hormone (TSH), prolactin (Prl), estradiol (E_2), total testosterone (T_{total}), dehydroepiandrosterone-sulfate (DHEA-S), cortisol (K), 17-hydroxyprogesterone (17-OHP), free thyroxine (T_4) hormones were determined in the blood serum:

Biochemical examinations. In all examined girls, indicators of carbohydrate metabolism – glucose, insulin were measured on an empty stomach, HOMA and CARO indexes were determined.

Determination of vitamin D in blood serum. The test method was used during the research. At this time, 75 μl of centrifuged blood serum is taken with a dispenser and buffer A and buffer B are mixed on it in stages. 75 μl from obtained content is taken and placed into the thermostat (37°C) for 10 minutes. Then buffer C (75 μl) is mixed on the obtained content and placed into the thermostat again for 5 minutes. At the last stage, 75 μl from obtained content were taken and it is poured into the test which designed for vitamin D., the test is inserted into the "Finecare" device within 15 minutes.

Ultrasound examination. During the ultrasound, the length, width, front-back size of the uterus, the length, width, thickness, volume of each 2 ovaries, as well as the thickness of the endometrium (M-echo) were determined:

Thickness, width, length of both lobes of thyroid gland, exographic dimensions of Isthmus, integral indicator of volume were determined.

Genetic examination. Karyotype analysis was performed by the normal classical method. Chromosomes obtained from the transplantation of peripheral blood were analyzed by GTG staining

method and 450-500 size banding, and 20 metaphases were observed. The operation consists of several stages. After 4-5 runs, it was done with a Nikon Eclipse Ni microscope.

Statistical processing of clinical material. The sign method and the Manna-Whitney-criterion were applied in the statistical analysis of the research.

RESULTS OF PERSONAL RESEARCH

Frequency of occurrence of general and genital infantilism in girls of the early reproductive period

The frequency of occurrence of hypogonadotropic and hypergonadotropic hypogonadism was studied as a result of clinical, functional, biochemical, genetic examinations in adolescent and young girls in the early reproductive period (image 1).

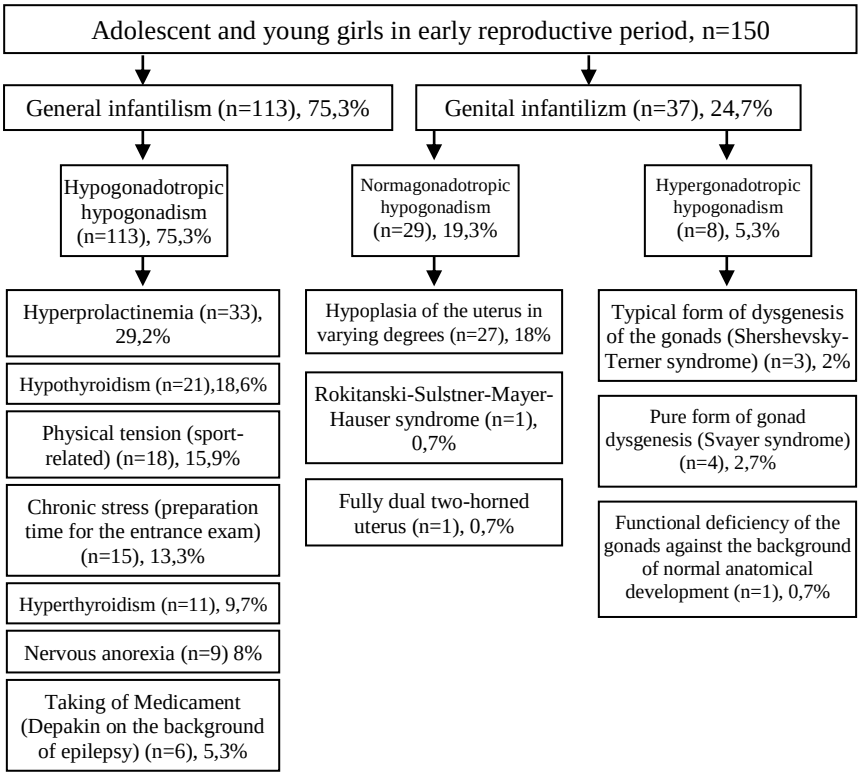

Image 1. Incidence of general and genital infantilism in adolescent and young girls during the early reproductive period

Characteristics of physical development in girls with general and genital infantilism in the early reproductive period

Anthropometric measurements of physical development of adolescents and young girls with general infantilism were determined in the conducted research. These measurements include height, weight, distance of arms in open position (AUP), shoulder width (SW), lower limb length (LLL), chest circumference (CC), and external measurements of the large pelvis, including Distantia spinarum, Distantia cristarum, Distantia trochanterica, Conjugata externa.

The obtained results were compared with similar indicators of practically healthy adolescents and young girls in the early reproductive period (table 1).

Table 1.

Characteristics of physical development in adolescent and young girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period

Indicators	Examination groups		P
	General infantilism (hypogonadotropic hypogonadism) (n=113)	Practically healthy girls (n=30)	
Height, m	1.46±0.06 (1.31-1.70)	1.65±0.02 (1.53-1.71)	<0.05
Weight, kg	51.54±0.19 (40-68)	59.2±0.67 (48-79)	<0.05
AUP, m	1.51±0.02 (1.46-1.75)	1.79±0.08 (1.62-1.89)	<0.05
Shoulder width, cm	34.25±0.12 (30-40)	38.0±0.16 (33-48)	<0.05
LLL, cm	85.1±0.13 (82-90)	93.14±0.18 (78-102)	<0.05
Chest circumference, cm	73.56±0.12 (50-81)	94.0±0.14 (90-106)	<0.05
Distantia spinarum, cm	22.36±0.16 (18-23)	24.73±0.14 (24-25)	<0.05
Distantia cristarum, cm	24.61±0.12 (22-26)	26.55±0.09 (25-28)	<0.05
Distantia trochanterica, cm	27.3±0.17 (22-29)	29.2±0.13 (27-30)	<0.05
Conjugata externa, cm	17.0±0.06 (15-19)	19.0±0.06 (18-20)	<0.05

In adolescents and young girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period, all anthropometric measurements reflecting physical development, including height, weight, AUP, SW, CC, external dimensions of the pelvis, were significantly less than similar sizes of practically healthy girls (P<0.05).

Characteristics of physical development in adolescent and young girls with genital infantilism (hyper-, normogonadotropic - hypogonadism) were studied (table 2).

Table 2.

Characteristics of physical development in adolescent and young girls with genital infantilism in the early reproductive period

Indicators	Examination groups		P
	Genital infantilism (n=37)	Practically healthy girlsn=30	
Length, m	1.63±0.08 (1.46-1.82)	1.65±0.02 (1.53-1.71)	>0.05
Weight, kg	58.1±0.14 (46-78)	59.2±0.67 (48-79)	>0.05
AUP, m	1.76±0.09 (1.69-1.91)	1.79±0.08 (1.62-1.89)	>0.05
Shoulder width, cm	38.2±0.04 (33-51)	38.0±0.16 (33-48)	>0.05
LLL, cm	97.2±0.11 (81-100)	93.14±0.18 (78-102)	<0.05
Chest circumference, cm	93.6±0.11 (60-100)	94.0±0.14 (90-106)	>0.05
Distantia spinarum, sm	25.8±0.06 (19-25)	24.73±0.14 (24-25)	>0.05
Distantia cristarum, cm	26.8±0.12 (26-31)	26.55±0.09 (25-28)	>0.05
Distantia trochanterica, cm	30.2±0.17 (23-31)	29.2±0.13 (27-30)	>0.05
Conjugata externa, sm	19.2±0.13 (18-21)	19.0±0.06 (18-20)	>0.05

In adolescent and young girls with genital infantilism in the early reproductive period, the indicator of LLL was statistically significantly higher than that of practically healthy girls (P<0.05). Other anthropometric indicators corresponded to the measurements of practically healthy girls (P>0.05).

Characteristics of sexual development in girls with general and genital infantilism in the early reproductive period

In the conducted study, the stages of development of secondary sexual characteristics were evaluated according to the J.Tanner scale in girls with general (hypogonadotropic hypogonadism) and genital (hyper-, normogonadotropic hypogonadism) infantilism, and the results were compared with the indicators of practically healthy girls. It has been determined that young and adolescent girls with general infantilism (hypogonadotropic hypogonadism) secondary sexual characteristics are noticeably delayed in development, and the hirsut figure reflects mild hirsutism.

Characteristics of the development of secondary sexual signs in adolescent and young girls with genital infantilism (normogenotropic hypogonadism) are presented in chart 1.

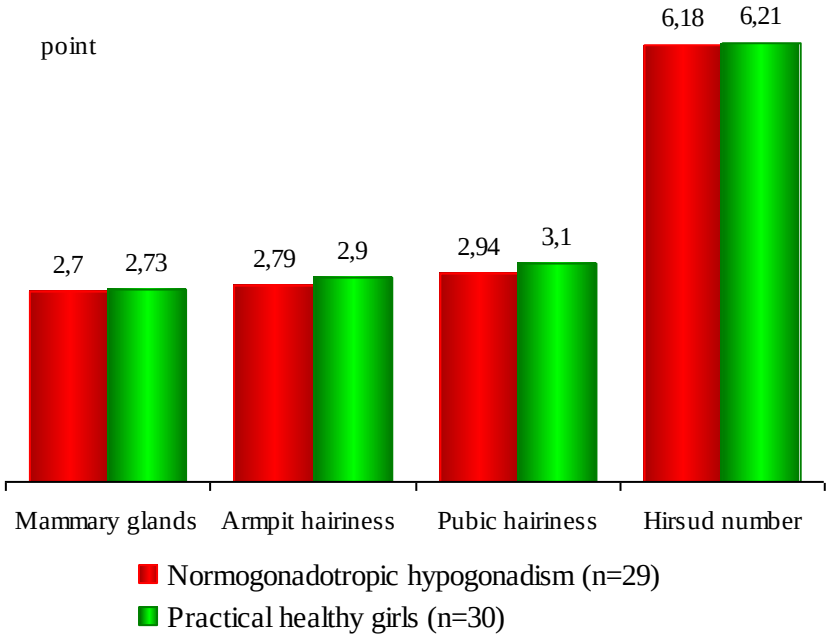

Chart 1. Characteristics of the development of secondary sexual characteristics in adolescent and young girls with genital infantilism (normogonadotropic hypogonadism) in the early reproductive period

Secondary sexual signs and hirsud figure in girls with genital infantilism (normogonadotropic hypogonadism) do not differ from similar indicators of practically healthy girls (P>0.05).

Thus, the development of secondary sexual signs in adolescent and young girls with genital infantilism (normogonadotropic - hypogonadism) was relevant to the development of practically healthy girls.

Characteristics of the development of secondary sexual signs in adolescent and young girls with genital infantilism (hypergonadotropic hypogonadism) in the early reproductive period were studied.

In girls with genital infantilism (hypergonadotropic hypogonadism), underdevelopment of mammary glands, increase of armpit and inguinal hairiness were determined (P<0.05). Medium-severe form of hirsutism was found in these girls.

In the conducted research, underdevelopment of mammary glands was observed in adolescent and young girls with hypogonadotropic and hypergonadotropic hypogonadism. Armpit hair growth had less in adolescent and young girls with hypogonadotropic hypogonadism, but significantly more in adolescent and young girls with hypergonadotropic hypogonadism. In adolescent and young girls with hypo and normogonadotrope - hypogonadism, pubic hair growth does not differ from practically healthy girls, while in hypergonadotropic hypogonadism, a statistically significant increase was observed.

Thus, in young and adolescent girls with general infantilism (hypogonadotropic hypogonadism), secondary sexual signs have significant delay in development, and a hirsut figure reflects mild hirsutism.

The development of secondary sexual signs in girls with genital infantilism (normogonadotropic hypogonadism) was consistent with the development of practically healthy girls. In girls with hypergonadotropic hypogonadism form of genital infantilism, underdevelopment of mammary glands, an increase in armpit and inguinal hair are determine (P<0.05), medium-severe form of hirsutism was discovered in these girls.

Results of echographic indicators of reproductive organs of girls with general infantilism in the early reproductive period

In the conducted research ultrasound, examination of the reproductive organs with a transabdominal transmitter carried out in adolescent and young girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period.

It was determined that the length of the uterus in adolescent and young girls with general infantilism (hypogonadotropic hypogonadism) was (3.9±0.12) cm, width (3.0±0.15) cm, front-back size (2.3±0,14) cm, the thickness of the endometrium (0.3±0.02) cm was statistically significantly lower than the physiological indicators ($P<0.05$). It should be noted that in these girls who were examined, the length, width, thickness, volume of the ovaries were noticeably lower ($P<0.05$).

Pathogenetic treatment was carried out in girls with hypogonadotropic hypogonadism for 6 Months-1 year. This treatment consisted of hormonal and non-hormonal correction. The main goal of hormonal treatment was the restoration of the initial estrogen deficiency.

Non-hormonal treatment included food regulation, group B, E, C vitamin therapy, adenoisotriphosphate acid (AA), physiotherapeutic treatments, needle reflexotherapy sessions, balneotherapy, therapeutic gymnastics, gynecological massage.

The main principles of treatment of general infantilism (hypogonadotropic hypogonadism):

- Restoration of the deficiency of female sex hormones
- Stimulation of physical development during puberty
- Development of secondary sexual characteristics
- Activation of osteosynthesis processes
- Solution of medical and social problems
- Creation of pregnancy and the ability to bear children.

After clinical, functional and radiological examination of adolescents and young girls with hyperprolactinemia (n=33) in the early reproductive period, it was determined that the main causes of hyperprolactinemia were functional (idiopathic) hyperprolactinemia (n=29) 87.9% and microprolactinoma (n=4) 12.1%. All patients were

prescribed the III generation dofaminergic drug dostinex (cabergoline). This drug was prescribed in a dose of 0.5-1 mg for 6-12 months. In the dynamics of treatment, physical and sexual development, prolactin level were evaluated. When the level of prolactin decreased to physiological indicators, was passed to the II stage of treatment and hormonal therapy was prescribed. A combined estrogen-gestogen preparation has been prescribed to stimulate sexual development. This drug was prescribed Femaston 2/10 containing 2 mg of 17β-estradiol and 10 mg of dydrogesterone. Hormonal treatment continued for 6 months. In the dynamics of treatment, non-hormonal antihomotoxic drugs are also prescribed. Of these preparations, Ovarium Compositum and Hormeel S were used. Antihomotoxic drugs were injected from 3 days to 1, 15 injections intramuscularly, and the effectiveness of the treatment was evaluated after 6 months.

Adolescent and young girls with hypothyroidism (n=21) were prescribed Levothyroxine under the supervision of an endocrinologist. This drug was taken in the amount of 1.6 mcg per 1 kg in the morning on an empty stomach 30 minutes before meals for 3 months. After 3 months, antihomotoxic drugs Ovarium Compositum and Hormeel S 1 ampoule were prescribed 20 intramuscular injections every 3 days and the effectiveness of the treatment was evaluated.

Regardless of the origin of hypogonadotropic hypogonadism, it has become important to take general strengthening measures, diet therapy (increasing or reducing caloric foods according to body weight), reduce physical and mental tension, adjusting the dose of psychotropic drugs and antiepileptic drugs.

Other causes of hypogonadotropic hypogonadism include sport-related physical exertion (n=18) and adolescent and young girls with anorexia nervosa (n=9) pathogenetic treatment was conducted with analogs of QnRh. From this drug, gonadoliberin was injected 1 subcutaneously every 90 minutes in pulse mode. The drug was prescribed for 6 weeks, 2 mg per day, 12 mg per week, 3 nights.

Despite the fact that the echographic indicators of the uterus and ovaries were higher compared to the similar indicators before the

treatment, they were statistically significantly lower than the similar echographic indicators of practically healthy girls (P<0.05).

In adolescent and young girls with general (hypogonadotropic hypogo-nadism) infantilism in the early reproductive period, the echographic indicators of the uterus and ovaries were statistically significantly lower than the echographic indicators of practically healthy girls (P<0.05).

Results of echographic indicators of the reproductive organs of girls with genital infantilism in the early reproductive period

In adolescent and young girls with genital infantilism (hypergonadotropic hypogonadism), echographic indicators of the uterus and both ovaries were significantly lower than the similar indicators of practically healthy girls (P<0.05).

The drug Femaston 2/10 was prescribed to adolescent and young girls with genital infantilism (hypergonadotropic Hypogonadism) by 5.3%, after clinical and laboratory tests for 6 Months-1 year. After this period, a repeated examination was carried out. After the pathogenetic treatment, an increase in echographic indicators of the uterus and both ovaries was observed (P<0.05).

At the same time, these indicators were statistically significantly lower than the indicators of practically healthy girls (P<0.05).

Echographic indicators of the uterus and ovaries were determined in adolescent and young girls with normogonadotropic hypogonadism (n=29) in the early reproductive period.

In adolescent and young girls with normogonadotropic hypogonadism, the length of the uterus was 5.9±0.14 cm, and the width was 5.1±0.11 cm significantly lower than the similar indicators of practically healthy girls (P<0.05).

The front-back size of the uterus was 3.6±0.28 cm, the thickness of the endometrium was 0.61±0.03 cm, and the echographic dimensions of both ovaries did not differ from the echographic indicators of practically healthy girls (P>0.05).

In girls with normogonadotropic hypogonadism, a diagnostic laparoscopy was necessarily performed to study the condition of the

ovaries (hormonally active tumors of the ovaries, anomalous gonads, false hermaphroditism and testicular feminization has been denied) before treatment. At the II stage, estrogen (microfolin, estrophem) and Dufaston were prescribed for 3 months in a minimal dose, or combined oral contraceptive (Yarina) was prescribed to these patients for 21 days, from the 5th to the 26th day of menstruation, for 6 months-1 year. set in the period. Physiotherapy and electroreflexotherapy were prescribed to these girls at the same time. In the dynamics of treatment, features of physical and sexual development with transabdominal transmitter (ultrasound), hormonal, carbohydrate metabolism changes were studied.

In adolescent and young girls with genital infantilism (hypergonadotropic hypogonadism), the echographic indicators of the uterus and both ovaries were statistically significantly lower than the echographic indicators of practically healthy girls.

As a result of pathogenetic treatment, an increase in echographic indicators of the uterus and both ovaries is observed in adolescent and young girls with hypergonadotropic hypogonadism, at the same time these indicators are lower than those of practically healthy girls ($P<0.05$).

In girls with normogonadotropic hypogonadism, the length and width of the uterus were determined statistically significantly lower. Other indicators were adapted to the similar indicators of practically healthy girls.

As a result of the pathogenetic treatment, all sizes of the uterus and echographic indicators of both ovaries did not differ from the sizes of practically healthy girls ($P>0.05$).

Echographic parameters of the thyroid gland in girls with general and genital infantilism during the early reproductive period

In the conducted research, an ultrasound examination of the thyroid gland was performed in 68 girls with general and genital infantilism. The length, width, thickness, volume of the right and left lobes and length of the isthmus were measured in the ultrasound

examination.

Druing the comparison the echographic indicators of the thyroid gland of girls with hypogonadotropic hypogonadism and girls with hypergonadotropic hypogonadism in the early reproductive period, a statistically significant decrease in the length of the right and left lobes, a significant increase in the width and thickness of both lobes, and an increase in the volume of the left lobe were observed ($P<0.05$).

In adolescent and young girls with hypergonadotropic hypogonadism, an increase in the length of the right and left lobe, a significant decrease in width, thickness, and a decrease in the volume of the left lobe were observed ($P<0.05$).

Comparing the echographic indicators of the thyroid gland of girls with normogonadotrope hypogonadism and girls with hypogonadotropic hypogonadism, an increase in the thickness of the right lobe and the length of the left lobe was observed.

Thus, in the hypogonadotropic hypogonadism form of general infantilism, a statistically significant increase in the width and thickness of the right and left lobes of the thyroid gland was observed. This can be associated to hypothy-reodism in 18.6% and hyperthyreodism in 9.7% of the causes of hypogonadotropic hypogonadism.

Features of hormonal changes in girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period, the effectiveness of pathogenetic treatment

In the conducted study, hormones of the hypothalamus-pituitary-thyroid-adrenal gland-ovary were determined in adolescent and young girls with general infantilism (hypogonadotropic hypogonadism) of various origins.

FSH 2.53±0.4 mIU/ml, LH 2.0±0.23 mIU/ml, E_2 28.44±1.1 pg/ml were statistically significantly lower in adolescent and young girls with general infantilism ($P <0.05$). At the same time, the amount of Prl (16.4±0.62 ng/ml) and $_{free}T4$ (1.35±0.04 ng/ml) was significantly higher.

It should be noted that despite an increase in K (143±15.2

ng/ml), TSH (2.16±0.26 mIU/ml), 17-OPH (0.35±0.02 ng/ml), DHEA-S (2.37±0.33 pg/ml), T_{total} (1.13±0.25 ng/ml), significantly did not differ from the similar indicators of practically healthy adolescent girls (P>0.05).

After pathogenetic treatment, the level of hormones in adolescent and young girls with general infantilism (hypogonadotropic hypogonadism) did not differ from the level of hormones in practically healthy girls (P>0.05). This reflects the effectiveness of the treatment.

Features of hormone changes in girls with genital infantilism (hyper-, normogonadotropic hypogonadism) in the early reproductive period, the effectiveness of pathogenetic therapy

In the conducted research, the hormones of the hypothalamus-pituitary-thyroid-adrenal gland-ovary were determined in adolescent and young girls with genital infantilism (hypergonadotropic hypogonadism).

In adolescent and young girls with hypergonadotropic hypogonadism, gonadotropin hormones, including FSH (42.7±4.78 mIU/ml), LH (21.14±1.6 mIU/ml), Prl (20.96±1.32 ng /ml), TSH (3.53±0.51) mIU/ml statistically significantly higher, DHEA-S (2.84±0.35 pg/ml), K (324.9±16.87 ng/ml), T_{total} (3.46±0.5 ng/ml) significantly higher, a small amount of E_2 (28.16±1.71 pg/ml) were observed (P< 0.05).

After the pathogenetic treatment, a statistically significantly decrease in gonadotropin hormones and adrenal gland hormone, and an increase in E_2 were prescribed (P<0.05).

Hormones determined as a result of pathogenetic treatment in adolescent and young girls with genital infantilism (hypergonadotropic hypogonadism) did not differ from similar indicators in practically healthy girls (P>0.05). This reflects the effectiveness of complex hormonal therapy.

In the conducted research, the results of hormones in girls with normogonadotropic hypogonadism in the early reproductive period were determined.

In adolescent and young girls with normogonadotropic

hypogonadism in the early reproductive period, an increase in prolactin and testosterone, and E_2 is at a low level is being observed ($P<0.05$). After pathogenetic treatment the results of hormones were consistent with the results of practically healthy young girls ($P>0.05$).

Features of the change in carbohydrate metabolism in girls with general and genital infantilism in the early reproductive period

In research indicators of carbohydrate metabolism were determined in 45 adolescent and young girls with hypogonadotropic hypogonadism of different origins.

In girls with general infantilism (hypogonadotropic hypogonadism), an inclination to insulininresistency was noted. This reveals itself with a significant increase in the HOMA index (4.21±0.13).

In adolescent and young girls with hypergonadotropic hypogonadism form of genital infantilism, insulin resistance reveals itself with an increase in insulin (19.79±0.76 uIU/ml), HOMA index (4.85±0.36), and a decrease in the CARO coefficient (0.28±0.02).

The results of indicators of carbohydrate metabolism in girls with genital infantilism (normogona-dotropic hypogonadism) in the early reproductive period were measured.

The indicators of carbohydrate metabolism in adolescent and young girls with genital infantilism (normogonadotropic hypogonadism) did not differ from similar indicators of practically healthy girls ($P>0.05$).

Results of genetic examination in girls with general and genital infantilism in the early reproductive period

In the conducted research, a genetic examination was carried out in 76 girls with general and genital infantilism in the early reproductive period.

In the genetic examination the karyotype was determined in the examined girls.

As a result of the research, it was determined that 3 (3.9%) women had Shershevsky-Turner syndrome chromosome structure

45X0, 4 (5.3%) women had a 46XY karyotype syndrome of Swyer , and 69 (90.8%) girl had a normal karyotype.

In this patients, 3 symptoms were determined, including short height, dysgenesis of gonads, and anomalies of various organs. These girls are characterized by bone dysplasia, hypoplasia of the spine, tendency to scoliosis and kyphosis, valgus curvature of the elbows and knee bones.

Micrognathia (small size of the lower jaw), high gothic palate, teeth anomaly were determined. These girls were assigned as having a short wide neck and the presence of a wing-like fold (sphinx neck). At the same time, in these girls, a spaced location of the nipples (hypertelorism), a mold-like thorax was determined.

Two of the three girls had eye abnormalities, including strabismus, nystagmus, epicanthia, and one girl had partial drooping of the eyelid (semitosis). 46XY karyotype was determined as a result of genetic examination in 4 girls. In pure gonadal dysgenesis (Swyer's syndrome), secondary sexual signs, including underdevelopment of the mammary glands, low hairiness in the armpit and inguinal areas, reduction of the echographic dimensions of the uterus in USM, intersex body type, atrophy of the endometrium, underdevelopment of the external genital organs and clitoris is being observed.

In adolescent and young girls with general and genital infantilism, according to genetic research, a normal karyotype was determined in 90.8%, pathology of the karyotype in 9.2%, Shershevsky-Turner syndrome (45XO) in 3.9%, Svayer syndrome (46XY) in 5.3%..

Features of the change in vitamin D in girls with general and genital infantilism during the early reproductive period

Features of the change in vitamin D in adolescent and young girls with general and genital infantilism are presented in table 3.

Deficiency of vitamin D is detected in girls with general (hypogonadotropic hypogonadism) and genital infantilism (hyper,-normogonadotropic hypogonadism). This is important in the pathogenesis of general and genital infantilism in the early

reproductive period.

Table 3.

Features of the change in vit D before treatment in girls with general and genital infantilism in the early reproductive period

Examination groups (n=70)	Before treatment	Comparison group, n=30	P
General infantilism (hypogonadotrope hypogonadism) (n=33), ng/ml	12.02±0.82 (3.79-22.2)	21.6±2.53 (12.53-31.78)	<0.05
Genital infantilism (hypergonadotrope hypogonadism) (n=8), ng/ml	15.27±2.1 (6.27-25)	21.6±2.53 (12.53-31.78)	>0.05
Genital infantilism (normogenotropic hypogonadism) (n=29), ng/ml	14.29±0.87 (3.36-23.3)	21.6±2.53 (12.53-31.78)	<0.05

The effectiveness of pathogenetic treatment in adolescent and young girls with general and genital infantilism reveals itself by a statistically significant increase in vitamin D ($P<0.05$).

Thus, the lack of vitamin D is important in the pathogenesis of general and genital infantilism. As a result of pathogenetic treatment, a statistically significant increase in vitamin D is observed ($P<0.05$).

RESULTS

1. In the early reproductive period, the frequency of occurrence of general infantilism (hypogonadotropic hypogonadism) 75.3%, and the frequency of occurrence of genital infantilism 24.7% is determined. Hyperprolactinemia in 29.2%, hypothyroidism in 18.6%, physical strain related to sports in 15.9%, and chronic stress in 13.3% are among the causes of general infantilism. Among the causes of genital infantilism (normogonadotropic hypogonadism), hypoplasia of the uterus of various degrees is noted in 18% of patients. In the hypergonadotropic hypogonadism form of genital infantilism, a pure

form of gonad's dysgenesis is detected in 2.7%, and a typical form of gonad's dysgenesis in 2% [1,5,12].

2. In height (1.46±0.06 m), weight (51.54±0.19 kg), arm distance in open position (1.51±0.02 m), width of the shoulders (34.25±0.12 cm), the length of the lower limbs (85.1±0.13 cm) and statistically significant decrease in the external dimensions of the pelvis are determined in girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period, which reflects physical developmental delay in girls with general infantilism (hypogonadotropic hypogonadism). The indicators of physical development in girls with genital infantilism (hyper-normogonadotropic hypogonadism) correspond to the indicators of practically healthy girls.

In adolescent and young girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period, from the secondary sexual signs: a noticeable delay in the development of mammary glands, armpit and pubic hair, a hirsud number 8.12±0.13 points is assigned, which reflects mild hirsutism. In girls with genital infantilism (normogonadotropic hypogonadism), the development of secondary sexual signs, the hirsud number 6.18±0.16 points corresponds to the development of practically healthy girls. In girls with genital infantilism (hypergonadotropic hypogonadism), underdevelopment of mammary glands, an increase in armpit and pubic hair is prescribed. The hirsud number is 15.9±0.18 points, which reflects medium-severe hirsutism [2,10,14].

3. In the early reproductive period, in the general (hypogonadotropic hypogonadism) and hypergonadotropic hypogonadism form of genital infantilism, the echographic indicators of the uterus and both ovaries are significantly lower than the echographic indicators of practically healthy girls.

In girls with normogonadotrope hypogonadism form of genital infantilism, the echographic indicators of the length and width of the uterus are statistically honestly lower than the similar indicators of healthy girls, the front-back size of the uterus, the thickness of the endometrium and the echographic indicators of both ovaries correspond to the echographic indicators of practically healthy girls

[3,13].

4. In girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period, follicul-stimulating (2.53±0.4 mIU/ml), luteinizing hormones (2.0±0.23 mIU/ml), estradiol (28.44±1.1pg /ml) statistically significant decreased, prolactin (16.4±0.62 ng/ml), free thyroxine (1.35±0.04 ng/dl) increased (P<0.05) [6,11].

5. In the hypergonadotropic hypogonadism form of genital infantilism, follicle-stimulating (42.7±4.78 mIU/ml), luteinizing (21.14±1.6 mIU/ml), prolactin (20.96±1.32 ng/ml), thyrostimulating hormone (3.53±0.51 mIU/ml), dehydroepiandrosterone sulfate (2.84±0.35 pg/ml), cortisol (324.9±16.87 ng/ml), testosterone (3.46± 0.5 ng/ml) is statistically significantly increased, while estradiol (28.16±1.71 pg/ml) is observed to be low. In girls with normogonadotropic hypogonadism, an increase in prolactin (16.72±0.44 ng/ml), testosterone (3.25±0.25 ng/ml), and low level estradiol (43.1±1.56 pg/ml) were observed [4].

6. Significant increase in the HOMA index (4.21 ± 0.13) is determined in girls with general infantilism (hypogonadotropic hypogonadism) in the early reproductive period. In the form of hypergonadotropic hypogonadism of genital infantilism, insulin on an empty stomach reveals itself with statistically significant increase in (19.79±0.76 uIU/ml), HOMA index (4.85±0.36), and a decrease in CARO index (0.28±0.02), which reflects the tendency to insulin resistance [8].

7. As a result of genetic examination, 90.8% of girls with general and genital infantilism normal karyotype is noted. Karyotype pathology is noted in 9.2%, of which Shershevsky-Turner syndrome chromosomal structure (45X0) is noted in 3.9%, Swyer syndrome (46XY) in 5.3% [7].

8. In the early reproductive period, the level of vitamin D in girls with general infantilism (hypogonadotropic hypogonadism) was 12.02±0.82 ng/ml, in girls with genital infantilism (hypergonadotropic hypogonadism) – 15.27±2.1 ng/ml, in girls with normogonadotropic hypogonadism form of genital infantilism 14.29±0.87 ng/ml is determined, which indicates that vitamin D

deficiency is important in the pathogenesis of general and genital infantilism [9].

PRACTICAL RECOMMENDATIONS

1. Girls with premature birth, intrauterine growth retardation of the fetus as a result of various obstetric and extragenital pathologies in the mother's womb, chronic somatic diseases, chronic inflammatory diseases of the genital organs should be noted as risk factors for general and genital infantilism.

2. Signs of delayed physical and sexual development during puberty should be detected in time and pathogenetic treatment should be carried out after clinical-diagnostic examinations.

3. In order to study the condition of the reproductive organs in girls with general and genital infantilism in the early reproductive period (congenital malformations of the uterus, hormonally active tumors of the ovaries, false hermaphroditism, dysgenesis of the gonads, testicular feminization), it is appropriate to conduct a diagnostic laparoscopy.

4. In girls with general and genital infantilism in the early reproductive period, it is important to carry out echographic examination of reproductive organs, hormones of the hypothalamic-pituitary-adrenal gland-ovarian system, indicators of carbohydrate metabolism, vitamin D and genetic examination.

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