doi: 10.37321/immunology.2023.4-01

UDC 616.697:618.177]-078-092:612.663.5(048.8)

FEATURES OF IMMUNOLOGICAL CHANGES IN INFERTILITY DIAGNOSIS

BABADZHAN V.D., BYRKA YE.O., KLIEPOVA A.A., SOLOVEI A.F., YARESKO A.V.

Kharkiv National Medical University, Kharkiv, Ukraine

Introduction. Sex hormones primarily affect immune responses, and the immune cells and components they create are typically involved in the control of gonadal and female reproductive system processes. In light of this, it can be said that the immune and reproductive systems are intimately related, which is why it is a good idea to take into account how they interact. Addressing the problem of infertility is highly important nowadays because, according to the WHO, every sixth person experiences this difficulty.

The inability to fertilize is known as infertility. A married couple is considered infertile if, in the absence of contraceptive use, they don’t become pregnant within 12 months of having active sexual relations and without using contraceptives. It is worth noting that 75% of couples who don’t use contraception and have regular sexual relations (2-3 times a week) usually become pregnant within one year.

According to data from the WHO, there are a number of primary causes of infertility in both men and women. Infertility in men is typically brought on by issues with sperm quality, such as irregular morphology and motility, ejaculation, absence, or low sperm count. Infertility in women can be brought on by a number of illnesses, including harm to the ovaries, uterus, fallopian tubes, organic and functional endocrine system problems, and other causes.

Immunological factors have a significant role in the development of infertility and account for more than 5% of both men’s and women’s causes. When a couple’s possession of particular organic elements cannot be used to explain why they are infertile, immunological mechanisms take on a greater significance and may become crucial.

The aim. To study and summaries modern immunological methods of laboratory diagnosis of the causes of infertility, namely the quantification of antisperm antibodies, determination of infertility biomarkers (exosomes), and HLA typing, which are relevant and require further study and implementation in the practice of doctors.

Materials and methods. An analytical review and analysis of the scientific literature in recent years, covering the study of immunological causes of infertility and, accordingly, the use of immunological methods of diagnosis and treatment of infertility.

Results: according to the material reviewed, we have identified three areas of research into the causes and diagnosis of infertility, which, in our opinion, require further and more detailed study for the successful overcoming of infertility in the future.

Discussion. Recently, cell therapy, as an innovative method for the treatment of infertility-related diseases, has gained the attention of scientists, and the results obtained in this area have proved promising [2]. Studies in this area have shown that the special properties and therapeutic possibilities of stem cells, as well as their role in tissue regeneration, are related to their secretion and paracrine effects. Thus, the topic of stem cell secrets has gained great interest in the field of regenerative medicine [3]. In this regard, we would like to start our discussion with exosomes, which are one of the most studied stem cell secretions.

Exosome research’s significance in infertility. Nanoscale extracellular vesicles known as exosomes are crucial for intercellular communication in a variety of physiological and pathological processes. They carry physiologically active substances such proteins, deoxyribonucleic acids (DNA), microribonucleic acids (miRNA), non-coding RNAs (ncRNA), and lipids and assist in maintaining the body’s homeostasis [4]. Exosomes are crucial for the regulation of critical cellular functions as intercellular communication, migration control, proliferation control, differentiation control, and extracellular matrix creation. Exosomes have also been demonstrated to have an impact on reproductive system functions in both men and women, including spermatogenesis, acrosome response, embryo implantation, and gametogenesis [5].

Women’s infertility may be linked to inflammatory conditions of the reproductive system. Exosome composition can act as brand-new biomarkers for inflammatory illnesses and immunopathological abnormalities that develop as a result of inflammatory processes. According to studies, neoplastic exosomes have a high concentration of miRNAs, which help to suppress T-cell proliferation and differentiation while also encouraging the induction of apoptosis [5, 6].

Determination of exosomes in endometriosis. Endometriosis is one of the most common diseases among women, which reduces the likeli-

hood of becoming pregnant. It is a long-lasting gynecological condition in which tissue that resembles uterine lining starts to proliferate outside of the uterus. Clinical signs of endometriosis include pelvic pain that does not coincide with menstruation, infertility, and an atypical distribution of stroma and glands that resemble endometrial tissue. Peritoneal fluid and exosomes from endometrial cells have been found to contain long non-coding RNAs (lncRNAs), microRNAs, and proteins that are involved in histone modification, the development of new blood vessels (angiogenesis), and immunological control. Exosomes may be crucial in the emergence of endometriosis because they promote neuroangiogenesis in the uterine wall [7]. The described endometriosis-specific characteristics of exosomes, such as miR-214-3p, extracellular vesicular legumain pseudogene 1 (EV-LGMNP1), and actin filament-related protein 1 antisense RNA 1 (AFAP1-AS1), open up new opportunities in the diagnosis and treatment of endometriosis [8, 9].

Determination of exosomes in polycystic ovary syndrome. Polycystic ovary syndrome (PCOS) is a common hormonal disorder of the reproductive system in women that predominantly affects women of reproductive age. A study was undertaken in 2020 to look into exosomes found in human follicular fluid as potential PCOS biomarkers. In this investigation, RNA from exosomes from human follicular fluid was isolated and sequenced. Exosomes found in human follicular fluid have been demonstrated in these investigations to be possible molecular indicators for the diagnosis of PCOS [10]. Exosomes can also be used to diagnose fertility problems in older women. In a study of animals, namely twenty-year-old mares, significantly higher levels of microRNAs of alveolar origin were observed in exosomes compared to young mares [11].

The study of exosomes and their contents as biomarkers for the diagnosis of diseases related to male fertility has also yielded initial results. Numerous studies have demonstrated the significance of exosome-related proteins, including the exosome protein annexin II, which can be exploited as a biomarker for male infertility and abnormalities of spermatogenesis [5]. The level of the enzyme prostaglandin D2-synthase (PTGDS) was notably low in males who had testicular vasectomy and tended to decline in azoospermia. PTGDS can be employed as a biomarker for the diagnosis of obstructive azoospermia, according to further research. When compared to men with non-obstructive azoospermia, PTGDS levels in individuals with obstructive azoospermia were considerably lower [10]. Based on the above, we can see that exosomes can play a role in the diagnosis of various diseases of the reproductive system in women and men.

Antisperm antibody testing’s significance in infertility: Antisperm antibodies (ASA) can be produced as a result of several disorders, which subsequently aid in the progression of infertility. IgG, IgA, and IgM, often known as ASA, are sperm antigen-specific antibodies. Ejaculate, cervical mucus, follicular fluid, and male and female serum are the fluids that contain these antibodies. It should be emphasized that IgG and IgA can also be found in vaginal secretions, unlike IgM, which is only present in serum. IgG is simultaneously made locally and discharged from the blood serum, whereas secretory IgA is solely made locally.

Antigens of spermatozoa, against which ASAs act, reduce sperm motility, which in turn prevents their movement via the reproductive tract of the female, negatively affects capacitation and acrosome reaction, the fertilization process, and interferes with implantation, growth and development of the embryo.

The hemizona assay (HZA), zona pellucida penetration assay (ZPA) and zona-free hamster egg-sperm penetration assay (SPA) were used to investigate the possible inhibitory effects of ASAs on the fertilization process in humans and mice [12]. The ZPA diagnostic test additionally revealed the effect of monoclonal antibodies (2C6, 1G12, 3B10, H6-3C4) on the entry of sperm into the lenticular membrane [13].

All diagnostic tests showed that two (2C6, 1G12) of the four monoclonal antibodies had a pronounced inhibitory effect. Monoclonal antibody (3B10) blocks ZPA and SPA, but does not inhibit HZA. A monoclonal antibody (H6-3C4) had no inhibitory effect on the fertilization process at all [13]. Based on the above, it has been established that ASAs interfere with the fertilization process at some stages, namely: some ASAs block the process of sperm maturation, which in turn prevents all phases of the fertilization process; other ASAs inhibit the process of capacitation and sperm binding to the zona pellucida; and others block the acrosome reaction, which reduces the ability of sperm to move through the zona pellucida and ooplasm [14]. It is important to note that in infertile men and women, ASAs are found in higher concentrations (9-12% higher than normal), but they are also found in fertile patients [14].

Women whose partners are found to have ASA most often have ASA as well, but such ASA reacts only with the sperm of the male partner and not with the sperm of other men. It should be noted that the presence of sperm in the female reproductive tract after sexual intercourse does not cause ASA. However, there is a possibility of ASA during sexual intercourse if the vaginal mucosa is damaged or if sperm enters the gastrointestinal tract [15].

Studies have established a link between the presence of inflammatory diseases in women and

an increase in the concentration of ASA. Thus, salpingitis is closely related to the stimulation of the body’s activated immune response and affects the formation of antibodies [16]. A positive correlation between the concentration of ASA in the blood and salpingitis-associated infertility in women has been established [17]. It is assumed that an increase in the level of immune reactivity of spermatozoa is a factor that affects the above phenomenon.

In most cases, women suffering from PCOS are characterized by a lack of ovulation, significantly elevated blood testosterone levels and obesity. PCOS is associated with a high risk of inflammation, injury and damage to the ovaries. There are claims that the above factors cause the formation of autoantigens and autoantibodies. However, a study involving 46 infertile patients with PCOS showed otherwise. The women had their serum ASA and sex hormones measured [18]. The results were as follows: 4-5 patients had low levels of circulating ASA in their serum, while none of the patients studied had elevated levels of ASA [19]. Thus, the claim of a close relationship between ASA and the pathogenesis of female infertility associated with PCOS was not confirmed.

A similar picture can be observed in endometriosis. A study conducted in 2012 involving 75 infertile women with minimal or mild endometriosis showed that none of the patients had elevated serum levels of ASA [20].

There is a claim that the formation of ASA is influenced by cross-immune reactions with exogenous antigens (microorganisms). A recent study has shown that human papillomavirus also affects the development of ASA. However, some of the causes of ASA remain unknown [21].

The significance of HLA typing of couples in infertility. In recent years, much attention has been paid to determining combinations of HLA genotypes in infertile couples, as some of them block fertilization, impairing the allodiscrimination process. HLA-typing of couples is performed in the following cases: during the diagnosis of infertility, before pregnancy planning, including in vitro fertilization, as well as in case of unsuccessful attempts, miscarriage and couples with close family ties.

A child who has inherited HLA-antigens has one gene of each locus from both parents. Therefore, the child is half alien to the mother’s body. This «foreignness» triggers an immune response aimed at preserving the pregnancy. A clone of immune cells is formed in the body of a pregnant mother, which in turn form special «protective» (blocking) antibodies. In normal pregnancy, «protective» antibodies to paternal HLA-antigens appear in the earliest stages of pregnancy.

The antigenic composition of the trophoblast is mainly represented by maternal class II histocompatibility antigens, including HLA-DQA1 genes, which is why they are used as immune markers.

In 70% of infertile couples, a high degree of similarity of HLA-DQA1 alleles (more than 50%) between a man and a woman was found, both in couples with miscarriages and in couples with unsuccessful in vitro fertilization (IVF) attempts. The HLA-DQA1 match between spouses causes similarities between fetal and maternal tissues, which in turn create a lack of antigenic stimulation of the woman’s immune system, which is necessary for pregnancy. Thus, the carriage of the HLA-DQA1*5 allele can be used as a marker of the degree of HLA-DQA1 compatibility of a couple [22].

The study showed that the presence of the HLA-DQA1*5 allele in both men and women increased the likelihood of high (>50%) overall HLA-DQA1 compatibility of the couple by 24.3 times in the miscarriage group, while the corresponding chances were 10.5 times higher in the IVF failure group [23].

Conclusion. We have reviewed the articles that included materials on the study of immunological methods of infertility research and identified three currently relevant methods for identifying the causes and diagnosis of this disease, which continue to require thorough study to solve the problems of infertility. Carriage of the HLA-DQA1*5 allele can be used as a marker of the degree of HLA-DQA1 compatibility of a couple. As well as the use of some exosome markers, such as endometriosis-specific exosome characteristics, such as miR-214-3p, EV-LGMNP1, AFAP1-AS1. At the same time, there is no doubt that there is a high correlation between elevated levels of ASA and female infertility, so special attention should be paid to ASA in the diagnosis of male infertility.

REFERENCES:

1. Roberts, C.W., Walker, W., Alexander, J. Sex-associated hormones and immunity to protozoan parasites. Clin. Microbi. Rev. 2001. Vol. 14(3). P.476-488. https://doi.org/10.1128/cmr.14.3.476-488.2001
2. Jahanbani, Y., Shafiee, S., Davaran, S., Roshangar, L., Ahmadian, E., Eftekhari, A. Dolati, S., Yousefi, M. Stem cells technology as a platform for generating reproductive system organoids and treatment of infertility related diseases. Cell Biol. Int. 2022. Vol. 46(4), P. 512-522. https://doi.org/10.1002/cbin.11747
3. Pourakbari, R., Ahmadi, H., Yousefi, M., Aghebati-Maleki, L. Cell therapy in female infertility-related diseases: emphasis on recurrent miscarriage and repeated implantation failure. Life Sci. 2020. Vol. 258. P. 118-181. https://doi.org/10.1016/j.lfs.2020.118181

4. Gurunathan, S., Kang, M.-H., Jeyaraj, M., Qasim, M., Kim, J.-H. Review of the isolation, characterization, biological function, and multifarious therapeutic approaches of exosomes. Cells. 2019. Vol. 8 (4). P. 307. https://doi.org/10.3390/cells8040307

5. *Kowalczyk, A., Wrzecińska, M., Czerniawska-Piątkowska, E., Kupczyński, R.* Exosomes–Spectacular role in reproduction. Biomed Pharmacother. 2022. Vol. 148. P. 112-752. https://doi.org/10.1016/j.biopha.2022.112752

6. *Ye, S.-B., Li, Z.-L., Luo, D.-H., Huang, B.-J., Chen, Y.-S., Zhang, X.-S., Li, J.* Tumor-derived exosomes promote tumor progression and T-cell dysfunction through the regulation of enriched exosomal microRNAs in human nasopharyngeal carcinoma. Oncotarget. 2014. Vol. 5 (14) P. 5439–5452. https://doi.org/10.18632/oncotarget.2118

7. *Freger, S., Leonardi, M., Foster, W.G.* Exosomes and their cargo are important regulators of cell function in endometriosis. Reprod. Biomed. Online. 2021. Vol. 43 (3), P. 370–378. https://doi.org/10.1016/j.rbmo.2021.05.022

8. *Nazri, H.M., Imran, M., Fischer, R., Heilig, R., Manek, S., Dragovic, R.A., Baker, C.M.* Characterization of exosomes in peritoneal fluid of endometriosis patients. Fertil. Steril. 2020. Vol. 113 (2). P. 364–373 doi:10.1016/j.fertnstert.2019.09.032

9. *Shen, Y., You, Y., Zhu, K., Fang, C., Chang, D., Yu, X.* Exosomes in the field of reproduction: A scientometric study and visualization analysis. Front Pharmacol. 2022. Vol. 13. https://doi.org/10.3389/fphar.2022.1001652

10. *Jahanbani, Y., Beiranvand, T., Mamaghani, P. Y., Aghebati-Maleki, L., Yousefi, M.* Exosome-based technologies as a platform for diagnosis and treatment of male and female infertility-related diseases. Journal of Reproductive Immunology. 2023. Vol. 156. https://doi.org/10.1016/j.jri.2023.103833.

11. *Mobarak, H., Heidarpour, M., Lolicato, F., Nouri, M., Rahbarghazi, R., Mahdipour, M.* Physiological impact of extracellular vesicles on female reproductive system; highlights to possible restorative effects on female age-related fertility. BioFactors. 2019. Vol. 45 (3) P. 293–303. https://doi.org/10.1002/biof.1497

12. *Gupta, S.K., Srinivasan, V.A., Suman, P., Rajan, S., Nagendrakumar, S.B., Gupta, N., Panda, A.K.* Contraceptive vaccines based on the zona pellucida glycoproteins for dogs and other wildlife population management. Am J Reprod. Immunol. 2011. Vol. 66(1). P. 51–62. https://doi.org/10.1111/j.1600-0897.2011.01004.x

13. *Shibahara, H., Hasegawa, A.* (Eds.). (2022). Gamete Immunology. Springer Nature Singapore Pte Ltd.

14. *Cui, D., Han, G., Shang, Y., Liu, C., Xia, L., Li, L., Yi, S.* Antisperm antibodies in infertile men and their effect on semen parameters: a systematic review and meta-analysis. Clin. Chim. Acta. 2015. Vol. 444. P. 29–36. https://doi.org/10.1016/j.cca.2015.01.033

15. *Selvaraj, K.; Selvaraj, P.* Chapter 24: Immunology in Infertility. In Principles & Practice of Assisted Reproductive Technology; Rao, K., Carp, H., Fischer, R., Eds.; JP Medical Ltd.: London, UK, 2014.

16. *Rajaratnam, A., D’Cunha, P., Furtado, Z., Fernandes, H.* Tuberculous salpingitis: A case report. J. Clin. Diag. Res. JCDR. 2013. Vol. 7 (6). P. 1186–1188. doi: 10.7860/JCDR/2013/4834.3032

17. *Liu, Q.Z., Zhu, W.J., Liu, H.P., Jiang, H.* Evaluation on antisperm antibody in infertile women with chronic salpingitis. J. Reprod. Contracept. 2014. Vol. 25 (3). P. 159–163. doi: 10.7669/j.issn.1001-7844.2014.03.0159

18. *Myogo, K.; Yamano, S.; Nakagawa, K.; Kamada, M.; Maegawa, M.; Irahara, M.; Aono, T.* Sperm-immobilizing antibodies block capacitation in human spermatozoa. Arch. Androl. 2001. Vol. 47 (2). P. 135–142. https://doi.org/10.1080/014850101316901343

19. *Bandoh, R.; Yamano, S.; Kamada, M.; Daitoh, T.; Aono, T.* Effect of sperm-immobilizing antibodies on the acrosome reaction of human spermatozoa. Fertil. Steril. 1992. Vol. 57 (2). P. 387–392. https://doi.org/10.1016/S0015-0282(16)54851-1

20. *Keenan, J.A., Sacco, A.G., Subramanian, M.G., Kruger, M., Yurewicz, E.C., Moghissi, K.S.* Endocrine response in rabbits immunized with native versus deglycosylated porcine zona pellucida antigens. Biol Reprod. 1991. Vol. 44 (1). P. 150-156. https://doi.org/10.1095/biolreprod44.1.150

21. *Gupta, S., Sharma, R., Agarwal, A., Boitrelle, F., Finelli, R., Farkouh, A., Shah, R.* Antisperm Antibody Testing: A Comprehensive Review of Its Role in the Management of Immunological Male Infertility and Results of a Global Survey of Clinical Practices. World J. Men’s Health. 2022. Vol. 40 (3). P. 380-398. https://doi.org/10.5534/wjmh.210164

22. *Shankarkumar, U., Pawar, A., Gaonkar, P., Parasannavar, D., Salvi, V., Ghosh, K.* HLA allele associations in idiopathic recurrent spontaneous abortion patients from India. J Hum Reprod Sci. 2008. Vol. 1 (1). P. 19-24. doi: 10.4103/0974-1208.39592

23. *Nowak J. K., Glapa-Nowak A., Banaszkiewicz A., Iwańczak B., Kwiecien J., Szaflarska-Popławska A., Walkowiak J.* HLA-DQA1*05 associates with extensive ulcerative colitis at diagnosis: an observational study in children. Genes (Basel). 2021. Vol. 12 (12). https://doi.org/10.3390/genes12121934

SUMMARY

FEATURES OF IMMUNOLOGICAL CHANGES IN INFERTILITY DIAGNOSIS

BABADZHAN V.D., BYRKA YE.O., KLIEPOVA A.A., SOLOVEI A.F., YARESKO A.V.

Kharkiv National Medical University, Kharkiv, Ukraine

The aim. To study and summarize modern immunological methods of laboratory diagnosis of the causes of infertility.

Materials and methods. An analytical review and analysis of the scientific literature in recent years, covering the study of immunological causes of infertility and, accordingly, the use of immunological methods of diagnosis and treatment of infertility.

Results and discussion. Infertility treatment is an urgent medical problem because, according to the WHO, every sixth person faces this problem during their lifetime. Immunological aspects play an important role in infertility and account for 5% of infertility among men and women. In cases where the cause of infertility cannot be explained by the presence of specific organic signs in a couple, the identification of immunological mechanisms of infertility becomes more crucial. The immunological causes of infertility are still underestimated, as the mother’s immune system plays a major role in the successful implantation of the embryo and the carrying of a pregnancy. The relevant areas of immunological research are HLA typing to determine the immunological «compatibility» of couples, the study of the role of antisperm antibodies (ASA) in the development of infertility, and the use of exosomes as biomarkers of reproductive system diseases that may be the cause of infertility. In accordance with the material reviewed, we have identified the main areas of research into the causes, diagnosis, and treatment of infertility, which require further detailed study for the successful overcoming of infertility in the future.

Conclusion. We have reviewed the articles that included materials on the study of immunological methods of infertility research and identified three currently relevant methods for identifying the causes and diagnosis of this disease, which continue to require thorough study to solve the problems of infertility. Carriage of the HLA-DQA1*5 allele can be used as a marker of the degree of HLA-DQA1 compatibility of a couple, as well as the use of some exosome markers, such as endometriosis-specific exosome characteristics such as miR-214-3p, EV-LGMNP1, AFAP1-AS1. There is also no doubt that there is a high correlation between elevated levels of ASA and female infertility, so special attention should be paid to ASA in the diagnosis of male infertility.

Key words: infertility, antisperm antibodies, exosomes, HLA typing.

РЕЗЮМЕ

ОСОБЛИВОСТІ ДІАГНОСТИКИ ІМУНОЛОГІЧНИХ ЗМІН ПРИ БЕЗПЛІДДІ

БАБАДЖАН В.Д., БИРКА Є.О., КЛЄПОВА А.А., СОЛОВЕЙ А.Ф., ЯРЕСЬКО А.В.

Харківський національний медичний університет, м. Харків, Україна

Мета. Вивчити та узагальнити сучасні імунологічні методи лабораторної діагностики причин безпліддя.

Матеріали і методи. Аналітичний огляд та аналіз наукової літератури останніх років, що висвітлює вивчення імунологічних причин безпліддя та, відповідно, застосування імунологічних методів діагностики та лікування безпліддя.

Результати та їх обговорення. Лікування безпліддя є актуальною медичною проблемою, оскільки, за даними ВООЗ, кожна шоста людина протягом життя стикається з цією проблемою. Імунологічні аспекти відіграють важливу роль у безплідді і становлять 5% безпліддя серед чоловіків і жінок. У випадках, коли причину безпліддя неможливо пояснити наявністю специфічних органічних ознак у подружжя, вирішального значення набуває виявлення імунологічних механізмів безпліддя. Імунологічні причини безпліддя все ще недооцінені, хоча визнається, що імунна система матері відіграє головну роль в успішній імплантації ембріона та виношуванні вагітності. Актуальними напрямами імунологічних досліджень є HLA-типування для визначення імунологічної «сумісності» пар, вивчення ролі антиспермальних антитіл у розвитку безпліддя, використання екзосом як біомаркерів захворювань репродуктивної системи, які можуть бути причиною безпліддя. Відповідно до розглянутого матеріалу, ми визначили основні напрями дослідження причин, діагностики та лікування безпліддя, які потребують подальшого детального вивчення для успішного подолання безпліддя в майбутньому.

Висновок. Аналіз імунологічних методів дослідження безпліддя дозволив виявили три актуальні на сьогоднішній день методи встановлення причин цього захворювання: наявність маркерів екзосом, специфічних для ендометріозу, таких як miR-214-3p, EV-LGMNP1, AFAP1-AS1 у жінок; носійство алелі HLA-DQA1*05 як маркеру ступеня HLA-DQA1 сумісності пари та підвищений рівень антиспермальних антитіл у чоловіків та жінок.

Ключові слова: безпліддя, антиспермальні антитіла, екзосоми, алель HLA-DQA1*05, HLA-типування.

Конфлікт інтересів: Подана у редакцію стаття на має конфлікту інтересів з науковими співробітниками та науково-дослідними установами.

Наукова значимість роботи: Наукова значимість роботи полягає у знайомстві читачів з новітніми видами імунологічних порушень, що спостерігаються при безплідді та можливостями їх діагностики, що відкриває перспективи до ефективного лікування. Стаття має важливе науково-практичне значення для лікарів акушерів-гінекологів, імунологів.

Наукова стаття є частиною науково-дослідних робіт кафедри внутрішньої медицини №2 і клінічної імунології та алергології: № 0123U100331 «Патогенетичне обґрунтування клініко-діагностичних, прогностичних та терапевтичних маркерів у хворих на ішемічну хворобу серця за умов поліморбідності» – ініціативна НДР, строки виконання – 2022-2025 рр.

Концептуалізація: Бирка Єлизавета.

Керування даними: Бабаджан Володимир Данилович.

Формальний аналіз: Клєпова Анастасія Артемівна.

Дослідження: Бирка Єлизавета Олександрівна, Клєпова Анастасія Артемівна, Соловей Альбіна Федорівна, Яресько Анастасія Володимирівна.

Методологія: Бабаджан Володимир Данилович.

Адміністрування проекту: Бабаджан Володимир Данилович.

Керівництво: Бабаджан Володимир Данилович.

Перевірка: Бабаджан Володимир Данилович.

Візуалізація: Соловей Альбіна Федорівна, Яресько Анастасія Володимирівна.

Написання оригінальної чернетки: Бирка Єлизавета Олександрівна, Клєпова Анастасія Артемівна.

Написання огляду і редагування: Соловей Альбіна Федорівна, Яресько Анастасія Володимирівна.

Conflict of interests. The manuscript submitted to the editorial board has no conflicts of interest with researchers or research institutions.

Scientific significance of the work: The scientific significance of the work is to acquaint readers with the newest types of immunological disorders observed in infertility and the possibilities of their diagnosis, which opens up prospects for effective treatment. The article is of great scientific and practical importance for obstetricians and gynecologists, immunologists.

The scientific article is a part of the research work of the Department of Internal Medicine №2 and Clinical Immunology and Allergology: No. 0123U100331 “Pathogenetic substantiation of clinical diagnostic, prognostic and therapeutic markers in patients with coronary heart disease in conditions of polymorbidity” – initiative research, terms of implementation – 2022-2025.

Conceptualization: Byrka Yelyzaveta.

Data management: Babadzhan Volodymyr.

Formal analysis: Kliepova Anastasiia.

Research: Babadzhan Volodymyr, Byrka Yelyzaveta, Kliepova Anastasia, Solovei Albina, Yaresko Anastasiia.

Methodology: Babadzhan Volodymyr.

Project administration: Babadzhan Volodymyr.

Supervision: Babadzhan Volodymyr.

Verification: Babadzhan Volodymyr.

Visualization: Solovei Albina, Yaresko Anastasiia.

Writing of the original draft: Byrka Yelyzaveta, Kliepova Anastasiia.

Writing the review and editing: Solovei Albina, Yaresko Anastasiia.

АВТОРСЬКА ДОВІДКА

- **Бабаджан Володимир Данилович**

  Доктор медичних наук, професор, Харківський національний медичний університет, кафедра внутрішньої медицини №2, клінічної імунології та алергології імені академіка Л.Т. Малої, м. Харків, Україна
  Адреса: 61002, м. Харків, вул. Пушкінська, 41
  Тел.: +380 67 573 23 38
  E-mail: vd.babadzhan@knmu.edu.ua
  ORCID: https://orcid.org/0000-0002-3939-4209

- **Бирка Єлизавета Олександрівна**

  Студентка Харківського національного медичного університету, кафедра внутрішньої медицини №2 і клінічної імунології та алергології імені академіка Л.Т. Малої, м. Харків, Україна
  Адреса: 61002, м. Харків, вул. Пушкінська, 41
  Тел.: +380 95 769 80 88
  E-mail: yobyrka.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0007-4812-751X

- **Babadzhan Volodymyr**

  Doctor of Medical Sciences, professor, Kharkiv National Medical University, Department of Internal Medicine No. 2 and of Clinical Immunology and Allergology named after Academician L.T. Mala, Kharkiv, Ukraine
  Address: 61002, Kharkiv, str. Pushkinska, 41
  Phone: +380 67 573 23 38
  E-mail: vd.babadzhan@knmu.edu.ua
  ORCID: https://orcid.org/0000-0002-3939-4209

- **Byrka Yelyzaveta**

  Student of Kharkiv National Medical University, Department of Internal Medicine No. 2 and Clinical Immunology and Allergology named after Academician L.T. Mala, Kharkiv, Ukraine
  Address: 61002, Kharkiv, str. Pushkinska, 41
  Phone: +380 95 769 80 88
  E-mail: yobyrka.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0007-4812-751X

- **Клєпова Анастасія Артемівна**

  Студентка Харківського національного медичного університету, кафедра внутрішньої медицини №2 і клінічної імунології та алергології імені академіка Л.Т. Малої, м. Харків, Україна
  Адреса: 61002, м. Харків, вул. Пушкінська, 41
  Тел.: +380 99 223 41 93
  E-mail: aakliepova.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0005-7030-9999

- **Соловей Альбіна Федорівна**

  Студентка Харківського національного медичного університету, кафедра внутрішньої медицини №2 і клінічної імунології та алергології імені академіка Л.Т. Малої, м. Харків, Україна
  Адреса: 61002, м. Харків, вул. Пушкінська, 41
  Тел.: +380 99 514 75 99
  E-mail: afsolovei.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0007-8794-8636

- **Яресько Анастасія Володимирівна**

  Студентка Харківського національного медичного університету, кафедра внутрішньої медицини №2 і клінічної імунології та алергології імені академіка Л.Т. Малої, м. Харків, Україна
  Адреса: 61002, м. Харків, вул. Пушкінська, 41
  Тел.: +380 99 114 16 58
  E-mail: avyaresko.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0003-5838-3972

- **Kliepova Anastasiia**

  Student of Kharkiv National Medical University, Department of Internal Medicine No. 2 and Clinical Immunology and Allergology named after Academician L.T. Mala, Kharkiv, Ukraine
  Address: 61002, Kharkiv, str. Pushkinska, 41
  Phone: +380 99 223 41 93
  E-mail: aakliepova.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0005-7030-9999

- **Solovei Albina**

  Student of Kharkiv National Medical University, Department of Internal Medicine No. 2 and Clinical Immunology and Allergology named after Academician L.T. Mala, Kharkiv, Ukraine
  Address: 61002, Kharkiv, str. Pushkinska, 41
  Phone: +380 99 514 75 99
  E-mail: afsolovei.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0007-8794-8636

- **Yaresko Anastasiia**

  Student of Kharkiv National Medical University, Department of Internal Medicine No. 2 and Clinical Immunology and Allergology named after Academician L.T. Mala, Kharkiv, Ukraine
  Address: 61002, Kharkiv, str. Pushkinska, 41
  Phone: +380 99 114 16 58
  E-mail: avyaresko.1m19@knmu.edu.ua
  ORCID: https://orcid.org/0009-0003-5838-3972

Стаття надійшла в редакцію 03.10.2023 р.