REBUPLIC OF AZERBAIJAN

On the rights of the manuscript

ABSTRACT

of the dissertation for the degree of Doctor of Sciences

THE NEW ASPECTS OF INFERTILITY DIAGNOSIS AND TREATMENT IN THE ASSISTED REPRODUCTIVE TECHNOLOGIES PROGRAM

Speciality: 3215.01 – Obstetrics and gynecology

Field of science: Medicine

Applicant**:** **Mahira Kamil Ismayilova**

Baku – 2024

The dissertation was performed at the department of Allergy and Immunology and in Immunological Laboratory of Azerbaijan Medical University, and the Department of Obstetrics and Gynecology of the Central Clinic Hospital

Scientific supervisor: doctor of medical sciences, professor **Jamila Fazil Gurbanova**

Official opponents: honored scientist, doctor of medical sciences, professor **Hijran Firudin Bagirova**

İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMİ KATİBİ
Tibb elmləri doktoru, professor
Nazim Adil oğlu Pənahov
06.03.24

doctor of medical sciences, professor **Leyla Musa Rzaguliyeva**

doctor of medical sciences **Rafiali Mashalla Novruzov**

doctor of medical sciences **Naila Akif Shahbazova**

Dissertation Council ED 2.06 of the Supreme Attestation Commission under the President of the Republic of Azerbaijan operating under Azerbaijan Medical University

Chairman of the Dissertation Council: doctor of medical sciences, professor **Fariz Hidayat Jamalov**

Scientific secretary of the Dissertation Council: doctor of medical sciences, professor **Eldar Allahverdi Aliyev**

Chairman of the scientific seminar: doctor of medical sciences, professor **Seadat Hasan Sultanova**

GENERAL CHARACTERISTICS OF THE WORK

Relevance of the topic and degree of its elaboration. Infertility is one of the urgent problems of medical, social and state importance not only in foreign countries, but also in Azerbaijan[1,2]. According to data provided by external sources, 15% of population in the reproductive period is infertile. According to the numerous studies, up-to-date the share of female infertility is 40%, and the share of male infertility is 45%, in 15% of cases, the cause of infertility is not known[3].

Currently, the in vitro fertilization (IVF) and associated programs and techniques known as assisted reproductive technologies (ART) have been recognized as the culmination in the treatment of infertility[4,5].

In the preparatory phase of therapy with the technique of in vitro fertilization, determination of the depth of initial examination of patients, correct diagnosis based on the causes of infertility,

---

1. Керимова С.Н. Применение экстракорпорального оплодотворения при длительном бесплодии / С.Н.Керимова, Э.М.Алиева - 2019. - с. 12-15.
2. Хорошкеева О.В. Роль антигенов главного комплекса гистосовместимости в реализации привычного выкидыша / О.В.Хорошкеева, Н.К.Тетруашвили, О.В.Бурменская [и др.] // Акушерство гинекология. - 2016. №3. - с. 5-10.
3. Cicinelli E. Prevalence of chronic endrometritisin repeated unexplained implantation failure and the IVF success rate after antibiotic theraphy / E.Cicinelli, M.Matteo, R.Tinelli [et. al.] // Hum. Reprod. - 2015. –Vol.30(2). - p.323-330.
4. Pau Nicolau. Alcohol consumption and in vitro fertilization: a review of the literature / N. Pau, E.Miralpeix, I.Sola [et. al.] // Gynecological Endocrinology. - 2014. – Nov., Vol.30, Issue 11. - p.759-763.
5. Franasiak J.M. Endometrial microbiome at the time of embryo transfer: next-generation sequencing of the 16S ribosomal subunit / J.M. Franasiak, M.D. Werner, C.R. Juneau [et. al.] // J.Assist. Reprod. Genet. -2016. – Vol.33. – p.129-136.

study of the state of reproductive function, as well as the somatic, endocrine, infectious and immunological status are urgent issues[6].

The efficiency of in vitro fertilization technique is associated not only with the quantity and quality of oocytes and embryos, but also with the state of endometrium[7,8].

An important condition for the successful implantation of the embryo transplanted into the uterine cavity is the readiness of endometrium to receive this embryo[9].

Immunogenetic compatibility of both partners plays a significant role due to HLA Class II genes, that carry out immunological interactions between the mother's body and the embryo through fetoplacental tissue at the beginning of pregnancy.

A high degree of compatibility of partners according to the HLA system can be the cause of insufficient immune response and lost pregnancy[10].

6. Васюхина А.А. Иммуногистохимические особенности эндометрия у женщин с трубно-перитонеальным бесплодием / А.А.Васюхина, Л.С.Целкович // Аспирантский вестник Поволжья. - 2016. №1-2, - с.13-16.
7. Курбанова Дж.Ф. Преждевременная недостаточность яичников. Тотальный овариальный резерв / Дж.Ф.Курбанова, Г.Х.Ганиева, З.Г.Ахмедова, В.А.Гусейнова / Müasir ginekologiya və perinatoligiyanın aktual məsələləri - 2014. № 4, - c. 44-47.
8. Курбанова Дж.Ф. Correlation among inhibin A and B, anti-mullerian hormone, follicle-stimulating hormone, luteinizing hormone and estradiol hormones in infertile women / Дж.Ф.Курбанова, A.A.Abdullayeva Journal of Medical, Biomedical and Applied Sciences – 2018, - s. 19-22.
9. Мальцева Л.И. Хронический эндометрит в практике акушера-гинеколога / Л.И.Мальцева, Г.Р.Смолина, Р.И.Шарипова [и др.] // Российский вестник акушера-гинеколога. - 2015. –Т.15. №5. - с. 102-105.
10. Zheng J. Analysis of the association of human leukocyte antigen DG gene polymorphisms with unexplained recurrent spontaneous abortion among ethnic Han Chinese from Wenzhou region / J.Zheng, H.Zhang, X. Xu [et.al.] //– 2016. – Vol. 33 № 1, - p.81-84.

Polycystic ovary syndrome (PCOS), which is quite common among women from the Azerbaijani population, is no less topical matter in the treatment of women infertility[11].

Women with PCOS are also at risk group due to developing ovarian hyperstimulation syndrome (OHSS) in the process of superovulation induction[12]. OHSS is one of the dangerous complications that occur during the application of ART. Besides the negative effect on the woman's health, the occurrence of OHSS also creates unfavorable conditions for the development of the implanted embryo[13].

An analysis of numerous studies has shown that, despite the constant enhancement of ART techniques, the probability of pregnancy within the IVF program is about 30%[14].

In most cases, among women who have undergone an IVF program due to infertility, pregnancy does not always end at the appointed time or does not develop at all due to the formation of thromboses in the fetoplacental system.

The causes of thrombosis are genetic defects of hemostasis and acquired disorders – antiphospholipid syndrome (AFS), which, by the nature of thrombophilia formation, can be equated with genetic defects

---

11. Азизова М.Э. Синдром поликистозных яичников с позиций современных представлений// - Баку: Азербайджанский Медицинский Университет / Казанский Медицинский Журнал, - 2015, Том 96, № 1, - с. 77-80.
12. Abbara A. Clinical parameters of ovarian hyperstimulation syndrome following different hormonal triggers of oocyte maturation in IVF treatment / A.Abbara, R.Islam, SA.Clarke [et.al.] // Clinical Endocrinology 88(6), - 2018, - p.920-927/
13. Kuc P. The dynamic of endometrial growth and the triple layer appearance in different controlled ovarian hyperstimulation protocols and their influence on IVF outcomes / P.Kuc, A.Kuczynska, M.Topczewska // Gynecol. Endocrinol. -2011. –Vol.27, № 11. – p.867-873.
14. Liselotte H. A fruitful alliance: the synergy between Atopobium vaginae and Gardenella vaginalis in bacterial vaginosis-associated biofilm /[et. al.] H.Liselotte, J.Vicky, S.Abdellati // Sexually Transmitted Infections. – 2016. - p.1-5.

of hemostasis[15]. In recent years, the method of preimplantation genetic diagnostics (PIGD) has been widely used in the practice of ART. PIGD allows to carry out the selection of genetic full-value embryos, which increases the chances of pregnancy occurring in IVF practice, allows to identify genetic mutations in a short period of time and to transfer only healthy embryos into the uterine cavity[16]. Selection of an embryo for implantation plays a very significant role for the successful end of the planned pregnancy and is based on morphological cellular analysis of embryos. Despite the evidences of correlation between embryonic morphology and the number of successful implantations, data from a number studies indicate a high percentage (30-40%) of morphologically "normal embryos" with various chromosomal disorders, mainly aneuplodia[17]. Notwithstanding with the sufficient number of relevant studies, currently, there is no single opinion on the importance of the influence of these or other factors on the efficiency of IVF programs, as well as the possibility of predicting the outcome of therapy at the stage of pregravid preparation of partners[18]. Analysis of literature proves a fairly stable, not high frequency of pregnancy - 38-40% in the transfer of embryos, even for women of up to 35 years[19].

15. Di Nisio M. Effects of multiple inherited and acquired thrombophiliya on outcoms of in-vitro fertilization / Di Nisio, A.Ponzano, GM.Tiboni [et. al.] // Trombosis research. Vol. 167. - 2018, - p.26-31.
16. Asissted Reproductive Technology. National Summary Report / National Center for Chronic Disease Prevention; Healthy Promotion of the Centers for Disease Control and Prevention in consulation; American Society for Reproductive Medicine and the Society for Asissted Reproductive Technology. – Atlanta (GA): US Dept of Healthy and Human Services. - 2015. - p.76
17. Capalbo A. The impact of biopsy of human embryo developmental potential during preimplantation genetic diagnosis // Hum. Reprod. – 2014. –Vol.29, № 6. - p.1173-1181.
18. Jenine K. Harris. Primer on binary logistic regression. Family Medicine and Community Health 9 (Suppl. 1), - 2021. - p.183-189.
19. Kupka M.S. Assisted reproductive technology in Europe , 2011: results generated from European registers by ESHRE / M.S.Kupka, T.D'Hooghe, A.P.Ferraretti [et. al.] // Human Reproduction . - 2016. -Vol.31. № 2. - p.233-248.

In conditions of significant heterogeneity of main clinical characteristics of partners in infertile marriage, the use of new statistical methods for analyzing the efficiency predictors of IVF is a priority, which conditioned the relevance of the current research methodology. In this regard, there is a need to develop and systematize criteria that help to predict efficient ways to achieve pregnancy in more frequent forms of infertility. On the one hand, such forecasting will allow to take advantage of the use of in vitro fertilization in the treatment of infertility, and on the other hand, it will significantly reduce unnecessary costs spent on carrying out this or that procedure. The aforementioned determined the relevance of this study.

Object and subject of research. The object of research was women with infertility (primary and secondary) who were sent to the Central Clinical Hospital of Baku for the therapy with IVF/ICSI (İntra Cytoplasmic Sperm injection) technique from 2007 to 2020.

For the achievement of tasks set, a study of 518 infertile patients who underwent 690 IVF/ICSI cycles was carried out.

According to the results of IVF/ICSI, all patients were divided into two groups: pregnant patients, i.e. with positive results of IVF/ICSI – Group A – main group (234 people) and patients with negative results of IVF/ICSI – Group B – control group (284 people), those who have not become pregnant after IVF/ICSI procedure.

In addition, according to the objectives of the research, women who got a therapy with the IVF/ISSI technique were divided into two sub-groups:

The 1st sub-group (55 people) with complications that may occur during ovulation stimulation – ovarian hyperstimulation syndrome (OHSS) and the 2nd sub-group (69 people) – without such complications (without OHSS).

The purpose of research – the aim was to create an optimal prognostic model of various results of in vitro fertillization in women with infertility based on the logistic regression method and to determine the probability of developing ovarian hyperstimulation syndrome.

The objectives of research

1. To analyze the anamnesis data, to study anthropometric, instrumental, histological, embryological, as well as clinical and laboratory data in infertile women with various results of in vitro fertilization program.
2. To study immunological and immunogenetic data in infertile women with various results of in vitro fertilization.
3. To determine the predictive value of the studied data by means of the statistical method named "Main components", to determine the parameters of selection of the studied women based on the method of factorial analysis, so that they can be included in the prediction formula of the results of in vitro fertilization in the future.
4. To determine more optimal statistical method of predicting the outcomes of IVF in infertile women according to the analysis of gynecological pathology, nature of ultrasound pathologies of pelvic organs and data of histological examination of endometrium.
5. To determine more optimal statistical method of predicting the outcomes of in vitro fertilization in infertile women based on the study of immunological and immunogenetic markers (CD4/CD8, anti-AFS thrombin IgM and IgG, HLA – DQB1*0201, HLA – DQB1*05, HLA – DQB1 0501 alleles).
6. To determine more optimal statistical method of the outcomes and forecast of in vitro fertilization in infertile women based on a multifactorial analysis of the studied parameters.
7. To study clinical and anamnestic, anthropometric, laboratory, immunological and immunogenetic data and to determine their predictive significance in order to create a predictive model of the likelihood progression of this complication of in vitro fertilization in infertile women with OHSS.
8. To develop an optimal statistical method for predicting the likelihood progression of OHSS in infertile women, considering their gynecological status.
9. To develop a logistic regression model for predicting the outcomes of in vitro fertilization technique in the framework of modern assisted reproductive technologies program.

Research methods. Examination of 518 patients with infertility, selected for in vitro fertilization and embryo transfer procedure, was carried out. According to the results of research, patients were divided into 2 groups: positive and negative IVF results. The research methods included: general clinical examination, routine laboratory tests (clinical blood analysis, hemostasiogram, hormonal, bacteriological examination, ejaculate examination), instrumental examinations (ultrasonography, hysterescopy, laparoscopy), analysis of the general status of patients involved in special laboratory diagnostic methods, immunogenetic and genetic studies, morphological analysis of endometrial biopsy specimen, pre-implantation genetic diagnosis of embryos, as well as clinical psychological analysis of patients. Prediction of the results of IVF and the likelihood of ovarian hyperstimulation syndrome was carried out based on the method of logistic regression and main components.

Main clauses put into defense.

At the stage of pregravid preparation of partners, it is necessary to determine the efficiency predictors of IVF method.

Important predictive factors that should be considered in determining the individual probability of a successful outcome of IVF program are: the age of the patient, the results of previous pregnancies, the number of mature oocytes, the number of good quality embryos on the day of transfer, AMH, HLA-DQB1*05, AFS IgM/T level, PCOS or OHSS, recurrent dysbiosis of the vaginal opening, chronic salpingo-oothecitis, the number of antral follicles, "endometrium at the proliferating stage".

Important risk criteria for the progression of OHSS in infertile women include: age, HWI, the number of antral follicles of the oophorons, PCOS, which significantly lowers the adaptive reserves of the female body.

The predictive model developed and recommended for clinical practice has a high informative characteristic (above 75%), high sensitivity and specificity, which makes it possible to identify the positive and negative outcomes of IVF.

The logistic regression model applied at the stage of pregravid preparation of partners allows to determine the probability of pregnancy in the result of IVF more accurately.

Scientific novelty of the research. In the course of this research, new scientific data were obtained:

- The main predictive factors of the efficiency of in vitro fertilization program in infertile women have been identified due to the application of the mathematical method of main components: results of previous pregnancies in case of secondary infertility (lost pregnancy), loss of spontaneous pregnancy, previous ART (number of mature oocytes), number of high-quality embryos on the day of transplantation, age, AMH level, HLA - DQB1*05, AFS IgM/T, PCOS or PCO, recurrent dysbiosis of the vaginal opening, chronic salpingo-oothecitis, number of antral follicles, endometrium at the proliferating stage.

- A model has been developed to predict the efficiency of in vitro fertilization, which allows to carry out personalized accompaniment of infertile women with different results of the ART program by the binary logistic regression method.

- Predictive coefficients of the proposed models for predicting the outcome of pregnancy induced by in vitro fertilization in infertile women based on the method of logistic regression are shown: general descriptiveness of the model based on such predictors as the age, AMH, previous ART (number of mature oocytes), previous ART (number of high quality embryos on the day of transplantation) is 94,29%, sensitivity is 89,0% and specificity is 96,4%. Another model is based on the following predictors: results of previous pregnancies in case of secondary infertility (lost pregnancy), loss of spontaneous pregnancy, previous ART cycle of IVF, with live birth, number of mature oocytes, number of high quality embryos and age, general descriptiveness of the model is 86,93%, sensitivity is 84,7% and specificity is 88,88%.

- The optimal predictive model with high sensitivity (83.63%) and specificity (83.82%) and significant predictive coefficient (83.74%) of the probability of OHSS progression was developed and proposed.

- More significant prognostic markers defining the likelihood of OHSS progression in infertile women were presented in the framework

of in vitro fertilization program: age, HWI, number of antral follicles of the oophorons, polycystic ovary syndrome or polycystic ovaries, and AMH.

- Mathematical method that allows to predict the successful outcome of the procedure and to determine the likelihood of OHSS progression was included to the preparatory stage of in vitro fertilization program.

Theoretical and practical significance of the research. Practical significance of the results of research lies in improving the efficiency of infertility treatment in women by applying the IVF/ISSI program.

In order to predict the occurrence of pregnancy within the framework of IVF program, predictive criteria which are positively and negatively correlated with IVF were determined. Thus, AMH, previous ART (number of mature oocytes), number of high quality embryos on the day of transplantation, number of antral follicles, endometrium in the proliferation phase are positively correlated with successful outcome of IVF, and Hla-DQB1*05, the outcome of previous pregnancies in case of secondary infertility (lost pregnancy), loss of spontaneous pregnancy, PCOS or PCO, recurrent dysbiosis of the vaginal opening, chronic salpingo-oothecitis are negatively correlated with unsuccessful outcome of IVF.

The assigned predictive markers will help to increase the chances of implantation and successful completion of pregnancy within the IVF program.

As a result of the research carried out, preliminary examination of patients who will be treated by applying IVF method will be conducted and recommendations on complex practical measures for pre-IVF preparation will be given. This will make it possible to increase the efficiency of the procedure, reduce the frequency of pregnancy complications and perinatal pathologies.

Prediction of likelihood of OHSS progression during IVF and extensive implementation of prognostic techniques into the clinical practice contribute to improving the results of therapy in infertile families and preventing serious complications of this syndrome.

With the use of pre-IVF predictive formulas, priority will be given to selective transfer of one embryo based on an integrative assessment of the relevant criteria, thereby preventing complications caused by multifetal pregnancies, as well as significantly reducing unnecessary costs for carrying out various procedures.

Approbation and application of the results of dissertation. Local and international research-to-practice conferences were held on the topic of this dissertation.

I International research-to-practice virtual conference, "Human genetics and prospects for the development of genetic diseases" – "Pre-implantation genetic diagnosis", Izmir, Turkey, p.48, September 26-27, 2020.

"İnfertil kadınlarda tüp bebek sonuçlarının tahmini", Türk Jinekoloji ve Obstertrik Derneği (TJOD) Online Sempozyumu - "Kısırlığı olan kadınlarda tüp bebek (invitro fertilizasyon) yöntemiyle tedavi olunma sonuçlarının tahmin edilmesi", Türkiyə Cumhuriyyəti, SS-100. , 4-6 Aralık 2020.

"Genetic aspects of Urology and Reproductive Medicine", XV Symposium of urologists and andrologists of Azerbaijan - "Role of genetic factors in case of In Vitro Fertilization", Azerbaijan, Baku, December 21, 2019.

Conference with organizational support of the association of "Support for the development of gynecology and perinatology" - "Characteristics of reproductive anamnesis and features of the course of pregnancy in women within the program of assisted reproductive technologies", Baku, February 28, 2020.

"Research-to-practice conference on human genetics and genetic diseases" - "Role of preimplantation genetic diagnostic in fertilization", Azerbaijan, Baku, May 30, 2020.

XIX symposium of urologists and andrologists of Azerbaijan – "Risk of aneuploidy in embryos in cases of pathozoospermia in men in assisted reproductive technologies", Azerbaijan, Guba, June 17-19, 2022.

Nakhchivan State University in the framework of Master Class – "Assisted reproductive technologies (artificial fertilization IVF", Nakhchivan AR, December 03, 2021.

Conference on “International standard of Clinical Practice” at the Georgian Association of “Medical Education and proving medicine” - "Predicting the likelihood of progression of ovarian hyperstimulation syndrome in infertile women during in vitro fertilization" ("Прогнозирование вероятности развития синдрома гиперстимуляции яичников у бесплодных женщин при проведении экстракорпорального оплодотворения"), Georgia, Chakvi c., July 9-17, 2022.

VI Uluslararası Koru Gebelik Doğum Lohusalık Kongresi – "Application of binary logistic regression method in development of optimal predictive model of in vitro fertilization results", Bolu, Turkey, April 26-30, 2023.

XX symposium of urologists and andrologists of Azerbaijan - "Pathozoospermia and pre-implantation genetic diagnostics of embryos", Gabala, June 9-11, 2023.

Research-to-science Regional Conference of the Europe and Asia Study Group of obstetrician-gynecologist of the Institute of Obstetrics and Gynecology of the Ministry of Health - "Modern approach to forecasting the IVF outcomes", Guba, June 23-25, 2023.

Research outcomes is included in the research and development program of the Institute of Obstetrics and Gynecology and in the research-to-practice activities of the Department of Obstetrics and Gynecology of the Central Clinic. A total of 40 articles and theses on the dissertation were published: 27 foreign, 13 local. Included in the international summarizing and indexing systems (databases) – 5 journals Web of Science, 4 SCOPUS. Without co-authors – 18 articles, 7 theses (3 local, 4 foreign), 11 speeches (7 local, 4 foreign).

The meeting of the preliminary discussion of the case was held with the participation of the colleagues of the I Department of Obstetrics and Gynecology and II Department of Obstetrics and Gynecology of Azerbaijan Medical University (March 9, 2023, protocol №08). The approval of the dissertation was held at the Scientific Seminar of the ED2.06 Dissertation Council established under AMU (November 29, 2023, protocol №03).

Name of the organization where the dissertation work is performed. Dissertation work is carried out in Allergology and Immunology Department of Azerbaijan Medical University, Obstetrics and Gynecology Department of the Central Clinic.

Total volume of the dissertation in characters with separate indication of the volume of the structural divisions. The introductory part of the dissertation, each of which consists of several sections, consists of 5 chapters, conclusion, results, practical recommendations, list of used literature and list of used abbreviations. The dissertation contains 79 tables, 5 graphs, 19 pictures. Introduction part (22066 characters), chapter I (100240 characters), chapter II (105177 characters), chapter III (74110 characters), chapter IV (30784 characters), chapter V (32106 characters), conclusion (35145 characters), results (3606 characters), practical recommendations (1569 characters), except for the list of used literature, total volume of the dissertation consists of 404803 characters. The total volume of the dissertation paper is 321 pages. More than 343 scientific literature and articles are used in the research.

DESIGN AND RESEARCH METHODS OF THE WORK

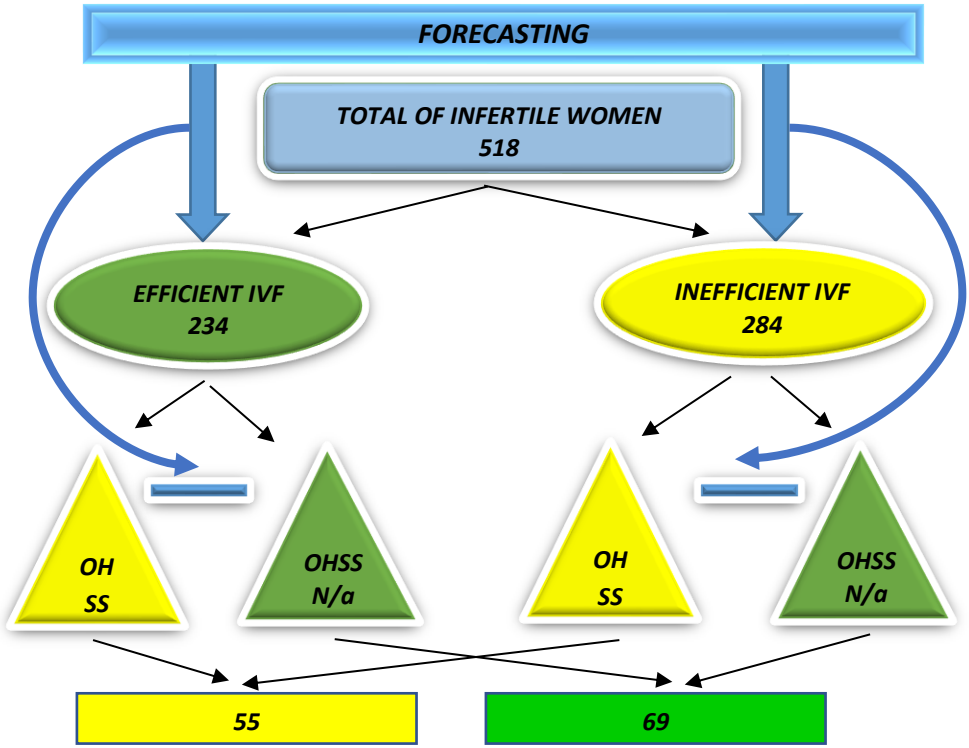
The object of research was women with infertility (primary and secondary) who were sent to the Central Clinical Hospital of Baku for the therapy with IVF/ISSI technique from 2007 to 2020.

For the achievement of tasks set, a study of 518 infertile patients who underwent 690 IVF/ISSI cycles was carried out.

According to the results of IVF/ISSI, all patients were divided into two groups: pregnant patients, i.e. with positive results of IVF/ISSI – Group A – main group (234 people) and patients with negative results of IVF/ISSI – Group B – control group (284 people), those who have not become pregnant after IVF/ISSI procedure.

In addition, the women who were treated by applying the IVF/ISSI technique were divided into two sub-groups in accordance with the objectives of the research: the 1st sub-group (55 people) with complications that may occur during ovulation stimulation – ovarian

hyperstimulation syndrome (OHSS) and the 2nd sub-group (69 people) – without this syndrome (without OHSS). Pic. 1.



Pic. 1. Design of the research.

Preliminary examination of couples

Preliminary examination of couples was carried out on an outpatient basis at the CCH of Baku city and included general clinical and special examination methods: general and special gynecological examinations; ultrasound examination of the pelvic organs; blood group and rhesus factor determination; clinical blood analysis; biochemical blood analysis; hemostasogram; examination of blood for syphilis, HIV (human immunodeficiency virus), hepatitis B and C; Examination of flora in the urethra and cervical canal, determination

of the degree of purity of the vaginal opening; cytological examination of smears from the cervix and colposcopy; examinations for infections (chlamydiosis, ureaplasmosis, mycoplasmosis, simple herpes virus, cytomegaly, toxoplasmosis, rubella); Blood analysis for FSH (folliculostimulating hormone), LH (luteinizing hormone), E2 (estradiol), Pr (prolactin), T (testosterone), cortisol, P (progesterone), TTH (thyrotropic hormone), STH (somatotropic hormone), Free T4 (thyroxin4), Free T3 (thyroxin3), AMH, histamin, serotonin, DHEAS, 17-OHP; opinion of the attending doctor about the patient's state of health and the possibility of prenatal care; opinion of other specialists according to the instruction; spermogram of a man; medical-genetic consultation; functional examination methods; ultrasound examination; endoscopic examinations: hysterescopy, laparoscopy. Immunological examinations, immunogenetic examinations, HLA-typification, clinical and psychological examination of a woman.

Therapy by applying the IVF technique included: 1. Diagnostics of the causes of infertility and selection of couples; 2. Stimulation of superovulation; 3.Monitoring of the growth and development of follicles (ultrasound and hormonal); 4. Transvaginal puncture of follicles and obtaining pre-ovulatory oocytes under the USI control; 5. Obtaining sperm and preparing it for in vitro insemination; 6. In vitro insemination of oocytes, cultivation of germ cells and embryos, fertilization of oocytes and determination of the fact of embryos splitting; 7. Transfer of embryos to the mother's uterus; 8. Maintaining the lutein phase of the therapeutic menstrual cycle; 9. Diagnostics of pregnancy, its follow-up and permission to give birth.

Stimulation of superovulation. Stimulation of superovulation was carried out with gonadotropic drugs: Puregon 300 BV/0.36 ml, Puregon 600 BV/0.72 ml, Puregon 900 BV/1.08 ml - G 036 A06 Follitropin beta, Organon (3.3 MCG), Gonal F – 450 BV/0.75 ml, follitropin Alpha G 03GA05, “Serona”Menogon 75 (menotropin) “Ferring Pharmaceuticals”, g03ga02 merional 75 (menotropin), G03GA02 “IBSA Institute biochimique, S.A", Menapur 75 BV, Ferring Internation Centery G036A02, Menagon 75, Organon

G03GA02, Metrodin 75 BV ”Serona“, G036A04 (urofollitropin), Fostimon 75/150 BV (urofollitropin), IBSA (Institut Biochimique, S.A" G03GA04. Dosage and scheme of drugs were prescribed individually, considering the hormonal status (levels of LH, FSH), as well as the results of ultrasound monitoring of the growth of follicles and the thickness of endometrium. We used the following protocols of superovulation stimulation:

"Long" protocol - With the application of prodrugs of QnRH agonists ((Lyukrin prodrug "ABBOTT Laboratories" (i-8-242 №009895 10.12.97 ppr), Zoladeks "AstraZeneca" (I №013307 / 02-2001 03.09.01), Decapeptil prodrug "Ferring Parmaceutical” (I - 8-248 № 008612 28.04.98 ppr), Diferelin ”Beafour Ipsen International" (I - №011452 / 01-1999 28.10.99)). These drugs were used on the 19th–22nd day of the menstrual cycle (middle of the lutein phase), and gonadotropins were used after achieving the desensitization of the pituitary gland.

"Antagonist" protocol - on the 2-3rd day of the menstrual cycle, gonadotropin hormones are administered, from the 6-7th day of stimulation, when the dominant follicle reaches 13-14 mm, antagonists of QnRH are applied (“Orgalutron” - 0.25 mg “Ganirelix”, “Organon” - 0.5 ml, H01CC01 (Germany), “Cetrotide” - 0.25 mg (Ceftrolex), “Merck UE ATHCARE, KGOA” (Germany), H01CC02

"Short protocol” – Agonists of QnRH were applied simultaneously with gonadotropic hormones from the 2^{nd}-3rd day of the menstrual cycle; gonadotropic hormones were applied from the 2^{nd}-3rd day of the menstrual cycle, after the diameter of 14mm of the leading follicle is obtained (6th - 7th day of stimulation) agonists of QnRH ((Orgalutran “Organon” (I №014324/01/2002 27.08.02), Serono “ (I №014978/01 – 2003 16.05.03)) were administered.

Puncture of follicles was carried out 35-36 hours after the use of the ovulatory dose of XH. All follicles with diameters larger than 14 mm were punctured and aspirated. In the process, a vaginal ultasound transmitter (7.5 MHs) with a special head - a lead for needle – was used. A needle with an outer diameter of 1.6 mm and a length of 25 cm, with an echo-contrast scratches on the tip visible when

performing transvaginal ultrasound was used. A system for aspiration of follicular fluid was connected to the needle, and the absorption of the follicle contents into the flask by creating negative pressure (about 120-150 mm. m.c.) in the aspiration line was carried out after the puncture. Aspiration fluid from one or several follicles was collected in a flask. As soon as these flasks were full, they were replaced with another ones. Subsequently, containers with flasks were transferred to the "K - System" laminar box with a vertical stream of sterile air and table with heated surface. The total amount of aspirated follicular fluid was recorded in ml, and then the liquid in each flask was poured into a sterile plastic Petri dish for determination of pre-ovulatory oocytes. The oocytes found and visually determined due to the massive silver cumulus (1-5 mm) were transferred to the nutritional medium in NUNC or Petri bowls with the help of sterile plastic capillaries connected by roller pipettes. The "Oocyte-corona-cumulus" complex after washing the cumulus out from blood impurities was investigated by binocular microscope at up to twenty and forty times magnification to determine the pre-ovulatory quality and maturity level of the obtained oocytes. Depending on the number of pre-ovulatory complexes obtained, they were placed in one or more wells (cavities) of 0.6 ml in fresh nutritional medium of NUNC bowls.

Initially, spermatozoa were microscopically evaluated in colored preparations in accordance with the WHO recommendations (WHO laboratory manual for the examination of human semen and sperm – cervical mucus interaction. Fourth edition, 2000, Cambridge). After the analysis, the ejaculate was transferred to Falcon flasks with sterile centrifuges in order to be washed out from the seed plasma. Washing-out was carried out in one of two ways: simple centrifugation and centrifugation on a density gradient. In simple centrifugation, the ejaculate was mixed with a three-to-five layer volume of the washing medium and centrifuged twice for 10 minutes in a 500-degree rotating shaker with intermediate homogenization of the sediment and substitution of the supernatant fluid. For flotation of more mobile spermatozoa, 0.5-1.0 ml of cultivating nutritional medium was added to the sediment, consisting of washed spermatozoa. For preparation of

spermatozoa in the density gradient, SilSelect, SupraSperm sets and, in some cases, a 55% and 80% Percoll gradient were used. During this technique, ejaculate was placed on the surface of a double density gradient and centrifugation was carried out for 20 minutes at 300 degrees. The sediment was aspirated with a thin needle, transferred to another flask and centrifuged twice for 10 minutes at 500 degrees with intermediate homogenization of the sediment in a rotating shaker and substitution of the supernatant fluid. The nutritional cultivation medium was also poured over the obtained sediment. The flask with the washed spermatozoa was incubated for 0.5 - 8 hours at a temperature of 36° on the surface of the table in laminar box until the oocytes insemination.

Ovum fertilization. Oocytes were fertilized by applying the intracytoplasmic sperm injection (ICSI) technique.

ICSI technique. Obtained preovulatory oocytes are released from "Corona radiata - Cumulus oophorus" complex cells by applying the sequential pipette method in the nutritional medium consisting of 33 units of hyaluronidase. In hyaluronidase medium, oocytes exposed for no more than 1 minute were transferred to wells (cavities) containing nutritional medium to be washed and purified from hyaluronidase. Oocytes released from "Corona radiata - Cumulus oophorus" complex cells were evaluated by their level of maturity: primary ovarian follicle phases (CV), M1 and M2, state of cytoplasm - presence of vacuoles, high granularity, color, thickness of zonae pellucida. Within several hours, oocytes in CV and M1 phases were transferred into the separate well (cavity) for further in vitro maturation. Mature preovulatory cells in the M2 phase, in which the 1st polar body is distinguished, were exposed to ICSI procedure.

In vitro cultivation of zygotes and embryos. The fertilized oocytes were kept in an incubator under the aforementioned conditions in one of the mediums listed below: Nutritient medium of INRA Menezo B2 (France); Nutritional medium of INRA Menezo Upgrade (France); Nutritional medium of FertiCult (Denmark); MediCult (Sweden) nutritional media complex, consisting of fertilization, first

days of development and growth of embryos to the blastocyst stage media; HTF nutritional medium (Irvin, USA).

16-20 hours after fertilization, oocytes were visually examined under an inverted microscope with binocular magnification (40 to 75 times magnification) and / or 200 times magnification. In order to be released from corona radiata cells, oocytes fertilized by the standard technique were imposed to pipetting. After the ICSI procedure, such manipulation for oocytes was not necessary. In the course of microscopic research, the presence of pronuclei and their number, the peculiarity of the location of pronuclei, as well as the state of the cytoplasm were determined. Zygotes with the characteristic features of fertilization pathology (three or more pronuclei, rough granularity or lysis of cytoplasm, vacuolization) were not used in the course of further work and were destroyed.

Selected normal zygotes were transferred into wells (cavities) with a fresh nutritional medium and cultivated for 30 hours or more (4.8 blastomeres, morula, blastocyst stages) until the moment they were transplanted into the uterine cavity. Pre-implantation embryos splitting features were monitored twice during the working day. After the transplantation of embryos and the expulsion of catheter, the catheter was examined in a microscope to see if the embryos remained in it. The number of transplanted embryos ranged from 1 to 3. Patients laid on their backs in a horizontal position for the next 2 hours after the transplantation, and then left the center. All procedures were carried out on an outpatient basis. When the Pre-Implantation Genetic Diagnosis (PGD) of embryos was carried out, the membranes of embryos were penetrated by a special laser by biopsy technique from the embryos on the 3rd day of cultivation, and 1-2 cell blastomeres were obtained by aspiration needle (20-40 MCN), fixed in the flask and sent to the genetic laboratory. Molecular cytogenetic analysis of the obtained samples was carried out by FISH (fluorescence in situ hybridization) technique. DNA of the chromosomes was hybridized with ready-made DNA probes (with probes of EBOT brand). The finished products were analyzed using Zeiss luminescent microscope. Number and structural anomalies were carried out on 9 chromosomes

(13, 15, 16, 17, 18, 21, 22, X, Y). Results of the analysis were submitted within 24 hours, and the embryos were transferred into the uterus on the 5th day of puncture at the blast level.

In order to ensure the full value of the lutein phase, all patients were additionally injected with XQ ("Profazi", Serono) 500-2000 BV i/m on the day of embryo transplantation, and then every fourth day of embryo transplantation. In addition, micronized progesterone ("Ulterogestan", "Esco - Iscoveseco", France, Gera progesterone, Biogest, Progestan) was used intravaginally at 600 mg/day. In cases where ovarian hyperstimulation syndrome (OHSS) was diagnosed, chorionic gonadotropic hormone was not prescribed. When endometrial development was delayed, estradiol-valerate (proginova, estrofem) was prescribed at 2-4 mg / day from the day of follicle puncture until the moment when the pregnancy was diagnosed, and then up to the 5-6th week of gestation, depending on the course of pregnancy.

On the 21st day after the puncture, the presence of CG in urine (qualitative analysis) or B-sub-units of CG in blood serum (quantitative analysis) was determined to diagnose pregnancy. Transvaginal ultrasound of the pelvic organs was performed to confirm the fact of pregnancy and to determine the localization and number of implanted embryos. In case of pregnancy with three or more embryos, instrumental reduction of their number was carried out at the insistence of patients. The number of embryos was reduced to two, and in case of emphatic protest of a woman, even to one. Selection of embryos depended on their size, localization in the uterus and the accessibility of manipulation to be carried out. Embryos of a larger size, with clear structural outlines, located near the bottom of the uterus were tried to be kept. The manipulation was carried out at 10-11 weeks of pregnancy, when the crown-to-rump length of the fetus was 45-50 mm. During these periods, the surgery is less traumatic and safer for the embryos to be kept.

The reduction technique of the number of embryos was as follows: after premedication and sanation of the anterior abdominal wall, a puncture of the fetus from the anterior or posterior wall of the

uterus was performed with a 25 cm long 22G needle under the control of ultrasound with an abdominal transmitter (C5-1). In this process, the goal was to get the needle into the chest and heart cavity of the fetus. The cannula of the needle was removed and 1-2 ml of KCl (Potassium chloride 75mg/ml) was injected into it, and expected until the moment when the heartbeat of the fetus stopped. The procedure was carried out simultaneously with 1-2 embryos, provided that they did not remove the needle from the uterus. No complications were observed during the reduction and the first 3 days after it. They US control was performed 3, 24 and 72 hours after the operation. In the postoperative period, all patients received antibacterial therapy (ampicillin or ampiox 1.0 g 4 times a day per os for 5 days). In cases where progressive ectopic pregnancy (tubal) was diagnosed, patients were hospitalized and laparoscopically performed tubectomy with "STORZ" equipment was carried out. The uterine pregnancies were carried out in accordance with the generally accepted principles of modern obstetrics.

The obtained data of clinical and laboratory examinations were processed by variational statistics methods in STATISTICA 10 (STATISTICA software package, USA, version 8 for Windows 10), statistical analysis system. The average value (M) of the obtained quantitative indicators and its standard error (m), and the absolute number of occurence of charasteristic features and its share (in %) were calculated. Characteristics of distribution for normality in all samples were determined according to the Kolmogorov – Smirnov, Shapiro - Wilki and Leven criteria. If the normal distribution was confirmed or the number of research objects was very large (more than 100), a parametric criterion - the Student's t-test, otherwise the Manna-Whitney criterion, which is a nonparametric criterion were used for comparative analysis. Statistical significance of the difference between groups according to the occurrence of characteristic features was defined based on the $\chi 2$ criterion of Pearson or Fisher's exact test. The use of the latter is more preferable, when the indicator in one of the cells in 2x2 tables is less than 5. Statistical significance of the

difference between the indicators is considered to be accepted at p<0,05.

The impact of individual symptoms of patients and their quantity coefficients on IVF results and its complications (presence of OHSS) was studied using logistic regression analysis in the Statistics 10 (USA) program. When the dependent quantity is binary (i.e., values such as Yes / No, Available/Not Available are taken, for example: the result of IVF is positive or the result of IVF is negative), logistic regression is used and its result is affected by independent variables (qualitative and / or quantitative) of various nature. The fact is that under the influence of the studied symptoms, the likelihood of accepting one of these two statements is assessed.

The logit of this probability is the ratio of the natural logarithm "positive effect" (p) probability to the "negative effect" (1p) probability.

$$Logit\ (p) = \ln \frac{\mathrm{p}}{1 - \mathrm{p}}$$

The (Logtip) value is continuous and assumes values in the interval from 0 to 1 (from negative effect to positive one). The work of the logistic regression procedure consists of formation and evaluation of an equation of the following type:

Logit (p) = Y = b0 + b1x1 + b2x2 + b3x3 + …
X1, x2, x3 – fixed variables.
b0, b1, b2, b3, - constant coefficients.

Then the probability of positive effect:

$$p = Y = \frac{1}{1 + e^{-Y}} = \frac{1}{1 + 2{,}72^{\,-Y}} = A$$

The probability of negative result of IVF is equal to "A", and the probability of positive result of IVF is equal to (1 – A), or the

probability of negative result of IVF is equal to (A x 100) %, and the probability of positive result of IVF is equal to [(1 – A) x 100]%. The average values of parameters (in numerical values) or the numbers 1 (when there is a symptom) and 0 (when there is no symptom) obtained in the course of the study are given, the value of Y is obtained.

The purpose of regression analysis is to measure the relationship between the dependent variable and one (double regression analysis) or several (multiple) fixed variables. Fixed variables are also called factorial, explanatory, determining, regressors and predictors. Dependent variable is sometimes called identifiable, explainable, "answer".

In the current research, fixed variables are separate signs characterizing patients with infertility, and dependent variables are the result of IVF, in particular – the occurrence of pregnancy (i.e., efficient IVF) or the failure of pregnancy after taking an IVF course (i.e., inefficient IVF). The dependent variable is also the development of OHSS or the absence of this complication.

In order to include important symptoms characterizing infertile women in the regression analysis, determination of the informativeness of previously independent symptoms is carried out. Selection of informative symptoms for formalization of classification functions is carried out on the basis of determining the reliability of the compared symptoms in patients with positive and negative results of IVF.

According to the data of the maximum values of linear classification functions (LCF), patients were distinguished into one or another forecasting group. To assess the efficiency of linear equations of forecasting, 2x2 conditional tables and indicators such as sensitivity and specificity were applied. Sensitivity is the share of persons with positive IVF results among the examined patients. This indicator characterizes the probability of real positive result of IVF. Its value was calculated by the formula SENSITIVITY – TP / TP + FN. Specificity is the share of persons with negative IVF results among patients. This parameter was calculated using the formula SPECIFICITY – TN / FP + TN.

TP – true positive; FN – false negative; TN – true negative; FP – false positive

Table 1

Efficiency of the obtained equations of regression

Solution according to the method tested	Actual state of objects	
	Positive	Negative
Positive	TP	FP
Negative	FN	TN

Definitions of features are as follows:

– TP (True Positives) – correctly classified positive patterns (true positive cases);

– TN (True Negatives) – correctly classified negative patterns (true negatives);

– FN (False Negatives) – positive patterns classified as negative (type I error). This is the so-called “false switch" case, in which the events of interest to us are not detected by mistake (false negative patterns);

– FP (False Positives) – negative patterns classified as positive (type II error). This is the false detection. So, in the absence of an event, an erroneous decision is made about its existence (false positive cases).

In most cases, while analyzing the quality of the diagnostic test, they work not with absolute parameters, but with relative ones – shares expressed in percentages, which are translated into definitions such as the sensitivity and specificity of the method.

Sensitivity is the share of true positive cases correctly identified by the method being tested:

$$Sp = \frac{TP}{TP + FN} x100\%$$

Specificity is the share of true negative cases:

$$Sp = \frac{TN}{TN + FP} x100\%$$

In regression analysis, selection of parameters for the research was carried out in the Statistica 10 Program (USA) close to predictors of the forecast or by the method of factor analysis. Factor analysis is a set of techniques that make it possible to reveal the aggregate features of hidden (unclear, latent) organized structures and the mechanism of development of the studied phenomena, processes based on the real existing relationships of the analyzed symptoms, the relationships of the examined objects themselves.

Techniques of factor analysis in the research practice are applied mainly for the purpose of compacting data describing the variability (dispersion) of elementary symptoms (R – factor analysis technique) or the variability of observed objects (Q – factor analysis technique), obtaining a small number of aggregate symptoms.

The algorithm of factor analysis is based on the use of a reduced matrix of double correlations (co-variations).

Reduced Matrix is a matrix on the main diagonal of which not units of complete correlation (values) or values of complete variance, but their reduced, slightly decreased values are placed. It should be noted that factor analysis is a mathematical model of the syndromological approach in medicine.

Factor analysis helps to combine a large number of symptoms into several groups that are identical to the concept of "disease syndrome". In this case, the first factor reflects the maximum information on the relationships of the case under study. Each of the following factors complemented the information on the relationship of symptoms.

RESULTS OF PERSONAL RESEARCH

In accordance with the goals and objectives of the study, as well as based on the results of IVF / ISSI, all examined patients were divided into two groups. Group A (234 women) included patients who got pregnant, that is, patients with positive IVF / ISSI results. Group B (284 women) included patients with negative IVF / ISSI attempts, i.e., patients who did not get pregnant after the procedure.

From the groups of women selected based on the retrospective studies, 311 patients were selected for further research, who were subsequently subjected to clinical-laboratory and instrumental examinations.

Clinical-anamnestic, antropometric, laboratory parameters, social status, characteristics of ultrasound data, histological, embryological indicators of women involved in the research have been analyzed in detail. Features of the reproductive anamnesis were presented. The psycho-emotional environment of women with different results of IVF was studied. Immunological parameters, genetic, immunogenetic data were studied. The average age of female patients with inefficient IVF procedures (Group B) was 34, 9 ± 4, 2, and in Group A (efficient IVF course) was 30, 9 ± 3, 4 years ($p < 0.01$).

Anthropometric parameters did not differ among the studied groups. No significant differences in social status, frequency of harmful habits were observed among the studied groups. Extragenital pathologies and previous inflammatory diseases of genital sphere also did not have significant differences between the compared groups.

Significant differences were found in the laboratory parameters of patients, particularly, in the hormonal profile: significantly higher figures of AMH and LH in the group with efficient IVF. At the same time, the level of cortisol in this group was significantly lower compared to the group in which IVF was inefficient. During the study of coagulatory parameters, low values of PI were also determined in Group A. In the group with positive results of IVF, significantly higher results of the histamine level and lower values of the serotonin level in the blood serum were determined.

The study of gynecological anamnesis determined an increase in the relative frequency of PCOS and salpingo - oothecitis in Group B, while ultrasound examination revealed a decr ease in the number of antral follicles.

No significant differences were revealed in hysterosalpingography, hysteroscopy and laparoscopy in the compared groups. At the same time, during histological examination of the endometrium, an increase in the percentage of women with endometritis and a decrease in the number of individuals in the proliferation phase of the endometrium in the group with negative IVF results were determined.

The study of reproductive anamnesis determined an increase in the total number of frequency of abortions, three and more abortions, an increase in the frequency of two and more cases of lost pregnancy in Group B. The analysis of menstrual function did not show significant differences in the comparison groups.

In particular, it is worth to note the high frequency of spontaneous pregnancies resulted in live birth and pregnancies occurred as a result of IVF and resulted in live birth in groups of women with efficient IVF.

Duration of infertility, its causes and the structure of an infertile marriage (primary or secondary marriage) did not affect the outcome of IVF.

Characteristics of previous treatments for infertility with ART and IVF results in patients showed that the number of IVF cycles resulted in live birth, the number of mature oocytes, the number of good quality embryos on the day of transplantation were significantly more frequent cases in the group with efficient IVF, while the number of split embryos in one cycle was higher in the group with non-efficient IVF.

Patients of Group B were characterized by changes in parameters of the immune system before IVF. In particular, an increase in the percentage of T-suppressors (CD8 +) and a decrease in the immunoregulatory index were determined. The consequence of

imbalance of the immune system is an increase of anti-thrombin, anti-β2-glycoprotein I and anti-phosphatidylserine antibodies titer.

Patients with negative IVF outcomes were carriers of HLA-DRB1*15 (5, 8 %) and HLA-DQB1*0201 alleles in significantly fewer cases and HLA-DQB1*05 and HLA – DQB1*0501 alleles in significantly more frequent cases.

In women with positive IVF outcomes, the frequency of HLA-DQA1/DQB1*0101/2-0501/2 haplotype was significantly lower, while 8 patients of this group had HLA-DQA1/DQB1*0201-0201 haplotype. In the group with negative IVF outcomes, no carriers of the aforementioned haplotype were noted.

The study of psycho-emotional environment of a woman determined the existence of several psychological types: anxious, anxious - depressive, depressive and neurotic. At the same time, no significant differences between comparison groups were determined. Difference between the groups was determined by stress level. A high level of stress was observed in significantly more frequent cases in the group with non-efficient IVF procedure outcomes.

The study of pre-implantation characteristics of embryos within the IVF program in the group with efficient IVF determined higher parameters of embryos without chromosomal pathology and low parameters due to relative frequency of embryos with chromosomal pathology compared to the group with negative IVF outcomes.

In the group with favorable outcomes of IVF, women over the age of 35 often had viable embryos, and in rare cases non-viable embryos. The characteristics of chromosomal pathologies in the studied women did not show significant differences between the comparison groups.

Characteristic features of women with ovarian hyperstimulation during the IVF-ICSI program

A study of anthropometric, clinical and laboratory, anamnestic parameters in women with OHSS and without complications as a result of IVF, showed that OHSS was significantly

more common in women in the lower age group (under 35 years) with deficiency in weight.

Social structure and occupational injuries do not affect the frequency of progression of OHSS. The red blood indicators did not reveal differences between the sub-groups, while the coagulation parameters in both sub-groups did not have great differences in general, except for PI (which was significantly higher in the sub-group without OHSS). A significant difference was observed in the hormonal profile parameters of women in comparison sub-groups. In the sub-group with OHSS, the level of LH, AMH, estradiol was significantly higher, and the level of FSH was significantly lower. Controversial changes have been obtained for indicators of cortisol. The hormone recorded in majority of women with OHSS (58,2%) was significantly higher compared to patients in the sub-group without OHSS. At the same time, the values of the mentioned hormone in 41.8% of women in the 1st sub-group were lower compared to the sub-group without OHSS. Patients with OHSS with ovarian cysts in the anamnesis are characterized by early or late menarche, irregularity of menstruation, painful and prolonged cycles. During the examination of women with OHSS, such gynecological diseases as PCOS, endometriosis, chronic endometritis, ovarian cysts were diagnosed significantly often, and hydrosalpinx was diagnosed in significantly less cases. Genital infections were also frequently detected in patients with OHSS: chlamydia, ureaplasma, mycoplasma, trichomonads. Duration, structure and causes of infertility did not have significant differences in the comparison sub-groups. Among the factors provoking OHSS may be glandular hyperplasia of the endometrium, which was observed in the 1st sub-group at a significantly high level.

Significant differences between the studied sub-groups were revealed during laparoscopic examination: fimbrioplasty, stomatoplasty, salpingo ovariolisis, uterine adhesions of I-IV stage were found in the 1st sub-group, and ovarian resection was detected in the 2nd sub-group more frequently. The level of ovarial reserve had high values in the 1st sub-group. Selection of agent that will stimulate hyperstimulation in the IVF program is also important. Conducting

stimulation by applying HMG resulted in formation of OHSS in significantly more frequent cases compared to FSH.

FORECASTING THE RESULTS OF IVF and OHSS

Forecasting of the results of IVF was carried out by means of logistic regression analysis. The analyzed parameters differed significantly between the compared groups of patients.

Logistic regression is applied to solve the problems of classifying the object under study into one of two previously mentioned groups. The mentioned model was used to predict the outcomes of IVF and its complications (OHSS) in infertile women, depending on some parameters studied by us (anthropometric, anamnestic, social, clinical, laboratory, psychoemotional, immunological, genetic, immunogenetic, etc.). At the same time, the degree of influence of these parameters on the result of IVF was analyzed, that is, the possibility of forecasting the outcomes of IVF and the frequency of progression of OHSS was studied.

The forecasting model is built on the basis of retrospective data and prospective researches. For this purpose, the initial data base (training data) was formed, representing the pattern of observations reflecting the number of rows equal to the number of objects observed (IVF results and existence of OHSS) and with the number of columns equal to the number of factors studied.

The predictive answer is the probability that a positive or negative result of IVF will occur, as well as the presence or absence of OHSS. The mentioned predictive results are dependent variables. The studied parameters (regressors and predictors) are fixed variables.

The proposed predictive model is based on the analysis of gynecological diseases at the time of examination (recurrent dysbiosis of the vaginal opening, PCO / PCOS, chronic salpingo-oothecitis), characteristic features of ultrasound pathologies of pelvic organs (the number of antral follicles) and data on histological examination of endometrium (endometritis and endometrium in the proliferation phase).

The regression analysis model for predicting the outcomes of IVF is as follows: the result is positive in case of pregnancy (pregnancy occurred - PO), and the result is negative in the absence of pregnancy (no pregnancy - NP). The presence and absence of pregnancy are dependent variables, while the features listed above are fixed variables.

In this case, the p-level of significance of the formed regression model was below 5%, that is, for the difference between the current model and the model consisting only of the estimate, the value of Wald's chi-square statistics is highly significant, $Chi^2(6) = 62,345$ p=, 00000 (table 2). Based on this, we can conclude that the selected variables listed above (predicting features) affect the outcomes of IVF. All coefficients of the equation, except for the coefficient for "endometritis", are significant at the level of 5% (p - level < 0.05).

The effect of all other factors can be evaluated by the odd ratio (OR) and their reliability interval (Table 2). The likelihood of a negative outcome of IVF significantly increases due to the "PCO" or "PCOS" - 7, 967 times. Then "recurrent dysbiosis of uterus" - 4, 65 times and "chronic salpingo-oothecitis" – 2, 77 times come. The probability of a positive outcome of IVF is also increased by the "number of antral follicles" - OR = 0, 94 and "endometrium in the proliferation phase", but the value of the last mentioned parameter was not high – OR = 0.49.

The results of calculation are described by the following regression equations:

Equation 1

Age = - 0,375 + 1,5 RDVO + 2,07 PCOS +1,02 CS - 0,058 NAnF + 0,2 E - 0,7 EPP

Note: RDVO - recurrent dysbiosis of the vaginal opening, PCOS - polycystic ovary syndrome, CS - chronic salpingo-oothecitis, NAnF - number of antral follicles in the oocytes, E - endometritis , EPP - endometritis in the proliferation phase.

The coefficient of the equation for "endometritis" is not statistically significant (p = 0.569), therefore, the mentioned predictor can be removed from the regression equation 5.2:

Table 2.

Coefficients of the regression equation to predict the results of IVF based on the results of gynaecological pathology analysis

	Model: Logistic regression (logit) N of 0's: 112 1's: 124 (Spreadsheet EXO 2) Dep. exists: IVF result is positive - 1, Negative - 0 Loss: Max likelihood (MS-err. scaled to 1) Final loss: 132,10482596 Chi?(6) = 62,345 p =,00000 Include cases: 1:234;238:521						
	const.b0	recurrent dysbiosis of the vaginal opening	PCOS	chronic salpingo-oothecitis	ultrasound number of antral follicles	histol endometritis	endometrium in the histol proliferation phase
Estimate	-0.37534	1.537431	2.07532	1.019017	-0.0582048	0.202821	-0.7093028
Standard Error	0.57395	0.3703873	0.5704074	0.3200732	0.0210621	0.356350	0.3483777
t (229)	-0.65396	4.150874	3.638313	3.183701	-2.763474	0.569163 9	-2.036017
p-value	0.513792	0.000046730	0.00033911	0.001655945	0.006184 05	0.569802	0.04289984
-95% CL	-1.50625	0.8076282	0.9514026	0.3883524	-0.0997053	-0.49932	-1.395738
+ 95% CL	0.755566	2.267234	3.199238	1.649682	-0.0167043 6	0.904966	-0.02286733
Wald's Chi-square	0.427666	17.22975	13.23732	10.13595	7.636786	0.323947	4.145364
p-value	0.513141	0.000033206	0.00027486	0.001455443	0.005722 23	0.569248	0.04175688
Odds ratio (unit ch)	0.687051	4.652622	7.967098	2.770471	0.9434566	1.224854	0.4919871
-95% CL	0.221738	2.242583	2.589339	1.474549	0.905104	0.606941	0.2476501
+ 95% CL	2.128817	9.65266	24.51385	5.205325	0.9834344	2.471848	0.9773921
Odds ratio (range)		4.652622	7.967098	2.770471	0.2201763	1.224854	0.4919871
-95% CL		2.242583	2.589339	1.474549	0.0748447 1	0.606941	0.2476501
+ 95% CL		9.65266	24.51385	5.205325	0.6477092	2.471848	0.9773921

Model: logistic regression (Logit). The dependent variable - IVF result is positive - (1), the result is negative (0). Chi2 - 62,345, p=0,0000, the number of observations. 1 - 234, 238 - 521

Note: Estimate - intercept term of the equation, Standard Error, p-value – significance level of coefficients of the equation - 95% CL + 95% CL - reliability interval, Wald's Chi-square, p-value - Wald's significance level

Equation 2

Logit (p)= Y = - 0,375 + 1,5 x RDVO + 2,07 x PCOS +1,02 CS - 0,058 x NAnF-0,7 x EPP

In the equation, the average values obtained during the study of parameters (in numerical values) or the number 1 (when there is a symptom) and the number 0 (when there is no symptom) are taken, thereby the value Y is obtained.

Further calculation takes such a form:

$$Logit\ p = Y = \frac{1}{1 + e^{-Y}} = \frac{1}{1 + 2{,}72^{-Y}} = A$$

The likelihood of a negative outcome of IVF is equal to the value “A”, and the likelihood of a positive outcome is equal to the value “1 - A”.

Quality of the formed model is assessed by the “disagreement ratio ” parameter. Sensitivity and specificity of the formed regression equation were calculated. To determine the sensitivity and specificity of the formed regression equation, the outcomes of IVF were additionally considered. Overall, the informativeness of the model is 71,6 % (169 / 236 * 100 % = 71,6 %). Odd ratio is 6,325; percentage of correct predictions is 71.61%; number of patients is 1:234; 238:521.

The odd ratio shows that to make a classification according to the regression model for gynecological pathology, is 6,3 times more correct than to randomly predict the result of IVF. The sensitivity of the formed model is 68,75%, and the specificity is 74,19%.

All observations with predicted values (probabilities) less than or equal to 0.5 were classified as unsuccessful (no pregnancy), while other observations with predicted values above 0.5 were classified as successful (pregnancy occurred).

The disagreement ratio is calculated as the ratio of the number of correctly classified observations to the number of improperly classified observations. The fact that the disagreement ratio is above 1 shows that the structured classification is better than the randomly conducted classification. As can be seen from the chart of the predictive model of logistic regression (chart 1), most of the predicted values of IVF predictors are under the observed values, which indicates the adequacy of the predictive model.

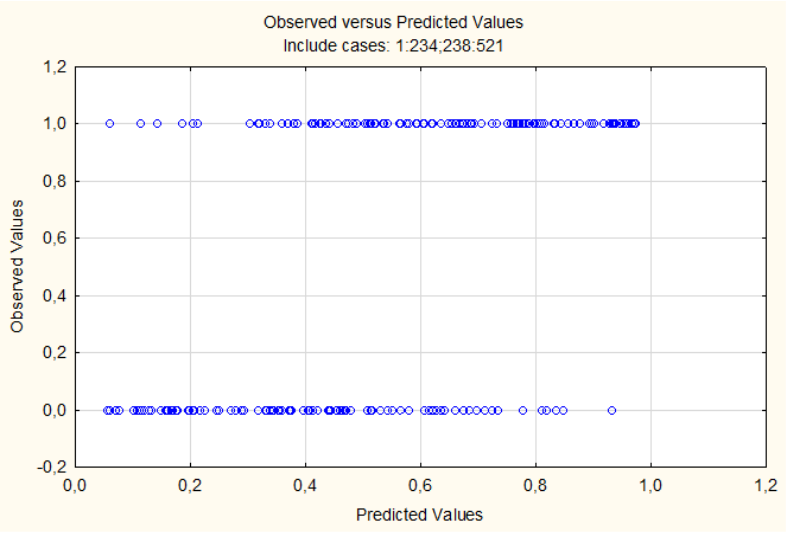


Chart 1. Predicted and observed values of IVF predictors for the structured forecast model of logistic regression.

Given the important role of immunological and genetic parameters in implementation of the IVF program, we selected the following immunological and immunogenetic markers for the formation of the second predictive model: CD4 / CD8 ratio, anti-AFS thrombin IgM, anti-AFS thrombin IgG, HLA-DQB1* 0201, HLA-

DQB1* 05 and HLA-DQB1* 0501 allele. Statistical analysis of the studied parameters by the method of logistic regression showed the reliable significance of the obtained model of the forecast ($p < 0,001$; $Chi2 = 115,43$, $p = 0,0000$).

The predictive unfavorable factor for the outcome of IVF is the presence of the HLA - DQB1*05 allele in patients. The presence of the mentioned allele increases the risk of a negative outcome by 23,7 times. Anti-AFS thrombin IgM also increases the risk of negative IVF outcome by 2,86 times (OR = 2, 86) (Table 3).

Comparing the obtained coefficients of the regression model, we obtain the 3rd regression equation:

Equation 3

Y = -1,04 – 1,86 x CD4/CD8 + 1,05 x AFS IgM/T - 0,24 x AFS IgG/T – 0,85 x HLA-DQB1* 0201 + 3,16 x HLA-DQB1* 05 + 1,5 x HLA-DQB1* 0501

CD4 / CD8, HLA-DQB1*05 and HLA-DQB1*0501 parameters are excluded from the regression equation due to the fact that the coefficients of equation for AFS IgM/T, AFS IgG/T and HLA-DQB1* 05 are valid at the level of 5% (p – level < 0.05) and for other parameters the regression coefficients are invalid. Consequently, the regression equation takes the following form (Equation 4).

Equation 4

Y =Logit (p)-1,04+1,05 x AFS IgM/T+0,24 x AFS IgG/T + 3,16 x HLA + DQB1 05

Calculations showed that the informativeness of the model is 83.87%, that is, in 83.87% of cases the obtained model correctly predicts the result of IVF in infertile women. Sensitivity of the mentioned model is 87.12%, and the specificity is 81.17%. The odd ratio shows that this model correctly predicts the result of IVF 29,2 times compared to the random prediction of the results. Estimation of the obtained model can also be presented according to the chart of probability and observed values, where a large correspondence of the predicted and observed values of the studied predictors of IVF outcomes is observed.

Table 3

Coefficients of the regression equation for predicting the outcomes of IVF based on the results of immunological and genetic parameters.

	Model: Logistic regression (logit) N of 0's: 70 1's: 85 (Spreadsheet EXO3) Dep. exists: IVF result is positive 1, Negative 0 Loss: Max likelihood (MS-err. scaled to 1) Final loss: 48,995274592 Chi2 (6) = 115,43 p = 0,0000 Include cases: 1: 285						
	Const.B0	CD4 / CD8	anti-AFS thrombin IgM	anti-AFS thrombin IgG	HLA-DQB1* 0201 allele	HLA-DQB1* 05 allele	HLA-DQB1* 0501 allele
Estimate	-1.04918	-1.86685	1.052878	-0.24842	-0.8539	3.1694	1.500169
Standard Error	2.028515	1.001122	0.203643	0.108294	0.63317	1.0239	0.8593105
t(511)	-0.51721	-1.86476	5.170204	-2.29398	-1.3486	3.0953	1.745782
p-value	0.605776	0.064194	0.000000	0.023198	0.17949	0.0023	0.08292402
-95% CL	-5.05777	-3.84519	0.650453	-0.46242	-2.1051	1.1460	-0.1979342
+ 95% CL	2.959409	0.11148	1.455302	-0.03442	0.39726	5.1929	3.198271
Wald's Chi-square	0.267514	3.477339	26.73101	5.262383	1.81898	9.5809	3.047754
p-value	0.605007	0.062223	0.000000	0.021797	0.17744	0.0019	0.08085847
Odds ratio (unit ch)	0.350223	0.154609	2.865888	0.780028	0.42572	23.794	4.482444
-95% CL	0.006359	0.021382	1.91641	0.629752	0.12182	3.145	0.8204238
+ 95% CL	19.28657	1.117937	4.28578	0.966162	1.48775	179.99	24.49016
Odds ratio (range)		0.106434	24529.45	0.089839	0.42572	23.794	4.482444
-95% CL		0.009909	515.0971	0.011270	0.12182	3.1456	0.8204238
+ 95% CL		1.143144	1168117	0.716123	1.48775	179.99	24.49016

Note: Estimate - intercept term of the equation, Standard Error, p-value - significance level of coefficients of the equation - 95% CL +95% CL - reliability interval, Wald's Chi-square, p-value - Wald's significance level

Forecasting the results of IVF by the basic components method and logistic regression. All women for whom the IVF procedure was carried out were described by numerous parameters: anthropometric data, anamnestic parameters, gynecological anamnesis, reproductive anamnesis, clinical, immunological, immunogenetic parameters, and etc. However, the peculiarity of the effect of above-mentioned factors on the outcome of treatment of infertility, in particular, on the outcome of IVF, has not been described. However, the large amount of data makes it difficult to interpret the results of research.

In order to distinguish the most fundamental symptoms and determine their numerical coefficients, we used the method of factor analysis - the main components method. Due to this method, all existing symptoms are combined in four groups of factors.

Each factor is characterized by a set of symptoms with relatively high value of numerical coefficients. Symptoms with lower numerical coefficients are excluded from the obtained factor groups.

According to the main symptoms, analysis of the obtained data revealed 4 grouping factors: factor 1 - gynecological factor; factor 2 - reproductive anamnesis; factor 3 - embryological parameter; factor 4 - combined parameters.

Transition from a large number of symptoms to a small number was carried out with the aim of removing low informative symptoms from the list and combining more frequent symptoms into one group.

Factor 1 was named "gynecological anamnesis“. Thus, the above-mentioned symptomocomplex included two symptoms with large numerical coefficients: "the result of previous pregnancies in case of secondary infertility" (0, 787) and "loss of spontaneous uterine pregnancy" (0, 788). The mentioned factor explains the dispersion of the system by 14.23%.

Factor 2 was named "reproductive anamnesis“. Thus, the above-mentioned symptomocomplex included a parameter with a large numerical coefficient – "pregnancy with live birth as a result of IVF" (- 0, 87). It should be noted that the “age” parameter (0, 72) with a high numerical coefficient was also included into the mentioned

factor. The numerical load of other parameters for the mentioned factor is not high. The mentioned grouping factor explains the dispersion of the system by 7.85%.

The 3rd grouping factor included the following parameters with large numerical coefficients: "previous ART – the number of mature oocytes" (0, 73) and "previous ART - the number of high-quality embryos on the day of transplantation" (0, 72). The mentioned grouping factor is conventionally called "embryological parameters" and explains the dispersion of the system by 7.36%.

Factor 4 - "Combined parameters", which explains the dispersion of the system by 6.53%, included numerous symptoms with small numerical coefficients (mycoplasmosis, age, PCOS or PCO, chlamydiosis). Therefore, the mentioned factor was excluded from further studies.

All parameters are combined in four symptomocomplexes group, which explains the used dispersion of the system by 35.94%. At the same time, the greatest strength is possessed by the 1st grouping factor - “Gynecological anamnesis”, which determines the variability of the established dispersion model by 14.23%, the 2nd grouping factor - “reproductive anamnesis + age” with a 7.85% contribution to the variability of the system, the 3rd grouping factor – “embryological parameters” which is responsible for 7.36% of the dispersion of the system, the 4th grouping factor - “combined parameters” - 6.53%. Moreover, the numerical coefficients of the symptoms covered by the grouping factors were determined.

So, predictively significant parameters characterizing women during preparation for IVF were obtained by the method of factor analysis from the entire range of studied symptoms, which significantly differed between groups of women with negative and positive results of IVF. Parameters with high numerical coefficients obtained as a result of factor analysis were used to forecast the results of IVF.

The mentioned parameters are: "age”, “results of previous pregnancies in case of secondary infertility – lost pregnancy (NP / LP)”, “loss of spontaneous uterine pregnancy (SHI)”, “pregnancy with

live birth as a result of IVF (PWD / DH)", "previous ART - number of mature oocytes (AMO)", "previous ART - number of high-quality embryos on the day of transplantation (NHQE)".

The model of the regression analysis is as follows: the result is positive (1) - pregnancy occurred (PO) and the result is negative (0) - no pregnancy (NP). PO (1) and NP (0) are dependent variables, while the symptoms listed above are fixed variables.

Coefficients of the equation turned out to be significant for the parameters listed below at a level of 5% (p - level < 0.05): "results of previous pregnancies in case of secondary infertility - lost pregnancies (4, 702)", "loss of spontaneous uterine pregnancy (5, 48)", "previous ART - the number of mature oocytes (- 0, 22)", "previous ART - the number of high-quality embryos on the day of transplantation (-2, 28)" and "age (0, 72)".

In this specified case, the p-level significance of the formed regression model turned out to be below 5%, the statistical value of the Wald's Chi-square for the difference between the current model and the model consisting only of estimates is of high importance. Based on this, it can be concluded that the selected variables listed above (predictive symptoms) affect the result of IVF. The result of the regression analysis for the prediction of the results of IVF is statistically reliable ($\chi 2 = 117,80$ p = 0, 0000).

The results of calculation showed the regression equation as follows: (Equation 5).

Equation 5

Y=5,61+4,7 x RPP/LP +0,72 x A+5,84 x LSP-0,41 PIVF/LB– 0,22 NMO –2,28 x NHQE

Note: PRR/LP - results of previous pregnancies in case of secondary infertility - lost pregnancies; LSP - loss of spontaneous uterine pregnancy; PIVF/LB - previous IVF with ART cycle, with live birth; NMO - the number of mature oocytes; NHQE - the number of high-quality embryos; A - age.

Equation 6

Logit (p)= Y = 5,61 + 4,7 x PRR/LP + 5,84 x LSP + 0,72 x A – 0,22 NMO – 2,28 x NHQE

To assess the efficiency of predictive equations of logistic regression, such parameters as sensitivity and specificity, calculated based on a 2 x 2 conjugation table.

Hypersensitivity is the share of persons with positive results of IVF among the examined patients. This parameter characterizes the likelihood of a real positive outcome of IVF. Specificity is the share of persons with negative outcomes of IVF among patients.

To determine the sensitivity and specificity of the formed regression equations, the positive and negative results of IVF in patients were additionally analyzed. The regression equation is statistically significant ($p < 0,001$). As it can be seen from the above, the developed forecasting model is capable of predicting the results of IVF by 86.93% based on the afore-mentioned parameters. Such a combination of symptoms can suggest the outcome of IVF and is reliable, moreover, the forecast is quite high. The sensitivity of the mentioned forecast is 84.7% and the specificity is 88.8%.

The specified parameters are able to predict the positive and negative outcomes of IVF in infertile women well before carrying out this procedure. The odd ratio shows that the classification according to the model is 44,3 times more correct than randomly predicting the result of IVF.

High predictive significance of the formed model of the results of IVF and the obtained logistic regression equation is confirmed by the developed chart of predicted and observed values of predictors. The chart demonstrates fairly large correspondence of predicted and observed values of predictors.

Another predictive model of the result of IVF based on age, AMH and embryological parameters was presented. The predictive model included the followings: age, AMH, previous ART - the number of matured oocytes, and previous ART - the number of high-quality embryos on the day of transplantation.

Equation 7

Logit (p) = Y= 0,379 + 0,175 x A + 1,19 x AMH + 0,39 x NMO + 2,59 x NHQE

Note: Logit (p) = Y = result of IVF

As it can be seen from regression equation 7, three parameters of the equation – AMH, NMO and NHQE are inversely proportional to unsuccessful results of IVF, that is, the higher the level of AMH, the greater the NMO and NHQE, the lower the probability of a negative result of IVF. The age of women is directly proportional to the negative result of IVF, that is, the greater the age, the higher the negative result of IVF.

The overall predictive significance of the predictive model is quite high – 94.29 %, OR = 338.92, sensitivity of the model is 89.09%, and specificity of the model is 97.64% (Table 4).

Table 4

Sensitivity and specificity of the regression equation for predicting the results of IVF

Solution on the method tested	Actual state of objects		
	Positive	Negative	% of correct forecasts
Positive	49	2	89.09091
Negative	6	83	97.64706

Note: Odd ratio – 338.92, percentage of correct forecasts - 94.29%, number of observations - 1:234; 238:521.

The adequacy of the formed model is confirmed by the regression chart, in which a high correspondence of predicted and observed values is observed.

Thus, the prediction of the results of IVF was carried out by applying a model of logistic regression, according to a complex of symptoms significantly differing among women with positive and negative results of IVF. Prediction was made based on the parameters of gynecological and reproductive anamnesis (recurrent dysbiosis of the vaginal opening, PCOS, chronic salpingo-oothecitis, ultrasound features of pelvic pathologies, mainly the number of antral follicles) and data of histological examination of endometrium (endometritis and endometrium in the proliferation phase). The predictive significance of this model was 71.61%. Sensitivity of the model was 68.75%, and the specificity was 74.19%. The specified predictive model is at intermediate level for its predictive power.

Predictive model, formed on the basis of immunological parameters, turned out to be somewhat stronger. Its prognostic value is 83.87%. Sensitivity of this model is 87.12% and specificity is 81.17%. HLA–DQB1*05 parameter has a great predictive power. The presence of the mentioned parameter in women increases the likelihood of a negative result of IVF by several times. Parameters for the last two predictive models were obtained by means of factor analysis – basic components method. Due to these statistics, parameters with high numerical loads over the grouping factors were selected. The parameters are: "results of previous pregnancies in case of secondary infertility – lost pregnancies (RPP/LP)“, ”loss of spontaneous uterine pregnancy (LSP)“, "previous ART – the number of matured oocytes (NMO)“, "previous ART - the number of high-quality embryos on the day of transplantation (NHQE)“ and ”age (A)". The predictive model formed based on these data was quite efficient. Its predictive value was 86.93%. Sensitivity of the predictive model is 84.7%, and specificity is 88.8%. The mentioned model predicts the result of IVF 44,3 times more correctly than any random prediction that we will make.

The second predictive model of IVF outcome, in which the parameters were selected through the factor analysis, was the most efficient. The predictors for this model: "Age”, “AMH”, “NMO” and “NHQE”. The predictive value of this model is the highest and equals to 94.29%, with sensitivity of 89.09% and specificity of 97.64%.

Forecasting the likelihood of progression of OHSS during IVF in infertile women. Logistic regression analysis of generally accepted clinical and laboratory predictors of OHSS progression was carried out to predict the likelihood of OHSS development during the IVF procedures. Predictors are: age, BMI, PI, estradiol, FSH, LH, cortisol, AMH, analysis of menstrual function, presence of ovarian cyst, presence of gynecological diseases at the time of examination (chronic endometritis, PCO or PCOS, endometriosis, hydrosalpinx, ovarian cyst), salpingo ovariolysis, ovarian reserve parameters, various methods of stimulation.

In women with OHSS these indicators were studied by the method of logistic regression: age, BMI, laparoscopy data (salpingo ovariolysis, polycystosis ovaries syndrome or polycystosis ovaries), ovarian reserve (number of antral follicles in the right ovary, number of antral follicles in the left ovary), as well as histological changes in endometrium - presence of glandular hyperplasia of endometrium.

The results of obtained forecast showed that the general model of regression analysis turned out to be statistically significant ($\chi 2$ =80, 249, p = 0,000), that is, this predictive model is adequate and can predict the likelihood of the presence or absence of OHSS.

OHSS is a dependent variable, while the other parameters listed above are fixed variables. Parameters such as age, BMI, GHE, number of antral follicles of the right and left ovaries, and salpingo ovariolysis were related to OHSS. Age and BMI were inversely proportional to OHSS, while GHE, NAnF in the right and left ovarian, AMH and salpingo ovariolysis were directly proportional. We obtain the following regression equations by putting down the coefficients for fixed variables.

Equation 8.

Logit (p) = Y = -2,48 - 0,11x Age - 0,14 x BMI + 0,86 x GHE +0,31x NAnFLO + 0,21 x NAnFRO + 3,72 x PCOS + 0,21 x AMH + 0,97 x SOL

Logit (p) = Y - probability of progression of OHSS

Note: A - age, BMI - body mass index, GHE - glandular hyperplasia of endometrium, NAnFRO - the number of antral follicles in the right ovary, NAnFLO - the number of antral follicles in the left ovary, PCOS - polycystosis ovaries syndrome, AMH - antimullerian hormone, SOL – salpingo ovariolysis.

The statistical analysis showed that reliable significant coefficients were set for these parameters: age, BMI, polycystosis ovaries syndrome, the number of antral follicles in the right ovary, the number of antral follicles in the left ovary, and AMH. The coefficients in parameters of salpingo ovariolysis (- 0,97), glandular hyperplasia of endometrium (- 0, 86) are not statistically significant, and therefore they should be included in the final formula of logistic regression.

Equation 9

Logit (p) = Y = - 2,48-0,11 x Age-0,14 x BMI + 0,31 x NAnFLO + 0,21 x NAnFRO + 3,72 x PCOS + 0,21 x AMH

According to the equation 9, it can be seen that reliable informative indicators are age, BMI, number of antral follicles in the right ovary, number of antral follicles in the left ovary, polycystosis ovaries syndrome and AMH.

An increase in BMI and age reduces the likelihood of OHSS, an increase in the level of NAnF values, AMH and PCOS in the right and left ovaries increases the likelihood of progression of OHSS during the IVF procedure. It should be noted that the largest coefficient is set for the parameters of PCOS and the number of antral follicles in the ovaries. Further, there are levels of AMH, BMI and age, with coefficients of 0.14 and 0.11, respectively.

Certain value is obtained by entering the average values of statistically significant symptoms obtained in the studied population (especially Azerbaijani) into the formula of the logistic regression equation. This value serves as a threshold between the presence and absence of OHSS. To predict the likelihood of progression of OHSS in examined women, the obtained values are entered into the regression equation. OHSS is diagnosed if the obtained values are below the threshold value, and in case if the obtained values are above the threshold, then the likelihood of developing OHSS is sharply reduced.

As shown above, the formed predictive model is statistically reliable ($p < 0, 05$). Overall, the predictive value of this model is 83.74%. Sensitivity of the model is 83.63%, and specificity is 83.82.

Forecasting the probability of OHSS formation during the implementation of IVF according to the formed model is 26,48 times more accurate than forecasting the probability of OHSS without this predictive model.

High predictive significance of the formed model and the logistic regression equation for predicting the progression of OHSS during the IVF procedure is confirmed by the developed chart of

predicted and observed values of predictors The chart shows a large correspondence of predicted and observed values of predictors, in which the parameters used are indicated by the points of predicted and observed values.

Consequently, age, BMI, level of AMH, number of antral follicles in the right and left ovaries, and PCOS are predictive markers of OHSS. At the same time, in absence of OHSS, age and BMI are positively correlated, while NAnF in the right and left ovaries, and PCOS are negatively correlated.

The study of possibility of forecasting IVF and OHSS was carried out by the method of logistic regression by using the statistical software package Statistica 10 (USA). The reliability of the results of statistical analysis and the predictive model itself was determined due to $\chi 2$ parameter and $p < 0.05$ value. All formed models of regression turned out to be highly significant, that is, they could reliably predict the results of IVF and progression of OHSS during the implementation of IVF procedure.

The first analysis on forecasting the result of IVF according to a certain set of symptoms referred to gynecological anamnesis showed high predictive significance for the prediction of the results of IVF (PCOS, RDVO, CS, NAnF and EPP). The predictive significance of this model, i.e., the percentage of correct predictions, is 71.61%. The sensitivity and specificity of the mentioned model were not very high and were equal to 68.75% and 74.19%, respectively.

Taking into account the important role of immunological changes during the IVF, the second predictive model, i.e., the second forecasting, was carried out with the main immunological and immunogenetic indicators. The predictive model formed according to immunological parameters showed high predictive informativeness of such an immunological marker as HLA - DQB1 * 05. The presence of this marker significantly increases the likelihood of a negative result of IVF. The value of the predictive model, formed based on immunological parameters, was 83.87%, which is significantly higher than the model formed according to the gynecological anamnesis data. The sensitivity and specificity of the forecast were 87.14% and

81.17%, respectively, which was also higher than that of the previous model.

During the preparation of infertile women for IVF, preliminary selection of parameters obtained as a result of the application of factor analysis (basic components method) was carried out for the formation of the subsequent two predictive models of IVF based on the parameters of those women. The conducted factor analysis revealed symptoms with high numerical coefficients, which can influence the outcomes of IVF.

Subsequent two predictive models were formed on the basis of parameters that have high numerical coefficients during factor analysis. These parameters are – the result of a previous pregnancy – lost pregnancy, loss of spontaneous pregnancy, the number of matured oocytes, the number of high-quality embryos. As is obvious, the parameters of gynecological and reproductive anamnesis were obtained by means of factor analysis.

The predictive model of IVF result, obtained based on these parameters, had greater predictive significance and was 86.93%. The sensitivity and specificity of the mentioned forecast is high and is 84.72% and 88.88%, respectively. The forecast carried out according to the mentioned parameters turned out to be more informative compared to the previous models. The second model of forecasting the IVF result, in which the parameters were selected by applying the factor analysis, turned out to be the most efficient. The predictors for this model were age, AMH, AMO and NHQE. The predictive value of this model is the highest and equals to 94.29%, while the sensitivity was 89.09% and the specificity was 97.64%.

The prediction of the likelihood of OHSS progression was carried out according to several parameters: body-mass index, glandular hyperplasia of endometrium, number of antral follicles in the right and left ovaries, polycystic ovaries syndrome and salpingo ovariolysis. The results of the regression analysis showed that reliable informative indicators are age, BMI, number of antral follicles in the right and left ovaries, polycystosis ovaries syndrome and the level of

AMH. Selection of these parameters was based on the simplicity and economic feasibility of the results obtained.

The predictive model developed based on these parameters was highly informative and was 83.74%. The sensitivity of the predictive model is 83.63%, and the specificity is 83.82%. The indicated parameters reflect the adequacy of this model.

RESULTS

1. According to anthropometric, anamnestic, clinical and laboratory studies, women with positive IVF results showed an increase in AMH, LH, histamine, a decrease in cortisol and serotonin, an increase in the number of mature oocytes and good quality embryos, while an increase in the number of cases of salpingo-oothecitis, endometritis, abortions and lost pregnancies were observed in women with negative IVF outcomes [2, 3,11,16].
2. Immunological and immunogenetic studies have shown that in women with negative IVF results, the titer of antibodies to T-suppressors (CD8+), β2-glycoprotein I and phosphoditilserine, HLA – DQB1 05 and HLA – DQB1 0501 alleles were increased, while pre-implantation genetic analysis of embryos determined a high number of embryos without chromosomal pathology in women with positive IVF results [10, 22, 23, 26, 28, 30, 31, 33, 40].
3. The main predictors of the outcome of IVF in infertile women are: results of previous pregnancies in case of the secondary infertility (lost pregnancy), loss of spontaneous pregnancy, previous ART (number of mature oocytes), number of high-quality embryos on the day of transplantation, age, AMH level, HLA-DQB1*05, AFS IgM/T, PCOS or PCO, recurrent dysbiosis of vaginal opening, chronic salpingo-oothecitis, number of antral follicles, endometrium in the proliferation phase [4, 5, 6, 9, 15, 20, 21].
4. AMH, previous ART (number of mature oocytes), number of high-quality embryos on the day of transplantation, number of antral follicles, endometrium in the proliferation phase are positively

correlated with the successful outcome of IVF, while HLA-DQB1*05, results of previous pregnancies in case of secondary infertility (lost pregnancies), loss of spontaneous pregnancy, PCOS, recurrent dysbiosis of the vaginal opening, chronic salpingo-oothecitis are negatively correlated with the successful outcome of IVF [1, 7, 12, 17, 31, 34].

5. It is possible to determine the individual probability of pregnancy as a result of IVF by determining the accuracy of the forecast by applying a predictive model developed based on a logistic regression at the stage of pregravidar preparation of married couples [14, 25, 29, 32, 35].
6. Models with greater informativeness than all other ones developed to predict the IVF results are those based on the following predictors: age, AMH, previous ART (number of mature oocytes), previous ART (number of high-quality embryos on the day of transplantation), which have an overall informativeness of 94.29%, sensitivity of 89.0% and specificity of 96.4%. Another model is also based on the following predictors: results of previous pregnancies in case of secondary infertility (lost pregnancy), loss of spontaneous pregnancy, previous ART cycle of IVF with live birth, number of mature oocytes, number of high-quality embryos and age. General informativeness of the model - 86.93 %, sensitivity - 84.7% and specificity - 88.88 % [8, 29, 36, 38].
7. In infertile women, the following fixed predictors of the outcome of IVF should be considered as more powerful at the stage of pregravidar preparation: previous ART (number of high-quality embryos on the day of transplantation), number of mature oocytes, AMH and the age of patients, which are more informative parameters in predictive models [15, 34, 40].
8. The main predictors for the progression of OHSS during the IVF procedure in infertile women are: age, BMI, number of antral follicles of the ovaries, polycystosis ovaries syndrome or polycystosis ovaries and AMH. Age and BMI are negatively correlated with the likelihood of OHSS progression, while an increase in the value of NAnF in the left and right ovaries, level of

AMH and PCO are positively correlated with the likelihood of progression of OHSS during IVF [19, 21, 24, 37, 39].

9. The predictive model for forecasting the probability of progression of OHSS in the course of IVF procedure in infertile women was designed by using the logistic regression method with accurate prediction of 83.74% , sensitivity of 83.63% and specificity of 83.82% [13, 35, 37].
10. Significantly different parameters among the examined infertile women with different outcomes of IVF may not always serve as predictive factors to forecast the results of IVF or the likelihood of progression of OHSS during the IVF procedure [10, 18, 27, 29].

PRACTICAL RECOMMENDATIONS

1. When predicting the results of IVF, it is necessary to be premised upon the main parameters of infertile women predicting the positive or negative outcome of IVF (results of previous pregnancies in case of secondary infertility – lost pregnancy, loss of spontaneous pregnancy, previous ART – number of mature oocytes, number of high-quality embryos on the day of transplantation, age, AMH level, HLA – DQB1*05, AFS IgM/T, PCOS, endometrium in the proliferation phase).
2. Before conducting IVF based on an integrative assessment of these parameters, it is necessary to predict the result of therapy individually for each woman by using the predictive formula. Thus, forecasting will allow to use the IVF in maximum efficiency, selectively transplant one embryo, and will reduce unnecessary costs on the other hand.
3. In order to obtain more accurate prediction of the IVF result, it is necessary to apply a predictive model with high informativeness (above 75%), high sensitivity and specificity before carrying out the procedure.
4. It is recommended to set some parameters in order to assess the risk of OHSS in the preparation phase for patients who have

applied for the treatment of infertility with the IVF program (age, BMI, number of antral follicles, polycystosis ovary syndrome).

5. When conducting IVF in infertile women, it is necessary to calculate the likelihood of progression of OHSS based on the predictors due to a favorable prognosis of pregnancy, obtained through predictive parameters (age, BMI, number of antral follicles, polycystosis ovary syndrome).

List of published scientific works on the topic of dissertation

1. Исмайлова М.К. Роль лапароскопии в успешной реализации программы экстракорпорального оплодотворения у женщин с трубным фактором бесплодия // Elmi–praktiki jurnal Cərrahiyyə, Бакı, 2009, səh. 45-49
2. Исмайлова М.К. Оценка эндокринного и инфекционного статуса женщин, включенных в программу экстракорпорального оплодотворения // Elmi-praktiki jurnal Sağlamlıq, Bakı 2009, səh .69-73
3. Исмайлова М.К., Мехдиева Ю.Д. Диагностика внутриматочной патологии при помощи гистероскопии среди женщин азербайджанского региона с целью повышения вспомогательных репродуктивных технологий // Материалы V Регионального научного форума Мать и дитя, Геленджик, 2011, стр. 207-208.
4. Исмайлова М.К., Мехдиева Ю.Д. Роль гистероскопии в повышении эффективности ВРТ // Медицинский вестник Башкортостана ИМЖС, ТОМ 6, №6, 2011, стр. 44-47.
5. Исмайлова М.К., Мехдиева Ю.Д. Выявление внутриматочной патологии при помощи гистероскопии среди женщин азербайджанского региона с целью повышения вспомогательных репродуктивных технологий // Журнал “Вестник новых медицинских технологий”, Том 18, №4, Российская Федерация, 2011, стр. 165-167.

6. Исмайлова М.К., Мехдиева Ю.Д. Гистероскопия как альтернативный метод повышения эффективности вспомогательных репродуктивных технологий среди женщин азербайджанского региона // Журнал Врач-Аспирант, 2011, № 4 (47), стр. 585-591.
7. Исмайлова М.К., Мехдиева Ю.Д. Гистероскопия как дополнительный метод повышения эффективности вспомогательных репродуктивных технологий среди женщин азербайджанского региона // Материалы XII Всероссийского научного форума Мать и дитя, Москва, 2011, стр. 319-320.
8. Исмайлова М.К., Мехдиева Ю.Д. Гистероскопия как альтернативный метод повышения эффективности вспомогательных репродуктивных технологий // Журнал Клиническая и экспериментальная хирургия, №2, 2011, Стр.14-21.
9. İsmayilova M.K., Mekhdiyeva Y.J. Using of hysteroscopy forrevealing endometrial pathologies among women in the Azerbaijan region to increase the assisted reproductive technologies // Sağlamlıq, Бакı, №5, 2012, səh. 55-59.
10. Исмайлова М.К., Мехдиева Ю.Д. Частота встречаемости генетических тромбофилий среди женщин, проходивших программу экстракорпорального оплодотворения // Электронный научно - практический журнал Клиническая и экспериментальная хирургия, №1 (7), 2013, стр.24-28.
11. Исмайлова М.К., Мехдиева Ю.Д. Эндометрит как фактор риска неудачных попыток ЭКО // Sağlamlıq , Бакı, №1, 2013, səh. 67-72.
12. Исмайлова М.К., Мехдиева Ю.Д. Генетические тромбофилии среди женщин, проходивших программу экстракорпорального оплодотворения // Журнал Врач-Аспирант, Воронеж, №2 (57), 2013, стр. 89-95.
13. Исмайлова М.К. Эктопическая беременность после ЭКО // Научно-практический журнал Практическая Медицина, Казань, № 7 (76), 2013, стр. 169-171.

14. Исмайлова М.К., Мехдиева Ю.Д. Особенности течения беременности и родов после ЭКО // Клиническая и экспериментальная хирургия. ЭНП №3 (9) 2013, стр. 37-43.
15. Исмайлова М.К., Мехдиева Ю.Д. Беременность и роды после ЭКО, особенности течения // ЗИПЖ Врач-аспирант, 2013, №5, 3 (60), стр. 467-473.
16. Исмайлова М.К., Мехдиева Ю.Д. Влияние оперативного лечения яичников на результаты индукции суперовуляции у женщин в программе ВРТ // Российский медицинский журнал, №1, 2014, стр.25-27.
17. Исмайлова М.К. Особенности раннего неонатального периода детей, родившихся после ЭКО // Sağlamlıq, 2014, Bakı, №2, səh. 74-77.
18. Исмайлова М.К., Мехдиева Ю.Д. Коррекция тромбофилических мутаций в программе ВРТ у женщин с идиопатическим бесплодием, преэмбриональными потерями и привычными выкидышами в анамнезе // Электронный НПЖ Клиническая и Экспериментальная Хирургия. 2014, №1, стр.25
19. İsmayilova M.K. Cabergoline as a preventive measure against ovarian hyperstimulation syndrome in assistive reproductive programs // Bode: International journal of Scientific Research and Innovative Technology, UK, vol 2 N 2 February, 2015, P-57-62.
20. Исмайлова М.К. Синдром поликистозных яичников в программе вспомогательных репродуктивных технологий новые аспекты профилактики // Müasir ginekologiya və perinatologiyanın aktual məsələləri jurnalı 2016, Bakı, №3 səh. 34
21. Исмайлова М.К. Роль антигенов главного комплекса гистосовместимости и иммуноцитотерапии в успешной реализации программы экстракорпорального оплодотворения // Azərbaycan, Allerqologiya və klinik immunologiya jurnalı 2018, Bakı, №2, səh.17-25.
22. Ismayilova M.K. İmplantasiya qabağı genetik diaqnostika – ekstrakorporal mayalanmanın uğurunun əsas amili kimi // Azərbaycan Tibb Jurnalı 2018, Bakı, № 4, səh. 23-29

23. Исмайлова М.К. Роль предимплантационной генетической диагностики в программе вспомогательных репродуктивных технологий // Müasir ginekologiya və perinatologiyanın aktual məsələləri jurnalı №4, 2018, Bakı, səh.39-44
24. Ismayilova M.K. On the role of preimplantation genetic diaqnosis in assisted reproductive technologies program // İnsan genetikası və genetik xəstəliklər: problemlər və inkişaf perspektivləri. Birinci Beynəlxalqelmi-praktik virtual konfransın məqalələr toplusu 2020, Bakı, səh.106
25. Исмайлова М.К. Разработка математической модели прогнозирования результативности экстракорпорального оплодотворения на основе бинарной логистической регрессии // Акушерство и гинекология, г.Москва, 2020, приложение №4, стр.105-106.
26. Исмайлова М.К. Оценка продукции цитокинов у пациенток с бесплодием на этапе подготовки к экстракорпоральному оплодотворению // Azərbaycan Allerqologiya və klinik immunologiya jurnalı №1, 2020., Bakı, səh.41- 47.
27. İsmayilova M.K. İnfertil kadınlar tüp bebek sonuçlarının tahmini // Türk Jinekoloji ve Obstertrik Derneği (TJOD) Online Sempozyumu, 4-6 Aralık 2020, Türkiyə Cumhuriyyəti, SS-100.
28. İsmayilova M.K. Pre-implantation genetic diagnosis // The first scientific – practical virtual conference science and technology in modern society problems, prognoses and solutions. Turkey, İzmir September 26-27, 2020, p. 48.
29. İsmayilova M.K. Pre-implantation genetic diagnosis in the program of assisted reproductive technology // The first scientific – practical virtual conference science and technology in modern society: problems, prognoses and solutions. Turkey, İzmir September 26-27, 2020, p.137-141
30. İsmayilova M.K. Binary logistical regression as an optimal model for prognosis of the result of in vitro fertilization // Репродуктивное здоровье, tom 12, N3, 2022, p. 364-373

31. İsmayılova M.K. Оцінка продукції цитокінів у пацієнток з безпліддям на етапі підготовки до екстакорпорального запліднення // Клінічна медицина №2 (80), 2022, p. 70-73.
32. Semikhodskii A. and Ismayilova M.K. Detection of Chromosomal Aneuploidies in Human Blastomeres Using FISH Increases the Success of IVF by Improving the Chances of Embryo Progress to Delivery // Cytology and Genetics, 2022, vol.56, No.3 p.209-214
33. Исмайлова М.К. Прогнозирование исходов экстракорпорального оплодотворения у женщин с бесплодием // Казанский Медицинский журнал, том CIII, №4, 2022
34. Ismayilova M.K. Application of the logistic regression method to predict the results of in vitro fertizilization // World of Medicine and Biology, No 4 (82) 2022, p. 69-74
35. Ismayilova M.K., Sonsuzluğu olan qadınlarda ekstrakorporal mayalanma zamanı yumurtalıqların hiperstimulyasiyası sindromunun yaranma ehtimalının proqnozlaşdırılması // Azərbaycan Tibb Jurnalı 2022, Bakı, № 4, səh. 73-79
36. Исмайлова М.К., Курбанова Дж. Ф. Оптимизация результатов лечения мужского бесплодия методом выявления анеуплоидии эмбрионов при экстракорпоральном оплодотворении // Müasir ginekologiya və perinatologiyanın aktual məsələləri jurnalı 2022, Bakı, № 4, səh. 38 – 46.
37. İsmayılova M.K. Köməkçi reproduktiv texnologiyalar proqramında sonsuzluğu olan qadınlarda yumurtalıqların hiperstimulyasiya sindromunun inkişafetmə ehtimalının proqnozlaşdırılmasında loqistik reqressiyanın tətbiqi // Ümummilli lider Heydər Əliyevin 100 illik yubileyinə həsr olunmuş elmi-praktiki konfransın məcmuəsi, Bakı 2023, səh. 208 – 210
38. İsmayılova M.K., Ekstrakorporal mayalanma zamanı preimplantasiya genetik diaqnostika üsulu ilə kişilərdə patozoospermiyadan asılı olaraq embrionların aneuploidiyasının aşkarlanması // Akademik Zərifə xanım Əliyevanın 100 illik yubileyinə həsr olunmuş elmi-praktiki konfransın məcmuəsi, Bakı 2023, səh. 193- 195.

39. Исмайлова М.К. Курбанова Дж.Ф. Взаимосвязь психоэмоционального состояния женщин с результатами экстракорпорального оплодотворения. Международный научно-практический журнал // Репродуктивное здоровье. Восточная Европа. 2023, том 13, № 6, стр. 599-605.
40. Ismayilova M.K. The impact of immune status characteristics on the results of in vitro fertilization in patients with infertility // World of Medicine and Biology, 4 (86) 2023. p.61-65.

LIST OF ABBREVIATIONS

AFS - antiphospholipid syndrome
AMH - antimullerian hormone
AMO - amount of mature oocytes
ART - Assisted Reproductive Technologies
BMI – body mass index
CIO - controlled induction of ovulation
CV - Cellular Variation
DHEAS - dehydroepiandrosterone-sulfate
E2 - estradiol
ET - embryo transplantation
FSH – follicle stimulating hormone
GHE - glandular hyperplasia of endometrium
GnRH – gonadotropin releasing hormone
HLA - human leukocyte antigens
HMG - human menopausal gonadotropin
ICSI - intracytoplasmic sperm injection
IVF - in vitro fertilization
LH - luteinizing hormone
LSP - loss of spontaneous pregnancy
M 1, 2 - Maturation 1, 2
NAnFLO - number of antral follicles in the left ovary
NAnFRO - number of antral follicles in the right ovary
NHQE - number of high-quality embryos
17-OHP - 17-hydroxyprogesterone
OHSS - ovarian hyperstimulation syndrome
OR - odd ratio
PCOS - polycystic ovaries syndrome
PCR - polymerase chain reaction
PGD - preimplantation genetic diagnosis
PI - prothrombin index
PIVF / LB - previous IVF cycle, with live birth
Pr - prolactin
RPPSI - results of previous pregnancies in case of secondary infertility
SOL - salpingoovariolysis
STH - somatotropic hormone
T - thyroxine
TTH - thyrotropic hormone

The defense of the dissertation will be held on «08» April 2024 at «____» at the meeting of the Dissertation Council ED 2.06 working under the Azerbaijan Medical University

Address: AZ 1022 Baku city, A.Gasimzade str. 14.(conference hall).

It is possible to get acquainted with the dissertation work in the library of Azerbaijan Medical University.

The electronic version of the dissertation and abstract has been posted on the official website of the Azerbaijan Medical University (www.amu.edu.az).

The abstract was sent to the required addresses on «06» March 2024.

Signed for print: 04.03.24
Paper format: 60x84 1/16
Volume: 79812 characters
Number of hard copies: 20