[Dedov II, Troshina EA, Antonova SS, et. al. Autoimmune diseases of the thyroid gland: the state of the problem. *Problemy endokrinologii* [*Problems of endocrinology*]. 2002; 48(2): 6-13 (In Russ.).] doi: /10.14341/probl11500.

2. Воронцова Т.В. Аутоиммунные реакции в щитовидной железе и радиация / Т.В. Воронцова // Иммунопатология, аллергология, инфектология. – 2000. – № 2. – С. 20–27 [Vorontsova TV. Autoimmune reactions in the thyroid gland and radiation. *Immunopatologiya, allergologiya, infektologiya* [*Immunopathology, allergology, infectology*]. 2000; 2: 20-27 (In Russ.).]

3. Добродеева Л.К. Иммунологическое районирование / Л.К. Добродеева // Сыктывкар: Изд. КНЦ УрО РАН, – 2001. – 212 с. [Dobrodeeva LK. Immunological zoning. Syktyvkar: NTS UrO RAN; 2001 (In Russ.).]

4. Иммунодефицитные состояния / В.Р. Гофман, Н.М. Калинина, С.А. Кетлинский [и др.]. – СПб.: Фолиант, 2000. – 568 с. [Hoffman VR, Kalinina NM, Ketlinsky SA et. al. Immunodeficiency conditions. St. Petersburg: Folio. – 2000 (In Russ.).]

5. Ким Л.Б. Влияние полярного стажа на кислородотранспортную функцию крови у северян различного возраста / Л. Б. Ким // Арктика и Север. – 2014. – №17. – С. 150– 162 [Kim LB. The effect of polar experience on the oxygen transport function of blood in northerners of various ages. *Arktika i Sever [Arctic and North]*. 2014; 17: 150–162 (In Russ.).]

6. Козинец Г.И. Исследование системы крови в клинической практике / Г.И. Козинец, В.А. Макаров. – М.: Триада– Х – 1997. – 480 с. [Kozinets GI. Studies of blood system in clinical practice. Moscow: Triada-X. - 1997; 480 p. (In Russ.).]

7. Новиков В.В. Растворимые формы мембранных антигенов клеток иммунной системы / В.В. Новиков, А.В. Караулов, А.Ю. Барышников // Иммунология. – 2007. – № 4. – С. 249–253 [Novikov VV. Soluble forms of membrane antigens of the cells of the immune system. *Immunology.* 2007; 4: 249–253.

8. Патология человека на Севере / А.П. Авцын, А.А. Жаворонков, А.Г. Марачев [и др.]. – М.: Медицина, 1985. – 416 с. [Avtsyn AP, Zhavoronkov AA, Marachev AG. et al. Human pathology in the North. M.: Medicine. – 1985 (In Russ.).]

9. Содержание аутоантител у практически здоровых людей / Л.К. Добродеева, Л.В. Сенькова, Г.Т. Лютфалиева [и др.]. – Физиология человека, 2006. – Т. 32, № 1. – С. 99–107 [Dobrodeeva LK, Senkova LV, Lutfalieva GT, et al. The content of autoantibodies in practically healthy people. *Fiziologiya cheloveka [Human physiology]*. 2006; 32 (1): 99–107 (In Russ.).]

10. Шубик В. М. Проблемы экологической иммунологии / В.М. Шубик .- Л.: Медицина, – 1976. – 240 с. [Shubik VM. Problems of Ecological Immunology. - L: Medicine. – 1976 (In Russ).]

11. Шубик В.М. Иммунологическая реактивность юных спортсменов / В.М. Шубик, М.Я. Левин. - М., 1982. – 136с. [Shubik VM. Immunological reactance of young athletes. - Moscow. – 1982 (In Russ.).]

12. Яровинский Б.Г. Количественное определение IgE и IgG к ДНК у больных атопическим дерматитом и атопической аллопецией методом ИФА / Б.Г. Яровинский, В.А. Егоров, А.В. Фридлиб // Клин. лаб. диагностика. – 2001. – № 11. – С. 38. [Yarovinsky BG. Quantitative determination of IgE and IgG to DNA in patients with atopic dermatitis and atopic alopecia by ELISA. *Klin. lab. Diagnostika [Clinical laboratory diagnostics]*. 2001; 11: 38 (In Russ.).]

13. Kon K, Maeda N, Sekija M et al. A method for studying oxygen diffusion barrier in erythrocytes: Effects of haemoglobin content and membrane cholesteroll. *J. Physiol.* (Gr. Brit.). 1980; 309: 569–590.

14. Lafstram B. Intravascular aggregation and oxygen consumption: aggregation of red blood cells produced by high molecular weight dextran or by hypothermia. *Acta anaesthesiol.* Scand. 1959; 3 (1): 41–51.

15. Liu R, Van L, Kaer ALa Cava et al. Autoreactive T cells mediateNK cell degeneration in autoimmune disease. *J. Immunol*. 2006; 176: 5247–5254.

16. Nagy ZA, Kusnierczyk P, Klein J. Terminal differecation of T–cells specific for mutant H–2K antigene. *J. Immunology*. 1981; 11: 167–172.

17. Naka T, Nishimoto N, Kishimoto T. The paradigm of IL–6: from basic science to medicine Arthr Res. 2002; 4(3): 233–42

18. Rodman TC, Stephen E, Sullivan JJ. et al. Innate natural antibodies. Primary roles indicated by specific epitopes. *Hum. Immunol.* 1997; 55(2): 87–95.

DOI 10.25789/YMJ.2021.75.08

УДК 618.145

CHUKHNINA Elena Galievna – Postgraduate at Department of Pathological Anatomy and Forensic Medicine, FSBEI HE SUSMU of the Ministry of Health of Russia, Chelyabinsk, https://orcid.org/0000-0001-6929-0892, e-mail: chuhninaeg@yandex.ru; **VOROPAEVA Ekaterina Evgenievna** – MD, associate professor, professor of the Department of Pathological Anatomy and Forensic Medicine FSBEI HE SUSMU of the Ministry of Health of Russia, Chelyabinsk, https://orcid.org/0000-0003-0800-3380; **KAZACHKOV Evgeny Leonidovich** – MD, Professor, Head, Department of Pathological Anatomy and Forensic Medicine FSBEI HE SUSMU of the Ministry of Health of Russia, Chelyabinsk, https://orcid.org/0000-0002-4512-3421; KA**ZACHKOVA Ella Alekseevna** – MD, Professor of the Department of Obstetrics and Gynecology, FSBEI HE SUSMU of the Ministry of Health of Russia, Chelyabinsk, https://orcid.org/0000-0002-1672-7058; **POLINA Miroslava Leonidovna** – PhD in Medical Sciences, Gynecologist at the Women's Health Medical Center, Moscow, Russia, https://orcid.org/0000-0003-3883-3967; **DOUGLAS Natalya Ivanovna** – Grand PhD in Medical Sciences, Head of the Department of Obstetrics and Gynecology, Medical Institute of North-Eastern Federal University named M.K. Ammosov, Yakutsk, Russia, https://orcid.org/

E.G. Chukhnina, E.E. Voropaeva, E.L. Kazachkov, E.A. Kazachkova, M.L. Polina, N.I. Douglas

EFFICIENCY OF HOMEOBOX GENE EXPRESSION ASSESSMENT FOR PREDICTING OUTCOMES OF ASSSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS

An analysis of the effect of *HOXA10* and *HOXA11* expression in the endometrial stroma of late reproductive women with tubal infertility factor on the outcomes of assisted reproductive technology (ART) programs was performed.

There was a tendency to a statistically significant decrease in the expression of *HOXA11* in the endometrial stroma during effective attempts to treat infertility.

Using the ROC (Receiver operator characteristic) method of analysis and calculations of the area under the ROC curve (AUC), it was found out that favorable levels of *HOXA11* expression for successful blastocyst implantation and live births in infertile women with their own and donor oocytes.

Keywords: *HOXA10*, *HOXA11*, expression, assisted reproductive technologies, implantation.

The potential role of *HOXA10* and *HOXA11* in the processes of implantation and functional regulation of tissues of the reproductive tract is recognized, however, the causes and consequences of expression features are actively discussed.

The ability to regulate the anatomical and functional identity of body segment structures by homeobox genes has been determined since the period of embryogenesis [10]. The relationship between the development of anomalies in *Hox/HOX* genetic mutations with a violation of not only organogenesis, but also the regulation of the encoding of transcription factors affecting the activity of "downstream" genes has been established.

Data on the *HOXA* genes and their probable role for implantation in women are insufficient and contradictory. The expression of *HOXA10* in the endometrium

of adult women occurs during the menstrual cycle [7], it is more pronounced in the functional layer compared to the basal one [18].

The role of *HOXA10* and *HOXA11* as moderators of activation or suppression of lower target genes [9] is based on the ability to regulate endometrial differentiation and proliferation by binding receptors to female sex hormones [4,18]. During implantation, the increased expression of *HOXA* mRNA genes is due to the transformation of stroma cells into decidual ones [15].

Abnormal expression of *HOX* genes is believed to be the cause of a violation of the implantation process, recurrent spontaneous abortions, conditions associated with infertility (endometriosis-associated, unclear genesis, polycystic ovary syndrome) [5,10,12,14].

There are reports that an increase in the expression of *HOXA11* in the endometrium is associated with an increase in the frequency of implantation [4,16,21]. Indicators of *HOXA11* proteins in infertile and fertile women, healthy and with gynecological diseases differ in various reports [10,11].

The mechanisms of endometrial receptivity disorders during the "implantation window" are connected to abnormal protein synthesis due to mutations and epigenetic abnormalities.

Conclusions about the aberrantly high expression of *HOXA10* mRNA in the fallopian tube mucosa during ectopic pregnancy were made by Unlu C. et al. (2016) [16]. There were no differences in the parameters of *HOXA10* and *HOXA11* proteins in the cells of the epithelium and stroma of the endometrium during the "implantation window" in the groups of women whose infertility was associated with low ovarian reserve, tubal-peritoneal factor, endometriosis, except for the sample with infertility of unclear genesis compared with fertile ones [3].

In other sources, the expression of *HOXA10* with H-score gradation in the groups with recurrent miscarriage and implantation failures was lower than in the control group, both in the glandular epithelium and the endometrial stroma [6]. The inconsistency and ambiguity of the data concerning the role of *HOXA10* and *HOXA11* in the regulation of endometrial receptivity, the assessment of the degree of its damage and the effectiveness of pregravid preparation determined the objective of our study.

The aim of the study was to evaluate the effect of *HOXA10* and *HOXA11* expression in the endometrial stroma of women of late reproductive age with tubal infertility factor on the outcomes of ART programs.

Material and methods. A prospective cohort study included 89 women of late reproductive age with tubal-peritoneal infertility who underwent ART programs at the Center of Obstetrics and Gynecology No. 1 LLC.

The sample included 68 women using their own oocytes, 21 – donor ones.

Inclusion criteria for the study: age 36-44, ovulatory cycle, normozoospermia or minor pathozoospermia of the husband (donor), embryos of good and excellent quality.

Exclusion criteria: infertility associated with the absence of ovulation; endometriosis, uterine fibroids of four cm or more, uterine factor of infertility, HIV infection, hepatitis B and C, severe pathozoospermia, systemic diseases; somatic diseases in the stage of exacerbation or decompensation.

Among women using their own oocytes, the first group consisted of 18 women with the onset of pregnancy, the second – 50 women with a negative result. At the second stage, these women were divided according to the live birth rate (the frequency of delivery of a live fetus(es) (take-home baby): the third group (n=14) – with a favorable outcome of ART programs, the fourth (n=54) – with a negative result.

In the sample using donor oocytes in ART programs (n=21), the following groups were distinguished: the first group consisted of 9 women with the onset of pregnancy, the second (n=12) – with a negative result. In order to analyze the frequency of live births, groups were formed: the third (n=6) – with the completion of ART programs with childbirth, the fourth (n=15) – with a negative result. The control group consisted of 20 healthy women (no chronic gynecological diseases) of reproductive age who applied for pregnancy planning.

In the cycles preceding the programs of assisted reproductive technologies, endometrial sampling was performed by aspiration biopsy using a Pipelle catheter during the expected "implantation window" (on the 17-25th day of the menstrual cycle, depending on the ultrasound monitoring data and on the 7th day after the peak of luteinizing hormone (LH)) (n = 89). Pathoanatomic examination of the material was carried out in accordance with the existing provisions.

An immunohistochemical study of endometrial biopsies was performed using standard sets of polyclonal antibodies from GeneTex, USA (rabbit polyclonal antibodies *HOXA10* and *HOXA11* receptor). Morphofunctional assessment of the endometrium was performed using the licensed Morphology 5.2 software. The results of the reaction of the *HOXA10* and *HOXA11* receptors were identified by calculating in percentage terms the relative density of stained endometrial stromal cells. Only clinically confirmed pregnancy (sonographic presence of the ovum) and live births were taken into account. The study was approved by the Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education "South Ural State Medical University" of the Ministry of Health of Russia, it was conducted after the prior informed consent of the patients.

All statistical calculations were performed using the licensed statistical software package IBM SPSS Statistics v. 22 (IBM Corp., Armonk, NY, USA). The normality of the distribution of variables was checked taking into account the sample size using the Shapiro-Wilk criterion.

The results of the study are presented as a median with an interquartile range of Me (Q1-Q3). To compare groups by qualitative characteristics, Pearson's chi-square criterion or Fisher's exact criterion were used (in cases of the number of cells in which the expected frequency was> 0%). The Mann-Whitney U–test was used to determine statistically significant differences between the two independent groups. To identify the relationship between the signs, the Pearson and Spearman correlation coefficient was calculated, depending on the data distribution variant. To determine the threshold values (cut-off point), a ROC analysis was performed. To build a predictive model and estimate the OR (odds ratio), we used the method of multiple logistic regression, calculated 95% CI (confidence interval) for the OR. The significance level (p) when testing statistical hypotheses was taken to be $p<0.05$.

Research results and discussion. The duration of the menstrual cycle in the sample using own oocytes was 28 (28;28.5), donor – 28 (28;29) (p=0.771) without statistical differences (p>0.05). The endometrium of all patients (n=89) taken on the seventh day after confirmed ovulation, when stained with hematoxylin and eosin, corresponded to the stage of the secretion phase.

The pregnancy rate (PR) in the group of patients with their own oocytes in ART programs was 26.5% (n=18). The live birth rate in the group of patients with their own oocytes in ART programs was 21.7% (n=14).

In the group of women with the onset of pregnancy using their own oocytes in

Table 1

The nature of HOXA10 and HOXA11 expression in the sample using own oocytes. Me (Q1; Q3)

Gene	Groups				p
	I (n=18)	II (n=50)	III (n=14)	IV (n=54)	
HOXA10	6.2 (3.7;9.4)	7.2 (3.8;8.2)	7.6 (5.2;8.3)	6.0 (3.6;9.3)	p_{1-2}= 0.754 p_{3-4}= 0.623
HOXA11	5.1 (4.3;6.1)	7.4 (5.4;8.7)	5.0 (4.3;6.1)	7.1 (5.3;8.7)	p_{1-2}= **0.001** p_{3-4}= **0.006**

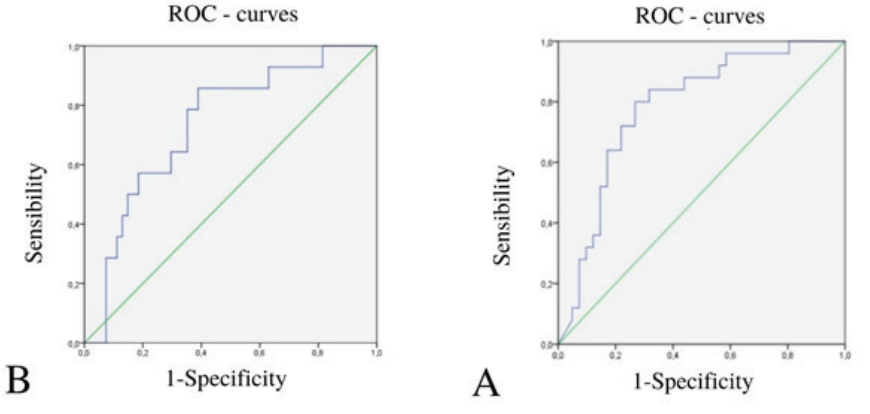

Fig. 1. ROC-curve of the relationship between HOXA11 expression in endometrial stroma cells and A. implantation and B. live birth in patients with their own oocytes in IVF/ICSI cycles

IVF/ICSI protocols, a tendency to a decrease in the expression of *HOXA10* and *HOXA11* was revealed (Table 1).

The level of *HOXA11* expression in stroma cells was statistically significantly lower in the group with pregnancy than in the group with ineffective attempts to treat infertility in ART programs (p=0.001).

The analysis of the frequency of live births in the sample showed the correlation of favorable outcomes of IVF/ICSI protocols with a lower *HOXA11* expression in the endometrial stroma (p=0.006). No such connection was found for *HOXA10* (p=0.623).

Using the method of ROC analysis and calculations of the area under the ROC curve (AUC), the prognostic significance of the expression of the *HOXA10* and *HOXA11* homeobox proteins in the endometrium was assessed in relation to the outcomes of ART programs (Figure 1).

The threshold value of *HOXA11* expression in endometrial stroma cells after successful implantation (group 1) at the cut-off point was equal to 6.1%. At a parameter value of ≤6.1%, the endometrium was characterized as favorable for implantation.

The sensitivity and specificity of the method were 80.0% and 73.0%, respectively. It was found that an increase in the expression of *HOXA11* in stromal cells by 1% reduces the probability of a decrease in implantation by 1.6 times.

The AUC values of *HOXA10* expression in the endometrium turned out to be statistically insignificant, which makes it impossible to calculate the prognostic coefficients of the onset of implantation (Table 2).

The importance of using *HOXA11* expression in endometrial stromal cells as a marker of the effectiveness of IVF/ICSI programs is shown.

In women with ART programs that ended in live fetal delivery (group 1C), the AUC of *HOXA 11* expression in the endometrial stroma was statistically significant (p=0.005). The value of the *HOXA 11* expression threshold parameter in the stromal cells of the endometrium, prognostically favorable for live birth, was equal to the same threshold parameter with a favorable prognosis for implantation and amounted to 6.1%. With an expression of less than 6.1%, the endometrium is characterized as favorable for the prognosis of live birth. The sensitivity and specificity of the method were 80% and 63%, respectively.

Table 2

Area under the ROC-curve (AUC) for the prognosis of implantation and live birth in patients with their own oocytes in IVF / ICSI cycles

Gene	AUC for the implantation prognosis	AUC for the live birth prognosis	*confidence interval (CI)95%*	*p*
HOXA10	0.525±0.074	0.462±0.074	0.380-0.670 0.316-0.608	p_1= 0.735 p_2= 0.666
HOXA11	0.767±0.064	0.744±0.071	0.642-0.892 0.567-0.849	p_1= **0.000** p_2= **0.005**

Table 3

Expression of HOXA10 and HOXA11 in women with different outcomes of ART programs using donor oocytes

Gene	Groups				p
	I (n=9)	II (n=12)	III (n=6)	IV(n=15)	
HOXA10	7.5 (3.7;7.9)	8.9 (3.5;10.8)	7.6 (6.6;8.5)	7.0 (3.6;9.7)	p_{1-2}= 0.320 p_{3-4}= 0.938
HOXA11	5.1 (4.1;5.8)	8.6 (6.6;10.0)	5.2 (4.8;5.8)	7.6 (5.9;9.2)	p_{1-2}= **0.001** p_{3-4}= **0.043**

Table 4

Area under the ROC-curve (AUC) of endometrial expression of HOXA10 and HOXA11 in women with donor oocytes in ART programs for the prognosis of implantation and live birth

Gene	AUC for the implantation prognosis	AUC for the live birth prognosis	*Confidence interval (CI) 95%*	*p*
HOXA10	0.630±0.130	0.489±0.125	0.243-0.734 0.375-0.884	p_1= 0.938 p_2= 0.320
HOXA11	0.917±0.067	0.789±0.103	0.785-1.000 0.586-0.991	p_1= **0.001** p_2= **0.043**

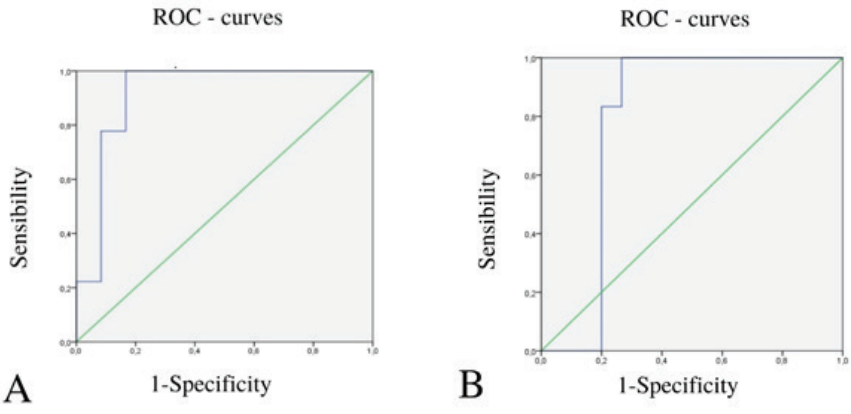

Fig. 2. ROC-curve of the relationship between HOXA11 expression in endometrial stroma cells and A. implantation B. live birth in patients with donor oocytes in ART programs

The pregnancy rate (PR) in the group of patients with donor oocytes in ART programs was 42.9% (n = 9). The live birth rate in women using donor oocytes was 30% (n = 6). Table 3 shows the expression of the studied immunohistochemical markers at different outcomes of ART programs in patients with donor oocytes.

The analysis of the positive outcomes of ART programs (pregnancy rate) using donor oocytes showed a lower expression of *HOXA10* and *HOXA11* in the endometrial stroma at the pregravid stage. The *HOXA11* index was statistically significantly lower compared to *HOXA10*.

Cases of pregnancy termination with live births also occurred predominantly in women with a lower *HOXA11* value (p = 0.043). The results of the ROC analysis are shown in Table 4.

The AUC of *HOXA11* expression in endometrial stromal cells is statistically significant for implantation and live birth in women with donor oocytes in ART programs.

The threshold value of *HOXA11* expression in endometrial stroma cells at the cut-off point, indicating a high probability of implantation in women with donor oocytes in ART programs, was 6.4%. The sensitivity and specificity of the method were 100.0% and 83.0%, respectively.

The probability of live birth in the group of women using donor oocytes increased at the threshold value of *HOXA11* expression in endometrial stroma cells at the cut-off point of 5.8% (p = 0.043). The sensitivity and specificity of the method were 83.0% and 80.0%, respectively.

Discussion. Low levels of *HOXA11* expression in stromal cells of the pregravid endometrium corresponded to a higher probability of implantation and live birth in a sample of women with their own and donor oocytes in IVF/ICSI programs. Calculations using ROC analysis confirmed the prognostic significance of *HOXA11*.

The low informative value of *HOXA10* as a marker of implantation can be interpreted from the standpoint of observations by other authors who noted a decrease in *HOXA10* mRNA in the middle phase of secretion in the endometrium of infertile women with hydrosalpinx, as opposed to fertile ones. Salpingectomy, on the contrary, led to a significant 15-fold increase in the expression of *HOXA10* in the glandular epithelium and endometrial stroma in comparison to the preoperative index [13].

The lack of involvement in the regulation of *HOXA10* protein implantation, identified by other authors [2], suggests the influence of the genotype on the "downstream" genes. Previous observations showed the absence of implantation during embryo transfer to mice with the *Hoxa10* genotype (-/-), with hemorrhage and tissue disorganization [1]. Probably, such changes are associated with insufficient decidualization of the endometrium.

The lowest *HOXA11* values in the group of women with live births with their own and donor oocytes in IVF/ICSI programs corresponded to the creation of optimal conditions for pregnancy, but the lack of similar observational experience in the literature indicates the need for further research.

Conclusions: The assessment of *HOXA11* expression in endometrial stromal cells is informative for predicting the probability of implantation and live birth in women of late reproductive age with tubal-peritoneal infertility in ART programs. For successful blastocyst implantation in women with their own and donor oocytes, favorable *HOXA11* expression levels are <6.1% and <6.4%, respectively; live births – <6.1% and <5.8%, respectively.

Reference

1. Bagot CN, Troy PJ, Taylor HS. Alteration of maternal Hoxa10 expression by in vivo gene transfection affects implantation. *Gene Ther.* 2000;7(16):1378-1384. doi:10.1038/sj.gt.3301245

2. Bourdiec A, Ahmad SF, Lachhab A, Akoum A. Regulation of inflammatory and angiogenesis mediators in a functional model of decidualized endometrial stromal cells. *Reprod Biomed Online*. 2016 Jan;32(1):85-95. doi: 10.1016/j.rbmo.2015.09.011.

3. Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. Hum Reprod Update. 2011;17(2):242-53.

4. Celik O, Unlu C, Otlu B, Celik N, Caliskan E. Laparoscopic endometrioma resection increases peri-implantation endometrial HOXA-10 and HOXA-11 mRNA expression. *Fertil Steril.* 2015;104(2):356-65.

5. Cermik D, Selam B, Taylor HS. Regulation of HOXA-10 expression by testosterone in vitro and in the endometrium of patients with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2003;88(1):238-43.

6. Doherty LF, Taylor HS. Leiomyoma-derived transforming growth factor-β impairs bone morphogenetic protein-2-mediated endometrial receptivity. *Fertil Steril.* 2015;103(3):845-52.

7. DU H, Taylor HS. Molecular regulation of mullerian development by Hox genes. *Ann N Y Acad Sci.* 2004;1034:152-65.

8. Jana SK, Banerjee P, Mukherjee R, Chakravarty B, Chaudhury K. HOXA-11 mediated dysregulation of matrix remodeling during implantation window in women with endometriosis. *J Assist Reprod Genet.* 2013;30(11):1505-12.

9. Lee B, Du H, Taylor HS. Experimental murine endometriosis induces DNA methylation and altered gene expression in eutopic endometrium. *Biol Reprod.* 2009 Jan;80(1):79-85.

10. Makker A, Goel MM, Nigam D, Bhatia V, Mahdi AA, Das V, Pandey A. Endometrial Expression of Homeobox Genes and Cell Adhesion Molecules in Infertile Women With Intramural Fibroids During Window of Implantation. *Reprod Sci.* 2017;24(3):435-444.

11. Margioula-Siarkou C., Petousis S., Milias S., Ravanos K., Kalogiannidis I., Mavromatidis G. et al. Endometrial expression of Leukemia Inhibitory Factor (LIF), LIF-receptor and HOXA-11 but not HOXA-10 is significantly impaired in women with unexplained infertility during implantation window. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 2016; 206: e165-6.

12. Matsuzaki S, Canis M, Darcha C, Pouly JL, Mage G. HOXA-10 expression in the mid-secretory endometrium of infertile patients with either endometriosis, uterine fibromas or unexplained infertility. *Hum Reprod.* 2009 Dec;24(12):3180-7.

13. Mlodzik M, Fjose A, Gehring WJ. Molecular structure and spatial expression of a homeobox gene from the labial region of the Antennapedia-complex. *EMBO J.* 1988 Aug;7(8):2569-78.

14. Modi D, Godbole G. HOXA10 signals on the highway through pregnancy. *J Reprod Immunol.* 2009;83(1-2):72-8.

15. Szczepańska M, Wirstlein P, Skrzypczak J, Jagodziński PP. Expression of HOXA11 in the mid-luteal endometrium from women with endometriosis-associated infertility. *Reprod Biol Endocrinol.* 2012;10;10:1.

16. Unlu C, Celik O, Celik N, Otlu B. Expression of Endometrial Receptivity Genes Increase After Myomectomy of Intramural Leiomyomas not

Distorting the Endometrial Cavity. *Reprod Sci.* 2016 Jan;23(1):31-41.
17. Yang Y., Chen X., Saravelos S.H., Liu Y., Huang J., Zhang J., Li T.C. HOXA-10 and E-cadherin expression in the endometrium of women with recurrent implantation failure and recurrent miscarriage. *Fertil. Steril.* 2017; 107(1): 136-43. e2.
18. Zheng J, Luo X, Bao J, Huang X, Jin Y, Chen L, Zheng F. Decreased Expression of HOXA10 May Activate the Autophagic Process in Ovarian Endometriosis. *Reprod Sci.* 2018 Sep;25(9):1446-1454.

DIAGNOSTIC AND TREATMENT METHODS

DOI 10.25789/YMJ.2021.75.09

УДК 616.281-089.843-06

N.A. Lebedeva, M.A. Diab Hassan, A.S. Machalov, I.I. Gogolev, N.R. Ilyina, D.S. Tomin, V.V. Karpov

COCHLEAR IMPLANTATION IN THE REPUBLIC SAKHA (YAKUTIA)

The article presents a statistical analysis of children's composition after cochlear implantation carried out in Otorhinolaryngology Department of Pediatric center of Republican Hospital No1 National Medical Center in the period from 2017 to 2019. The results of hearing and speech rehabilitation were obtained according to the scale for assessing the prospects of using children's cochlear implantation and categories of hearing perception were defined as well.

Keywords: cochlear implantation, otorhinolaryngology, audiology, rehabilitation, hearing, speech.

Introduction. The ability to perceive sound is one of the important features of the human body, which allows us to fully cognize the picture of the world around us. Hearing loss or congenital inability to hear in childhood patients is a serious burden not only in their socialization, but also in the learning process. [11] Attempts to restore hearing have been actively undertaken since the middle of the 20th century. [10]

The ability to restore hearing function in deaf people using direct electrical stimulation of the afferent fibers of the auditory nerve with a multichannel electrode system has become one of the most important achievements of medical science today. [4, 12] Cochlear implantation (CI) is the only method of treating patients with total deafness, which functionally provides intelligible speech perception. [7, 12] The regulatory document that controls the selection of candidates for surgery is the instructional material approved by the letter of the Ministry of Health of the Russian Federation of 15.06.2000 No. 2510 / 6642-32 "On the implementation of criteria for the selection of patients for cochlear implantation, methods of preoperative examination and prediction of effectiveness rehabilitation of implanted patients". The main selection criterion for CI is damage to the majority of hair cells. The selection of children is carried out in accordance with the division of patients into the pre-lingual and post-lingual categories, which have an important prognostic value. [5] For early diagnosis of hearing loss in the Russian Federation, universal audiological screening of newborns and children of the first year of life is carried out, including registration of otoacoustic emission and short-latency auditory evoked potentials. [1, 3] The optimal hearing and speech result in CI, in children with congenital deafness and hearing loss in the first year of life, can be achieved before the age of 3 years, the minimum recommended age is 6-12 months. [5, 8]

As part of the implementation of the decree of the Head of Sakha Republic (Yakutia) dated August 22, 2016 No. 1372 "On measures to improve high-tech types of medical care and innovative treatment methods in Sakha Republic (Yakutia)", as well as the signing of a Cooperation Agreement between the Ministry of Health of Sakha Republic (Yakutia) (Minister Okhlopkov M.E.) and Federal State Budgetary Institution 'National Medical Research Center otorhinolaryngology of the Federal Medical and Biological Agency' of Russia (director Daihes N.A.) in 2017 for the first time performed cochlear implantation operations in children aged 1 to 2 years. Since 2018, on the basis of Republican hospital No1 National center of medicine, a specialized day hospital has been put into operation to configure and replace the CI speech processors. [9, 13]

After the operation and connection of the implant, a telemetry session and speech processor (SP) settings are conducted in the Day Hospital of Republican hospital No1 National center of medicine at the appointed time. An integrated approach to hearing and speech rehabilitation is observed, in addition to classes with a teacher of speech rehabilitation, speech therapist, psychotherapist, children additionally study at home, according to the recommendations of specialists, with weekly video reports from their parents. [1, 2, 6]

The study of the obtained results of hearing and speech rehabilitation in children is currently very relevant.

Purpose of the study: to determine the effectiveness of hearing and speech rehabilitation of children after cochlear implantation, performed on the basis of the ENT department of Republican hospital No1 National center of medicine for the period 2017-2019.

Materials and methods. The study was carried out according to the medical records of an inpatient patient and data from the workflow automation system for medical institutions, based on the Day Hospital and ENT department of Republican hospital No1 National center of medicine from 2017 to 2019. The work is in accordance with the ethical principles of conducting scientific medical research with human participation. The parents of each patient signed an authorization

LEBEDEVA Natalya Afanasyevna – M.D., Ph.D., associate professor Medical Institute M.K.Ammosov NEFU, lebedeva-lor@mail.ru; **DIAB Hassan Mohamad Ali** – M.D., Ph.D., professor of Otorhinolaryngological National Medical Research Center, hasandiab@mail.ru, **MACHALOV Anton Sergeevich** – M.D., Ph.D., the Head of Audiology, Cochlear Implantation and Auditory rehabilitation department of Otorhinolaryngological National Medical Research Center, anton-machalov@mail.ru, **GOGOLEV Innokentiy Ivanovich** – M.D., the Head of ENT department of RH1 NCM, innokentiy.gogolev@mail.ru, **ILYINA Nadezhda Romanovna** – M.D., the Head of Speech center of RH1 NCM, nadyailina13@gmail.com, **TOMIN Dmitriy Sergeevich** – ENT resident Medical Institute M.K.Ammosov NEFU, dmitry_tomin@mail.ru, **KARPOV Vasiliy Vasilevich** – ENT resident Medical Institute M.K.Ammosov NEFU, dark.gray2099@gmail.com