Chukhnina E.G., Polina M.L., Douglas N.I.

THE ROLE OF ABBERRANT HOXA GENE EXPRESSION IN THE GENESIS OF GYNECOLOGICAL DISEASES

DOI 10.25789/YMJ.2021.74.28

The review presents current data on the effect of endometrial expression of the homeobox genes *HOXA10* and *HOXA11* on implantation processes in healthy fertile women and in common gynecological diseases. The features of gene expression, potentially unfavorable for implantation and leading to infertility, are described. The variability of receptivity markers expression before and after myomectomy, salpingectomy and the removal of ovarian endometriomas was shown.

Keywords: *HOXA10* and *HOXA11* genes, expression, endometrium, implantation.

Purpose: to determine the role and expression pattern of *HOXA* genes in the genesis of various gynecological diseases.

Homeobox genes «*Hox / HOX*» (Gr. homios – similar) of mammals are homologues of the gene complexes of the fruit fly Drosophila melanogaster Antennapedia and Bithorax.

These selector genes are expressed in the process of organogenesis and regulate the anatomical and functional identity of the body segment structures of the embryo by encoding transcription factors that control a number of «downstream» genes, completely unknown) [48].

The name «*Hox*» is used for the homeosis genes of vertebrates, «*HOX*» for humans. The complete set of 39 *Hox / HOX* genes in humans and mice is carried out in four clusters (*HOXA, HOXB, HOXC and HOXD*), each of which contains 9-13 genes of 7, 17, 12 and 2 chromosomes, respectively. The *Hox / HOX* gene homeobox is represented by a sequence of 183 base pairs encoding a 61 amino acid homeodomain, similar to the bacterial helix / anti-helix model. Homeodomains are a helix-loop-helix-coil-helix structure that is responsible for recognizing and binding specific DNA sequences that regulate the expression of target genes.

CHUKHNINA Elena Galievna – Postgraduate at Department of Pathological Anatomy and Forensic Medicine, FSBEI HE SUSMU of the Ministry of Health of Russia, Chelyabinsk, e-mail: chuhninaeg@yandex.ru; **POLINA Miroslava Leonidovna** – PhD in Medical Sciences, Gynecologist at the Women's Health Medical Center, Moscow, Russia, e-mail: polina.ml@mail.ru; **DOUGLAS Natalya Ivanovna** – Grand PhD in Medical Sciences, Head of the Department of Obstetrics and Gynecology, Medical Institute of North-Eastern Federal University, Yakutsk, Russia, e-mail: nduglas@yandex.ru.

The homeodomain mediates protein binding to the promoter areas of target genes containing the 5 '- TAAT-3' sequence. The *Hox / HOX* genes are characterized by collinearity, indicating expression along the anteroposterior body axis in a sequence identical on the chromosome. The *HOX* axis of the human genital system coincides with that of mice [49].

The specificity of temporal and spatial expression of *Hox / HOX* genes is manifested in the control of the female reproductive tract organogenesis. The *Hox9, Hoxa10, Hoxa11* and *Hoxa13* genes in mammals regulate the differentiation of Mullerian ducts into adult reproductive structures. It was found that they are prematurely and simultaneously expressed in the paramesonephral duct in early embryogenesis (exclusion from the collinearity principle) in the phase when the Mullerian ducts are devoid of stromal or epithelial differences [12,49].

The ability of *Hox / HOX* genes to regulate the morphogenesis of body segments explains the development of abnormalities in homeobox mutations. Loss of the function of the *Hom-C3'labial* gene in the fruit fly leads to impaired involution of the embryo's head segment, salivary glands, and cephalopharyngeal apparatus [40]. It is possible to develop an additional pair of wings instead of a pair of stoppers or to transform the antenna into Drosophila legs [34]. With the dominant position of the gene, which is located behind the 5 'mutated gene, posterior transformation is probable. In case of 3 '*Hox* gene mutation or deletion, changes in the body segment by the type of anterior transformation are likely to happen.

The homology of the *HOX* genes of different mammalian clusters allows to compensate for the loss of function [14]. The *Hoxa10* deletion in mice results in the transformation of the proximal uterine body into a tubular and narrow structure similar to the fallopian tube, controlled by the *Hoxa 9* gene [7].

Several of the *Hox / HOX* genes are involved in the unique transformation of the female reproductive system in the postnatal period – during the menstrual cycle and pregnancy.

HOXA9 is expressed in the fallopian tubes, *Hoxa11* – in the lower segment of the uterus, cervical glands and epithelium, *Hoxa13* – in the ectocervix and the upper part of the vagina (in the epithelium) [18,49].

The *HOXA10* protein is found in the nucleus and cytoplasm of epithelial and stromal cells in the endometrium of mice and baboons [1]. In adults, *Hoxa10 / HOXA10* is expressed in the endometrium during the menstrual cycle [18]. Hybridization of *Hoxa10* mRNA in situ reveals more pronounced expression in the functional layer of the endometrium compared to the basal one, moderate expression in the myometrium and distal intestine [49]. The *Hox / HOX* genes regulate cell differentiation and endometrial proliferation by influencing the relationship of receptors and female steroid hormones, the secretion peak of which occurs during the «implantation window» [1,12,49].

The *HOXA10* expression is also modulated by testosterone and vitamin D [23].

About 40 genes regulated by *HOXA10* have been described, including moderators of endometrial receptivity [41]. The *Hoxa10 / HOXA10* and *Hoxa11 / HOXA11* genes act as important transcriptional moderators that either activate or suppress downstream target genes [25].

Important targets for embryo implantation include cell adhesion molecules, signal transduction factors and metabolic mediators [42].

Emx2 is a divergent homeobox gene that is the mammalian homologue of the Drosophila empty helix gene. The *Emx2* gene of vertebrates is located outside the *Hox* cluster and is expressed in the

developing vertebrate brain and genitourinary system, in the embryo – in the epithelial components of the pronephros, mesonephros, ureteral kidneys, wolffian and Mullerian ducts. In mouse embryos, *Emx2* expression is significantly reduced in the male gonad, but remains in the female gonad. *Emx2* null mutants do not develop kidneys, gonads or a reproductive tract [17].

In adults, *EMX2* is found in the human uterus. *EMX2* expression showed dynamics depending on the phase of the human reproductive cycle [16]. *EMX2* is cyclically expressed in the adult endometrium, having an antiproliferative effect; it doubles in the peri-implantation endometrium [15]. *Hoxa10*-regulated *Emx2* expression is fundamental to embryo implantation. *Hoxa10* / *HOXA10* suppresses the expression of the homeobox gene *Emx2 / EMX2* [37].

The *HOXA10* expression changes in mice and primates are associated with defects in uterine functions leading to infertility [42], due to a decrease in endometrial receptivity, hemorrhage and disorganization in the implantation zone [36]. Violation of protein synthesis occurs due to mutations and epigenetic devations, DNA modification with the same nucleotide sequence. The attachment of a methyl group to cytosine in the CpG dinucleotide at the C5 position of the cytosine ring reduces gene expression, up to «epigenetic shutdown» with the development of endometriopathies, endometriosis and endometrial cancer.

The *HOXA-10* gene regulates the activity of the β3-integrin subunit [25] and the development of endometrial pinopodia [11]. During decidualization, the expression of *HOXA10* and *HOXA11* and the vascular endothelial growth factor *VEGF* increase [8].

An increase in the expression of the *HOXA* genes mRNA in decidual cells transformed from the stroma makes mucosa more susceptible to embryo implantation [42].

Changes in *HOX* genes expression are connected to a decrease in implantation and diseases associated with infertility (of unknown origin, PCOS, endometriosis), and recurrent spontaneous abortions [13,26,28,33]. Endometrial polyps, disorders of blood flow in the vessels of the uterine mucosa and chronic endometritis are also noted among the pathological conditions of the endometrium [20].

The role of *Hoxa / HOXA10* in implantation is confirmed by the aberrantly high expression of HOXA10 mRNA in the fallopian tube mucosa during ectopic pregnancy [47].

A decrease in the level of *HOXA10* mRNA in endometrial biopsies of women with hyperandrogenism is associated with a decrease in fertility in PCOS [30]. Endometrial tissue obtained by pipel biopsy in the secretory phase was immediately placed in liquid nitrogen and stored at -72 ° C; after RNA extraction Northern blot analysis was performed.

In a prospective study, Kara M. et al. (2019) studied the endometrium of 53 women of reproductive age with abnormal uterine bleeding not associated with uterine fibroids and polyps in the proliferative phase of the menstrual cycle. The expression of *HOXA-10* mRNA in glandular epithelial cells of the endometrium in the group with polycystic ovary syndrome (PCOS) (n = 33) was significantly lower than in healthy fertile women (0.60 ± 0.14 versus 1.23 ± 0.21) ($p < 0.05$). A similar tendency was observed for the *HOXA-11* and leukemia inhibitory factor (LIF) genes ($p < 0.05$) [38].

The *HOXA* genes leading role in the genesis of endometriosis is confirmed by data on abnormal endometrial receptivity during the "implantation window" on the background of changes in the DNA methylation profile [43].

In a sample of infertile women with peritoneal endometriosis diagnosed during laparoscopy (n = 31) without drug therapy, a decrease in the expression of *HOXA-10* and *HOXA-11* mRNA in the secretory endometrium was revealed by quantitative real-time PCR (PCR-RT) in the last three months. Western blot analysis also showed a decrease in the expression of endometrial proteins in endometriosis compared to the control group (n = 26) [29].

The analysis of *HOXA-10* expression in the endometrium of women with infertility of idiopathic genesis, various forms of endometriosis, uterine myoma and healthy fertile in the middle of the secretory phase was carried out by PCR-RT, the same protein – by an immunohistochemical method. The *HOXA-10* mRNA expression level in the endometrial glands was significantly lower than in the stroma, but without intergroup differences. No protein expression was found in the glands. Overexpression of the *HOXA-10* protein in the endometrial stroma in women with peritoneal endometriosis was determined more often (100%) than in other groups with infertility (on the background of infiltrative endometriosis (72.7%), ovarian endometriomas (70.0%), uterine fibroids (68.8%), of unexplained genesis (55.6%)) [5].

Violation of epigenetic regulation at the heart of the pathogenesis of endometriosis confirms the hypermethylation of the *HOXA10* gene promoter and a decrease in its expression in the eutopic endometrium of animal models (mice and baboons) [45].

Changes in genomic DNA methylation at the *HOXA10* locus in the stroma of endometrioid heterotopies, including foci on the peritoneum, ovaries and lung parenchyma, are associated with progesterone resistance and increased local estradiol production [48].

The *Hoxa10 / HOXA10* gene in embryogenesis implements the introduction of immature mesenchymal cells into the endometrial tissue; it also determines the endometrioid profile of immature cells among adults. Homeobox genes "switching off", medical or surgical, is considered to be the way to prevent endometriosis. Characteristic of healthy fertile women, a halving of the *Emx2* level from the index in the peri-implantation endometrium is absent in endometriosis [37].

The predominant expression of the *HOXA10* protein was observed in stromal cells in comparison to the glandular eutopic and ectopic endometrium of fertile and infertile women. Szczepańska M. et al. (2010) revealed a significant decrease in the transcript ($p = 0.019$) and protein ($p = 0.048$) of the *HOXA10* gene in women with endometriosis-associated infertility [15].

A later study by the authors (2012) confirmed low expression of mRNA and *HOXA11* protein levels in endometriosis compared to healthy women ($p = 0.003$ and $p = 0.004$, respectively) and tubal-peritoneal infertility ($p = 0.041$ and $p = 0.001$, respectively) in the middle of the luteal phase using Western blotting and PCR-RT [32]. In both studies, excessive methylation of the CpG islet in the 1st exon of the *HOXA11* gene was determined in endometriosis in comparison to other groups ($p < 0.001$) [4,15].

A decrease in the *HOXA10* gene mRNA expression in the eutopic endometrium in the middle of the luteal phase in endometriosis-related infertility was associated with excessive methylation of the promoter in the study by Fambrini M. (2013) [9].

Similar observations took place in women with ovarian endometriomas in the middle luteal phase in comparison to healthy women. There was an increase in methylation of the *HOXA10* promoter in the eutopic endometrium with endometriosis rather than with intact mucosa (8.7% versus 6.2%, $p = 0.037$ and 11.9 versus 9.2%, $p = 0.032$ for sequences 1 and 2, respectively). The methylation level was significantly higher in the eutopic tissue

in endometriosis than in the ectopic tissue: the average difference for sequence 1 and 2 was −3.6 (p = 0.001) and −6.0 (p = 0.0001), respectively [35].

An increase in the expression of microRNA 135b in the secretory phase of the uterus correlates with a decrease in *HOXA-10*, confirming the aberrant receptivity of the endometrium among women with endometriosis [21].

Reduction in the level of *HOXA10* methylation was noted in the blood of fetuses of women with endometriosis who took folic acid (n = 22), in contrast to the control group (n = 15) [6].

A possible mechanism of endometrial receptivity disorder in uterine myoma in the study by Doherty L.F. et al. (2015) [44] was associated with a decrease in the expression of *HOXA10* mRNA due to the activation of transforming growth factor (*TGF-β3*) after applying the medium of cultured myomatous node cells.

Makker A. et al. (2017) evaluated the expression of the *HOXA10* and *HOXA11* genes in the "implantation window" of women with infertility and uterine myoma without cavity deformation (n = 18) in comparison to healthy fertile women (n = 12). Indicators of mRNA and proteins studied by quantitative PCR-RT and immunohistochemistry, respectively, were lower in infertile women, however, a statistically significant decrease was observed only for *HOXA10* mRNA (p = 0.03) and the same protein (p = 0.001) [27].

In the endometrium of women with intramural, submucosal leiomyomas without uterine cavity deformation, there was a tendency towards a decrease in the expression of *HOXA-10* and *HOXA-11* mRNA in the middle of the luteal phase in comparison to the fertile ones and uterine septum, but without statistically significant differences. After myomectomy of intramural nodes, three months later, a statistically significant increase in the expression of *HOXA10* (12.8 times) and *HOXA11* (9 times) was revealed. Removal of submucosal myomas had no significant effect on gene expression [24].

In a case-control study by Alizadeh Z. et al. (2013) no differences in the endometrial expression of *HOXA11* and *HOXA10* mRNA on days 19-23 of the menstrual cycle were found among infertile women with uterine fibroids larger than 5 cm (n = 12). After myomectomy, there was an increase in *HOXA11* by 1.24 times (p = 0.7) and *HOXA10* by 2.39 times, but without statistically significant differences (p = 0.15) [19].

The decrease in the expression of *HOXA-10* and *HOXA-11* mRNA in the secretory endometrium of infertile women with endometrioma (n = 20) and benign ovarian cysts (n = 5) in comparison to healthy women (n = 5) was statistically insignificant. Removal of the endometrioma was accompanied by a considerable rise in the expression of *HOXA-10* mRNA (12.1 times) and *HOXA-11* (17.2 times), in contrast to preoperative parameters (p = 008 and p = 035, respectively) [31].

A number of studies have shown a decrease in *HOXA-10* mRNA in the middle phase of secretion in the endometrium of infertile women with hydrosalpinx as opposed to fertile women. Salpingectomy resulted in a statistically significant 15-fold increase in the *HOXA10* expression in both the glandular epithelium and the endometrial stroma compared to the preoperative indicator [32].

The evaluation of *HOXA10* and *HOXA11* proteins in epithelial and stromal cells of the endometrium on the 7-8th day after ovulation by calculating the histochemical index (h-score) in a prospective study of infertile women (n = 65) did not reveal statistically significant differences in the groups (with low ovarian reserve (n = 22), tubal-peritoneal factor (n = 13), endometriosis (n = 5)), except for the sample with infertility of unknown origin (n = 15) in comparison to healthy patients (p = 0.005) [10].

A statistically significant decrease in the expression of the *HOXA10* gene mRNA was found in the endometrium of women with endometrial polyps (n=21) – by 2.9 times (p = 0.016), *HOXA11* – 5.5 times (p = 0.03) compared to the control (n = 9), regardless of size and quantity [2].

In the samples of the secretory endometrium of women of reproductive age with infertility, a lower expression of *HOXA10* mRNA (p = 0.047) was detected by 0.69 times compared to the control. The expression of miRNA-135b was 1.81 times higher (p <0.01). The *HOXA10* gene expression increases significantly in the middle of the luteal phase and remains high from the moment of implantation to the end of the reproductive cycle [3].

In a cohort study by Yang Y. et al. (2017) 18 healthy women, 12 with habitual implantation failure under the age of 40 (transfer of at least four good quality embryos for at least three fresh or frozen cycles) and 20 – with recurrent miscarriage, evaluated the expression intensity of *HOXA-10* and E-cadherin. The calculation was carried out according to the H-score equation: H score = ∑Pi (i + 1), where i is the intensity of staining (0 = negative; 1 = weak; 2 = moderate; 3 = strong), Pi is the percentage of cells stained at each intensity (0% -100%). H-scores were measured separately in stromal cells and glandular epithelium.

The *HOXA-10* expression was localized in the nuclei of stromal cells and the cytoplasm of glandular epithelium cells. The *HOXA-10* H-scores in the groups with recurrent miscarriage and implantation failures were lower than in the control group, both in the glandular epithelium and in the stroma [16].

Endometrial samples obtained during hysteroscopy of 84 women with gynecological diseases (submucosal (n = 13) and intramural uterine myoma (n = 13), endometriosis (n = 27), uterine septum (n = 6), Asherman syndrome (n = 8), hydrosalpinx (n = 4) or uterine polyps (n = 11)) were distinguished by methylation of at least one CpG cluster in the *HOXA10* promoter area in comparison to healthy controls (n = 7). High methylation in a number of CpG islets of the *HOXA10* gene promoter was detected in endometrial polyps, submucosal and intramural myomas. Women with endometriosis, in contrast to healthy controls, were distinguished by a decrease in methylation. A correlation was found between gene expression in submucous uterine myoma and DNA methylation of 1 CpG cluster in the second intron area (CpG 4.5.6; r = 0.72, p = 0.02), as well as in endometriosis (r = −0.9, p = 0.04) [39].

In 25 biopsies of the eutopic endometrium of women of reproductive age with infertility on the background of chronic endometritis, bisulfite sequencing revealed methylation in the promoter area of the *HOXA10* gene in 84% and the *HOXA11* gene in 64%. The correlation with the duration of infertility was determined: up to one year the methylation level was 5.7%, more than 10 years – it was close to 50% [46].

The methylation status of the *HOXA10* and *HOXA11* genes suggests a probable molecular marker of infertility in various gynecological diseases. The leveling of abnormal DNA methylation of genes is associated with the drugs indole-3-carbinol and epigallocatechin-3-gallate, which indirectly affect endometrial receptivity [22]. The endometrium of women with the most common gynecological diseases is characterized by a specific pattern of the *HOXA10* gene methylation.

It is assumed that data on the nature of the *HOXA* gene expression in various gynecological diseases will help in the development of specific therapeutic agents for fertility management.

The authors declare no potential conflicts of interests

Литература

1. Аномальное гиперметилирование генов *HOXA10* и *HOXA11* при бесплодии, ассоциированном с хроническим эндометритом / Сухих Г.Т., Осипьянц А.И., Мальцева Л.И. [и др.] // Акушерство и гинекология. -2015. – 12. – С. 69-74. [Sukhikh GT, Osipyants AI, Maltseva LI, Smolina GR, Poloznikov AA, Muizhnek EL, Kiselev VI. Abnormal hypermethylation of genes *HOXA10* and *HOXA11* in infertility associated with chronic endometritis. *Akusherstvo i ginekologiya* [*Obstetrics and gynecology]*. 2015; 12: 69-74].

2. Киселёв В.И. Регуляция активности генов и новые лекарственные средства / Киселёв В.И., Пальцев М.А. // Вестник РАН. -2016; 86(6): 512-9. [Kiselev BI, Paltsev MA. Regulation of gene activity and new drugs. *Vestnik RAMS [Bulletin of the Russian Academy of Sciences].* 2016; 86(6): 512-9.

3. Шуршалина А.В. Морфо-функциональные перестройки эндометрия в «окно имплантации» / Шуршалина А.В., Демура Т.А. // Акушерство и гинекология. – 2011. - 7-2: С. 9-13. [Shurshalina AV, Demura TA. Morpho-functional restructuring of the endometrium into the 'implantation window'. *Akusherstvo i ginekologiya [Obstetrics and gynecology]*. 2011; 7-2: 9-13.

4. Alizadeh Z, Faramarzi S, Saidijam M, Alizamir T, Esna-Ashari F, Shabab N, Farimani Sanoee M. Effect of intramural myomectomy on endometrial *HOXA10* and *HOXA11* mRNA expression at the time of implantation window. *Iran J Reprod Med*. 2013 Dec;11(12):983-8.

5. Andersson KL, Bussani C, Fambrini M, Polverino V, Taddei GL, Gemzell-Danielsson K, Scarselli G. DNA methylation of *HOXA10* in eutopic and ectopic endometrium. *Hum Reprod*. 2014 Sep;29(9):1906-11.

6. Ashary N, Laheri S, Modi D. Homeobox genes in endometrium: from development to decidualization. *Int J Dev Biol*. 2020;64(1-2-3):227-237.

7. Benson GV, Lim H, Paria BC, Satokata I, Dey SK, Maas RL. Mechanisms of reduced fertility in *Hoxa-10* mutant mice: uterine homeosis and loss of maternal *Hoxa-10* expression. *Development*. 1996;122(9):2687-96.

8. 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.

9. Browne H, Taylor H. *HOXA10* expression in ectopic endometrial tissue. *Fertil Steril*. 2006 May;85(5):1386-90.

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

11. Carvalho FM, Aguiar FN, Tomioka R, de Oliveira RM, Frantz N, Ueno J. Functional endometrial polyps in infertile asymptomatic patients: a possible evolution of vascular changes secondary to endometritis. *Eur J Obstet Gynecol Reprod Biol*. 2013 Sep;170(1):152-6.

12. 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 Aug;104(2):356-65.

13. 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 Jan;88(1):238-43.

14. Daftary GS, Taylor HS. Hydrosalpinx fluid diminishes endometrial cell *HOXA10* expression. Fertil Steril. 2002 Sep;78(3):577-80.

15. Daftary GS, Troy PJ, Bagot CN, Young SL, Taylor HS. Direct regulation of beta3-integrin subunit gene expression by *HOXA10* in endometrial cells. *Mol Endocrinol*. 2002 Mar;16(3):571-9.

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

17. Du H, Daftary GS, Lalwani SI, Taylor HS. Direct regulation of *HOXA10* by 1,25-(OH)2D3 in human myelomonocytic cells and human endometrial stromal cells. *Mol Endocrinol*. 2005 Sep;19(9):2222-33.

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

19. Du H, Taylor HS. The Role of Hox Genes in Female Reproductive Tract Development, Adult Function, and Fertility. *Cold Spring Harb Perspect Med*. 2015 Nov 9;6(1):a023002.

20. Fambrini M, Sorbi F, Bussani C, Cioni R, Sisti G, Andersson KL. Hypermethylation of *HOXA10* gene in mid-luteal endometrium from women with ovarian endometriomas. *Acta Obstet Gynecol Scand*. 2013 Nov;92(11):1331-4.

21. 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 Nov;30(11):1505-12.

22. Kara M, Ozcan SS, Aran T, Kara O, Yilmaz N. Evaluation of Endometrial Receptivity by Measuring *HOXA-10, HOXA-11*, and Leukemia Inhibitory Factor Expression in Patients with Polycystic Ovary Syndrome. *Gynecol Minim Invasive Ther*. 2019 Aug 29;8(3):118-122.

23. Kulp JL, Cakmak H, Taylor HS. HOX Genes and Endometriosis. In: Giudice LC, Evers JLH, Healy DL, editors. *Endometriosis: science and practice*. Oxford: Blackwell Publishing Ltd; 2012. p. 184–9.

24. Kulp JL, Mamillapalli R, Taylor HS. Aberrant *HOXA10* Methylation in Patients With Common Gynecologic Disorders: Implications for Reproductive Outcomes. *Reprod Sci*. 2016 Apr;23(4):455-63.

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

26. 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 Mar;24(3):435-444.

27. 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.

28. 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.

29. McGinnis W, Levine MS, Hafen E, Kuroiwa A, Gehring WJ. A conserved DNA sequence in homoeotic genes of the Drosophila Antennapedia and bithorax complexes. *Nature*. 1984 Mar 29-Apr 4;308(5958):428-33.

30. Mirabutalebi SH, Karami N, Montazeri F, Fesahat F, Sheikhha MH, Hajimaqsoodi E, Karimi Zarchi M, Kalantar SM. The relationship between the expression levels of miR-135a and *HOXA10* gene in the eutopic and ectopic endometrium. *Int J Reprod Biomed*. 2018 Aug;16(8):501-506.

31. Miyamoto N, Yoshida M, Kuratani S, Matsuo I, Aizawa S. Defects of urogenital development in mice lacking Emx2. *Development*. 1997 May;124(9):1653-64.

32. 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.

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

34. Petracco R, Grechukhina O, Popkhadze S, Massasa E, Zhou Y, Taylor HS. MicroRNA 135 regulates *HOXA10* expression in endometriosis. *J Clin Endocrinol Metab*. 2011 Dec;96(12):E1925-33.

35. Piltonen TT. Polycystic ovary syndrome: Endometrial markers. *Best Pract Res Clin Obstet Gynaecol*. 2016 Nov;37:66-79.

36. Quinonez SC, Innis JW. Human HOX gene disorders. *Mol Genet Metab*. 2014 Jan;111(1):4-15.

37. Rackow BW, Jorgensen E, Taylor HS. Endometrial polyps affect uterine receptivity. *Fertil Steril*. 2011 Jun 30;95(8):2690-2.

38. Saare M, Modhukur V, Suhorutshenko M, Rajashekar B, Rekker K, Sõritsa D, Karro H, Soplepmann P, Sõritsa A, Lindgren CM, Rahmioglu N, Drong A, Becker CM, Zondervan KT, Salumets A, Peters M. The influence of menstrual cycle and endometriosis on endometrial methylome. *Clin Epigenetics*. 2016 Jan 12;8:2.

39. Salih SM, Taylor HS. *HOXA10* gene expression in human fallopian tube and ectopic pregnancy. *Am J Obstet Gynecol*. 2004 May;190(5):1404-6.

40. Szczepańska M, Wirstlein P, Luczak M, Jagodzinski P, Skrzypczak J. Expression of *HOXA-10* and *HOXA-11* in the endometria of women with idiopathic infertility. *Folia Histochem Cytobiol*. 2011;49(1):111-8.

41. Szczepańska M, Wirstlein P, Luczak M, Jagodziński PP, Skrzypczak J. Reduced expression of *HOXA10* in the midluteal endometrium from infertile women with minimal endometriosis. *Biomed Pharmacother*. 2010 Dec;64(10):697-705.

42. 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 Jan 10;10:1.

43. Taylor HS, Arici A, Olive D, Igarashi P. *HOXA10* is expressed in response to sex steroids at the time of implantation in the human endometrium. *J Clin Invest*. 1998 Apr 1;101(7):1379-84.

44. Taylor HS, Vanden Heuvel GB, Igarashi P. A conserved *Hox* axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the *Hoxa* cluster genes. *Biol Reprod*. 1997 Dec;57(6):1338-45.

45. Taylor HS. The role of *HOX* genes in human implantation. *Hum Reprod Update*. 2000 Jan-Feb;6(1):75-9.

46. Troy PJ, Daftary GS, Bagot CN, Taylor HS. Transcriptional repression of peri-implantation EMX2 expression in mammalian reproduction by *HOXA10*. *Mol Cell Biol*. 2003 Jan;23(1):1-13.

47. 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.

48. 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.

49. 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.

O.M. Zamorschikova, S.S. Sleptsova, S.S. Sleptsov, S.I. Malov

HDV INFECTION: A PREDICTOR OF SEVERE HEPATIC FIBROSIS (LITERATURE REVIEW)

DOI 10.25789/YMJ.2021.74.29

Abstract: About a third of the world's population has serological signs of previous or current HBV infection, and 350 million people suffer from chronic hepatitis B. It is generally known that the combined damage of the liver with hepatitis B (HBV) and delta (HDV) viruses significantly increases the risk of adverse outcomes such as liver cirrhosis and hepatocellular carcinoma. However, the lack of official registration of HDV in Russia contributes to the belittling of the threat posed by it. In addition, many aspects of the pathogenesis and improvement of HDV diagnostic methods still require detailed study. The problem is of particular importance for the Republic of Sakha (Yakutia), since the share of chronic hepatitis D in the etiological structure of chronic viral hepatitis accounts for 24.5%, in some areas the number of people with antibodies to HDV infection among HBsAg-positive population reached 31% [8]. In the European part of Russia, antibodies to the HD virus were detected in 1.3-5.5% of individuals with HBsAg [3].

The aim of this study is to study the epidemiological and pathogenetic aspects of HDV infection using the example of the Republic of Sakha (Yakutia).

The rate of progression of chronic hepatitis D infection in patients is not the same, while the factors that determine the unfavorable outcome of this infection need to be clarified [14,16,28]. In addition to the genetic characteristics of the virus, the role of interferon genes in the formation of liver fibrosis was noted, due to their binding to the receptors of host cells and their influence on the process of viral reproduction within the cell. The results of clinical studies indicate their predictive effects in Asian populations (Japan, China, Taiwan). There are works indicating the influence of polymorphism (rs368234815) of the IFNL4 gene on the incidence of hepatocellular carcinoma [17]. Taking into account the above, the clinical and epidemiological situation for hepatitis D can serve as the subject of studying the influence of the virus genotype and polymorphisms of candidate genes on the formation of HDV-associated hepatocellular carcinoma, as well as on the likelihood of achieving a stable virological response and / or spontaneous clearance in patients with different rates of liver disease progression.

Keywords: Hepatitis D virus, hepatitis B virus, chronic hepatitis, epidemiology, predictors, gene polymorphism, INFL 3, INFL 4, liver cirrhosis, hepatocellular carcinoma.

Introduction. Despite some progress in studying the characteristics of the epidemiology of hepatitis D, the risk of its progressive course remains high. Chronic hepatitis D is a severe form of liver disease characterized by an aggressive course and leading to the rapid development of liver cirrhosis and hepatocarcinoma [3, 6, 7].

Due to the lack of an official registration of this disease in the Russian Federation, the epidemiological situation is assessed fragmentarily by based on the available results of selected scientific studies. In hepatitis B, super-infection with the delta virus causes progression of the disease and leads to a more rapid development of liver cirrhosis than mono-infection of hepatitis B. [1, 2, 12].

Purpose of the study: is to study the epidemiological and pathogenetic aspects of HDV infection using the example of the Republic of Sakha (Yakutia).

Research results: The Republic of Sakha (Yakutia) is one of the disadvantaged territories of the Russian Federation in terms of the prevalence of parenteral viral hepatitis [9]. According to the Rospotrebnadzor Administration for the Republic of Sakha (Yakutia), the incidence of chronic viral hepatitis in 2018 amounted to 67.8 people / 100 thousand people, which is higher than the incidence rates in the Far Eastern Federal District (48.1 people / 100 thousand people) and the Russian Federation (42.2 people / 100 thousand people. The frequency of detection of antibodies to hepatitis D virus according to scientific research in Yakutia is heterogeneous, ranging from 17.2% to 31.7% [8]. In the federal register "Chronic viral hepatitis in the Republic of Sakha (Y)", only 15,068 people were registered, of which the share of chronic hepatitis D accounted for 15.5%. Chronic viral hepatitis D is detected more often in men of working age and is characterized by a progressive course, with the development of cirrhosis of the liver (LC) and hepatocellular carcinoma (HCC). In the etiology of all cirrhosis, the proportion of delta infection is 38.4%, and in HCC - 28.5%, among all deaths from viral hepatitis in Yakutia in 2019, 43% suffered from chronic viral hepatitis D. According to the analysis cases of detection of hepatocellular carcinoma in the Republic of Sakha (Yakutia), this pathology exceeds the average incidence in the country, and the incidence of malignant neoplasms of the liver is ten times higher than the average in the Russian Federation both among men and women [5, 9, 11].

A feature of the hepatitis D virus is its ability to replicate in the human body in the presence of hepatitis B virus [4, 25]. The causative agent of HDV infection was first identified by Italian scientists in 1977 when analyzing 83 liver biomaterials in HBsAg carriers [20, 21]. The

ZAMORSCHIKOVA Olga Mikhailovna – Postgraduate student of Infectious Diseases, phthisiology and dermatovenerology Department, North-Eastern Federal University named after M.K. Ammosov, Institute of Medicine. Yakutsk, Russia. E-mail: olya-botty@mail.ru; **SLEPTSOVA Snezhana Spiridonovna** – Doctor of Med. Sci., assistant professor, Head of Infectious Diseases, phthisiology and dermatovenerology Department, North-Eastern Federal University named after M.K. Ammosov, Institute of Medicine. Yakutsk, Russia. E-mail: sssleptsova@yandex.ru; **SLEPTSOV Spiridon Spiridonovich** – Cand. of Biol. Sci., assistant professor, senior researcher of clinic-populational and medico-social researches laboratory, Yakutian Science Center of complex medical problem. Yakutsk, Russia. E-mail: sachaja@yandex.ru; **MALOV Sergey Igorevich** - Cand. of Med. Sci., assistant of Infectious Diseases Department, Irkutsk State Medical University. Irkutsk, Russia. E-mail: Lynx2000@mail.ru, +7(908)66264