Saint Petersburg State University

Dzhemlikhanova
Liailia Kharriasovna

PERSONALIZED PROGRAMMING OF IMPROVEMENT OF ASSISTED REPRODUCTION METHODS EFFECIENCY DURING INFERTILITY TREATMENT IN WOMEN WITH UTERINE FIBROIDS AND GENITAL ENDOMETRIOSIS

3.1.4. Obstetrics and Gynecology

Dissertation for a postdoctoral degree in Medicine
Translation from Russian

Scientific Consultant:
MD, PHD
A.M. Gzgzyan

Saint Petersburg
2024

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INTRODUCTION

Study Rationale

Currently, there is a tendency to expand the indications for the application of assisted reproductive technology methods; the contribution of ART methods to infertility treatment in a number of countries ranges from 2 to 7% of the total number of deliveries [154]. However, despite the rapid development and introduction of new technologies, the achieved efficiency indicators of IVF (IVF+ICSI) programs for the recent 5–10 years remain virtually at the same level, and the delivery rate does not exceed 28.0% [151, 152, 154, 183]. The urgent tasks facing ART centers to improve efficiency are the problems of low ovarian reserve and poor response to ovarian stimulation, fertility recovery in 'thin' endometrium, management of women with repeated failures of IVF programs, which include patients with severe forms of endometriosis and uterine myoma. In recent years, ART centers have seen a marked increase in the number of patients with uterine myoma, up to 20-30% [59], or genital endometriosis, up to 40-50% [341]. The prognosis of IVF programs efficiency in such women deteriorates due to the fact that surgical correction of uterine myoma and genital endometriosis is often required, whereas surgical treatment, in turn, aggravates failure factors (diminished ovarian reserve, endometrium injury, etc.).

The impact of uterine myoma on the results of IVF (IVF+ICSI) programs is estimated controversially by experts, especially in the presence of intramural leiomyomas not distorting the endometrial cavity. Researchers indicate probable factors of the negative impact of uterine intramural leiomyomas on fertility, including changes in the uterine artery blood flow, disturbances in the expression of the endometrium receptivity factors during the 'implantation window period' [116, 173, 214]. [116, 173, 214; at the same time, the role of conservative myomectomy in improving the conditions of implantation is unclear; there is a significant number of studies devoted to genetic factors involved in pathogenesis of uterine myoma [27, 50, 55, 199, 271; no ideas have been formulated about peculiarities of pregravid preparation in different variants of polymorphisms of sex steroids metabolism genes.

Guidelines on fertility recovery [14] are mainly focused on recovery of spontaneous fertility, usually reduced to the restoration of the organ's anatomical structure, but do not offer rehabilitation tactics specifically as applied to pregravid preparation prior to an IVF (IVF+ICSI) program.

In genital endometriosis, the main mechanisms of infertility development are associated with the presence of adhesions, loss of the ovarian reserve, changes in the pelvic cavity and in the oocyte microenvironment [257, 350, 353, 365], and with endometrial receptivity disorders [132, 178, 196]. IVF (IVF+ICSI) programs allow compensating for the tubal factor infertility and the factor of negative influence of components in the pelvic cavity that are 'toxic' to the oocyte, but not the diminished ovarian reserve and altered endometrial receptivity. Currently, the debates regarding appropriateness of the surgical stage for diagnosis and treatment of endometriosis are ongoing, and the significance of hormonal treatment both for natural fertility recovery and for infertility treatment planning is controversial. The guidelines for surgical treatment of women with endometriosis and infertility [36] conflict with the risks of impairing the reproductive prognosis because of ovarian tissue loss in the presence of ovarian endometriomas. The current approach suggests restrained tactics regarding indications for surgical treatment, but a significant number of women have a history of numerous surgical interventions performed in the previous decade, which determines suboptimal conditions for the ART program prognosis. Guidelines for hormone therapy prescription during the pregravid preparation period have a moderate level of evidential support. Detailed characterization of eutopic endometrial disorders as a pregravid preparation can form a focused view on the most probable characteristics of the structural and functional organization of the endometrium aimed at achieving pregnancy and determining the conditions for implementation of infertility overcoming mechanisms.

It should be noted that the currently available general-purpose variants of pregravid preparation of women for ART programs cannot be recognized as effective in the presence of diseases with various pathogenetic mechanisms of fertility disorders and decreased efficiency of infertility treatment methods – genital

endometriosis and uterine myoma. A detailed characterization of the efficiency of each stage of the treatment cycle is necessary for reliable determination of prognostic factors.

Considering the presence of significant non-modulable risk factors for IVF (IVF+ICSI) program failure – age, ovarian reserve condition – it is necessary to determine a tactic for obtaining the optimal number of mature oocytes and embryos of the best quality and preparation of the receptive endometrium depending on the systemic features associated with the pathogenesis of infertility in the existing disease.

The aim of the study is to create a personalized, pathogenetically justified approach to programming efficiency of assisted reproductive technologies in women with uterine fibroids and genital endometriosis on the basis of a combined evaluation of clinical and molecular-biological parameters.

Study Objectives:

1. Evaluate the clinical anamnestic characteristics and efficiency of IVF (IVF+ICSI) programs in women with uterine fibroids and genital endometriosis of various degrees of severity.
2. Determine specific features of ovarian stimulation, fertilization, embryo culture within IVF (IVF+ICSI) programs in women with uterine fibroids and genital endometriosis of various degrees of severity.
3. Perform a comparative analysis of indices of vascular resistance to the uterine artery blood flow in uterine fibroids and genital endometriosis at the stage of pregravid preparation and within the IVF (IVF+ICSI) program dynamics.
4. Assess the condition of the endometrium in women with uterine fibroids and genital endometriosis at the stage of pregravid preparation and identify prognostic risk factors for failure of IVF (IVF+ICSI) programs.
5. Determine the frequency of polymorphisms of genes associated with synthesis and metabolism of sex steroids in uterine fibroids in women planning infertility treatment by IVF (IVF+ICSI) methods.

6. Identify clinical anamnestic and clinical morphologic factors of the prognostic efficiency of an IVF (IVF+ICSI) program in uterine fibroids and genital endometriosis using dispersion analysis methods.
7. Elaborate an algorithm for preimplantation preparation in women with genital endometriosis with a target to maximize the efficiency of IVF (IVF+ICSI) programs.

Academic Novelty

- For the first time, the use of multivariate analysis of variance, including clinical anamnestic, molecular biological and vascular indices allowed to determine the factors of prognostic efficiency of ART programs in women with uterine intramural myoma and severe forms of external genital endometriosis, which form a personalized approach, with high reliability.
- For the first time, the significance of genetically determined control of estrogen metabolism (catechol-O-methyltransferase gene polymorphism) determining a personalized approach to the tactics of management of women with uterine myoma and infertility associated with the risk of recurrent course and progression of uterine myoma was established.
- For the first time, morpho-functional and immunohistochemical characteristics of eutopic endometrium associated with the pregnancy rate within ART programs were determined in women with severe EGE at the stage of pregravid preparation.
- For the first time, a stable decrease of blood flow resistance indices (PI, RI, SDR) in spiral arteries at all stages of IVF (IVF+ICSI) protocol (at the beginning of stimulation, on the day of oocyte final maturation trigger introduction, on the day of embryo transfer) associated with a decrease in the efficiency of IVF (IVF+ICSI) programs was shown in women with uterine intramural myoma.

- For the first time, the possibility of personalized pre-conception hormone therapy for women with EGE entering IVF (IVF+ICSI) programs was justified pathogenetically.

Defended Provisions

1. Uterine fibroids (intramural form) and severe genital endometriosis, including combination thereof, are associated with significantly lower rates of clinically verified pregnancy as a result of ART programs as compared to women without uterine myoma and genital endometriosis and represent independent factors of negative prognosis of ART programs.
2. In women with uterine intramural myoma, persistent decrease of blood flow resistance indices in spiral arteries in the dynamics of IVF (IVF+ICSI) protocol is a factor that deteriorates the prognosis of IVF (IVF+ICSI) programs efficiency.
3. In women with EGE, the efficiency of IVF (IVF+ICSI) programs determines the ability of eutopic endometrium to physiological secretory transformation. Preconception hormone therapy has pathogenetic significance and is accompanied by an increase in progesterone receptor expression and an associated increase in the clinical pregnancy rate.
4. Genetically determined features of estrogen metabolism control associated with G/G polymorphism in the catechol-O-methyltransferase (COMT) determine the risk of recurrent and progressive course of the disease gene in women with uterine myoma and allow justifying the expediency of active reproductive setting for the terms of IVF (IVF+ICSI) program planning.
5. Dynamic study of blood flow indices in spiral arteries, assessment of catechol-O-methyltransferase (COMT) gene polymorphism, evaluation of progesterone receptor expression in the endometrium by immunohistochemical study and preconception hormone therapy determine personalized programming of the ART method efficiency in women with uterine intramural myoma and severe forms of external genital endometriosis.

Practical Value

- In women with EGE, the preimplantation preparation plan for an IVF (IVF+ICSI) program should include hormone gestagen treatment lasting 3–6 months, unless such treatment has been performed less than 12 months prior to the program. If there is a need for an 'urgent' ovarian stimulation under diminished ovarian reserve and/or in women of an older reproductive age, delayed transfer of frozen embryos after the preimplantation preparation is indicated.
- For women with multiple uterine fibroids planning infertility treatment, determination of polymorphism of the catechol-O-methyltransferase (COMT) gene is indicated; identification of G/G polymorphism in the catechol-O-methyltransferase (COMT) gene allows estimating a high risk of uterine fibroids recurrence after conservative myomectomy in the period from 6 to 36 months – therefore, it is necessary to inform women about the high risk of recurrent course of the disease after surgical treatment. It is recommended to plan application of ART programs for infertility treatment as soon as possible after completion of rehabilitation after surgical treatment. For the first time, the possibility to program optimal terms of starting IVF (IVF+ICSI) protocols in women with uterine fibroids to account for genetic factors of the disease recurrence and progression risk on the basis of genetic factors of COMT enzyme activity control was substantiated.

Issue Testing

In the course of work on the dissertation, the results of the study have been repeatedly reported at scientific and scientific-practical congresses and conferences: II National Congress ‘Discussion Issues of Contemporary Obstetrics’ (Saint Petersburg, May 28-30, 2015), report ‘Efficiency of IVF Programs and Delivery Outcomes in Patients with External Genital Endometriosis’; XVI All-Russian Scientific Forum ‘Mother and Child’ (Moscow, 2015), report ‘Evaluation of IVF Program Efficiency and Pregnancy Outcomes in Patients with External Genital

Endometriosis'; VIII International Scientific Congress 'Operative Gynecology – New Technologies' (Saint Petersburg, October 20-24, 2016), reports 'Molecular and Biological Mechanisms of Proliferation', 'Conservative Myomectomy and Efficiency of IVF Programs'; Regional Scientific and Practical School 'Topical Issues of Obstetrics and Gynecology in the North-West Federal District' (Svetlogorsk, May 11-12, 2017), report 'Principles of Surgical Treatment of Reproductive System Diseases in Women Planning Pregnancy with ART Application'; Medical Forum 'Education Week at the Elizavetinskaya Hospital', (Saint Petersburg, November 2017), report 'Current Approaches to Overcoming Infertility in Women with Uterine Fibroids and Endometriosis'; 34th Annual Meeting of the ESHRE (Barcelona, Spain 1-4 July 2018), 'Excessive Intrauterine Interventions Negatively Affect In Vitro Fertilization (IVF). Outcomes in Women with Repeated IVF Failure'; IX International Scientific Congress 'Operative Gynecology – New Technologies' (Saint Petersburg, October 24-27, 2018), report 'Preparation for ART Programs for Patients after Surgical Treatment of Uterine Cavity Diseases'; II Medical Forum 'Education Week at Elizabeth Hospital', (Saint Petersburg, November 2018), report 'Current Approaches to the Treatment of Genital Endometriosis in Women with Infertility'; XIII International Congress on Reproductive Medicine (Moscow, January 21-24, 2019), report 'Planning ART Programs in Women with Uterine Cavity Pathology'; III International Conference 'Hemostasis, Thrombosis and Reproduction: An Interdisciplinary Approach" (Saint Petersburg, May 13-15, 2019), report 'Features of Preparation and Implementation of ART Protocols in Patients with Endometriosis'; Medical Forum 'III Education Week at Elizabeth Hospital' (Saint Petersburg, November 11-17, 2019), report 'Approaches to Correction of Uterine Cavity Pathology in Women with Infertility; All-Russian Scientific and Practical Conference for Obstetricians and Gynecologists 'Ott Readings' (Saint Petersburg, November 26-27, 2019), report 'Hyperplastic Diseases of Reproductive Organs in Patients Planning ART'; IV All-Russian Scientific and Practical Conference 'Medicine for the Future: From Pregnancy Planning to Childbirth' (Saint Petersburg, October 29-30, 2021), report 'Features of

ART Programs Planning in Genital Endomentriosis'; Ott Academy Christmas Meeting (Saint Petersburg, December 17-18, 2021), report 'Features of ART Protocols in Patients with Various Hyperplastic Diseases of Reproductive Organs'; IV All-Russian Scientific and Practical Conference for Obstetricians and Gynecologists 'Ott Readings', 'Reproductive Medicine in the Era of Changing Priorities: Facts and Goals" (Saint Petersburg, November 10-11, 2022), report 'Predictors of Efficiency of IVF Programs in Women with Uterine Fibroids: Evaluation of Endometrial Blood Flow'; VII Congress of Obstetricians-Gynecologists of the Republic of Tajikistan, (Dushanbe, November 26, 2022), report 'Surgical Aspects of the Pregravid Preparation of Women Planning Assisted Reproductive Technology Programs'; III Scientific and Practical Conference with International Participation 'Health of a Woman, a Fetus and a Newborn' (Saint Petersburg, April 21-22, 2023), report 'ART Programs in Women with Uterine Fibroids: Peculiarities of Endometrial Blood Supply'; III All-Russian Scientific and Practical Conference 'Endocrinology of Reproduction. Professor V.V. Potin's School' (Saint Petersburg, June 9-10, 2023), report 'Doppler Velocimetry of Endometrial Blood Flow within the Natural Cycle and within IVF Programs'; Conference devoted to topical issues of clinical implementation of modern biotechnologies in reproductive medicine 'Medicine for the Future: From Pregnancy Planning to Childbirth' (Saint Petersburg, November 24-25, 2023), report 'Infertility in Women with Uterine Fibroids.'

The developed algorithms for conducting preconceptional preparation when planning ART programs for women with uterine fibroids and women with genital endometriosis are used in teaching educational disciplines implemented by the Department of Obstetrics, Gynecology and Reproductology of Saint Petersburg State University and in the clinical practice of the Department of Assisted Reproductive Technologies of the Federal State Budgetary Scientific Institution 'Research Institute of Obstetrics, Gynecology and Reproductive Technology named after D. O. Ott.'

Author Contributions

The dissertation topic, structure and main provisions were developed by the author with the participation of a research adviser on the basis of long-term dedicated studies devoted to the problems of improving the efficiency of ART programs. The aim and objectives were formulated by the author independently, as well as all stages of scientific research, including the collection of clinical material, echographic and Doppler studies, statistical processing of the obtained findings and their interpretation. The author personally conducted all stages of assisted reproductive technology cycles of a significant number of observations included in the study on the basis of the Department of Assisted Reproductive Technologies of the Federal State Budgetary Scientific Institution 'Research Institute of Obstetrics, Gynecology and Reproductive Technology named after D. O. Ott' of Saint Petersburg (Head of the Department – prof. A.M. Gzgzian, M.D.).

Publications

In total, the author has published more than 110 scientific papers, including 17 publications on the subject of the dissertation, including 12 publications within the list of the State Commission for Academic Degrees and Titles and 5 publications in the *Scopus* scientometric database.

Structure and Volume of the Dissertation

The text of the manuscript is stated on 274 pages of typewritten text. It consists of the table of contents, introduction, literature review, chapters with description of research materials and methods, results of the dissertation, discussion of the results, conclusions, practical recommendations, lists of abbreviations and references. The work is illustrated with 33 figures and 93 tables. The bibliographic list includes 37 Russian and 349 foreign publications.

Key Research Findings

- In women with uterine fibroids, genetically determined control factors of estrogen metabolism, which increase the recurrent disease risk, were

identified, which allows formulating recommendations for rational planning of infertility treatment [Section 3.7, publications n. 18, 19, 22, 81, 82].

- The informative technique of endometrial blood flow assessment within the IVF (IVF+ICSI) programs was determined; for women with uterine intramural leiomyomas, the negative significance of persistently diminished blood flow resistance in the spiral arteries within IVF (IVF+ICSI) programs, which determines the decreased efficiency of ART programs, was defined [Sections 3.1, 3.2, 3.3, publications n. 6, 7, 20, 26, 35].
- The morphofunctional and immunohistochemical characteristics of the eutopic endometrium within the natural cycle associated with IVF (IVF+ICSI) program failure were determined, which allowed formulating the factors of post-transfer period failure in genital endometriosis [Sections 3.1, 3.4, 3.5; publications n. 9, 10, 21, 32, 135, 210].
- The efficiency of pre-conception preparation for women with genital endometriosis aimed at increasing the efficiency of IVF (IVF+ICSI) programs was determined [section 3.6, publication n. 37].

Chapter 1. LITERATURE REVIEW

1.1.1. Genetic aspects of uterine myoma development

Uterine fibroids represent a widespread disease of the female reproductive system, diagnosed in every fourth woman in different regions of the world [31; the detection rate varies from 20-50% according to clinical observations [145, 379] to 70-80% according to post-mortem examinations [5, 181]; it is detected in 5-10% of women with infertility and in 1-2.4% – as the only infertility factor [23, 110]; it is the cause of pregnancy failure [256].

Despite the significant prevalence of uterine fibroids in women, there are practically no methods of efficient disease treatment at the present time. Considerable interest of researchers in the issues of genetic factors in fibroids development is stipulated by the necessity of both clarification of pathogenesis mechanisms and elaboration of optimal management tactics.

Uterine fibroids refer to hormone-dependent proliferative diseases of the female reproductive system with multifactorial inheritance type. The correlation of the disease with the level of sex steroids has been shown in numerous studies for more than 50 years. In addition, fibroids development is also determined by the balance of growth factors of the angiogenesis and apoptosis systems [1, 88, 277, 306, 372]. Researchers' opinions on the role of genetic factors in the development of uterine fibroids diverge; there is an idea of a distinct hereditary nature of the disease with a 2.5-fold risk increase relative to the population, whereas the estimated inheritability of the disease ranges from 26 to 69% [180, 189].

Currently, there are several approaches to evaluation of genetic factors of uterine myoma development – comparative assessment of the intact myometrium and leiomyoma tissue to identify pathologic pathways using exome sequencing and microRNA studies [88, 179, 262] or identification of genes relevant for myometrial hyperplastic processes development. Uterine myoma has a monoclonal origin; thereby, as the tumor grows, somatic mutations accumulate in its tissue. To date, rather many variants of somatic mutations identified in uterine myoma cells have

been described (the most frequent of them are mutations in MED12 and HMGA2 genes [15].

Whole genome sequencing allowed identifying several loci associated with the risk of uterine myoma development; however, it proved difficult to substantiate the biological effect of the identified loci on the development of predisposition to uterine fibroids in a significant number of cases [42]. A significant number of factors indicating the hereditary nature of the disease have been identified: racial characteristics – an increased incidence of the disease in African-American women [383], a high risk of fibroids myoma development in women having uterine fibroids in the first degree of kinship as compared to women without such relatives [4, 167], a higher concordance of fibroids myoma development in monozygotic twins as compared to dizygotic twins [189, 284]. Ethnicity has also been shown to impact the clinical course of the disease – African-American women are two to three times more likely to develop symptomatic fibroids as compared to Caucasian women [68, 300, 374, 376]. At the same time, a study comparing large cohorts of women originating from various ethnic groups with leiomyoma failed to identify any specific loci correlating with a higher incidence of the disease [186]. It is likely that the increased incidence and severity of the clinical course may be associated with a combination of certain genetic factors and environmental factors, which do not represent independent risk factors for the disease – for example, a correlation of allelic polymorphism of glutathione-S-transferase GSTM1 and methionine synthase reductase MTRR genes has been shown: it was demonstrated that in case of detection of a combination of the GSTM1 del/del genotype with the MTRR 66G/G or MTRR 66A/G genotype, there is a predisposition to rapid growth of uterine myomas [265].

A large-scale study based on UK Biobank material, examining samples from 15,000 women with uterine fibroids, allowed identifying 22 genome regions associated with the disease. Among them, genes determining genome stability, genes encoding estrogen receptors, and a combination of genes associated with the formation of reproductive organs were identified [181]. Estrogens and progesterone

are known to be the main endogenous regulators of uterine myoma development. Increased expression of the Bcl-2 protein (apoptosis suppression factor) is stimulated by estradiol and progesterone [83], and the combined effect of estrogens and progesterone ensures the greatest effect on stimulation of uterine myoma proliferation, while one of the effects of estrogens is an increase in the expression of progesterone receptors [311].

Biological activity of hormonal factors is determined by the activity of their biosynthesis (determined primarily by enzyme systems), status of the receptor apparatus, and metabolic features. Variants of estrogen receptor polymorphism have been shown to be associated with a predisposition to uterine fibroids [63]. To date, several polymorphic loci have been identified in the ERα estrogen receptor gene, of which the PvuII and XbaI restriction site polymorphisms are the most studied ones; there are studies indicating functional significance of such polymorphisms [62], and the effect of estrogen impact on the PP genotype receptor (with the 'mutant' allele) appears to be more active than contact with the PP or PP genotype receptor; there are also indications that the P allele of the estradiol receptor gene is associated with the risk of uterine fibroids and adenomyosis development [147, 271]; however, there are contrary data [55].

Studies of genetic features of progesterone metabolism and receptivity are also a subject of debate: Renner S.P. et al. (2008) [323] showed that single-nucleotide polymorphisms +331G/A and V600L in a progesterone receptor gene are not associated with an increased risk of uterine myoma development. At the same time, it is known that an allele of the progesterone receptor gene with Alu insertion forms a receptor with an altered response, ensuring an increased biological effect of progesterone; however, studies of the relative risk of uterine myoma development did not reveal dependence on a variant of polymorphism [199].

Data on the impact of genes regulating steroid hormone metabolism on etiopathogenesis of uterine hyperplastic processes are few and still remain controversial. The catechol-o-methyl-transferase (COMT) gene encodes a protein responsible for steroid hormone metabolism (it is suggested that changes in the

structure of this gene may be responsible for inactivation of estrogens, thus affecting the hormone profile) [50, 338]. Catechol estrogens are inactivated in the body in two ways – by conjugation with glutathione (with the participation of the enzyme glutathione-S-transferase) and by methylation (with the participation of the enzyme catechol-O-methyltransferase). Catechol-O-methyltransferase, by methylating 2-hydroxyestadiol, increases the concentration of 2-methoxyestradiol (2-MeO-E2), which, in turn, has an antiproliferative cytostatic property and reduces the possibility of DNA damage, i.e., has an antitumor effect. Besides, catechol-O-methyltransferase converts 2-hydroxyestrogen to 2-methoxyestrogen. 2-hydroxyestrogen functions as an antiestrogen in many tissues. Transversion of G to A in the COMT gene results in the substitution of the Valine amino acid for methionine at position 158 of a protein, thus determining a functionally significant polymorphism [231]. In the G/G genotype, catechol-O-methyltransferase converts 2-hydroxyestrogen into its methylated form more efficiently and faster, thus reducing the number of antiestrogens and contributing to the formation of a more active estrogen profile. People with the A/A genotype are characterized by a lower estrogen profile [50]. Heidari M. et al. in their study (2019) found an association of AA+GG genotypes with an increased risk of uterine myoma development (in contrast to the GA genotype) [190]. COMT enzyme activity was shown to be significantly higher in human leiomyoma tissue as compared to the surrounding intact myometrium [301], thus suggesting a significant role of COMT in myoma formation. The G/A allele of the COMT gene (Val158), which produces a highly active protein, is found significantly more frequently in African American women as compared to Caucasian women, reinforcing the previously identified cause-and-effect relationship [50]. In vitro experiments with cell cultures have shown an association between highly active COMT polymorphisms and the level of cell proliferation; at the same time, this effect does not depend on ethnicity [50]; there is a significant association between the presence of large myomas and the Val158 COMT polymorphism [337, 338].

Aromatase encoded by the CYP19A1 gene is the key enzyme required for estrogen and androgen synthesis. Local aromatase activity and expression of mRNA and CYP19 protein are significantly higher in uterine lioemyomas as compared to intact myometrium in women of different ethnic groups [80]. High local aromatase levels are associated with a local increase in estrogen synthesis and promote proliferative activity stimulation in tumors [218].

Considering the scattered data on the detection rate of polymorphisms of estrogen and progesterone metabolism and receptor genes in women with uterine fibroids, there is no possibility to assess the nature of their impact on the clinical course of the disease, which requires further research – in terms of possibilities of disease prediction, clinical course prognosis and clarification of the role and place of surgical treatment of uterine myoma for women planning to realize the reproductive function.

1.1.2. Current Ideas on Pathogenesis of Fertility Disorder in Uterine Fibroids

The negative impact of uterine fibroids on reproductive function is described primarily in terms of the high incidence of pregnancy complications, such as miscarriage, fetal position abnormalities, uterine contractility abnormalities in labor, and bleeding in the postpartum and early postpartum periods. The idea of the etiologic role of uterine myoma in the development of infertility is debated, although a number of authors consider that 5 to 10% of female infertility problems can be directly attributed to the presence of myoma [343]. It is well known that submucosal uterine myoma reduces the likelihood of pregnancy not only in the population but also with application of assisted reproductive technology resources [6, 110, 294; thereby, it has been shown previously, that myomectomy improves reproductive outcomes and, if uterine fibroids are the only cause of infertility, solves the problem [173, 175, 203, 204, 274, 294, 330], whereas there is no consensus concerning the negative impact of uterine intramural myoma on the realization of reproductive function. In recent years, the number of patients of assisted reproductive technology (ART) centers who have uterine myoma and/or have undergone conservative

myomectomy, has markedly increased, while the discussion regarding the influence of myoma on the efficiency of in vitro fertilization (IVF) programs continues [116, 173, 345]. The incidence of uterine myoma in women with infertility at the age of 33–40 years can reach 8% and among ART patients – 26% [59, 76].

In 2020, a meta-analysis by Rikhraj K. et al. was published, which included data from 15 studies (5029 women) and compared the effectiveness of IVF cycles in women with uterine fibroids and in women without uterine fibroids. It was shown that in uterine fibroids the incidence of clinical pregnancy was reduced by 32% and the incidence of labor by 44%. At the same time, analysis of studies that included women with uterine intramural leiomyomas only showed that the differences were always substantial, in contrast to cases with uterine subserosal leiomyomas. The authors also showed that the incidence of pregnancy failure in women with myoma tended to increase, but these differences were not statistically significant [355].

It is known that uterine intramural leiomyomas are detected in 58% of uterine myoma cases [316]. It is difficult to build a uniform concept of infertility pathogenesis in the intramural form of uterine myoma due to the fact that different researchers apply different inclusion criteria for the size of myomas – from 4 to 7 cm in diameter; the number and localization of myomas in relation to the uterine cavity are also accounted for differently. At the same time, it is considered that the presence of subserosal leiomyomas is usually not associated with impaired fertility.

Mechanisms of fertility impairment in uterine fibroids are associated with several factors: 1) changes in the length and structure of the cervix, impairing the conditions of sperm transport, 2) changes in the uterine vascular system associated with myoma and affecting angiogenesis in the endometrium and its receptivity [119], 3) changes in the structure of the endometrium at submucosal localization of leiomyomas, conjugated with changes in the spectrum of biologically active factors involved in formation of the 'implantation window' [59, 110], 4) changes in peristalsis and contractility of the myometrium [95, 121, 123]; 5) impaired passage through the ostia uteri (or their obstruction) due to specific location of uterine

myomas [59, 374]. Probably, such factors as excess body weight, ethnicity, etc. also play a certain role.

Among causes of the negative effect of uterine myoma on fertility, inflammatory changes in the endometrium (associated with release of vasoactive peptides) and disorders of the endometrial vasculature are also the subject of study [103, 230]. Somigliana et al. (2007) showed that anatomical changes in the uterine cavity in women with myoma are associated with changes in the histologic structure of the endometrium - stretching of the subendometrial zone structures is identified, elongation and stretching of glands, glandular cystic hyperplasia, polyposis, and dilatation of venules in the endometrium are detected in the endometrium; as shown in other studies, gland atrophy and chronic inflammatory process in the endometrium are also frequently detected, and it is assumed that paracrine influences, such as vasoactive amines and other proinflammatory factors secreted by leiomyomas, may play a role [102, 171, 315]. Studies by Eldar-Geva T. et al., Surrey E.S. et al., Yoshino O. et al. [95, 121, 123] proved that women with myoma have an increased contractility of myometrium, which correlates negatively with the pregnancy probability. It is also known that the pseudocapsule of uterine myomas has a high angiogenic activity [326].

In assessing the receptivity of the endometrium in uterine fibroids, data concerning evaluation of molecular mechanisms of uterine myoma impact on fertility are of considerable interest [195].

HOXA10/Hoxa10 is a transcription factor containing a homeobox sequence that is essential for embryonic development and is also an important factor in formation of the endometrium in an adult body throughout each menstrual cycle [219, 336]. HOXA10 expression is necessary for formation of a receptive endometrium [67, 335]. At present, it is a proven marker of full receptivity of the endometrium. It was shown that diminished HOXA10 expression is observed in genital endometriosis, PCOS, chronic salpingo-ophoritis and in conditions involving implantation disorders [84, 92, 196, 269, 303]. Women with uterine fibroids were also found to have diminished HOXA10 levels [345]. Rackow B.W. and Taylor H.S.

(2010) [308] showed a significant decrease in HOXA10 expression in the endometrial stroma in women with uterine submucosal myoma as compared to both control groups (in the absence of uterine myoma) and intramural myomas; at the same time, a number of authors note that the conservative histologic examination of the endometrium often cannot show reliable differences between healthy women and women with infertility [254, 255]. It is important that the identified abnormalities in the expression of key receptivity factors are usually observed throughout the endometrium, regardless of the submucosal myoma localization. In uterine intramural myoma, a tendency for HOXA10 decrease in endometrial stroma was reported [92, 197, 308]. At the same time, whether the change in the endometrial receptivity is associated with remoteness of the intramural myoma from the uterine cavity remains to be determined. mRNA expression evaluation in the luteal phase of the cycle in women with uterine fibroids is considered to be a marker of the endometrial receptivity [321].

The number of surgeries for uterine myoma comprises more than 70% of the total number of surgical interventions in gynecology [3]. Does myomectomy restore reproductive potential? There is data that in a comparative evaluation of the efficiency of expectant management (refusal of myomectomy) and myomectomy, the pregnancy rate in women after myomectomy within 5 years was 2 times higher – 25% and 12%, respectively [267]. Authors' opinions regarding the effect of conservative myomectomy on fertility recovery are contradictory: Zepiridis L.I. et al. (2016) [386] showed improved infertility outcomes with any types of conservative myomectomy, whereas SamejimaT. et al. (2015) [206] found that conservative myomectomy can solve the infertility problem only in women, in whom myoma was the only factor of infertility – particularly in case of submucosal localization; at the same time, removal of intramural myomas may have no effect on the efficiency of infertility treatment [294]. At the same time, many authors are unanimous that conservative myomectomy improves pregnancy outcomes (decreased risk of spontaneous miscarriage and incidence of preterm labor), thereby, however, increasing the incidence of abdominal delivery [165, 237].

The need for conservative myomectomy for uterine submucosal myoma is obvious to most specialists, but the formation of indications for conservative myomectomy for intramural nodes is a subject of debate. The list of indications for myomectomy includes the size of myomas (4 cm or more), their number, the presence of uterine cavity distortion, and total uterine volume [109, 116, 363, 386]. In the Russian Federation, the indications for conservative myomectomy before planning ART methods are regulated, including in accordance with clinical guidelines [13]: removal of uterine myomas with a diameter exceeding 4 cm is indicated. Indications for removal of subserosal myomas are usually associated with their size or impact on the pelvic organs.

Performing conservative myomectomy in women with infertility requires thorough preoperative preparation and examination with the use of various imaging methods (transvaginal ultrasound, MRI) to choose the optimal option of surgical intervention, since myomectomy is an injury to the myometrium, the need to use suture material, the risk of defects in the myometrium [122], recommendations for the prevention of incomplete scar formation in the myometrium limiting the use of electrosurgical techniques [364], surgical intervention in women with infertility are justified. The role of minimally invasive interventions - uterine artery embolization, remote ablation of uterine myomas under MRI control with the use of ultrasound or radiofrequency equipment in the treatment of women with infertility is still insufficiently studied. It is known, for example, that selective uterine artery embolization is often associated with a subsequent decrease in ovarian reserve [235, 370].

Despite the presence of evidence that myomectomy can improve fertility or increase the efficiency of infertility treatment, a meta-analysis of available publications published in the Cochrane database in 2012 [261] demonstrates the presence of contradictory data and poorly systematizable studies, which does not allow us to speak about the unambiguous positive effect of myomectomy for intramural myomas on fertility.

According to Zepridis L.I. et al., the important parameters for deciding on the necessity of myomectomy are: 1) expected impact of myoma on fertility, 2) the efficiency of surgical intervention, 3) additional clinical data related to the presence of myoma [386]; the authors conclude that submucosal myomas and myomas of intramural localization with a diameter exceeding 4 cm negatively affect reproductive potential, have pronounced clinical manifestations, and their removal will have a positive impact on fertility; whereas intramural myomas with a diameter of less than 4 cm and subserosal myomas generally do not affect fertility, and their removal will not improve a woman's reproductive potential.

1.1.3. Uterine Fibroids and Endometrial Blood Supply

Endometrial blood flow indices are a subject of study in terms of predicting both the onset of pregnancy and its possible complications [317]. It is known that the presence of uterine myoma alters endometrial vascularization, which can negatively affect the implantation process. Kamel A. and co-authors in 2018 conducted a study of endometrial vascularization in uterine fibroids using power volume Doppler ultrasonography [120] in women with single uterine intramural myomas from 1 to 7 cm in diameter. It was found that morphometric characteristics of the endometrium (thickness and volume) in women with uterine fibroids who applied for infertility treatment using ART methods did not differ from those in women without uterine fibroids – with male or idiopathic factor of infertility; however, when using power volume Doppler ultrasonography, increased endometrial vascularization was detected in women with uterine fibroids (significantly increased VI, FI and VFI indices), whereas no differences in blood flow indices (PI, RI) were observed in the uterine artery. It is important that a significant increase in endometrial blood flow was determined only for women with uterine myomas exceeding 4 cm. Ng E.H. et al. also found no differences in PI and RI blood flow indices in uterine arteries regardless of myoma size [130]. It is noted that depending on the part of the myometrium from which intramural uterine myomas develop – from the outer part of the myometrium as subserosal myomas or

from the connective area as submucosal ones – different clinicopathologic characteristics of the disease are determined [119].

The review by Stewart E.A. et al. (2016) [371] showed that in the uterus with myoma there is an 'angiogenesis dysregulation.' An important factor in the angiogenesis regulation is the TGF-β-related pathway that regulates cell growth, modulation of tissue remodeling, inflammation and apoptosis [283]. Ng E.H. et al. found no differences in the blood supply indices of the endometrium in women with uterine fibroids and in the absence of myoma during IVF (IVF+ICSI) programs [130]. At the same time, it is known that in uterine fibroids there is a decrease in blood flow resistance indices in all areas of the uterine artery. One of the possible mechanisms of hyperperfusion development may be the increased expression of the TGF-β gene in the endometrium of women with uterine fibroids [179]. TGF-β3 is one of the most significant representatives of the transforming growth factor family, and its secretion is significantly increased in the myometrium in uterine fibroids (it is a product of leiomyoma). Altered regulation of TGF-β3 production in the presence of leiomyomas leads to implantation disorders and excessive menstrual blood loss [322]; TGF-β3 also regulates the BMP-2 action and reduces the PAI-1, ATIII and thrombomodulin gene expression in endometrial stem cells. Under physiological conditions, there is a cyclic change in the PAI-1 (plasminogen activator inhibitor) activity in the endometrium, which is a modulator of fibrinolysis – it begins to increase in the late proliferative phase, reaching a maximum by the onset of menstruation. This gene expression pattern of the hemostasis system ensures normal blood loss during normal menstruation. However, in uterine fibroids, the PAI-1 expression in the endometrium increases 4-fold, thus provoking fibrinolysis disorders, impeding thrombolysis in the vessels, resulting in menorrhagia, often observed in women with uterine fibroids. Overexpression of TGF-β3 leads to overproduction of such extracellular matrix proteins as collagen-1, fibronectin, PAI-1, which is accompanied by leiomyoma growth. Thus, TGF-β produced by leiomyoma impairs the endometrial receptivity [59, 322] and PAI-1 production in the endometrium [334]. Researchers [322] are ready to assume that the therapeutic

use of drugs blocking TGF-β3 may be a promising direction for uterine myoma complications treatment. The experiment showed the therapeutic effect of high doses of vitamin D, which promote the activation of apoptosis and inhibition of Wnt/b-catenin pathway genes in leiomyoma cell culture, on the normalization of TGF-β3 and PAI-1 expression [251].

Evaluation of the endometrial blood supply is a significant indicator of endometrial receptivity, including within ART program cycles. Currently, the number of studies devoted to the evaluation of endometrial blood flow in embryo transfer cycles is small, and their results are often contradictory. Adequate endometrial blood supply in the middle of the secretion phase is one of the most important conditions for achieving pregnancy [325], while increased resistance to blood flow during this period is observed in women with recurrent miscarriage after ART programs [317]. Wang J. et al. (2018) used the results of three-dimensional power Doppler ultrasonography to evaluate the endometrial blood supply, which allowed to establish that on the day of embryo transfer, higher volume blood flow indices (VI, FI, VFI) in the endometrium positively correlate with the probability of pregnancy [131, 356; at the same time, the data of various researchers are often contradictory and the correlation of blood flow indices with the efficiency of ART programs in women with uterine fibroids is not always informative [130].

It was shown that endometrial blood flow indices are also associated with the level of cytokines (IL-15, IL-18, IL-18-binding protein) during the peri-implantation period and may reflect the endometrial receptivity [56, 138]. In the process of physiological transformation of the endometrium during the normal menstrual cycle, there is a well-regulated process of limited NK cell activation, which determines a regular change in the content of angiogenic and immunotropic cytokines. Cytokines are involved in local angiogenesis in the process of formation of the receptive endometrium. In particular, interferon-γ and TNF are essential for early implantation stages; dysregulation of different cytokine types production in the endometrium is accompanied by abnormalities in the endometrial histo- and angioarchitectonics. IL-15 is involved in the activation and maturation of NK cells in the endometrium and

is found predominantly in the perivascular cells of the stroma around the spiral arteries in the middle and late stages of the secretion phase. In an experiment in mice, the absence of NK cells resulted in a lack of proper changes in the spiral arteries required for pregnancy. Mature NK cells participate in the formation of structural changes in the spiral arteries via IL-15 and interferon-γ. The IL-15 expression is positively correlated with increased subendometrial blood flow (VFI), as is CD56+ cell count in women with repeated IVF and ET failures [138]. Thus, the decreased subendometrial blood flow with the decreased IL-15 expression is accompanied by insufficient activation of uterine NK cells and deficiency of proangiogenic factors. At the same time, under physiological conditions, endometrial blood flow indices should not increase excessively, which can be shown in the assessment of the volume blood flow index (VFI) by 3D power Doppler ultrasonography. It was also shown that women with high IL-15 expression levels do not have a physiologic decrease in local angiogenesis, which may be related to an excess of proinflammatory cytokines, while an excess of Th-1 may be associated with implantation failures [56]. Kitaya K. et al. (2005) showed changes in the IL-18 / IL -12 / IL-15 ratio in implantation failures, suggesting that IL-15 is directly involved in the postovulatory recruitment of NK cells. IL-18 is expressed around the thin muscle fibers of the spiral arteries, directly affecting the angiogenesis processes. The IL-18 and IL-15 expressions are determined to be significantly lower in the group of repeated implantation failures as compared to women with male factor infertility. IL-15 and subendometrial blood flow indices were determined to have a significant correlation ($r = 0.65$; $p = 0.0001$) with CD56+. The IL-18, IL-18 binding protein and the IL-15 mRNA correlated negatively with the PI in the uterine artery [232]. Thus, changes in blood flow indices may reflect dysregulation of cytokines in the endometrium and cause impaired implantation processes due to excessive activation of NK cells or inadequate angiogenesis before implantation.

A study of molecular biological factors in the endometrium and myometrium during the peri-implantation period may help to understand the causes of the decreased efficiency of IVF programs in women with uterine fibroids, since no

significant changes in the histoarchitectonics of the endometrium during this period were observed [254, 255]. It can be assumed that if the negative effect on implantation rate in submucosal myomas is related to the appearance of signaling molecules produced by the myomas in the endometrium, this effect is weakened in intramural myoma due to anatomic remoteness. The difficulty of summarizing clinical cases with uterine intramural myomas is due to the fact that this is a heterogeneous group in terms of such parameters as size, number of myomas, their localization and remoteness of the myoma capsule from the endometrium. In 2055, Lu N. [127] published the results of a study that evaluated the outcomes of IVF programs depending on the distance from the intramural myoma capsule to the uterine cavity: when the distance ranged from 1 to 3 mm, the implantation rate was reduced and the rate of miscarriage was increased as compared to women without uterine fibroids. The most biologically active area of a myoma is its pseudocapsule, and it is probably this area and its relation to the endometrium that will determine the effect on implantation. Thus, intramural uterine myomas may have a paracrine effect on the adjacent endometrium, causing implantation disorders.

1.1.4. Uterine Fibroids and Efficiency of Assisted Reproductive Technology Programs

Significant contradictions in publications are related to the evaluation of the impact of uterine intramural myoma on the efficiency of IVF (IVF+ICSI) infertility treatment. In 1998, Ramzy A.M. et al. conducted a study [374] of a relatively small group of women with uterine fibroids not deforming the uterine cavity in IVF programs, which showed no significant differences in the efficiency of IVF programs as compared to the control group (without uterine myoma). Later in 2002, Donnez J. et al. showed that pregnancy rates in women with myomas deforming the uterine cavity, not deforming the uterine cavity, and without myoma comprise 9%, 33.5% and 40%, respectively [110]. An analysis of data from more than 9000 IVF cycles in 2018 also showed that the presence of uterine intramural myomas not deforming the uterine cavity is associated with a decline in the efficiency of IVF

cycles (implantation rate, clinical pregnancy rate, and delivery rate decrease by 6%, 14%, and 19%, respectively), while the incidence of miscarriage increases by 27% [356]. A number of authors point out the importance of myoma localization: in the presence of type 3 myomas, in accordance with the international classification of the International Federation of Gynecology and Obstetrics (FIGO) of 2011 [266], especially if their diameter exceeds 2-3 cm, the efficiency of IVF (IVF+ICSI) programs decreases [124, 214, 339, 354].

Meta-analyses by Somigliana E. (2007), Pritts E.A. (2009), Sunkara S.K. (2010) [171, 294, 345] once showed that in uterine intramural fibroids not deforming the uterine cavity, there is a reduced pregnancy rate during IVF and ET programs and increased incidence of miscarriage as compared to women without uterine myoma [6], which is confirmed by a relatively recent meta-analysis [172]. At the same time, in the presence of only subserosal myomas, such a pattern is not observed [345]. Meanwhile, Somigliana E. et al. (2011) [173], based on the analysis of 239 IVF cycles, indicated the absence of differences in the incidence of pregnancy and childbirth in women with intramural myomas not deforming the uterine cavity with a diameter of less than 5 cm as compared to the control group of women without uterine myoma; the dependence of the results on the myoma size is also shown by Bonanni V. (2023) and Yan L. (2014) [116, 357]: the negative impact of uterine intramural myoma on the outcomes of IVF programs is determined already when the size of a myoma exceeds 2.85 cm (a decrease in the frequency of births was revealed). Works by different researchers [117, 173, 215, 267, 339, 355] provide different borderline values of myoma size, at which there is a decrease in the efficiency of IVF programs – from 4 to 7 cm. Thus, a significant number of authors show a decrease in the pregnancy rate, implantation rate and delivery after IVF (IVF+ICSI) in uterine intramural fibroids not deforming the uterine cavity.

Changes in myometrial and endometrial vascularization, changes in the functional activity of the endometrium due to changes in gene expression in the peri-implantation period appear to be possible causes of the pregnancy rate decrease.

Evaluation of the endometrial receptivity using gene expression spectrum analysis revealed only insignificant changes in the spectrum (3 out of 25 identified genes) during the implantation window in women with intramural myoma [134]. Undoubtedly, the negative effect of uterine intramural myoma not deforming the uterine cavity on the results of IVF (IVF+ICSI) programs is determined by the factors responsible for the decrease in fertility (myometrial contractility, endometrial receptivity, formation of the 'implantation window' under changes in the regular expression of implantation factor genes). Changes in the myometrial and endometrial vasculature or the peculiarities of estrogen receptors or their metabolism, expression of growth factors (TGF-β, VEGF) are also likely to affect the efficiency of ART programs [159, 179].

Despite a significant number of studies on the role of uterine myoma in impaired fertility and infertility treatment by ART methods, the data are contradictory and the need for further study of this issue is obvious. One of the possible directions may be an in-depth assessment of the state of the endometrium using molecular-biological and genetic methods in different uterine myomas, which will allow to form personalized management tactics to achieve maximum results in infertility treatment, rationally applying surgical and pharmacological methods.

The negative impact of uterine myoma on the outcomes of assisted reproductive technology programs is not offset after conservative myomectomy, except in cases of submucosal myoma removal [266, 345, 358]. Sarıdoğan E. et al. (2019) showed that in general, removal of intramural myomas had no significant effect on the outcomes of IVF programs, whereas removal of myomas with a diameter of 5-6 cm or more is considered necessary [312].

In 2019, Fortin C.N. et al. showed that the cumulative pregnancy rate in post-myomectomy women is higher as compared to women with uterine fibroids who did not undergo myomectomy or to women in the control group (without myoma); the improvement of ART programs results immediately – pregnancy rate increases already in the first IVF cycle. It should be noted, at the same time, that the delivery rate in these women does not increase significantly [126]. The positive effect of

myomectomy on fertility in the case of large myoma sizes and multiple myomas is shown in the work by Şükür Y.E. (2021) [327].

The waiting period between the conservative myomectomy and the IVF (IVF+ICSI) program (during which the myometrial scar formation takes place) usually comprises 3 to 6 months (depending on whether there was contact with the uterine cavity during surgery) [266], which should also be taken into account when planning infertility treatment in women with reduced ovarian reserve. Accordingly, when determining the indications for conservative myomectomy prior to ART programs, an individualized approach with careful evaluation of all risk factors and anticipated positive outcomes is important. Preparation of women with uterine intramural myoma for IVF remains unclear (in contrast to cases of submucosal myoma).

Data on the efficiency of assisted reproductive technology programs after treatment with minimally invasive modern methods – endovascular embolization of uterine arteries (EMA), focused ultrasound under control of magnetic resonance imaging (MRgFUS) – based on studies performed on numerous observations and having high reliability are currently insufficient.

1.2.1. Current Ideas on Pathogenesis of Infertility in Endometriosis

The negative impact of genital endometriosis on fertility is formed in multiple directions: unfavorable changes in the pelvic cavity; loss of ovarian reserve and suboptimal status of oocytes; and impaired endometrial receptivity [93].

The formation of an unfavorable environment in the abdominal cavity during EGE is provided by the secretion of numerous immunoreactive and proangiogenic factors by implants – IL-1β, IL-6, -7, -8, -17, -18, -33, TGF-α, VEGF, EGF, and others [164, 169, 188, 217, 365], – which has negative effects on gametes and embryos. Peritoneal macrophages have the ability to actively phagocytize spermatozoa; under their influence, the expression of metalloproteinases decreases [286, 383]. The formation of adhesions in the pelvic cavity in EGE also ensures a decrease in fertility.

The factors that have a negative impact on fertility in EGE undoubtedly include a decrease in the number of antral follicles and the associated decrease in markers of ovarian reserve, primarily AMH and antral follicle number. The most significant cause of loss of ovarian reserve is surgical treatment of endometriomas (including thermal damage to intact ovarian tissue, devascularization). In addition, there is an opinion that the presence of endometrioma outside surgical treatment is an independent factor of AMH reduction [342] associated with a shortened reproductive period in women with genital endometriosis. There is also an idea that endometrioid ovarian lesions have a negative impact not only on the number but also on the quality of oocytes; at the same time, the mechanisms of pathogenic effects on oocyte quality are debated: there is a discussion of the role of inflammatory response affected by the PI3K-PTEN-Akt signaling pathway activation, including the activation of autoimmune processes in the ovaries [139, 320]; increased apoptosis activity in granulosa cells, which causes impaired follicle development, altered oocyte microenvironment [164], decreased ovarian aromatase activity [228], altered balance of antioxidant defense factors, and mitochondrial dysfunction of cumulus cells, was shown [200, 228, 257, 350]. Researchers pay considerable attention to the factors of oxidative stress: the increase in the content of reactive oxygen species, nitric oxide (NO), lipid peroxidase in granulosa cells in endometriomas accompanied by a decrease in antioxidant activity, superoxide dismutase, glutathione peroxidase, a decrease in the content of copper, zinc, selenium, which is accompanied by a decrease not only in the number of mature oocytes, but also in the frequency of fertilization, was shown [213, 257, 350].

At the same time, clinical data do not always confirm the fact of negative impact of endometriosis on oocyte quality: Filippi F. et al. (2014) [275] compared endometrioma-affected and intact ovaries and found no significant differences in the number of follicles, the number of mature oocytes obtained and the number of viable embryos. De Ziegler D. et al. (2010) indicate that in women with EGE, oocyte quality is not altered by a diminished response to controlled superovulation

stimulation [93]. The frequency of embryo aneuploidy in women with and without EGE does not differ according to Juneau C. (2016) [285].

A study of embryo condition peculiarities by time-lapse microscopy also allowed to evaluate additional data: when culturing embryos of women with genital endometriosis, a shortening of the duration of the first cell cycle and a decrease in the number of embryos of good quality were revealed – however, with the same pregnancy rate [353].

Endometrium is one of the critical determinants of fertility. The endometrium contains a complex of autocrine, paracrine, and endocrine signaling pathways, including sex steroids, cytokines, chemokines, and intracellular pathways, whose interaction determines endometrial receptivity. Whether endometrial receptivity is impaired in women with genital endometriosis is a matter of debate; there are a significant number of studies evaluating different parameters of changes in receptivity of the endometrium leading to impaired implantation or pregnancy failure in endometriosis.

Various aspects of disorders in the eutopic endometrium associated with impaired receptivity were described in the literature: altered ultrastructure of the eutopic endometrium, including disruption of pinopodia formation [245, 263]; increased expression of estrogen receptor (ER) alpha, altered balance of ERα and ERβ in the eutopic endometrium, including genetically determined [149, 150, 260, 332], decreased concentration of progesterone receptors and resulting progesterone resistance [178, 202, 233, 295]; disturbances in the expression of HOXA10, HOXA11 genes in the peri-implantation period [52, 187, 196, 383], changes in the expression of laminin-1 [158]; changes in the balance of immunoreactive molecules in the endometrium (CD8, 20, 138; IL-17, IL-6 [28]; increased expression of BCL6, Kras, aromatase, changes in STAT3, SIRT1 signaling pathways [51,132]. Decreased expression of other endometrial factors – integrin α and β3 and L-selectin, which play an important role in implantation processes [44, 136, 157, 161, 239, 252]. It is assumed that changes in gene expression in the endometrium are associated with changes (decrease) in the biological effect of progesterone and estrogen overactivity

[90, 302, 385]. A decrease in the expression of leukemia inhibitory factor (LIF), necessary for normal implantation [298], which is determined normally in the endometrium during the implantation window, was demonstrated [74, 241].

In endometriosis, inflammation is one of the pathophysiologic mechanisms of the disease formation associated with progesterone resistance and estrogen prevalence [246], which is accompanied by dysfunctions of the endometrium [43, 221, 222, 227]. Inflammation is considered to be the cause of impaired endometrial receptivity in endometriosis [207, 222, 227]. In the presence of proinflammatory reactions in the endometrium, there is a local and systemic change in the expression of cytokines [57, 201, 207, 209, 224, 304], accompanied also by an increase in the content of macrophages [253].

One of the most significant changes in endometriosis is the induction of the p450 aromatase expression in the endometrium [41, 65], and it is on this factor that inflammation has a stimulating effect. Brosens J. (2004) [191] showed that the increased expression of aromatase is associated with IVF failures. Excessive local estrogen production leads to inhibition of key factors of blastocyst-endometrium contact – for example, integrins α and β3, – while a decrease in integrin expression is associated with impaired IVF outcomes and can be modified by the administration of aromatase inhibitors within the stimulation cycle [263].

Normally, decreased progesterone levels at the very end of the luteal phase result in significant proinflammatory changes in the endometrium necessary for the onset of menstrual bleeding. It is likely that deficiency of progesterone action in endometriosis may contribute to the premature inflammatory response [129].

Proinflammatory changes in the eutopic endometrium of women with EGE are accompanied by excessive activation of signaling pathways that support the process of inflammatory changes and potentiate progesterone resistance [223]; excessive production of interleukin-17 in the endometrium of women with endometriosis [106] is accompanied by increased production of IL8, which in turn affects the PTEN/AKT signaling pathway. Under the influence of IL6 overproduction, STAT3 (signal transducer and activator of transcription 3), a key

transcription factor responsible for the implementation of the inflammatory response program, is steadily activated. Normal STAT3 activation plays an important role in the decidualization of stromal cells of the endometrium, determines angiogenesis in the endometrium and participates in the formation of receptivity of the endometrium. Excessive and untimely activation of STAT3 in genital endometriosis is accompanied by disease progression and infertility [234, 281, 360].

Disruptions in the activation of several other signaling pathways in the endometrium of women with endometriosis are described: increased activity of AKT and MAPK, which disrupt decidualization processes, suppressing, in particular, the expression of FOS, NOTCH1, estrogen receptor beta, and progesterone receptor genes; a significant number of gene expression changes in the endometrium associated with secretory transformation of the endometrium are described [111, 148, 162, 281]. The activity of the Wnt/b-catenin signaling pathway is also impaired in the presence of progesterone deficiency [216]. A decrease in the level of glycodelin A (immunomodulatory glycoprotein) [240] is suggested to be considered as a potential noninvasive biomarker of endometriosis.

The implantation success is determined by the physiologic balance of type 1 and type 2 T-helper cells and the immunogenic factors they secrete. Excessive activity of type 1 T-helper cells is associated with fetal loss, while the activity of type 2 T-helper cells is aimed at maintaining pregnancy. At the onset of pregnancy, a 10-fold increase in the expression of type 2 T-helper cells 6 and 10 is detected. It is known that progesterone has a suppressive effect on type 1 T-helpers and is an inducer of cytokine release by type 2 T-helpers [137]. It is obvious that the positive effect of progesterone administration on pregnancy failure is realized due to its selective immunosuppressive effect, as well [268]. In progesterone deficiency, also caused by progesterone resistance in EGE, the process of control over the state of 'immune tolerance' in the endometrium is disturbed, and the processes associated with implantation are disturbed [11, 53]; a number of authors also point to the high frequency of chronic endometritis in endometriosis [193].

Progesterone deficiency in the endometrium is also associated with increased expression of the BCL6 oncogene, the expression of which is also increased in the inflammatory response, including in women with EGE [51, 132, 233]. In turn, the inflammatory response in progesterone resistance has an immune-mediated effect on the functions of the endometrium, including the expression of genes associated with the formation of the "implantation window" [79, 178, 240]. [79, 178, 240, 297]. The expression of genes involved in the remodeling of the extracellular matrix, angiogenesis and proliferation has been shown to be altered in the endometrium of women with EGE [205], which forms a vicious circle of progesterone resistance and proinflammatory changes in the endometrium [86]. Inflammation, in turn, induces impaired secretory transformation of the endometrium as a manifestation of progesterone resistance in response to progesterone receptor dysfunction. There is also an idea of a possible role of the bacterial component in the development of proinflammatory changes in the endometrium as a stage in the pathogenesis of endometriosis [66]; chronic endometritis is also a known factor of fertility disorders [85, 144, 243].

Thus, in endometriosis, the expression of progesterone-dependent genes is impaired by biomarkers of the endometrial receptivity during the implantation window – adhesion molecules (integrins, cadherins, selectins, immunoglobulins), cytokines, growth factors, and prostaglandins) [239]. In the endometrium of women with GE, the expression of the IPFR-binding protein and prolactin is significantly reduced [178], and the expression of the αvβ3 integrin is reduced, which ultimately leads to diminished expression of HOXA10 (involving gene hypermethylation mechanisms), which in turn regulates the expression of the IPFR-binding protein. The expression of HOXA11, another important component involved in the interaction with the blastocyst during the implantation window, is also reduced (normally, with adequate progesterone levels, it is upregulated in the middle of the secretion phase). A number of cytokines (LIF, IL6, IL11) affecting the expression of estrogen and progesterone receptors have an altered secretion profile in the endometrium [349]. Thus, the markers of the endometrial receptivity demonstrate

pronounced interrelations in proinflammatory and hormonal factors. In order to increase the ART program efficiency, it is important to restore adequate expression of the factors of endometrial receptivity using personalized immunomodulatory therapy, which will allow to reduce surgical aggression in endometriosis therapy.

Adenomyosis is a condition in which endometrium-like tissue (epithelial and stromal components) are located in the myometrium and surrounded by hypertrophic muscle fibers.

EGE and adenomyosis are estrogen-dependent diseases among women of reproductive age, often occurring in combination. In 1995, Souza et al. stated that the incidence of adenomyosis in young women with infertility and dysmenorrhea is as high as 54% [359]. Up to 35% of women with advanced endometriosis have adenomyosis [48]. The etiology of adenomyosis is not completely clear. There are ideas that adenomyosis is a consequence of direct invasion of endometrial cells into the myometrium, for example, due to trauma during intrauterine interventions or the appearance of microtrauma during uterine contractions, in which there is a disruption of the structure of the connective zone [71, 229], local trauma and activates reparative processes accompanied by a local increase in the level of estradiol [177], which in turn additionally stimulates peristalsis and thus forms conditions for the 'invasion' of the endometrium into the myometrium; according to another theory, adenomyosis may develop as a result of metaplasia of embryonic Müllerian ducts or stem cells of the endometrium. The growth of adenomyosis foci is usually stimulated by estrogens and suppressed by progestogens [282]. Modern methods of genetic analysis of eutopic of the endometrium in adenomyosis show the presence of a significant number of genes whose expression differs from normal (more than 1000) [184].

he existing hypotheses of adenomyosis formation do not explain the full range of clinical manifestations. The most frequent clinical manifestations of adenomyosis are menorrhagia, infertility, implantation failure, and pregnancy failure. It was shown that adenomyosis negatively affects fertility and the outcomes of ART programs [105, 328]: normal myometrial contractility is altered due to changes in its

architectonics, but the decrease in the endometrial receptivity is likely to be the most important; changes in the expression of known implantation markers are shown: the expression of HOXA10 genes is decreased [174, 198]; the expression of LIF during the 'implantation window' is impaired, and the activation of the FOXO1A pathway occurs [94]. A number of pro-inflammatory factors such as IL-1b, corticotropin-releasing hormone [155], as well as NK cells, macrophages and a range of cytokines are elevated [91, 366]. Levels of catenin and selectin, proteins involved in the regulation of cell adhesion, are increased and levels of integrin and osteopontin are decreased [133, 156, 307]. A decrease in estrogen metabolism in eutopic endometrium was also demonstrated. Increased resistance to estradiol is associated with a decrease in the number of progesterone receptors, particularly PR-B [211]. Matrix metalloproteinases are involved in the remodeling of the extracellular matrix. The highest expression is observed during the m.c. proliferative phase and is regulated by estrogens. In adenomyosis, the activity of such important stimulators of angiogenesis as MMP and VEGF is significantly increased in eutopic endometrium, which ensures higher vascular density, and there is an even higher level of MMP-2 and -9 expression correlating with the VEGF expression and micro-vessel density in ectopic endometrium as compared to eutopic endometrium [160, 377].

Thus, the eutopic endometrium in women with adenomyosis has certain metabolic and molecular changes characterized by active proliferation, decreased apoptosis, the possibility of local estrogen production and progesterone resistance. These features enhance the ability of the endometrium to infiltrate the connective zone with the myometrium and ectopic growth into the myometrium [71].

Currently, the surgical stage is still the 'gold standard' for diagnosing adenomyosis, which also allows to perform the removal of altered tissues; this treatment has the greatest effect in the case of pain syndrome.

Most authors consider hormone treatment in adenomyosis necessary in terms of suppressing ovarian function [324]. The symptoms of adenomyosis are usually attempted to be managed by hormone therapy (GnRHa, progestins, in particular

dienogest or LNG-containing intrauterine system). Interestingly, Satoshi Inoue et al. (2019) showed that in a significant number of cases, foci of adenomyosis contain KRAS mutations, which reduces the efficiency of dienogest treatment [369].

IVF (IVF+ICSI) programs in women with genital endometriosis allow correcting some of the factors that impair fertility: morpho-functional changes in the fallopian tubes, violations of normal anatomy in the pelvic cavity, negative impact of peritoneal fluid on gametes and embryos. However, the decrease in the ovarian reserve, disorders of folliculogenesis and decrease in the 'quality' of oocytes and embryos, impaired function of the endometrium cannot be corrected by the technologies of ART programs alone. At the same time, the decrease of the ovarian reserve and changes in the state of oocytes and embryos are currently not available for correction after the occurrence (only primary prevention is discussed), whereas leveling the negative effect of the state of the endometrium during EGE on fertility is a task that can be solved.

1.2.2. Current Approaches to Fertility Recovery in Women with Endometriosis

The tactics of infertility treatment in women with endometriosis depend on the rational evaluation of many factors, and currently remains the subject of much debate [75]. The complexity of an optimal treatment elaboration is largely determined by the diversity of clinical forms of the disease and the balance of infertility factors in each couple. When forming the tactics, it is necessary to account for the stage of endometriosis, the woman's age, the status of ovarian reserve, the presence of other infertility factors, and the duration of infertility [12]. When planning approaches to infertility therapy, it is also necessary to consider the indications for surgical treatment (pain syndrome, the presence of masses in the ovaries (endometriomas), etc.), which may require delaying the long-awaited pregnancy. In 2010, Adamson G.D. and Pasta D.J. proposed the 'Endometriosis Fertility Index,' which takes into account a significant number of the above factors and allows to predict the chances of spontaneous pregnancy in the coming years

[47]. Considering the high frequency of decreased ovarian reserve in women with genital endometriosis, obtaining a prognosis for pregnancy will provide an opportunity to form optimal management tactics for women with infertility.

Considering the spectrum of changes associated with genital endometriosis ensuring fertility disorders, the therapeutic strategy should take into account such factors as morpho-functional changes of fallopian tubes, disturbances of normal anatomy in the pelvic cavity, negative influence of peritoneal fluid on gametes and embryo, decreased ovarian reserve, changes in the functional status of oocytes and embryos, and disorders of the endometrial receptivity. Obviously, impaired fallopian tube patency and male factor infertility will certainly be indications for the use of ART methods. In a number of cases, there are indications for surgical treatment of endometriosis (the surgical stage currently in most cases allows establishing the diagnosis of genital endometriosis). The efficiency of surgical treatment of endometriosis in terms of fertility recovery is presented by a number of authors as sufficient without additional hormonal influence [78, 235, 309], which is reliably proven in the case of minor EGE degrees [146, 287]; at the same time, there are studies showing that proinflammatory changes in the endometrium are also reduced after surgical treatment [329]. The role of surgical treatment in the process of infertility management in women with severe forms of endometriosis is debated [107, 146, 259, 381]: the endometrial receptivity will not change after surgery, and the risks of losing the ovarian reserve during ovarian intervention seem to be rather high in a number of cases [276].

Considering the factors determining fertility disorders in women with genital endometriosis, combined treatment is justified in infertility. In a number of cases, combined treatment of endometriosis ensures fertility recovery due to the effect on the infertility development mechanisms, including in eutopic endometrium. Particularly, the efficacy of endometriosis treatment with GnRHa drugs is largely determined by blocking ovarian function, including by reducing the level of estradiol when anovulation is achieved. Suppression of the ovarian function by GnRHa drugs causes a decrease in angiogenesis, suppresses cell proliferation, induces apoptosis

and reduces VEGF secretion [118, 344] and expression of proinflammatory factors (IL17) [106] in eutopic endometrium.

Dienogest is a selective progestin of the 4th generation, a derivative of 19-norsteroiods, highly selective to progesterone receptors [247]. The spectrum of biological effects of the drug in long-term use has a therapeutic effect on women with endometriosis. Dienogest at a dose of 2 mg per day can cause anovulation, contributing to a decrease in estrogen production, reduces the production of prostaglandin E2, proinflammatory cytokines (IL-6, IL-8); besides, in case of dienogest administration, the activity of aromatase and angiogenesis factors – vascular endothelial growth factor (VEGF), nerve growth factor (NGF) – decreases both in eutopic endometrium and in implants [100, 101]; the expression of progesterone A and B receptors increases while the expression of estrogen receptors beta and alpha decreases, which allows overcoming progesterone resistance [97]. Long-term administration of dienogest induces decidualization and atrophy in endometrioid foci, has anti-inflammatory effect, anti-angiogenic effect, antiproliferative effect [40, 99, 314, 367].

Hayashi et al. compared the levels of progesterone and estradiol receptors in endometrioma tissue in women after endometriosis treatment with those in the endometrium of women without endometriosis. It was shown that in the tissue of endometriomas in women after treatment, significantly higher levels of progesterone B receptor expression were detected as compared to women not treated with dienogest or GnRHa and to the level of progesterone B receptors in the eutopic endometrium of healthy women. Interestingly, the expression of progesterone A receptors in endometriomas in women in dynamics before and after dienogest PR-A treatment did not differ, whereas it increased after GnRHa administration. The expression of estradiol α and β receptors decreased after dienogest (but not GnRHa) treatment [97].

The efficiency of progesterone receptor modulator drugs in women with endometriosis is also being studied [296]. Another direction in the therapy of endometriosis is inhibitors of prostaglandin production, aromatase inhibitors. There

are also published studies on the efficiency of resveratrol, which is an antiproliferative and anti-inflammatory factor [362]. In animal experiments, a decrease in the area of implants, a decrease in the level of VEGF and MCP-1 in blood serum was shown.

Adenomyosis has a pronounced negative impact on fertility, both in terms of spontaneous pregnancy and assisted reproductive technology (ART) outcomes, due to endometrial/myometrial dysfunction, impaired endometrial receptivity, fetal egg implantation processes, placenta formation and attachment, and increased risk of spontaneous miscarriage [328, 368]. According to a systematic review and meta-analysis, adenomyosis reduces the probability of clinical pregnancy after IVF/ICSI by 28% (hazard ratio (HR) 0.72 (95% CI, 0.55-0.95) and significantly increases the risk of early pregnancy loss (HR 2.12 (95% CI, 1.20-3.75) as compared to women without adenomyosis [329]. Currently, the disease is increasingly diagnosed in women with infertility, as many of them delay their first pregnancy until > 30 years.

There is evidence that GnRHa therapy during 1–3 months increases the pregnancy rate in women with adenomyosis; probable mechanisms of the increase in the endometrial receptivity are represented by the reduction of inflammatory response and angiogenesis, and activation of apoptosis. A reduction of local hyperestrogenism, which contributes to the normalization of uterine peristalsis, is also possible [249]. There are data on the combined positive effect of GnRHa therapy and gestagens on fertility [324], as well as at a combination of GnRHa therapy with the use of high-intensity focused ultrasound in women with adenomyosis [128].

The data on the effectiveness of surgical treatment (adenomyomectomy) in infertility management are still insufficient [274]. In recent years, laparoscopic adenomyomectomy has become an alternative to laparotomy for the treatment of focal adenomyosis, but the risk of uterine rupture during pregnancy is increased after such access [125]. Hysterectomy in women with adenomyosis who have fulfilled their reproductive function also cannot be considered an optimal solution to the problem in the light of current data.

Medical treatment allows to manage the clinical symptoms of adenomyosis and preserve fertility, but there are no drugs approved specifically for the treatment of adenomyosis and there are no specific guidelines for the best management of such patients. Choosing the optimal infertility treatment for patients with adenomyosis is difficult because of the lack of clear evidence of a relationship between fertility and the severity and/or form of adenomyosis.

Vannuccini et al. presented a detailed review of drugs for the drug therapy of adenomyosis [375]. Currently, some non-hormonal (for example nonsteroidal anti-inflammatory drugs) and hormonal drugs (for example progestins, combined oral contraceptives (COCs) and Gonadotrophin-releasing hormone analogue (GnRHa) are used for treatment of pain and heavy menstrual bleeding with no approved indications. One of the main directions of drug treatment of adenomyosis is the use of progestins [39] and, in particular, dienogest. Inhibition of adenomyosis cell proliferation against the background of dienogest application occurs, among other things, due to induction of apoptosis processes. In addition, in uterine tissue samples taken after hysterectomy in women who received dienogest, significant changes in histological characteristics were found: a decrease in cell proliferation, nerve growth factor expression and nerve fiber density [98], which explains the clinical evidence of the favorable efficacy profile of dienogest for the treatment of pain associated with adenomyosis [310]; the effect on the normalization of macrophages and natural killer cells expression was also shown [347]. Administration of dienogest increases the efficiency of IVF programs by 48.6% in patients with stage II-III adenomyosis, probably, also owing to the improvement of the endometrial receptivity due to overcoming resistance to progesterone and powerful complex anti-inflammatory effect. It was shown that the drug increases the number of natural killer cells infiltrating the glandular structures of the endometrium, which causes a potential favorable effect on embryo implantation and its protection after discontinuation of treatment of adenomyosis in patients who need pregnancy [24]. Comparative studies of the efficiency of various combination regimens with dienogest monotherapy (e.g., combined use of aromatase inhibitors with GnRHa) are being conducted [313].

Thus, drug treatment plays an important role in the comprehensive management of patients, especially those with diffuse adenomyosis, who need to restore fertility. Drug treatment is often a more appropriate choice for managing symptoms of pain and bleeding than surgical treatment. In addition, such treatment can improve pregnancy rates within ART programs.

For women with EGE or adenomyosis, who do not plan to realize their reproductive function immediately after comprehensive treatment of endometriosis, achieving pregnancy in the long term may be difficult, primarily due to a critical decrease in the ovarian reserve; currently, when counseling such patients, it is possible to discuss methods of 'delayed motherhood,' – particularly, oocyte cryopreservation. Oocyte cryopreservation by vitrification is a safe and effective method for women with endometriosis. It is indicated when there is a risk of ovarian damage, especially before surgery [170, 272]. The data on the efficiency of using vitrified oocytes and the chances of having a child require further evaluation; it is debated at what point of treating women with endometriosis it should be used. Currently, it seems premature to recommend the routine use of oocyte banking in women with endometriosis.

1.2.3. Efficiency of IVF (IVF+ICSI) Programs in Endometriosis

Assisted reproductive technologies are currently the most important method of fertility recovery in women with genital endometriosis. The evaluation of the efficiency of ART methods in this case remains controversial, and the tactics of preparing women with genital endometriosis for IVF (IVF+ICSI) and methods of superovulation stimulation to increase the efficiency of infertility treatment are also a subject of discussion.

The pathogenesis of fertility disorder in endometriosis determines the influence of this disease on the effectiveness of ART methods, including the presence of changes in the endometrial receptivity [77] and the loss of the ovarian reserve.

A significant number of authors indicate that the pregnancy rate in women with EGE in IVF programs is lower than in women without EGE, with a decrease in pregnancy rate of up to 35%. Regarding the efficiency of individual stages, the authors point to a decrease in the number of obtained oocytes, fertilization rate, and implantation rate [69, 114, 341]. The prognosis of IVF worsens when several infertility factors are combined [212]. At the same time, there is evidence that when evaluating the ART program efficiency in women with preserved ovarian reserve under 35 years of age, EGE does not affect the efficiency of IVF – except for cases with endometriomas (characterized by a reduced response to stimulation) [331].

A comparison of IVF results in EGE stage I-II and EGE stage III-IV shows that pregnancy rates are significantly lower in severe forms of endometriosis. The results of IVF in EGE stage I-II are comparable to those of women with tubal and male factor infertility [115, 275, 340, 381]. Whereas in EGE III-IV stages, in the presence of endometriomas, deep infiltrative endometriosis, the efficiency of IVF is significantly reduced [115, 163, 225, 333, 340, 351].

Evaluation of the efficiency of IVF programs (IVF+ICSI) in programs involving the use of donor oocytes (based on the evaluation of 240 cycles) showed that the embryo transfer to women with EGE reduced implantation rates, clinical pregnancy and delivery rates as compared to the results of transfer of embryos obtained using donor oocytes to women without genital endometriosis [194]; these results indicate a significant role of altered endometrial receptivity in fertility impairment in endometriosis.

Pacchiarotti A. et al. (2020) compared the quality of embryos obtained from young women (not older than 37 years) with reduced ovarian reserve and having severe forms of genital endometriosis with embryos obtained from women without endometriosis and having normal ovarian reserve – while there was a regular reliable decrease in the number of oocytes obtained in endometriosis, the frequency of oocytes obtained at the MII stage was also reduced (70% and 83%, respectively); however, the morphologic characteristics of embryos, implantation rate, and pregnancy rate were comparable in both groups. The authors suggested that in

women with severe forms of endometriosis, despite reduced ovarian reserve, the quality of the obtained embryos is not affected, nor is the pregnancy rate reduced [319]. Similar results were also demonstrated in animal experiments [168, 318, 378].

There are indications of high frequency of endometriosis detection in women with infertility of unclear genesis and repeated failures in ART programs [192], which allows to present endometriosis as an obvious cause of IVF (IVF+ICSI) program failures [51, 132] and even to recommend laparoscopic intervention for women with repeated ART program failures, including for the purpose of endometriosis diagnostics [238].

Most authors recognize the need for new high-quality placebo-controlled studies to provide statistically significant data [60].

Thereby, the question arises whether the treatment of endometriosis (surgical, hormonal, aromatase inhibitor, etc.) affects the effectiveness of infertility treatment and pregnancy outcomes. The notion that genital endometriosis is a factor decreasing the ART program efficiency dictates the need to evaluate different methods of preparation for IVF (IVF+ICSI) in endometriosis. On the one hand, variants of surgical preparation have been proposed and a number of authors point to its effectiveness [259], but the role of these methods in changing endometrial receptivity is minimal, and the risks of losing the ovarian reserve in the case of ovarian intervention are high [276]. De Ziegler D. Et al. (2019) showed that nowadays women at the older reproductive age often start infertility treatment with IVF (IVF+ICSI) methods. Therefore, the tactics aimed at shortening the period from the first infertility treatment to the beginning of IVF (IVF+ICSI) program are reasonable. The authors point out that the possibility of avoiding the surgical stage before IVF will allow to shorten the time 'until pregnancy,' suggesting that this does not improve the outcome of IVF, but may reduce the ovarian reserve (except in cases of hydrosalpinx or endometriomas requiring surgical treatment) [60].

Likes C.E. et al. showed that comparison of the efficiency of IVF programs and/or transfer of cryopreserved embryos in women after surgical or hormone treatment of endometriosis to women with infertility of unclear genesis and,

consequently, not treated (but in whom endometriosis was detected after another unsuccessful transfer), any type of EGE treatment leads to a considerable increase of the ART program efficiency [259].

The role of hormone therapy performed prior to IVF (IVF+ICSI) programs is also controversial: Barnhart K. et al., Hughes E. et al. state that there is no reliable data for the fact that treatment of EGE prior to IVF improves the results of IVF, and treatment with GnRHa, gestagens, OCs is effective for the treatment of EGE symptoms, but does not have a pronounced impact on the efficiency of infertility treatment, delaying the time before infertility treatment [69, 279]. On the other hand, a number of studies showed that the use of GnRHa for 3–6 months before IVF increases the clinical pregnancy rate by 4 times [250]; it is also described that the combined use of GnRHa with aromatase inhibitor drugs can increase the efficiency of IVF programs as compared to women treated with GnRHa alone [38]. Some publications are devoted to the use of tablet preparations of GnRH antagonists prior to ART programs [291]; further studies are required to obtain reliable results. The efficiency of different types of hormone therapy in women after unsuccessful ART programs was shown [143, 245]; a number of studies indicate that dienogest therapy for severe EGE improves IVF outcomes [143, 292, 381].

Given the high incidence of chronic endometritis in women with EGE (38.5% versus 14.1% in women without EGE) [87, 193], treatment of chronic endometritis is suggested as a preparatory therapy.

A well-known study published in the Cochrane Library in 2019 [248] evaluated the efficiency of prescribing GnRHa for a duration of at least 3 months before starting IVF programs (IVF+ICSI). The authors were forced to admit that the summary result of the analysis of randomized controlled trials is characterized by low quality due to the significant heterogeneity of available publications, lack of possibility to perform blinded randomized trials, significant heterogeneity of study groups in different publications, including the severity of EGE. It was shown that the delivery rate in untreated women comprised 36%, whereas in women treated with GnRHa between 3 and 6 months ranged from 9% to 31%. Considering the lack

of possibility of randomization, it should be assumed that in the group of women who did not receive treatment, women with small forms of endometriosis were more frequent, while treatment was prescribed as a rule for advanced degrees of EGE severity.

Another factor discussed as affecting the outcomes of ART programs in women with genital endometriosis is the choice of a superovulation stimulation method in IVF (IVF/ICSI) programs.

A significant number of publications reported the benefits of a super-long protocol with GnRH agonists, but it is known to have a high risk of cycle cancellation due to lack of ovarian response (8, 90). There is evidence of some increase in implantation rate with superovulation in women with endometriosis in a long protocol with GnRH agonists as compared to a short protocol with GnRH antagonists, but the choice of such a protocol requires higher doses of FSH drugs, and the efficiency of a long protocol with reduced ovarian reserve is debated [89, 280]. It seems that a short protocol with GnRH antagonists is a universal option that is optimal for both OHSS risk and reduced ovarian reserve. In recent years, there has been a discussion of the feasibility of segmentation of the IVF (IVF+ICSI) cycle, when embryos obtained in the superovulation cycle are cryopreserved, allowing for additional preparation in terms of hormonal therapy of endometriosis – in such cases, the use of GnRH agonists as a trigger for final oocyte maturation may be considered reasonable; Dominique de Ziegler et al. (2019) suggest that such tactics may reduce the risks of endometriosis progression [60].

A meta-analysis published in 2020 [346] compared super-long and long protocols with GnRHa – the fertilization and implantation rates in the analysis including only randomized trials were not significantly different depending on the type of protocol. However, the clinical pregnancy rate was significantly higher in women who received the super-long protocol. However, in non-randomized studies (cohort studies), super-long protocols had higher fertilization and implantation rates; when comparing super-long and short protocols in non-randomized studies, fertilization and pregnancy rates were higher in super-long protocols. The duration

of stimulation in the analysis of randomized studies did not differ, while in cohort studies it was obviously longer in superlong protocols (when comparing both long and short protocols). Comparison of the clinical pregnancy rate depending on the severity of EGE in randomized and cohort studies showed no difference between the super-long protocol, long and short protocols in terms of clinical pregnancy rate in EGE I-II stages, while in EGE III-IV stages the super-long protocol was significantly more efficient than the long protocol, but did not differ in efficiency from the short protocol in randomized studies, while in cohort studies there were no differences. The authors state that III-IV stage EGE is characterized by more pronounced proinflammatory changes and changes in the abdominal anatomy, as well as more significant disturbances of the endometrial receptivity, which requires prolonged suppression of estrogenic stimulation. The risks of excessive inhibition of the hypothalamic-pituitary system during the supravalvular protocol and, accordingly, the cancellation of cycles are also of importance. Thus, it seems that in I-II stage EGE a long protocol is sufficiently effective, and in III-IV stage EGE a supra-long protocol is required. The obtained results indicate that the accuracy of evaluation of different variants of superovulation stimulation depends largely on the way of formation of clinical groups for research and the method of statistical processing of the obtained data. It should be recognized that no unambiguous advantages of certain schemes of superovulation stimulation for women with endometriosis were demonstrated.

A higher pregnancy rate after a superlong stimulation protocol is consistent with the data that treatment with GnRHa before IVF affects the quality of the obtained oocytes and the structure of the endometrium [278]. GnRHa treatment reduces the concentration of IL-1, TNF, nitric oxide in peritoneal fluid [185]. Zhao F. et al. (2020) [244] showed that a comparison of short protocols with GnRH agonists and GnRH antagonists and a long protocol with GnRH agonists showed no significant differences in the key evaluated efficiency indicators – the number of obtained oocytes, the fertilization rate, good quality embryo rate, and the delivery rate. It is expected that the short protocol with GnRH antagonists requires a lower

dose of gonadotropin preparations for stimulation and, accordingly, requires somewhat lower material costs. The choice of stimulation protocol in the IVF (IVF+ICSI) program for women with endometriosis in conditions of decreased ovarian reserve in ovarian endometriomas is a difficult task for a reproductologist.

The efficiency of IVF (IVF+ICSI) programs in women with adenomyosis is also controversial. There are authors indicating that the pregnancy rate in women with asymptomatic adenomyosis does not differ from the pregnancy rate in women without adenomyosis, and if asymptomatic adenomyosis is the only imaging criterion of asymptomatic adenomyosis, the infertility rate does not increase [64]. At the same time, there are a number of studies showing that the presence of adenomyosis has a negative impact on pregnancy rates in ART programs [105, 384], and the risk of miscarriage in women with adenomyosis is increased 2.12 times as compared to women without adenomyosis (as well as the risk of preterm birth) [113]. According to Martínez-Conejero J.A. (2011), when analyzing the efficiency of ART cycles with the use of donor oocytes, there are no differences in pregnancy rates between women with adenomyosis, EGE and the control group (without genital endometriosis); however, the incidence of miscarriage is increased, on the basis of which the authors conclude that the presence of adenomyosis does not worsen the conditions for implantation, but increases the miscarriage risk [49].

Many recognize the need for pregravid preparation when planning ART programs for adenomyosis; pretreatment with GnRHa was shown to increase pregnancy rates in ART programs for adenomyosis [108, 220, 249]. Dueholm M. et al. report significant differences [112], whereas in the work by Park C.W. the differences are not reliable [290].

In summary, it may be concluded that clinical studies demonstrate a decreased implantation rate in ART programs, an increased incidence of early pregnancy loss and preterm delivery in women with adenomyosis. One of the most discussed markers of adenomyosis in publications is the thickening of the connective zone, the magnitude of which correlates with the degree of negative impact on reproductive potential. It should be noted that a thorough statistical analysis is hampered by

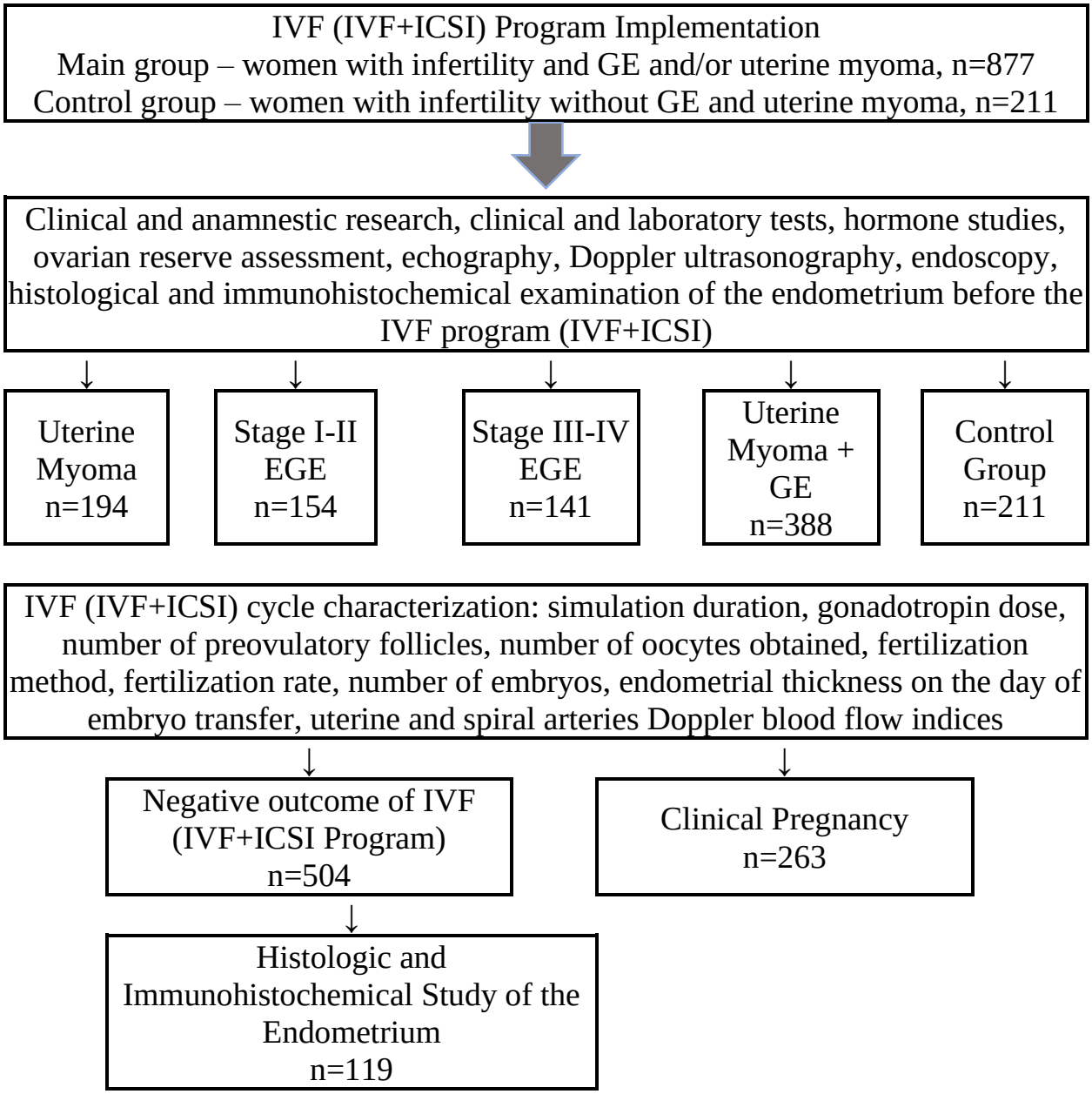
differences in the diagnostic criteria for adenomyosis used in studies by different authors. Most publications show that the outcomes of IVF (IVF+ICSI) programs and embryo transfer in women with adenomyosis worsen in comparison with women without adenomyosis, but there is insufficient reliable data on the efficiency of hormone therapy prior to IVF in terms of efficiency improvement. There is also no sufficient data on the role of surgical treatment of adenomyosis in improving the efficiency of IVF programs.

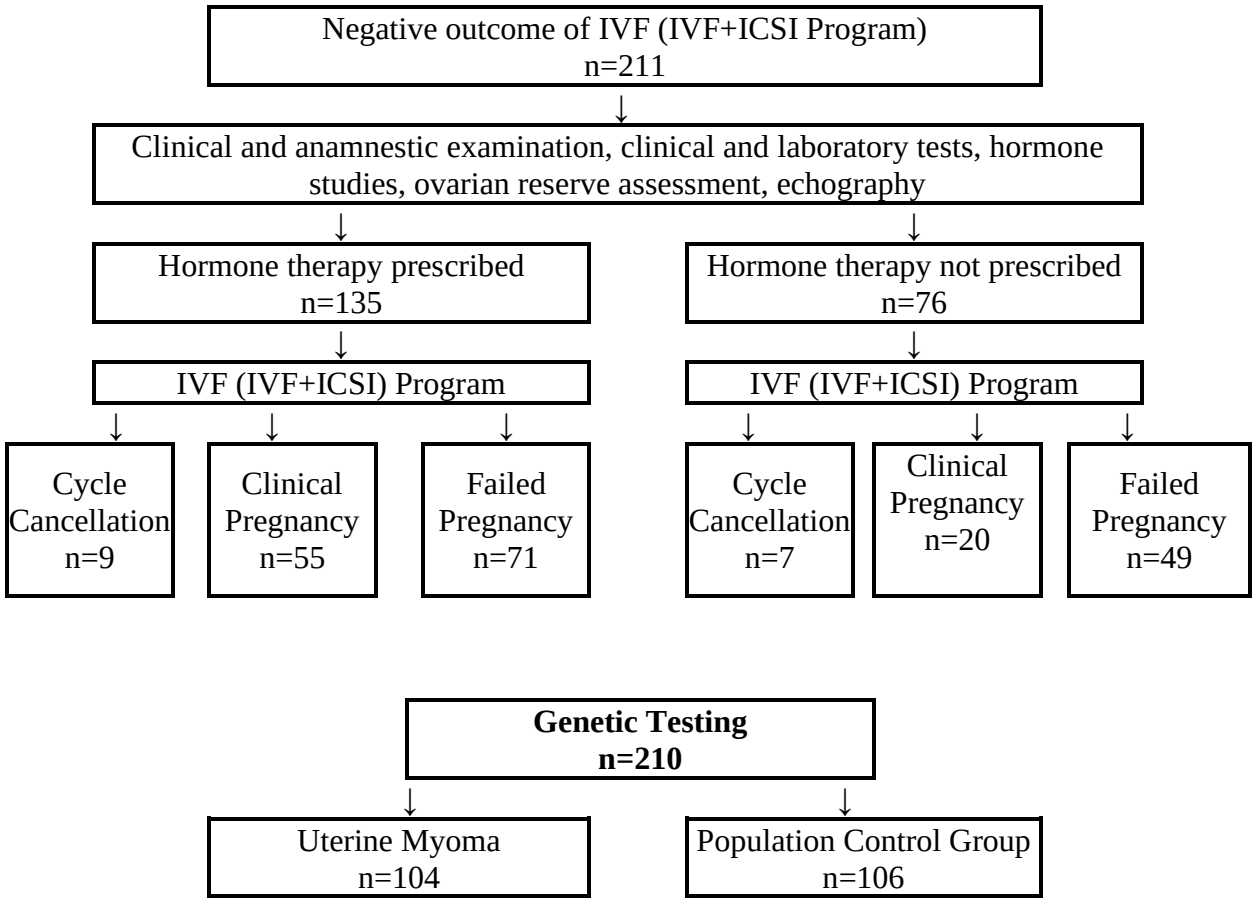
There are not many studies evaluating the course and outcomes of pregnancies resulting from IVF (IVF+ICSI) in women with genital endometriosis. Most often, researchers point to an increased incidence of miscarriage [141], preterm delivery, gestosis, and operative delivery [166], including in the work based on data from the Swedish national registry (more than 8000 women) [142], while Hong Lin (2015) showed, upon analysis of more than 50000 pregnancies, that only the preterm delivery rate increases [270]. The work of Italian authors [289] demonstrates a significant increase in the incidence of placenta previa in women with genital endometriosis (6%) as compared to women without endometriosis (1%), whereas the preterm delivery rate did not differ; likewise, there were no differences in the incidence of gestosis, gestational diabetes, low or high birth weight relative to the gestational age, the incidence of live births and neonatal problems. A study by Yang P. et al. (2019) based on data analysis of IVF programs results of more than 3000 women, showed no miscarriage risk increase in women with genital endometriosis [308].

Thus, up-to-date publications demonstrate a significant variation of data on the efficiency of IVF (IVF+ICSI) programs in genital endometriosis; the results of studies often depend on the applied approach to patient selection and the method of statistical processing of the obtained data.

Chapter 2. MATERIALS AND METHODS

Study Design





Inclusion criteria for patients of the main group:

- age from 20 to 40 years;
- presence of a verified diagnosis of external genital endometriosis and/or uterine myoma;
- treatment of infertility of different genesis by IVF (IVF+ICSI) methods;
- ovarian stimulation in a short IVF protocol using GnRH antagonists;
- voluntary consent for participation.

Inclusion criteria for control group patients:

- age from 20 to 40 years;
- no evidence of external genital endometriosis and/or uterine myoma;
- treatment of infertility of different genesis by IVF (IVF+ICSI) methods;
- ovarian stimulation in a short IVF protocol using GnRH antagonists;
- voluntary consent for participation.

Non-inclusion criteria for patients of the main group and control group:

- presence of diseases included in the list of contraindications to the use of assisted reproductive technologies in accordance with Appendix No. 2 to the Decree of the Ministry of Health of the Russian Federation dated August 30, 2012, No. 107n "On the Procedure for the Use of Assisted Reproductive Technologies, Contraindications and Restrictions to their Use";
- abnormal karyotype of one of the spouses.

The study was approved by the local medical research ethics committee of the Federal State Budgetary Scientific Institution 'Research Institute of Obstetrics, Gynecology and Reproductive Technology named after D. O. Ott' (Statement No. 77 dated 12.05.2016).

2.1. General Clinical Characteristics of Examined Patients

2.1.1. Women with Uterine Fibroids and/or Genital Endometriosis, Who Underwent IVF (IVF+ICSI) Infertility Treatment

A study of 877 women with uterine fibroids and genital endometriosis who underwent infertility treatment by ART methods in the Department of Assisted Reproductive Technologies of the Research Institute of Obstetrics, Gynecology and Reproductive Technology named after D.O. Ott from 2010 to 2013 was conducted. The average age of the women comprised 34.23 years (from 24 to 45 years), of which 559 women aged up to and including 35 years, and 336 women aged over 35 years.

The number of examined women with uterine fibroids comprised 410 (45.8%) women. The diagnosis was established based on the results of echographic examination and/or surgical intervention and verified histologically. Among them, uterine subserosal fibroids (types 6 and 7 according to the FIGO classification, 2011) were detected in 174 women (42.4%), uterine intramural fibroids (types 3-5 according to the FIGO classification, 2011) – in 279 women (68.0%), submucosal myomas (types 0-2 according to the FIGO classification, 2011) were removed in 24

women (5.85%). Multiple uterine myomas were observed in 62 cases (15.1%), of which 52 had intramural-submucosal myomas, and 7 cases had a history of submucosal myoma removal. In most cases there was a combination of subserosal and intramural myomas (51 women); a combination of intramural myomas and removal of submucosal myomas in anamnesis was present in 4 women; in 3 cases there was a combination of subserosal and submucosal myomas (in anamnesis).

Adenomyosis was detected in 93 women (10.4%), diagnosed during hysteroscopy and according to the results of morphologic study of the material obtained during multifocal core needle biopsy of the myometrium; in 75 cases there was a combination of uterine myoma and adenomyosis.

In the main group, EGE was verified in 397 (44.4%) women based on the results of endoscopic examination (laparoscopy) with subsequent morphologic examination of surgical material. Stage I-II EGE was diagnosed in 204 women (51.4%), stage III-IV EGE – in 193 women (48.6%) – in 193 women (48.6%), of whom 51 women (12.8%) had endometriomas. Recurrence of endometriosis was detected in 24 women (6.0%).

Primary infertility was diagnosed in 518 (57.9%) women and secondary infertility – in 377 (42.1%).

The average menarche age comprised 13.03 years. Regular cycle was determined in 831 (92.8%) women, 64 women had abnormal uterine bleeding (7.15%).

A history of pregnancy was noted in 377 (42.1%) women. 10.4% of all pregnancies ended in childbirth (35 women had a single birth in the past, 3 women had two births, of which 6 (14.6%) were delivered by caesarean section, and 5 (12.2%) had preterm deliveries. 41.6% of all pregnancies ended in abortions, 10.2% of all pregnancies were undeveloped, 19.0% were spontaneous abortions, and 18.8% were ectopic pregnancies.

Anomalies of genital development were detected in 20 (2.22%) women. Chronic salpingitis – in 566 (63.2%), chronic endometritis – in 143 (15.9%), synechiae in the uterine cavity – in 31 (3.5%).

408 women underwent surgical interventions in the abdominal cavity (from 1 to 5 operations). The number of peritoneal operations in women ranged from 0 to 3 (0.14 on average), laparoscopies from 0 to 5 (0.6 on average), and hysteroscopies from 0 to 7 (0.82 on average).

Ovarian surgical interventions (1 to 3) were performed in 325 (36.3%) women in the past, including ovarian resection in 210 (23.5%), ovarian cauterization for PCOS, 'multifollicular ovaries' in 103 (11.5%). Unilateral ovariectomy was performed in 10 (1.1%) patients.

Contraception was used in the past by 196 (21.9%) women, of which barrier contraception – 6 (0.67%), combined hormonal contraceptives – 182 (20.3%), IUD – 33 (3.7%).

Hormone therapy before the IVF program (IVF+ICSI) was performed in 251 (28.0%) women, of which progesterone preparations were used in 154 (61.4%). The indications for hormone therapy were treatment of endometrial hyperplasia, correction of endogenous progesterone deficiency, and hormone therapy in the complex treatment of chronic endometritis.

Ovulation stimulation in the history was performed in 97 women (1 to 4 cycles), intrauterine insemination was performed in 49 women. IVF (IVF+ICSI) was performed in 186 women in the past, and cryopreserved embryo transfer was performed in 27 women. Unsuccessful IVF (IVF+ICSI) protocols occurred in 177 women.

Extragenital diseases in history were diagnosed in 286 (32%) women. Benign thyroid diseases (diffuse nodular nontoxic goiter, autoimmune thyroiditis, nodular goiter) were detected in 54 (6%) women, benign breast diseases – in 158 (17, 7%), 17 of them had a history of surgery for breast diseases, hyperprolactinemia – in 4 women, body weight deficit – in 2 women, obesity – in 9 women, cardiovascular diseases – in 6 women, gastrointestinal diseases – in 7 women, chronic hepatitis C – in 29 women. Drug allergies were indicated by 21 women. By the beginning of the IVF (IVF+ICSI) program, all chronic somatic diseases in the examined women were in remission or medically compensated.

2.1.2. Women, Who Underwent IVF (IVF+ICSI) Infertility Treatment in Absense of Uterine Fibroids and Genital Endometriosis

The control group consisted of 211 women, whose examination did not reveal hyperplastic diseases of the reproductive system organs (uterine fibroids, genital endometriosis, hyperplastic processes in the endometrium, ovarian masses). Inclusion criteria were the presence of indications for infertility treatment by assisted reproduction technology methods, whereas exclusion criteria were the presence of contraindications for ART programs, the presence of hyperplastic diseases of the uterus, endometrium or ovaries both at the time of examination and in history.

The mean age comprised 32.07±0.32 (23 to 44 years), with 160 women aged up to and including 35 years and 52 women aged over 35 years.

The age of menarche was 13.13±0.26 years. A regular menstrual cycle was observed in 180 (87%) women. Hyperpolymenorrhea was reported by 5 (2%) women and dysmenorrhea by 115 (55%) women. Pregnancies in history (1 to 6) were in 104 women, with an average value of 0.938±0.08; 27 (13%) women gave birth, 7 (25.9%) had cesarean section, 34 women had abortions, 11 of them had 2 to 4 induced abortions (average value 0.289±0.04) and 24 (11%) women had spontaneous abortions, 20 (19.2%) women had blighted ovum. There were 44 (21%) women operated for ectopic pregnancy.

6 (3%) women had a history of hyperprolactinemia.

55 (26%) women used contraceptives, including hormonal contraception – 45 (21%) and IUD – 8 (4%) women.

Chronic salpingitis was diagnosed in 131 (62%) cases, chronic endometritis in 36 (17%) cases, including two women who had previously undergone surgical treatment for uterine synechiae.

144 (62.25%) women had a history of abdominal surgery – from 1 to 5 operations (average 1.1), including 41 (20%) women, who underwent peritoneal surgery, and 120 (56.87%) women, who underwent surgery by laparoscopic access. Ovarian surgeries were performed in 53 (25.12%) women, ovarian resections in 23

(11%), ovarian cauteries and biopsies in 22 (10%), unilateral ovariectomy was performed in 5 (2%) women, and ovarian interventions were performed in 23 women to treat PCOS.

The duration of infertility comprised 6.35±0.26 years. Primary infertility was observed in 107 (51.0%) women, secondary infertility in 104 (49.0%) women. Combined causes of infertility were observed in 89 women, with an average of 2.16 infertility factors. Male factor infertility was presented in 109 (52.0%) women, tubal factor in 120 (57%) women, idiopathic infertility in 7 (3%) women, endocrine factor infertility in 69 (33%) women, uterine factor infertility in 6 (3%) women. Other causes of infertility were identified in 4 (2%) women.

Hormone therapy was performed previously in 75 (36%) women, including progesterone preparations were taken by 11 (6%) women.

On average, ovulation stimulation was observed in 39 (18.39%) women – 2 to 6 cycles (0.39 on average), 20 women (9.43%) had a history of 1-2 intrauterine insemination procedures (0.166 on average), 87 (41.04%) women had a history of 1 to 6 IVF (IVF+ICSI) programs (0.735 on average), of which 72 (33.96%) women underwent failed IVF (IVF+ICSI) programs (0.51 on average).

Nicotine addiction was recognized by 9 (4%) women.

By the beginning of the IVF (IVF+ICSI) program, all chronic somatic diseases in the examined women were in remission or medically compensated. Extragenital diseases were diagnosed in 78 (37%) women, including cardiovascular diseases in 12 (6%) women, gastrointestinal diseases in 9 (4%) women, hepatitis in 9 (4%) women, and drug allergies in 23 (11%) women, thyroid diseases were detected in 20 (9%) women, benign breast diseases – in 23 (11%) women, of whom 4 (2%) underwent surgical interventions, body weight deficit – in 2 (1%), 1–2-degree obesity – in 16 (8%) women, average BMI comprised 24.04±0.28 m^2/kg.

2.1.3. Population Control Group

The population control group included 106 women – a population sampling of women of the same race, whose place of birth and residence was limited to one region. The age of the examined women ranged from 24 to 61 years.

The inclusion criteria for the population control group for this study were:

1) age – over 18;
2) sex – female;
3) race – Caucasian;
4) region of residence – northwest Russia;
5) voluntary participation in the study.

2.2. Study Methods

2.2.1. Clinical Anamnestic Study

The heredity, past and concomitant gynecologic and extragenital diseases were analyzed. Particular attention was paid to the study of gynecological anamnesis – characteristics of the menstrual cycle (age of menarche, duration of formation, nature of disorders) and reproductive function (number of pregnancies, their course, outcome), the nature, volume and efficiency of previous conservative or surgical treatment of reproductive diseases, as well as the age of appearance of the first clinical symptoms and diagnostic signs of uterine myoma and genital endometriosis were taken into account.

2.2.2. Hormonal Evaluation

The content of FSH, LH, AMH, estradiol, prolactin in blood was determined by immunoenzymatic technique on day 3-5 of the menstrual cycle.

2.2.3. Pelvic Ultrasound

Pelvic ultrasound was performed with the help of a Samsung-Medison SonoAce X6 ultrasound scanner (Republic of Korea) using a transvaginal transducer with a frequency of 4-9 MHz. During ultrasound examination, the uterus size, thickness and structure of the endometrium, the size of the ovaries and signs of their functional activity were determined (the state of the follicular apparatus, the presence of dominant follicle and corpus luteum, their sizes; the presence of other cavity formations, as well as the dynamics of folliculogenesis in cycles of superovulation stimulation in IVF (IVF+ICSI) programs). Uterine dimensions were determined by obtaining a longitudinal section image. The length of the uterine body was measured from the midpoint of a perpendicular drawn from the apex of the angle between the body and cervix to the opposite uterine wall to the furthest point of the fundus. Perpendicular to this measurement, the anteroposterior dimension of the uterine body was determined at its widest part. The uterine width was determined in the widest part in the transverse scan. The uterine volume was calculated using the formula 'length X anteroposterior dimension X width of the uterine body X 0.523' [2]. When evaluating the myometrium, the presence of uterine myomas, their size and localization, uterine wall asymmetry, hypoechogenic areas in the myometrium, linear striation, hyperechogenic inclusions in the myometrium and changes in the connective zone between the myometrium and endometrium – increase up to 3-4 mm and changes in the structure – with inhomogeneous thickness and structure were detected.

The endometrial thickness was measured as the anteroposterior dimension of the midline uterine echo (M-echo). The connective zone was visualized in 2D scanning mode at the border of the myometrium and the endometrium as a hypoechogenic area subendometrially. When examining the ovaries, the maximum dimensions in two mutually perpendicular planes were measured.

2.2.4. Doppler Velocimetry of the Uterine Artery Blood Flow

Doppler velocimetry in uterine vessels in the IVF cycle was performed with the help of a Samsung-Medison SonoAce X6 ultrasound scanner (Republic of Korea) using a transvaginal transducer with a frequency of 4-9 MHz. After measuring the size of the uterus, the thickness of the endometrium, the size of the ovaries and intra-ovarian structures (follicles, corpus luteum), color Doppler imaging with Doppler velocimetry of blood flow velocity curves in uterine and ovarian vessels was performed. Blood flow was studied in uterine arteries and their branches – arcuate, radial, spiral. Visualization of uterine arteries was performed at the level of the uterine isthmus, before the vessel entered the myometrium, of arcuate arteries – in the outer third of the myometrium, of radial arteries – in the middle third of the myometrium, of spiral arteries – in the thickness of the endometrium. After locating the investigated vessel, the blood flow velocity curves were recorded using color Doppler mapping. For this purpose, a stable image of the curves was obtained for at least three cardiac cycles.

When analyzing blood flow velocity curves, the following parameters were determined:

- peak systolic velocity (PSV) – this parameter reflects myocardial contractile activity and elasticity of the walls of the investigated vessel (cm/sec);
- end diastolic velocity (EDV), which characterizes the resistance to blood flow in the peripheral vasculature (cm/sec);
- average velocity (Avg), (cm/sec).

In addition, the so-called 'angle independent indices' were calculated (automatically) on the basis of blood flow velocity ratio:

- pulsatility index (PI),
- resistance index (RI),
- systolic-diastolic ratio (SDR).

Pulsatility index was determined as the quotient of the difference between PSV and EDV divided by Avg. The resistance index was calculated as the ratio of

the difference between PSV and EDV to PSV. The systolodiastolic ratio reflects the ratio of the maximum systolic blood flow velocity PSV to the end-diastolic blood flow velocity EDV. Peripheral resistance indices were calculated automatically [35]. Figure 1 shows the curve of blood flow velocity in the spiral arteries with a calculation of PI, RI, SDR, measured in a woman from the control group on the day of the final oocyte maturation trigger injection within the IVF program.

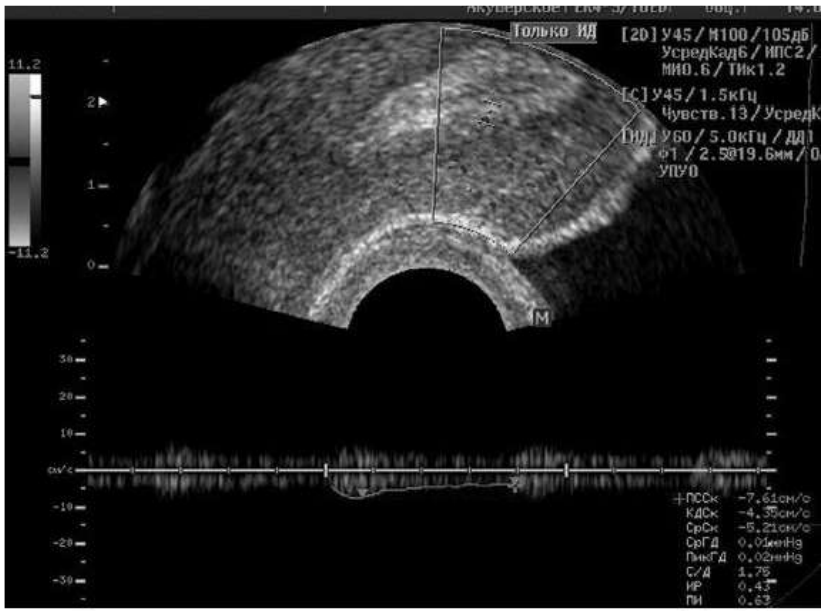


Figure 1.

Image of the blood flow velocity curve in the spiral arteries on the day of administration of the final oocyte maturation trigger within the IVF program, control group.

The efficiency of IVF (IVF+ICSI) programs was assessed by registering the onset of clinical pregnancy by visualization of the fetal egg in the uterine cavity during the US study on day 20-25 after embryo transfer.

Ovulatory menstrual cycle was confirmed by determining the level of progesterone in blood serum not less than 35.0 nmol/L on the 20-22 day of the studied menstrual cycle.

2.2.5. Hystology and Immunohistochemistry

Endometrial biopsy was performed to clarify the status of the endometrium in women entering IVF (IVF+ICSI) programs or after a failed IVF (IVF+ICSI) protocol. Endometrial biopsy was performed under the following conditions: day 5

from the start of progesterone medication (administration of micronized progesterone at a dose of 400 mg vaginally) or day 7 after an ovulation trigger injection (or endogenous LH surge); the M-echo value on the day of biopsy according to ultrasound comprised 7 mm or more.

Qualitative morphological assessment of the endometrium was performed on the basis of assessment of compliance of the morphological picture of the endometrium with the following criteria: early, middle, late phase of secretion, lag in the development of the endometrial stroma (incomplete phase of secretion due to the lack of synchronous development of epithelial and stromal components of the endometrium). Morphological signs of chronic endometritis included the following: mononuclear infiltration in the endometrial stroma, edema of the endometrial stroma, basal hyperplasia of the endometrium, hypoplastic endometrium [30, 34].

Hystology and immunohistochemistry were performed in the pathology division of the Pathomorphology Department of the Federal State Budgetary Scientific Institution 'Research Institute of Obstetrics, Gynecology and Reproductive Technology named after D.O. Ott'.

The signs of chronic inflammatory reaction, expression of sex steroids and expression of markers of immune competent cells were determined in the endometrium by immunohistochemistry.

The surgical and biopsy material of the endometrium was fixed in 10% neutral formalin (pH 7.2) and processed according to the standard protocol. Slices 3-5 μm thick were prepared from the obtained blocks. Hematoxylin and eosin were used for plain staining. During light microscopy, the correspondence of the structure of the endometrium to the day of the menstrual cycle, the state of the glands, stroma and vascular component of the endometrium, and the presence or absence of histologic signs of inflammatory and pathologic changes were evaluated. The study was performed using the Olympus CX31 microscope (Japan) at ×100, ×400 magnification.

Immunohistochemistry was performed on 5 μm thick paraffin sections placed on slides coated with poly-L-lysine film (*Sigma*, Japan). Dako Cytomation LSAB2

System-HRP (*Dako*, Denmark) was used as an imaging system. For the immunohistochemical reaction, we used a standard one-step protocol with antigen retrieval (high-temperature tissue treatment) in 0.01 M citrate buffer pH 7.6. Visualization of the immunohistochemical reaction was performed according to a standard scheme. Immunohistochemical method of the study included: quantitative and qualitative assessment of estrogen receptor (ERa), progesterone receptor (PR) expression in biopsy specimens of the endometrium using antibodies to ERα receptors (clone 1D5) and PR receptors (clone PR 636) in standard dilution 1:50 produced by *Dako Cytomation* (Denmark). Sex hormone receptor expression was assessed by the Histochemical Score=ΣP(i)×I semi-quantitative method, where I is the intensity of staining expressed in points from 0 to 3; P(i) is the percentage of cells stained at different intensities. Staining intensity: 0 – no staining, 1 – weak staining, 2 – moderate staining, 3 – strong staining. The maximum count value should correspond to 300 units. In addition, the character of receptor expression distribution in the studied material was taken into account (as modified by Tolibova G.H., 2015 [28]).

To evaluate immunologic criteria of chronic inflammatory reaction in the endometrium, the presence of markers of immunocompetent cells CD8+ (cytotoxic T lymphocytes), CD20+ (B cells), CD56+ (NK cells), CD138+ (plasma cells (CD138) was determined by counting the number of cells in the field of view at a magnification of 400×. The antibodies used included CD8+ [clone CD8/144B], CD20+ [clone L26], CD56+ [clone 4B12], CD138+ [clone M115], at a standard dilution of 1:50 and at a standard dilution of 1:25 produced by *Dako Cytomation* (Denmark). Immunohistochemical criteria for the degree of severity of chronic endometritis were evaluated according to the classification suggested by Tolibova G.H. et al., 2015 [28].

2.2.6. Assessment of Polymorphism of Estrogen and Progesterone Receptor Genes, Catechol-O-Methyltransferase Gene, CYP19 gene

The study of polymorphism of estrogen receptor *α* gene – *Xbal* and *Pvull*- was performed. The appearance of the *XbaI* restriction polymorphism in the estrogen receptor α (*ERα*) gene is caused by the replacement of adenine (A) by guanine (G) in the intronic region (*dbSNP rs*9340799, *IVS1-351A>G*) (Colin E., 2003). Another variant of the *ERα* gene polymorphism is caused bythe appearance of an additional site for the PvuII restriction endonuclease as a result of a single nucleotide substitution of thymine (T) for cytosine (C) (*dbSNP rs*2234693, *IVS1-397T>C*). In the specialized literature, the normal allele *A of the *ERα* gene is designated as **x*, and the polymorphic allele **G* is designated as **X*. The **T* allele is designated **p*, and the **C* allele is designated as **P*.

The frequency of various variants of progesterone receptor gene polymorphism (*PGR*) in women with uterine fibroids was analyzed. The polymorphic variant of the progesterone receptor gene containing an *Alu* insertion in the G intron, size 306, was designated as *Progins* (allele T2) [46]

The polymorphism of the *COMT* gene was analyzed: transversion of G to A in the fourth exon of the *COMT* gene leads to the replacement of the valine amino acid with methionine at position 158 of the protein, thus determining the polymorphism of this gene, which is functionally significant: in the presence of the A/A genotype, the enzymatic activity of 2-methoxyestradiol is reduced almost 4-fold [231], whereas in the G/G genotype catechol-O-methyltransferase converts 2-hydroxyestrogen to its methylated form more efficiently and more rapidly and thus reduces the amount of antiestrogen, creating higher levels of active forms of estrogen in tissues. DNA samples were obtained in a standardized manner from peripheral blood lymphocytes. DNA isolation from peripheral blood lymphocytes was performed according to the methodology given in the Sambrook's manual [264] with certain modifications.

The frequencies of genotypes and alleles of *ERα* and *PGR* genes, *COMT* and *CYP 19* genes in 104 women with uterine fibroids and 106 women from the population control group were analyzed by polymerase chain reaction. The 25 μl amplification mixture included 15 nM of each primer, 67 mM Tris-HCl, pH 8.8, 16.6 mM ammonium sulfate, 6.7 mM $MgCl_2$, 6.7 μM EDTA, 10 mM mercaptoethanol, 170 μg BSA, 1.0 mM each dNTP and 1U Taq-DNA polymerase (produced by *Bion*, Moscow)

The following PCR conditions were used for amplification of *ERα* and *PGR* gene fragments: after denaturation (94°C, 7 min), 30 cycles of amplification were performed in the following mode: 94°C – 40 sec; 55°C – 40 sec; 72°C – 1 min. Amplification products were analyzed in 7.5% polyacrylamide gel with subsequent staining with ethidium bromide and UV visualization. To identify alleles of the *ERα* gene, the resulting PCR product was cleaved by restriction products *PvuII* and *XbaI*. The restriction products were subjected to electrophoresis in a 7.5% polyacrylamide gel and analyzed in transmitted UV light after staining with ethidium bromide.

The following PCR conditions were used for amplification of *COMT* gene fragments: after denaturation (94°C, 7 min), 30 cycles of amplification were performed in the mode: 94°C – 40 sec; 55°C – 40 sec; 72°C – 1 min (modified oligonucleotides with restriction site creation were used: F5' – CGGATGGGGTGGATTTCGCTcG – 3'; R5' – ACTATCACCAGGCCCCCCTCAG- 3'). To identify alleles of the *COMT* gene, the obtained PCR product was decomposed by BstFN1 restrictionase, and the restriction products were subjected to electrophoresis in a 7.5% polyacrylamide gel, followed by ethidium bromide staining and UV visualization.

2.3. Statistical Analysis of the Findings

Statistical processing of the obtained data was performed on a personal computer using the *Microsoft Excel* standard package and *Statistica for Windows*

version 6.0, *StatSoft Inc.* (USA) and SPSS-19 application programs using parametric and nonparametric statistics methods.

Descriptive statistics included calculation of mean (M), standard error of mean (m). Evaluation of intergroup differences in sign values was performed using the Student's *t* test and Mann-Whitney rank *U* test. Differences were considered statistically significant at $p<0.05$ (95% significance level) and $p<0.01$ (99% significance level). Data are presented as percentages, mean values and a 95% confidence interval.

Analysis of variance was performed to evaluate the relationship between the studied parameters. Also, canonical discriminatory analysis was performed, which allows to construct a linear combination of different features. The significance of the differences between the indicators of the function was assessed through Wilks' λ.

The Shapiro-Wilk test was used to test the agreement of the metric indicators' distribution. If the sample distribution agreed with the normal distribution, the mean and standard deviation or error of the mean were used to describe the characteristics of the sample; if the null hypothesis of agreement with the normal law was rejected, the median and quartiles of the distribution were used to describe the metric indicators. Categorical data are presented as empirical laws of distribution. The non-parametric Wilcoxon test was used to compare two samples for homogeneity; in the case of three or more samples, the Kruskall-Wallis test was used. Fisher's exact test was used to test the independence of categorical data. Canonical correlation analysis was used to reveal the structure of correlation dependence between two sets of metric indicators. The separability of the populations according to a set of traits was tested using linear discriminant analysis. Stratification of the population into two age groups was done to improve classification. Discriminant functions separating the populations by outcome characteristics were used as the dependent variable in single factor analysis of variance with a grouping variable responsible for different nosologic forms of diseases. Van der Waarden and Dunnett multiple comparison methods were used to identify the most significantly different subgroups.

Statistical processing of the results of gene polymorphism determination was performed using the GraphPad InStat computer program, version 3.05.32. When comparing individual frequencies of genotypes, Fisher's test was used; when comparing groups, the standard χ^2 test was used. Relative risk (OP) of disease development at a certain genotype was calculated by the standard formula $OP=a/b \times d/c$, where a and b are the number of patients with and without mutant genotype, respectively, and c and d are the number of people in the control group with and without mutant genotype, respectively. OP is given with a 95% confidence interval. The confidence interval limits were calculated using the formulas $OPmin = OP (1-1.96/ \sqrt{\chi^2})$ and $OPmax = OP (1+1.96/ \sqrt{\chi^2})$.

Chapter 3. RESULTS OF THE DISSERTATION

3.1. Findings of Comparative Clinical Epidemiological Analysis and Clinical Effeciency of IVF (IVF+ICSI) Programs in Women with Uterine Fibroids and Genital Endometriosis

We analyzed 1088 case histories of women who underwent infertility treatment using ART methods in the Department of Assisted Reproductive Technologies of the Federal State Budgetary Scientific Institution 'Research Institute of Obstetrics, Gynecology and Reproductive Technology named after D. O. Ott' from 2012 to 2014, of whom 895 women with uterine fibroids and genital endometriosis made up the main group. The control group consisted of 211 women, whose complex examination before planning IVF (IVF+ICSI) infertility treatment did not reveal the above diseases.

3.1.1. Clinical Characteristics of Women with Uterine Fibroids and Genital Endometriosis, Who Entered the IVF Protocol

The main group consisted of women aged 24 to 45 years. Among them, 549 women (62.6%) were under 35 years of age and 328 women (37.4%) were 35 years and older. The mean age comprised 34.23 years.

The control group included women aged 22 to 43 years, of whom 143 women (67.8%) were under 35 years old and 68 women (32.2%) were over 35 years old.

The main group included 410 (46.8%) women with uterine fibroids verified by echographic examination and/or on the basis of morphologic examination of the surgical material. Among them, subserosal uterine fibroids (types 6 and 7 according to the FIGO classification, 2011) were detected in 174 women (42.4%), uterine intramural myoma (types 3-5 according to the FIGO classification, 2011) – in 279 women (68.0%), submucosal myomas (types 0-2 according to the FIGO classification, 2011) were removed in 24 women (5.85%). Multiple uterine myomas

were observed in 62 cases (15.1%), of which 52 had intramural-submucosal myomas, and 7 cases had a history of submucosal myoma removal. In most cases there was a combination of subserosal and intramural myomas (51 women); a combination of intramural and submucosal myomas in anamnesis was present in 4 women; in 3 cases there was a combination of subserosal and submucosal myomas (in anamnesis).

Adenomyosis was detected in 75 women (8.6%) – it was diagnosed during hysteroscopy and according to the results of morphologic study of the material obtained during multifocal trepan biopsy of the myometrium; in 75 cases there was a combination of uterine myoma and adenomyosis.

In the main group, EGE was verified in 397 (45.3%) women based on the results of endoscopic examination (laparoscopy) with subsequent morphologic examination of the surgical material. Stage I-II EGE was diagnosed in 204 women (51.4%), stage III-IV EGE – in 193 women (48.6%), of whom 51 women (12.8%) had endometriomas. Recurrent endometriosis was identified in 24 women (6.0%).

With regard to the inclusion and non-inclusion criteria, 877 women were included in the study; considering the high frequency of the combination of the hyperplastic diseases of the reproductive system organs under study, the main group of women was divided into subgroups according to isolated nosologic forms and a group with a combination of the above diseases:

1. uterine fibroids – 194 women;
2. stage I and II EGE – 154 women;
3. stage III and IV EGE – 141 women;
4. a group with various combinations of uterine fibroids, EGE, adenomiosis – 388 women.

The mean age of women who enetred the IVF protocol in subgroups 1, 4, and 5 was significantly higher than the mean age of women in the control group (Table 1).

Table 1
Age characteristics of women, who entered IVF programs

Group	n	M	m	p, vs control group
Control group	211	32.7	0.32	>0.05
Subgroup 1 – uterine fibroids	**194**	**35.67**	**0.47**	**<0.001**
Subgroup 2 – I-II st. EGE	154	33.33	0.54	>0.05
Subgroup 3 – III-IV st. EGE	141	33.02	0.61	>0.05
Subgroup 4 – combination of uterine myoma and genital endometriosis	**388**	**34.3**	**0.28**	**<0.001**

When analyzing the characteristics of the menstrual cycle, no significant differences were found between the groups in terms of such parameters as menarche onset age, and regular menstrual cycle frequency. Duration of infertility, number of pregnancies, structure of primary and secondary infertility did not differ significantly between the groups. In subgroup 3 (stage III-IV EGE), the delivery rate was the lowest, and the spontaneous abortion rate was the highest (Table 2).

Table 2
Comparative characteristics of obstetric and gynecologic history of women with uterine fibroids and/or genital endometriosis and women from the control group, who entered IVF (IVF+ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p, KW (Kruskall-Wallis)
n	211	194	154	141	388	
Regular m.c.	87%	94%	96%	100%	89%	>0.05
Abnormal uterine bleeding, %,	2%	8%	5%	9%	9%	>0.05
Infertility duration, years	6.35±0.26	7.56±0.51	6.64±0.51	5.53±0.53	7.81±0.31	<0.05
Primary infertility, %	56	41	61	58	64	>0.05
Secondary infertility, %	44	59	49	42	36	>0.05
Number of pregnancies in history	0.938±0.08	1.08±0.12	0.87±0.14	0.76±0.16	0.66±0.08	>0.05
Number of abortions in history	0.289±0.05	0.4±0.06	0.25±0.06	0.24±0.10	0.25±0.04	>0.05
Роды, % of women	**13**	**10**	**8**	**2**	**5**	**<0.05**
Premature delivery, % of women	1	2	0	2	0	>0.05
Blighted ovum, %	9	10	5	9	11	>0.05
Spontaneous abortion, %	**12**	**11**	**9**	**20**	**9**	**<0.05**
Ectopic pregnancy, %	21	21	20	16	9	>0.05
Chronic salpingitis, %	62	71	67	52	43	>0.05
Chronic endometritis, %	17	8	12	13	20	>0.05

When analyzing the structure of infertility causes, it was revealed that the rate of male factor infertility in all examined women comprised 56.15%. Besides, the

male factor was significantly more frequent in women in the control group (52.1%) compared to the main group (40%), p=0.0078; in women in the main group; no differences in the male factor rate between subgroups were found. Expected significant differences were identified in the rate of infertility due to endometriosis between the control and main groups (0% and 46%, respectively, p=0). In terms of other infertility factors, no significant differences were found between the groups: tubal factor infertility was recorded in 53.4% of the examined women (56.9% in the control group and 51.96% in the main group, p=0.25); anovulatory infertility – in 29.29% (33.2% in the control group and 28.0% in the main group, p=0.21); unexplained infertility was determined in only 3% of women in both the main and the control group; uterine factor infertility was identified in 1.9% of women, (2.8% in the control group and 1% in the main group, p=0.23). Other forms of infertility were determined in 1.9% of women (1.9% in the control group and 2% in the main group, p=1).

Analysis of the infertility factor rate among women in the main group showed that anovulatory infertility was significantly more frequent in women with uterine fibroids (Table 3).

Table 3

Comparative analysis of the structure of infertility causes in women with uterine fibroids and/or genital endometriosis and in women from the control group, who entered IVF (IVF+ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p, KW (Kruskall-Wallis)
n	211	194	154	141	388	
Male factor, %	**52**	**40**	**41**	**38**	**39**	**p=0.0078 p_{1-4} =0.65**
Tubal factor, %,	57	64	47	38	50	p=0.25 p_{1-4} =0.081
Unexplained infertility, %	3	6	3	0	3	p=0.81 p_{1-4} =0.45
Anovulatory infertility, %	**33**	**36**	**24**	**24**	**23**	**p=0.21 p_{1-4} =0.043**
Uterine factor infertility, %	3	2	2	0	2	p=0.23 p_{1-4} =0.94
Other infertility causes, %	2	1	2	1	2	p=1 p_{1-4} =0.37

In the control group, more than half of the women had a single cause of infertility, whereas women in the main group had a predominance of cases with 2-3 infertility factors. The average number of combined causes of infertility was the highest in the control group and the lowest in women with uterine fibroids and/or genital endometriosis (Table 4).

Table 4

Comparative quantitative analysis of infertility causes in women with uterine fibroids and/or genital endometriosis and in women from the control group, who entered IVF (IVF+ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4
n	211	194	154	141	388
Number of infertility causes, M±m	2.16±0.04	1.34±0.08*	1.82±0.09**	1.89±0.11	1.63±0.06*

*p<0,005 vs control group

** p<0,01 vs control group

Thus, the analysis of the infertility causes revealed that in the main group the factors determined by the state of the female reproductive system dominate, whereas in the control group, with the exclusion of genital endometriosis and uterine myoma, the male factor infertility has a significantly higher specific weight. Among women from the main group, there is a remarkable increase in the anovulatory infertility rate in women with uterine fibroids. In women with genital endometriosis, the number of infertility causes is significantly lower than in the control group and in uterine myoma, which demonstrates the predominant role of endometriosis-related factors of fertility impairment.

More than 80% of all women had a history of pelvic and hysteroscopic surgery. Among women with endometriosis, the highest average number of abdominal surgeries (1 to 5) was observed, as well as the average number of ovarian surgeries, which has a negative impact on the ovarian reserve (Table 5). The highest frequency of hysteroscopic interventions was observed in the group of women with a combination of uterine myoma and genital endometriosis (1.25±0.07), which is significantly higher than in the control group ($p<0.05$).

Table 5

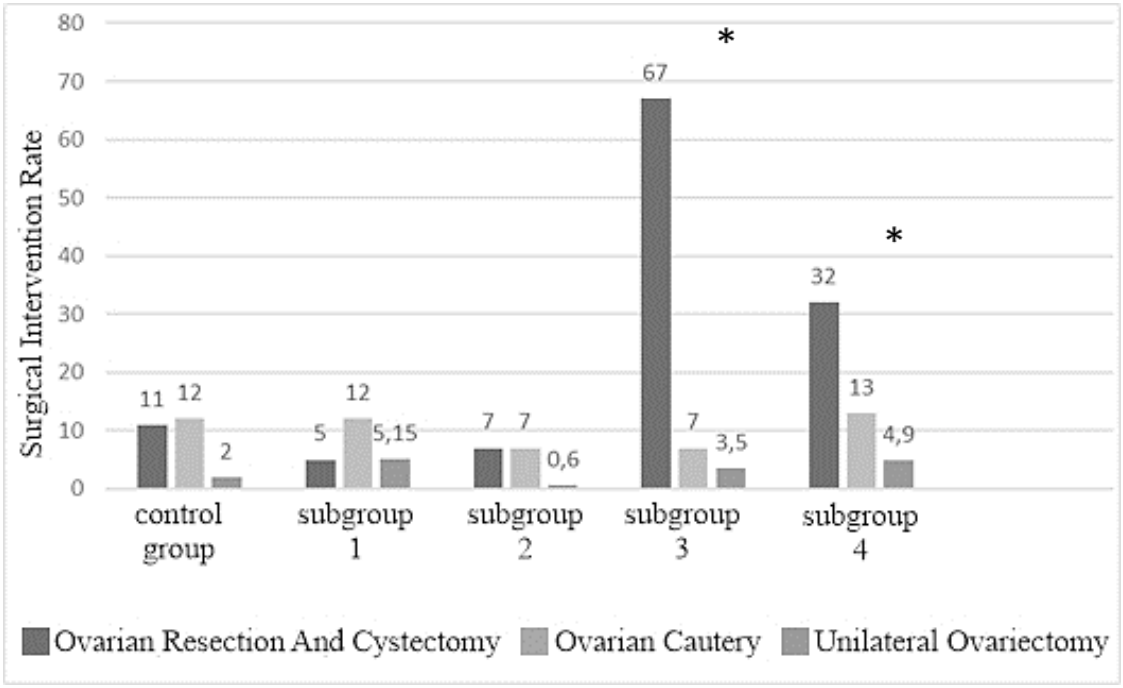
Number of pelvic surgeries and rate of intrauterine interventions in history of women with uterine fibroids and/or genital endometriosis, who entered IVF (IVF/ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4
n	211	194	154	141	388
Number of surgical interventions in the abdominal cavity, M±m	1.19±0.12	1.17±0.1	**1.58±0.09***	**1.6±0.09***	1.47±0.08
Number of operative interventions on ovaries, M±m	0.28±0.03	0.16±0.04	0.21±0.04	**0.9±0.09***	**0.54±0.06****
Number of intrauterine interventions, M±m	0.47±0.06	0.42±0.05	0.72±0.08	0.63±0.07	**1.25±0.07****

*p <0,05 vs control group

**p <0,01 vs control group

Evaluation of the surgical intervention volume showed that ovarian resection and cystectomy were performed significantly more often in the groups of women with stage 3-4 EGE and with a combination of uterine myoma and genital endometriosis (p<0.001); the rate of ovarian cautery in all groups did not differ significantly. Forty women had a history of unilateral ovariectomy, whereas analysis of such operation frequency did not reveal any significant differences between the groups (Figure 2).



*p<0,001 vs the rate of ovarian resection and cystectomy in the control group

Figure 2

Comparative analysis of the ovarian surgery rates in women with uterine fibroids and/or genital endometriosis, who entered IVF (IVF+ICSI) programs

A comparative analysis of the ART program application in the history of the examined women was performed. No significant differences were found between the control group and the groups of women with uterine fibroids and with minor forms of endometriosis when comparing the average number of ovulation stimulation cycles, the number of intrauterine insemination procedures and IVF (IVF+ICSI) programs in the history (Table 6). Comparison of the number of ART program failures in anamnesis showed significantly higher rates in women with stage III-IV EGE and with a combination of uterine myoma and genital endometriosis. It should be noted that in the group with severe forms of endometriosis, all previously performed IVF cycles (IVF+ICSI) failed.

Table 6

Comparative analysis of the history of ovulation stimulation and ART procedures in women with uterine fibroids and/or genital endometriosis, who entered IVF (IVF+ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4
n	211	194	154	141	388
Number of ovulation stimulation cycles, M±m	0.39±0.07	0.23±0.08	0.51±0.12	0.49±0.15	0.40±0.07
Number of IUI cycles, M±m	0.17±0.04	0.09±0.05	0.25±0.08	0.22±0.10	0.15±0.05
Number of IVF cycles, M±m	0.74±0.08	0.62±0.11	0.57±0.11	0.62±0.16	0.80±0.09
Number of failed IVF, M±m	0.31±0.06	0.54±0.09	0.49±0.10	0.62±0.16*	0.76±0.09*

p<0,05 vs control group

Previous hormone therapy was indicated by 36% of women in the control group and 28% of women in the main group (p=0.06).

In the main group, hormone therapy was significantly less frequently used in women with uterine fibroids (16%), p<0.05.

We analyzed the frequency of hormone therapy in external genital endometriosis: hormone therapy was used slightly more often in severe forms of EGE – thereby, gonadotropin-releasing hormone agonists significantly prevailed in the structure of hormone therapy (Table 7).

Table 7

Comparative analysis of the frequency of use of various types of hormone therapy in anamnesis of women with EGE, who entered IVF (IVF+ICSI) programs

	All women with EGE n=295	Stage I-II EGE n=154	Stage III-IV EGE n=141

	abs.	%	abs.	%	abs.	%
Undewent EGE hormone therapy, total	171	58	81	52.6	90	63.8
Performance of various types of hormone therapy (relative to the number of women who received hormone therapy)						
GnRHa preparations	99	57.9	43	53.1	56	62.2
CHC	53	31.0	26	32.1	27	30.0
Other treatment (synt. progestagens)	35	20.5	21	25.9	14	15.6
Natural progesterone preparations	24	14.0	14	17.3	10	11.1

Extragenital diseases in the stage of compensation were detected in 373 women (33.7% of all examined women). There were no significant differences between the groups in the frequency of various categories of diseases, p>0.05 (Table 8).

Table 8

Comparative analysis of the extragenital disease rate in women with uterine fibroids and/or genital endometriosis who entered IVF (IVF+ICSI) programs

	control group		subgroup 1		subgroup 2		subgroup 3		subgroup 4	
n	211		194		154		141		388	
	абс.	%	абс.	%	абс.	%	абс.	%	абс.	%
All extragenital diseases	78	37.0	67	34.5	51	33.1	41	29.1	129	33.2
Cardiovascular diseases	13	6.2	13	6.7	8	5.2	3	2.1	16	4.1
Gastrointestinal diseases	8	3.8	6	3.1	6	3.9	3	2.1	12	3.1
Obesity	17	8.1	8	4.1	6	3.9	0		16	4.1
Liver diseases (viral hepatitis)	8	3.8	15	7.7	11	7.1	10	7.1	27	7.0
Thyroid disorders	4	1.9	16	8.2	6	3.9	11	7.8	23	5.9
Benign breast diseases	23	10.9	43	22.2	20	13.0	34	24.1	66	17.0
Drug allergies	23	10.9	16	8.2	8	5.2	10	7.1	31	8.0
Other	18	8.5	51		14		30		63	

Comparative evaluation of indicators characterizing ovarian reserve in women with uterine fibroids and/or genital endometriosis, who entered IVF (IVF/ICSI) programs

Comparison of mean values of FSH and LH levels in women from the control and studied groups did not reveal any significant differences (Table 8), and no significant differences were revealed when comparing these indicators in the age categories of 35 years and younger and over 35 years. An increase in estradiol level was found in women with stage I-II EGE (146.95± 12.85) as compared to women of the control group (93.8±4.8), p=0.04.

AMH level was significantly lower in women with EGE irrespective of severity – including women in the group with a combination of uterine myoma and genital endometriosis – than in the control group (p≤0,05). Antral follicle count was significantly decreased not only in women with EGE, but also in women with uterine fibroids as compared to the women from the control group (Table 9).

Table 9

Comparative evaluation of indicators characterizing ovarian reserve in women with uterine fibroids and/or genital endometriosis, who entered IVF (IVF/ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4
n	211	194	154	141	388
FSH	6.81±1.78	6.73±0.27	6.95±0.26	7.68±0.49	6.93±0.21
LH	5.73±0.33	4.81±0.21	4.91±0.28	4.75±0.35	5.07±0.18
Estradiol	93.8±4.8	121.95±12.85	**146.95±12.85 p=0.04**	147.16±23.16	125.03±7.96
AMH	2.64±0.2	**1.77±0.23 p=0.006**	**1.79±0.23 p=0.001**	**1.3±0.24 p<0.001**	**1.72±0.15 p<0.001**
Antral follicle count	10.54±0.29	**8.14±0.32 p<0.001**	**8.45±0.39 p<0.001**	**7.18±0.51 p<0.001**	**7.62±1.45 p<0.001**
Single ovary, % of women	1.9	5.2	0	5.0	4.9

Note: *p*-value is presented when there is a significant difference from the indicators of the control group

Thus, women with uterine fibroids and EGE entered the IVF (IVF+ICSI) program, having reduced indicators of ovarian reserve; thereby, a significant increase in the number of surgical interventions on the ovaries was determined only in severe forms of EGE and in the combination of genital endometriosis and uterine myoma.

3.1.2. Efficiency Indicators of Multifollicular Ovarian Stimulation in IVF (IVF+ICSI) Programs in Women with Uterine Fibroids and/or Endometriosis

Analysis of the main parameters of the IVF (IVF+ICSI) cycle revealed that the average total dose of FSH preparations was significantly higher in women from subgroups 1, 3 and 4 as compared to women without uterine myoma and genital endometriosis. At the same time, there were no significant differences between all groups in the duration of superovulation stimulation. Comparison of the effective dose of gonadotropins showed that in women with severe EGE and in combination

of uterine myoma with genital endometriosis, a significantly higher amount of FSH preparations was required (Table 10).

Table 10

Comparative analysis of stimulation efficiency indices in IVF cycles (IVF+ICSI) in women with uterine fibroids and/or genital endometriosis

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p
n	211	194	154	141	388	
Total FSH dose (IU)	1675.9±40.9	1985.5±88.9 *p=0.005	1856.4±73.2	2193.8±112.2 *p=0.005	2086.4±72.2 *p<0.001	p<0.001
Effective dose of gonadotropins (FSH), IU	154.8±31.2	231.8±22.8	242.3±53.3	310.4±49.5 *p=0.01	264.8±44.8 *p=0.02	p=0.008
Stimulation duration (days)	8.8±0.09	9±0.14	8.8±0.15	9.4±0.3	9.2±0.12	p=0.85

*- *p* vs control group

Superovulation stimulation in women with uterine fibroids, with severe forms of EGE and in combination of uterine myoma with genital endomentriosis required more gonadotropin preparations.

In the process of superovulation stimulation, 22 women in the main group showed an unsatisfactory response to the prescribed dose of gonadotropin preparations, so transvaginal puncture was canceled (8 women in subgroup 1, 3 in subgroup 2 and 3 in subgroup 3, 8 in subgroup 4). In the control group, all women underwent transvaginal follicle puncture.

The indicators of the superovulation stimulation efficiency confirmed the correspondence of the indicators of reduced ovarian reserve to the number of obtained oocytes and bipronuclear zygotes. A significant decrease in the number of punctured follicles and obtained oocytes, including MII stage in women with uterine fibroids, EGE and in the combination of uterine myoma and genital endometriosis was revealed. In women with stage III-IV EGE, the number of obtained mature oocytes was 1.8 times lower as compared to women in the control group ($p<0.05$). However, the fertilization efficiency of the obtained oocytes did not differ between the studied groups (Table 11). The embryo quality was assessed in accordance with the classification suggested by Gardner D.K., 2003 [176].

Table 11

Comparative analysis IVF (IVF+ICSI) cycle efficiency in women with uterine fibroids and/or genital endometriosis

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p
n	211	186	151	138	380	
Number of punctured follicles	13.1±0.5	10.2±0.6	9.3±0.6	8.0±0.9	9.4±0.6	p<0.001
Number of obtained oocytes	11.9±0.7	8.9±0.6	8.1±0.5	7.0±0.8	8.3±0.5	p<0.001
Number of obtained MII stage oocytes	8.6±0.5	7.7±0.7	5.9±0.6	4.7±0.6	7.0±0.7	p<0.001 $p_{к-2}$=0.0 $p_{к-3}$=0.0
Frequency of IVF+ICSI fertilization, %	49	44	52	48	48	p>0.05
Number of bipronuclear zygotes	7.3±0.3	5.0±0.3	4.6±0.3	4.3±0.5	5.1±0.4	p<0.001
Fertilization efficiency (number of 2p zygotes / number of oocytes), %	75.2±2.1	67.4±3.4	68.7±3.4	67.9±3.4	72.5±2.9	p>0.05
Number of embryos of optimal quality on the 4th day of cultivation	5.2±0.2	4.2±0.3	4.5±0.4	4.3±0.6	5.5±0.5	p>0.05
Rate of obtaining embryos of satisfactory quality, %	75.2±5.6	72.0±3.3	76.5±3.1	66.2±5.6	79.6±2.9	p>0.05

Thus, despite the negative impact of reduced ovarian reserve on the quantitative indicators with respect to the obtained oocytes and the number of zygotes, the oocytes obtained from women with uterine fibroids and/or genital endometriosis have the same fertilization rates, as well as no reliable differences were found during embryo culturing in the dynamics as compared to women from the control group.

The frequency of protocol cancellation due to stimulation failure in women with uterine fibroids and/or genital endometriosis did not differ, while in comparison with women from the control group it was significantly more frequent (p=0.03), Table 12. The development of ovarian hyperstimulation syndrome in women with uterine fibroids and/or genital endometriosis was significantly less frequent (p=0). Complications of transvaginal follicle puncture occurred with the same frequency in all groups of women (p=0.1).

Table 12

Comparative analysis of the rates of stimulation failure, development of ovarian hyperstimulation syndrome, complications after follicle OR and canceled embryo transfer in women with uterine fibroids and/or genital endometriosis

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p,

						main and control groups
n	211	194	154	141	388	
Protocol cancellation (stimulation failure), %	0	4.1	1.9	2.1	2.1	0.0337 p_{1-4} =0.7941
OHSS development rate, %	18.0	6	5	2	8	0 p_{1-5} =0.3388
OR complications, %	5.2	2	4	2	2	0.1135 p_{1-4} =0.1019

Stimulation failures were significantly more frequent in women from the main group, while the incidence of OHSS was significantly less frequent as compared to women from the control group, reflecting a higher incidence of diminished ovarian reserve and diminished response to superovulation.

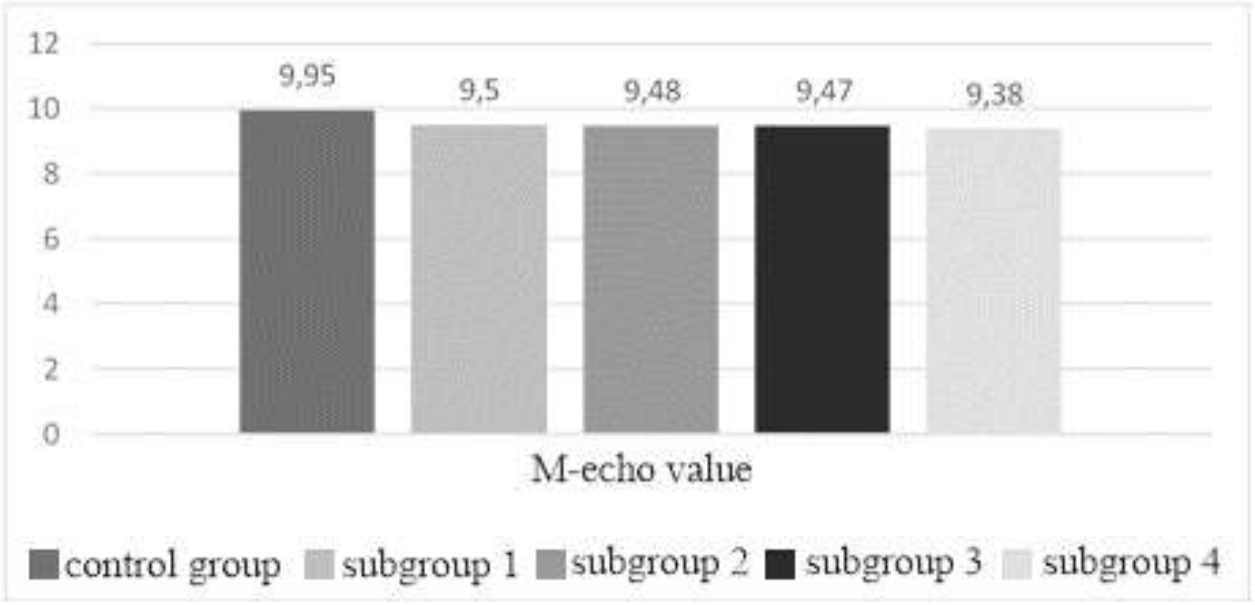
Embryo transfer cancellation (due to diminished endometrium, absence of embryos of satisfactory quality, development of acute respiratory viral infection, etc.) had the same frequency in the main group and the control group (p=0.8451); in the subgroup of women with severe EGE, the frequency of embryo transfer cancellation was significantly higher than in the subgroup of women with uterine fibroids (p=0.02) (Table 13).

Table 13

Comparative analysis of cancelled embryo transfer in women with uterine fibroids and/or genital endometriosis

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p
n	211	186	151	138	380	
Cancelled ET, abs./%	19/9,0	15/8,1	11/7,3	28/20,3	34/8,9	p_{1-3}=0,02, χ2=0,0016 p_{1-4}=0,06 χ2=0,87

Evaluation of the endometrial thickness on the day of embryo transfer showed no significant differences between the groups (Figure 3).



p>0,05

Figure 3

Comparative analysis of M-echo values on the day of embryo transfer in women with uterine fibroids and/or genital endometriosis

Cryopreservation was performed on 569 out of 1066 women (53.3%). In the main group, the cryopreservation rate among women with uterine fibroids and genital endometriosis (in subgroups 1-4) did not differ significantly (p=0.13), whereas it was significantly lower than in the control group (45.0% and 66.8%, respectively), p=0.0004 (Table 14).

Table 14

Comparative analysis of embryo cryopreservation rates within IVF (IVF+ICSI) programs among women with uterine fibroids and/or genital endometriosis

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4
n	211	186	151	138	380
Number of cryopreservation cases, abs.	141	97	51	54	194
Cryopreservation rate, %	66.8	52.1*	33.8*	39.1*	51.1*
$\chi 2$ or Fisher's two-sided test relative to the control group		8.87	38.6	25.95	13.74

*p<0,001 vs control group

Clinically defined pregnancy occurred in 36.6% of women. Pregnancy rate in women from the main group was significantly lower as compared to women from

the control group (34.3% and 45.8%, respectively, p=0.039), Table 15. Comparison of evaluation of IVF (IVF+ICSI) program efficiency within the age categories of women not older than 35 years and women 35 years and older showed a significant decrease in efficiency in the main group as compared to the control group only in women not older than 35 years (p=0,049). The delivery rate averaged 20.8% and was lower in women from the main group as compared to the control group (p=0.046). Comparison of the delivery rates in the age categories under 35 years and over 35 years showed a significant decrease in the delivery rate in the main group as compared to the comparison group in women over 35 years of age (5.2% and 15.9% respectively, p=0.048), Table 15.

Table 15

Comparative analysis of the IVF (IVF+ICSI) program efficiency in women with and without uterine fibroids and/or genital endometriosis (pregnancy rate, births per OR)

	total	control group	main group	p	$\chi 2$ or Fisher's two-sided test
	959	192	767		
Clinical pregnancy rate	36.6% (351/959)	45.8% (88/192)	34.3% (263/767)	**0.039**	**8.82**
Clinical pregnancy rate among women under 35 years old	43.2% 263/609	54.3% 70/129	40.2 % (193/480)	**0.049**	**8.19**
Clinical pregnancy rate among women older than 35 years old	25.1% (88/350)	28.6% 18/63	24.4% (70/287)	0.1	0.48
Delivery rate	20.8% 199/959	29.7% 57/192	18.5% 142/767	**0.046**	**11.66**
Delivery rate among women under 35 years old	28.6% 174/609	36.4% 47/129	26.5% 127/480	0.169	4.96
Delivery rate among women older than 35 years old	7.1% 25/350	15.9% 10/63	5.2% 15/287	**0.044**	**8.83**

Comparative analysis of pregnancy and delivery rates among women from the main group showed the lowest efficiency of the IVF (IVF+ICSI) program in women with severe EGE and with a combination of uterine myoma and genital endometriosis. Comparison of the pregnancy rate among women from subgroups with uterine fibroids, stage III-IV EGE and with a combination of uterine myoma and genital endometriosis showed significantly lower rates as compared to women from the control group (Table 16).

Table 16

Comparative analysis of IVF (IVF+ICSI) program efficiency among women with uterine fibroids and/or genital endometriosis

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p	$\chi 2$ or Fisher's two-sided test
	к	1	2	3	4		
Clinical pregnancy rate	45.8% (88/192)	35.1% (60/171)	43.6% (61/140)	31.8% (35/110)	30.9% (107/346)	к-1 **0.042** к-2 0.7 к-3 **0.04** к-4 **0.01**	к-1 **4.32** к-2 0.17 к-3 **5.69** к-4 **11.88**
Clinical pregnancy rate among women under 35 years old	54.3% 70/129	40.4% 42/104	51.1% 45/88	36.4% 24/66	36.9% 82/222	к-1 **0.047** к-2 0.7 к-3 **0.02** к-4 **0.02**	к-1 **4.44** к-2 0.21 к-3 **5.6** к-4 **9.98**
Clinical pregnancy rate among women older than 35 years old	28.6% 18/63	26.9% 18/67	30.8% 16/52	25.0% 11/44	20.2% 25/124	к-1 0.8 к-2 0.8 к-3 0.8 к-4 0.2	к-1 0.05 к-2 0.07 к-3 0.17 к-4 1.67
Delivery rate	29.7% 57/192	22.8% 39/171	19.3% 27/140	15.5% 17/110	17.1% 59/346	к-1 0.15 к-2 **0.04** к-3 **0.006** к-4 **0.001**	к-1 2.2 к-2 **4.64** к-3 **7.66** к-4 **11.66**
Delivery rate among women under 35 years old	36.4% 47/129	30.8% 32/104	28.4% 25/88	24.2% 16/66	24.3% 54/222	к-1 0.4 к-2 0.2 к-3 0.1 к-4 **0.02**	к-1 0.82 к-2 1.52 к-3 2.97 к-4 **5.84**
Delivery rate among women older than 35 years old	15.9% 10/63	10.4% 7/67	3.8% 2/52	2.3% 1/44	4.0% 5/124	к-1 0.4 к-2 **0.045** к-3 **0.02** к-4 **0.008**	к-1 0.84 к-2 **4.41** к-3 **5.2** к-4 **7.94**

Significant decrease in the pregnancy rate was determined for women with uterine myoma – OR 0.64, CI 0.42-0.98, for women with stage III-IV EGE, OR 0.55, CI 0.34-0.9, for women with a combination of uterine myoma and genital endometriosis, OR 0.53, CI 0.37-0.76, $p<0.05$; for women with stage I-II EGE, no differences from the comparison group were found, OR 0.91, CI 0.59-1.41, $p>0.05$.

To identify the factors associated with the IVF (IVF+ICSI) program outcomes, a comparative analysis of clinical and anamnestic data was performed among women from the control and the main groups, depending on the IVF (IVF+ICSI) program outcome – the onset of clinical pregnancy.

Comparative characteristics of factors affecting the IVF program outcomes in women from the control group

Analysis of the dependence on pregnancy occurrence after the studied IVF (IVF+ICSI) cycle did not reveal any differences in the characteristics of gynecological and somatic anamnesis, and the frequency of infertility factors was not significantly different among the women from the control group. Women who successfully completed an IVF (IVF+ICSI) program were expected to have significantly lower age (31.0±4.1 and 32.6±4.8 years, respectively, p=0.03) and higher ovarian reserve (AMH and antral follicle count) as compared to women who failed (Table 17).

Comparative assessment of the number of pelvic surgical interventions and the number of failed ART programs in history in women with IVF (IVF+ICSI) pregnancies and in women with failed pregnancies showed no differences.

Evaluation of the characteristics of the superovulation stimulation cycle and embryological stage performance showed that quantitative indicators – the number of oocytes, bipronuclear zygotes, and embryos of optimal quality – have a significant impact, while the frequency of obtaining embryos of satisfactory quality and the M-echo value on the day of embryo transfer did not differ depending on the outcome of IVF (IVF+ICSI) programs (Table 17).

Table 17

Evaluation of the performance of the stimulation stage and the embryologic stage of IVF cycles (IVF+ICSI) in women from the control group depending on the pregnancy onset

	Failed pregnancy				Clinical pregnancy				
	N	Median	LQ	UQ	N	Median	LQ	UQ	p
Age	**95**	**33.0**	**29.0**	**36.0**	**95**	**31.0**	**28.0**	**33.0**	**0.03**
AFC	**95**	**10.0**	**7.0**	**11.0**	**95**	**11.0**	**9.0**	**14.0**	**0.005**
AMH	**95**	**2.0**	**2.0**	**1.0**	**3.0**	**4.0**	**2.0**	**4.0**	**0.008**
Total dose of FSH preparations	95	1600	1350.0	2025.0	95	1537.5	1200.0	1775.0	0.065
Number of obtained oocytes	**95**	**9.0**	**6.0**	**13.0**	**95**	**12.0**	**9.0**	**15.0**	**0.0003**
Number of bipronuclear zygotes	**95**	**5.0**	**3.0**	**8.0**	**95**	**8.0**	**6.0**	**10.0**	**0.00001**
Ratio of the number of bipronuclear zygotes to the number of mature oocytes, %	**67**	**80.0**	**66.7**	**90.9**	**55**	**84.6**	**72.7**	**100.0**	**0.049**

Number of embryos of optimal quality on the 4th day of cultivation	**73**	**4.0**	**2.0**	**6.0**	**82**	**6.0**	**4.0**	**7.0**	**0.024**
Rate of obtaining embryos of satisfactory quality, %	73	75.0	57.0	100.0	82	66.7	53.3	87.5	0.1
M-echo value on the ET day	95	10.0	8.0	11.0	94	10.0	9.0	11.0	0.06

Correlation analysis using Spearman's criteria revealed a significant negative correlation between the age and pregnancy onset in women from the control group (rs=-0.16, p=0, 03) and a significant positive correlation with the number of antral follicles (rs=0.2, p=0.005), number of obtained oocytes (rs=0.26, p=0.0002), number of bipronuclear zygotes (rs=0.32, p=0.048) and number of embryos of satisfactory quality on the 4th day of culturing (rs=0.24, p=0.002).

Comparative characteristics of factors affecting the IVF program outcomes in women from the main group

Comparison of the mean age of women from the main group with completed pregnancy after IVF (IVF+ICSI) delivery with that of women with failure showed significant differences: 32 and 35 years (p<0.001). Similarly, pregnancy termination with delivery had significantly higher antral follicle count before the start of the protocol, whereas gonadotropin and AMH levels did not differ significantly (Table 18).

Table 18

Comparative characteristics of ovarian reserve parameters depending on the delivery rate after IVF program

Factor	Failed pregnancy			Successful pregnancy			p
	25%	M	75%	25%	M	75%	
FSH	5.40	6.75	8.31	5.59	6.44	8.11	0.78
LH	3.40	4.49	6.20	3.58	4.85	6.34	0.30
Estradiol	63.52	106.13	165.09	46.80	100.97	132.00	0.08
AMH	0.80	1.15	2.10	1.00	1.50	2.40	0.15
Antral follicle count	5.00	**7.00**	9.00	6.00	**9.00**	11.00	**0**

Diminished ovarian reserve was consistently associated with IVF failures (17% in failed outcomes and 10% in positive outcomes, p=0.044).

In positive IVF outcomes, the highest incidence was associated with transfer of 2 embryos (compared to transfer of 1 embryo).

In successful IVF cycles, a higher rate of embryo cryopreservation was observed – 56%, whereas in failed protocols the rate of cryopreservation was 36% ($p<0.0001$).

Evaluation of the IVF (IVF+ICSI) cycle in women with post-protocol pregnancy revealed that with fewer gonadotropins spent on stimulation, the number of obtained oocytes, including mature ones, and the number of fertilized zygotes were significantly higher, while the fertilization rate did not differ (Table 19).

Table 19

Comparison of the IVF (IVF+ICSI) program outcomes in women from the main group depending on the pregnancy rate

Factor	Failed pregnancy			Successful pregnancy			p
	25%	M	75%	25%	M	75%	
Total dose of FSH preparations	1500.00	**1950.00**	2475.00	1387.5	**1675.00**	2062.5	**0**
Stimulation duration, days	8,00	9.00	10,00	8.00	9.00	10.00	0.29
Follicles before OR	4,00	**7.00**	11,00	8.00	**10.00**	14.00	**0.00**
Obtained oocytes	3.0	**7.00**	10.0	6.00	**9.00**	13.00	**0.00**
Mature oocytes	2.00	**4.50**	8.00	5.00	**7.00**	11.00	**0.00**
Mature oocyte obtainment rate	66.70	83,30	100.00	63.05	85,7	94.70	0,94
Number of fertilized zygotes	2.00	**5.00**	8.00	5.00	**7.00**	10.00	**0.00**
Number of 2p zygotes	2.00	**4.00**	6.00	3.75	**5.00**	7.00	**0.00**
Fertilization rate	50.00	72,7	100.00	66.7	80.00	92.9	0.27
Number of embryos of optimal quality on day 3	2.00	4.00	6.00	3.00	4.00	6.00	0.20
Number of embryos of optimal quality on day 4	2.00	4.00	6.00	3.00	4.00	6.00	0.11
Endometrial thickness on the ET day	8.00	**9.00**	10.00	9.00	**10.00**	10.00	**0.00**

Comparative characteristics of factors affecting the IVF program outcomes in women with uterine fibroids

For women with uterine fibroids, the likelihood of pregnancy was lower in cases of endocrine factor infertility (OR 0.57 (CI 0.33 to 0.99), $p<0.05$, whereas the presence of male factor infertility as the main indication for ART programs was associated with an increased likelihood of pregnancy (OR = 2.1 (CI 1.24-3.56, $p<0.01$), and tubal factor infertility had no significant effect on the outcome (OR

0.66 (CI 0.39-1.11), p=0.14. Thus, increased frequency of anovulation and, accordingly, regular absence of secretory transformation of the endometrium in anamnesis is a factor of negative prognosis of ART program effectiveness for women with uterine fibroids.

Comparative assessment of the number of operations on pelvic organs, the number of operations on ovaries, the number of failed ART programs in women with pregnancy after IVF (IVF+ICSI) programs and in women with failed pregnancy did not reveal any differences.

The dependence of pregnancy rate on the localization of uterine myomas is shown in the presence of intramural myomas – in women with intramural myomas, the probability of pregnancy decreased (Table 20).

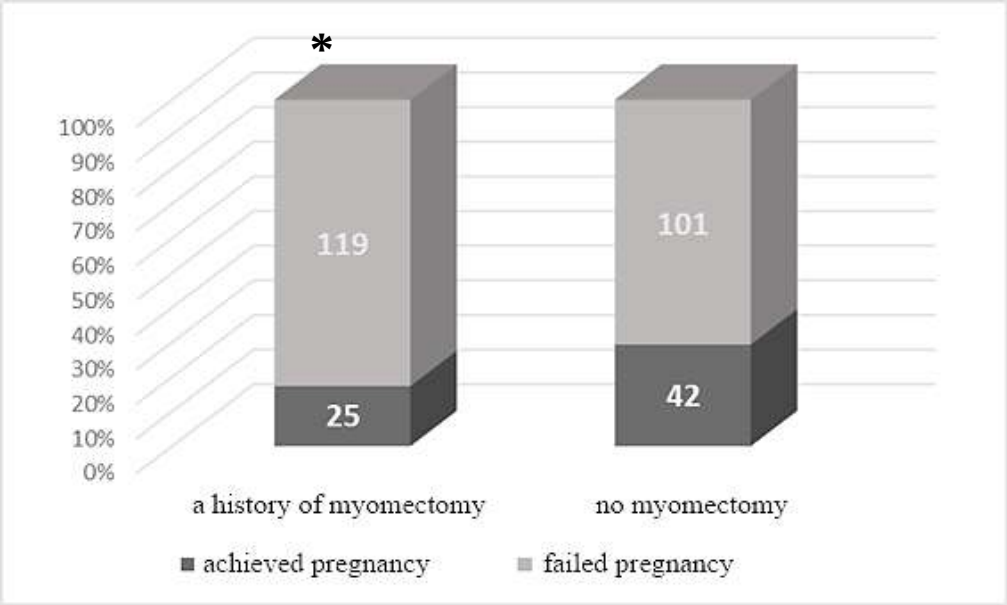
Table 20

Presence of uterine intramural myomas and subserosal myomas and pregnancy rate (Pearson Chi-square criterion was used)

	OR (95% CI)	p
Uterine subserosal myomas	1.2 (0.71-2.01)	0.503
Uterine intramural myomas	0.53 (0.31-0.93)	0.025
Multiple uterine myomas	0.41 (0.18-0.95)	0.037

The presence of adenomyosis was also a negative predictor of clinical pregnancy, OR 0.2 (0.04-0.91), $p<0.05$.

Women with a history of conservative myomectomy of intramural myomas were less likely to become pregnant as compared to women without a history of conservative myomectomy (17.4% and 29.4%, respectively, p=0.02), OR 0.51 (0.29-0.89, p=0.018), Figure 4.



*- p<0,05

Figure 4

Pregnancy rate among women with uterine fibroids depending on the performance of myomectomy in anamnesis

It was determined that the age of women with a successful pregnancy was significantly lower as compared to women with a failed pregnancy. BMI had no significant effect on pregnancy rate, and there were no women with BMI over 35 in the group. Antral follicle count and antimüllerian hormone levels in women with successful completion of the IVF (IVF+ICSI) program were significantly higher than in women with failure. The main indicators of the superovulation stimulation efficiency also had significant differences depending on the program outcome – the total dose of FSH preparations was lower, the number of obtained oocytes, bipronuclear zygotes, and embryos of good quality was higher in women with pregnancy, while the fertilization efficiency indicators – fertilization rate (the ratio of the number of bipronuclear zygotes to the number of MII stage oocytes) and the frequency of obtaining embryos of satisfactory quality did not differ (Table 21).

Table 21

Evaluation of IVF (IVF+ICSI) cycle efficiency in women with uterine fibroids depending on pregnancy onset

	Failed pregnancy				Clinical pregnancy				
	N	Median	LQ	UQ	N	Median	LQ	UQ	p
Age	**147**	**38.0**	**34.0**	**41.0**	**103**	**34.0**	**31.0**	**37.0**	**0**
AFC	**147**	**7.0**	**5.0**	**9.0**	**103**	**9.0**	**6.0**	**11.0**	**0.0004**

AMH	147	2.0	1.0	2.0	103	2.0	1.0	4.0	0.06
Total dose of FSH preparations, IU	**147**	**1875.0**	**1500.0**	**2475.0**	**103**	**1750.0**	**1350.0**	**2175.0**	**0.025**
Number of obtained oocytes	**147**	**7.0**	**4.0**	**10.0**	**103**	**10.0**	**7.0**	**15.0**	**0.000001**
Number of bipronuclear zygotes	**147**	**4.0**	**2.0**	**6.0**	**103**	**6.0**	**4.000**	**8.0**	**0.000008**
Ratio of the number of bipronuclear zygotes to the number of mature mature oocytes	98	70.5	50.0	100.0	84	79.9	60.0	100.0	0.18
Number of embryos of optimal quality on day 3 of culturing	**143**	**3.0**	**2.0**	**5.0**	**99**	**4.0**	**3.000**	**6.0**	**0.0001**
Number of embryos of optimal quality on day 4 of culturing	**82**	**3.0**	**2.0**	**5.0**	**78**	**4.5**	**3.000**	**6.0**	**0.000002**
Rate of obtaining embryos of satisfactory quality, %	84	75.0	54.5	100.0	82	80.0	66.7	100.0	0.08
M-echo value on the ET day	**143**	**9.0**	**8.0**	**10.0**	**103**	**10.0**	**8.5**	**11.0**	**0.001**

Correlation analysis with calculation of the Spearman coefficient revealed a significant negative association of clinical pregnancy onset with the age of women with uterine fibroids (rs=-0.34, p=0) and a positive association of AFC (rs=0.23, p<0.001), the number of oocytes obtained (rs=0, 31, p<0.001), the number of bipronuclear zygotes (rs=0.28, p<0.001), the number of embryos of satisfactory quality on the 4th day of culturing (rs=0.38, p<0.0001), and the M-echo value on the day of embryo transfer (rs=0.21, p=0.001).

Comparative characteristics of factors affecting IVF program outcomes in women with stage I-II external genital endometriosis

Women with pregnancy at the end of an IVF (IVF+ICSI) cycle, in contrast to women with a failed outcome, had a significantly lower defined age (31.8±3.8 and 34.6±4.9 years, respectively, p<0.0001). No differences in AMH and antral follicle number were found. The presence of male factor infertility as an indication for ART programs was associated with an increased likelihood of pregnancy (OR=1.9 (CI 1.08-3.36, p<0.01), as was tubal factor infertility (OR 2.03 (CI 1.16-3.56), p<0.05. The presence of adenomyosis acted as a negative prognostic factor (OR 0.2 (CI 0.04-0.91), p<0.05.

Women with stage I-II EGE with a failed IVF (IVF+ICSI) program were significantly more likely to have a history of ovarian surgery (0.3±0.06) as compared to women with a pregnancy (0.15±0.04), p=0.02.

Evaluation of indicators of the efficiency of superovulation stimulation and embryological stage, similarly to the indicators in women from the control group, showed that quantitative indicators (the number of obtained oocytes, bipronuclear zygotes, embryos of optimal quality) differed significantly in the positive outcome of IVF (IVF+ICSI) programs, while the frequency of obtaining embryos of optimal quality did not differ in women with different outcomes of the programs. It should be noted that the M-echo value on the day of embryo transfer was found to be a significant factor (M 9.0 and 10.0 mm for failure and pregnancy, respectively, p=0.0003) (Table 22). In contrast to women from the control group, women with stage I-II EGE showed differences in the total dose of FSH preparations spent on stimulation – the dose was determined to be lower at successful outcome as compared to unsuccessful outcome (M 1650.0 IU and 1875.0 IU respectively, p=0.008).

Table 22

Evaluation of IVF (IVF+ICSI) cycle efficiency in women with stage I-II EGE depending on pregnancy onset (Mann-Whitney test was used)

	Failed pregnancy				Clinical pregnancy				
	N	Median	LQ	UQ	N	Median	LQ	UQ	p
Age, years	**117**	**34.0**	**32.0**	**38.0**	**90**	**32.0**	**29.0**	**34.0**	**<0.001**
AFC	117	8.0	5.0	11.0	90	9.0	6.0	11.0	0.17
AMH, ng/ml	117	2.0	1.0	3.0	90	2.0	1.0	4.0	0.2
Total dose of FSH preparations, IU	**117**	**1875.0**	**1500.0**	**2400.0**	**90**	**1650.0**	**1425.0**	**1975.0**	**0.008**
Number of obtained oocytes	**115**	**6.0**	**3.0**	**11.0**	**90**	**9.0**	**4.0**	**12.0**	**0.01**
Number of bipronuclear zygotes	**111**	**3.0**	**2.0**	**5.0**	**90**	**5.0**	**3.0**	**7.0**	**0.0004**
Ratio of the number of bipronuclear zygotes to the number of mature mature oocytes	66	71.4	50.0	100.0	58	83.3	60.0	100.0	0.16
Number of embryos of optimal quality on day 3 of culturing	**91**	**3.0**	**2.0**	**5.0**	**74**	**4.0**	**3.0**	**7.0**	**0.002**
Number of embryos of optimal quality on day 4 of culturing	**63**	**4.0**	**3.0**	**6.0**	**61**	**5.0**	**3.0**	**6.0**	**0.024**
Rate of obtaining embryos of satisfactory quality, %	66	83.3	60.0	100.0	62	80.0	38.5	100.0	0.36
M-echo value on the ET day	**105**	**9.0**	**8.0**	**10.0**	**90**	**10.0**	**9.0**	**10.0**	**0.0003**

Correlation analysis with calculation of the Spearman coefficient revealed a significant negative correlation of the clinical pregnancy onset with the age of women with stage I-II EGE (rs=-0.3, p<0.001) and no dependence on AFC, while a

significant positive correlation was found for the number of oocytes obtained (rs=0, 2, p<0.01), the number of bipronuclear zygotes (rs=0.25, p<0.001), the number of embryos of satisfactory quality on day 4 of culturing (rs=0.21, p=0.02), as well as the M-echo value on the day of embryo transfer (rs=0.26, p<0.001).

Comparative characteristics of factors affecting IVF program outcomes in women with stage III-IV external genital endometriosis

In women with severe EGE, the presence of male factor as an indication for ART was a positive predictor of pregnancy (OR 2.83; CI 1.19-6.7, p=0.017).

Age was not identified as a factor significantly affecting the outcome of an IVF (IVF+ICSI) program (p=0.059).

In women with stage III-IV EGE, IVF (IVF+ICSI) program failure was noted with a significantly higher number of ART program failures in history as compared to women with an achieved pregnancy (0.3±0.11 and 0.5±0.16, p=0.04).

The number of ovarian interventions in women with a failed IVF (IVF+ICSI) program with stage III-IV EGE was significantly lower than in women from the control group (0.3±0.1 and 0.9±0.1, p=0.00003).

Similarly to women with stage I-II EGE, significant differences depending on efficiency were obtained in quantitative parameters of the stimulation and embryological stage – in the case of program failure, the total dose of FSH preparations was significantly higher, the number of obtained oocytes, bipronuclear zygotes, embryos of optimal quality was significantly lower than in women with pregnancy. Significant reliable difference was found in the M-echo value (higher in women with achieved pregnancy) (Table 23).

Table 23

Evaluation of IVF (IVF+ICSI) cycle efficiency in women with stage III-IV EGE depending on pregnancy onset (Mann-Whitney test was used)

	Failed pregnancy				Clinical pregnancy				
	N	Median	LQ	UQ	N	Median	LQ	UQ	p
Age, years	60	34.0	30.0	36.0	36	32.5	28.5	35.0	0.059
AFC	**60**	**6.0**	**1.0**	**13.0**	**36**	**8.5**	**2.0**	**18.0**	**0.005**
AMH, ng/ml	**60**	**1.0**	**1.0**	**2.0**	**36**	**1.0**	**1.0**	**3.0**	**0.04**
Total dose of FSH preparations, IU	**60**	**2100.0**	**1600.0**	**2650.0**	**36**	**1575.0**	**1350.0**	**2100.0**	**0.007**

Number of obtained oocytes	**58**	**5.0**	**2.0**	**8.0**	**36**	**8.0**	**4.0**	**12.0**	**0.004**
Number of bipronuclear zygotes	**56**	**2.0**	**1.5**	**5.0**	**36**	**5.0**	**2.0**	**7.5**	**0.012**
Ratio of the number of bipronuclear zygotes to the number of mature mature oocytes	41	66.7	50.0	87.5	24	77.5	68.35	100.0	0.19
Number of embryos of optimal quality on day 3 of culturing	**46**	**2.5**	**1.0**	**5.0**	**35**	**4.0**	**2.0**	**6.0**	**0.027**
Number of embryos of optimal quality on day 4 of culturing	**32**	**3.5**	**1.0**	**4.5**	**22**	**5.0**	**4.0**	**7.0**	**0.003**
Rate of obtaining embryos of satisfactory quality, %	32	85.7	57.8	100.0	24	80.0	70.7	100.0	0.68
M-echo value on the ET day	**54**	**9.0**	**8.0**	**10.0**	**35**	**10.0**	**9.0**	**11.0**	**0.0006**

Correlation analysis showed no significant association of the age of women with stage III-IV EGE with the onset of clinical pregnancy, whereas AFC positively correlated with the IVF (IVF+ICSI) program success (rs=0.29, p=0.004), as well as the number of obtained oocytes (rs=0.3, p=0.004), the number of bipronuclear zygotes (rs=0.26, p=0.01), the number of embryos of satisfactory quality on day 4 of culturing (rs=0.41, p=0.002) and the M-echo value on the day of embryo transfer (rs=0.37, p<0.001).

Comparative characteristics of factors affecting IVF program outcomes in women with a combination of uterine myoma and external genital endometriosis

A history of conservative myomectomy for intramural myomas was found to be a negative prognostic factor for pregnancy (OR 0.4, CI 0.19-0.84, p=0.014).

Depending on the outcome of an IVF (IVF+ICSI) program, the age was significantly different (M 36.0 and 33.5 years at failure and in women with pregnancy, respectively, p=0.0004).

In women with a combination of uterine myoma and genital endometriosis, a failed IVF (IVF+ICSI) program was noted in women with a significantly higher number of pelvic interventions in anamnesis as compared to women with achieved pregnancy (1.8±0.1 and 1.5±0.1, p=0.04).

Analysis of the efficiency of the superovulation stimulation stage, in the case of unsuccessful completion of an IVF (IVF+ICSI) program, showed that the total dose of FSH preparations was significantly higher, the number of bipronuclear zygotes and embryos of optimal quality on day 3 of culturing was lower as compared

to women with achieved pregnancy (Table 24). At the same time, the frequency of obtaining embryos of satisfactory quality and M-echo value on the day of embryo transfer did not differ - comparable quality of embryos and endometrial thickness do not determine the efficiency of IVF (IVF+ICSI) programs for women with a combination of uterine myoma and genital endometriosis, determining the significance of other indicators - reduction in the number of oocytes obtained and posttransfer stage.

Table 24

Evaluation of IVF (IVF+ICSI) cycle efficiency in women with uterine fibroids and genital endometriosis depending on pregnancy onset (Mann-Whitney test was used)

	Failed pregnancy				Clinical pregnancy				
	N	Median	LQ	UQ	N	Median	LQ	UQ	p
Age, years	**120**	**36.0**	**33.0**	**37.0**	**70**	**33.5**	**31.0**	**35.0**	**0.0004**
AFC	**120**	**6.5**	**4.0**	**9.0**	**70**	**7.0**	**6.0**	**10.0**	**0.026**
AMH, ng/ml	**120**	**2.0**	**1.0**	**3.0**	**70**	**2.0**	**1.0**	**4.0**	**0.04**
Total dose of FSH preparations, IU	**117**	**1950.0**	**1500.0**	**2525.0**	**70**	**1750.0**	**1350.0**	**2025.0**	**0.005**
Number of obtained oocytes	117	6.0	2.0	10.0	70	7.0	4.0	10.0	0.111
Number of bipronuclear zygotes	**114**	**3.0**	**1.0**	**6.0**	**70**	**5.0**	**3.0**	**6.0**	**0.022**
Ratio of the number of bipronuclear zygotes to the number of mature mature oocytes	**84**	**71.0**	**35.4**	**100.0**	**48**	**80.0**	**60.0**	**100.0**	**0.04**
Number of embryos of optimal quality on day 3 of culturing	**89**	**4.0**	**1.0**	**6.0**	**65**	**3.0**	**3.0**	**5.0**	**0.027**
Number of embryos of optimal quality on day 4 of culturing	44	4.0	2.0	6.0	45	4.0	3.0	5.0	0.61
Rate of obtaining embryos of satisfactory quality, %	52	75.7	50.0	100.0	45	75.0	57.1	100.0	0.32
M-echo value on the ET day	97	9.0	8.0	10.0	70	9.5	8.0	10.0	0.17

Correlation analysis revealed a significant negative correlation of clinical pregnancy onset with the age of women with a combination of uterine myoma and EGE (r_s=-0.26, $p<0.001$) and a positive correlation of AFC (r_s=0.16, $p=0.03$), the number of bipronuclear zygotes, the number of embryos of satisfactory quality on the 4th day of culturing (r_s=0.17, $p=0.02$); M-echo value on the day of embryo transfer had no correlation with the program outcome (r_s=0.11, $p=0.17$).

In the case of IVF (IVF+ICSI) program failure, the number of pelvic interventions in anamnesis of women with EGE and in women with a combination of uterine myoma and genital endometriosis was significantly higher as compared to their number in women from the control group (Table 25).

Table 25
Comparative analysis of the number of pelvic interventions in women from the control and main groups with failed IVF (IVF+ICSI) programs

	control group	subgroup 1	subgroup 2	subgroup 3	subgroup 4	p, Kruskal-Wallis test
n	211	194	154	141	388	
Number of operations on pelvic organs	1.2±0.1	1.3±0.09	1.6±0.11	1.7±0.1	1.8±0.1	0 к-1 1.0 к-2 0.01 к-3 0.006 к-4 0.0002

3.1.3. Evaluation of Explored Factors' Impact on the Results IVF (IVF+ICSI) Programs Using Discriminant Analysis Methods

To assess the impact of the studied diseases on the outcomes of IVF (IVF+ICSI) programs, discriminant analysis was performed and canonical correlation coefficients were determined. All the studied diseases had a negative effect on the outcome of IVF (IVF+ICSI) programs, with age and adenomyosis having the most pronounced negative effect (Tables 26, 27).

Table 26
Canonical weights for baseline characteristics

	Y
Age	0.013
Subserosal form of uterine myoma	0.031
Intramural form of uterine myoma	0.101
Multiple uterine myomas	0.023
Adenomyosis	0.021
St. I EGE	0.025
St. II EGE	0.052
St. III EGE	0.083
St. IV EGE	0.083
Retrocervical endometriosis	-0,145
Endometrial cysts	0.026
Simple endometrial hyperplasia without a history of atypia	0.029

Table 27
Final characteristics for estimation of canonical weights

	X
Oocytes obtained at OR	-0.003
Mature oocytes obtained at OR	-0.008
Clinically diagnosed pregnancy after IVF	-0.024
Delivery after a given IVF cycle	-0.057

Thus, uterine fibroids and genital endometriosis are identified as factors that have a negative impact on achieving the highest frequency of clinically diagnosed pregnancies and deliveries in the main group.

To illustrate the role of the studied factors in achieving the final characteristics, a graph of canonical values is provided below (Figure 5).

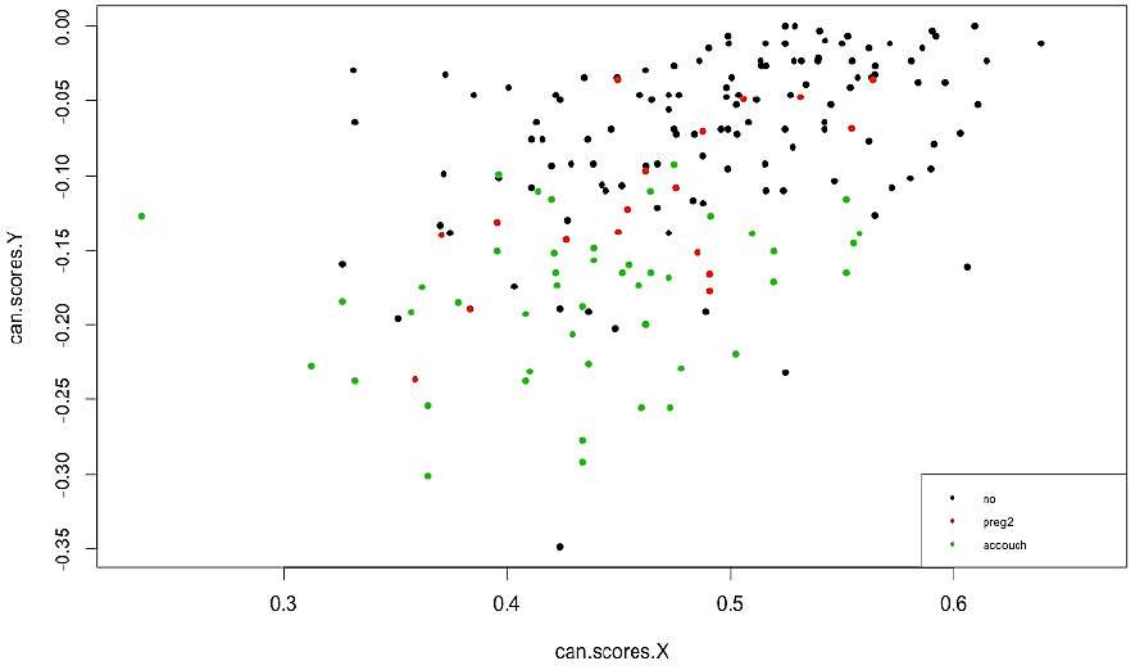


Figure 5
Graph of canonical values

In order to identify the most significant factors affecting the outcomes of IVF (IVF+ICSI) programs, we studied the values of signs in the main group. The presence of stage III EGE and multiple uterine myomas was found to be negatively correlated with the outcomes of ART: biochemical and clinical pregnancy and delivery (Table 28). In the analysis of biochemical pregnancy onset, only women with no subsequent verified clinical pregnancy were included; similarly, in the analysis of clinical pregnancy rate, only cases that did not result in delivery were included. A significant change in the outcome of IVF (IVF+ICSI) programs

depending on the presence of stage III EGE was revealed. The above analysis shows that a significant proportion of pregnancy loss with EGE occurs after clinical verification of pregnancy, leading to a significant reduction in the delivery rate.

Table 28
Comparison of the rate of various IVF (IVF+ICSI) program outcomes depending on the presence of st. III EGE

	No st. III EGE		St. III EGE		$\chi 2$ or Fisher's two-sided test	p
	n	%	n	%		
Negative IVF (IVF+ICSI) outcome	210	60.000	23	56.098	0.23	0.63
Biochemical pregnancy	13	3.714	1	2.439	NA	1.0
Clinical pregnancy	30	8.571*	10	24.390*	10	0.0016
Delivery after IVF (IVF+ICSI)	97	27.714	7	17.073	1.62	0.2033

p=0.02

The presence of multiple uterine myomas is also significantly associated with negative IVF outcomes (Table 29). In uterine fibroids, despite significant success of biochemical pregnancy, pregnancy loss is the most frequent at the early stage - before visualization of the fetal egg (up to 6 weeks).

Table 29
Comparison of the rate of various IVF (IVF+ICSI) program outcomes depending on the presence of multiple uterine myomas

	No multiple uterine myomas		Multiple uterine myomas		$\chi 2$ or Fisher's two-sided test	p
	n	%	n	%		
Negative IVF (IVF+ICSI) outcome	213	58.356	20	76.923	2.75	0.0975
Biochemical pregnancy	12	3.288	2	7.692	NA	0.2368
Clinical pregnancy	40	10.959	0	0.000	NA	0.0929
Delivery after IVF (IVF+ICSI)	100	27.397	4	15.385	NA	0.2508

p=0.05

Analysis of the negative impact of the combination of two factors on the outcomes of IVF (IVF+ICSI) programs highlighted the following combinations (at $p \leq 0.01$): multiple uterine fibroids and adenomyosis, multiple uterine fibroids and retrocervical endometriosis, adenomyosis and stage III EGE, multiple uterine fibroids and adenomyosis (see Appendix).

An automatic multiple discriminant analysis of the impact of the combination of various reproductive system disorders was performed in the main group; as a

result, 3 combinations with a distinct negative impact on the outcomes in IVF (IVF+ICSI) programs were identified.

In the population with the combination of uterine myoma and adenomyosis, as well as with the combination of uterine myoma and stage III-IV EGE, such negative factors as the presence of adenomyosis, intramural uterine myoma, endometrioid cysts, and all types of conservative myomectomy in the anamnesis were identified. Thereby, treatment for EGE had a significant positive effect on IVF outcome; treatment with GnRHa and treatment with synthetic gestagens had almost equal canonical weights (Table 30, Figure 6). The factor of age in the presence of uterine myoma and adenomyosis did not stand out as a discriminant function in this case.

Table 30

Results of the multiple discriminant analysis of factors determining the positive outcome of IVF (IVF+ICSI) programs in women with uterine fibroids and genital endometriosis

discriminant function 1	LD1	discriminant function 2	LD1
adenomyosis	-0.977	intramural uterine myoma	-0.712
chronic endometritis	-0.737	endometrial ovarian cysts	-1.878
history of hysteroscopy	0.675	EGE treatment - GnRHa preparations	2.608
number of abdominal surgeries	-0.868	EGE treatment - gestagens	2.038
number of ovarian surgeries	-0.989	male factor infertility	1.803
IVF+ICSI fertilization	-0.851	number of optimal quality embryos for transfer	0.658
number of infertility factors	1.363		
tubal factor	-1.514		
EGE as an infertility factor	-1.384		
idiopathic infertility	-3.269		
endocrine infertility	-1.564		
uterine factor infertility	1.965		
other causes of infertility	5.058		
intramural myoma removal in anamnesis	-1.956		
submucosal myoma removal in anamnesis	-1.430		
subserosal myoma removal in anamnesis	-1.413		
oocyte cryopreservation	0.958		

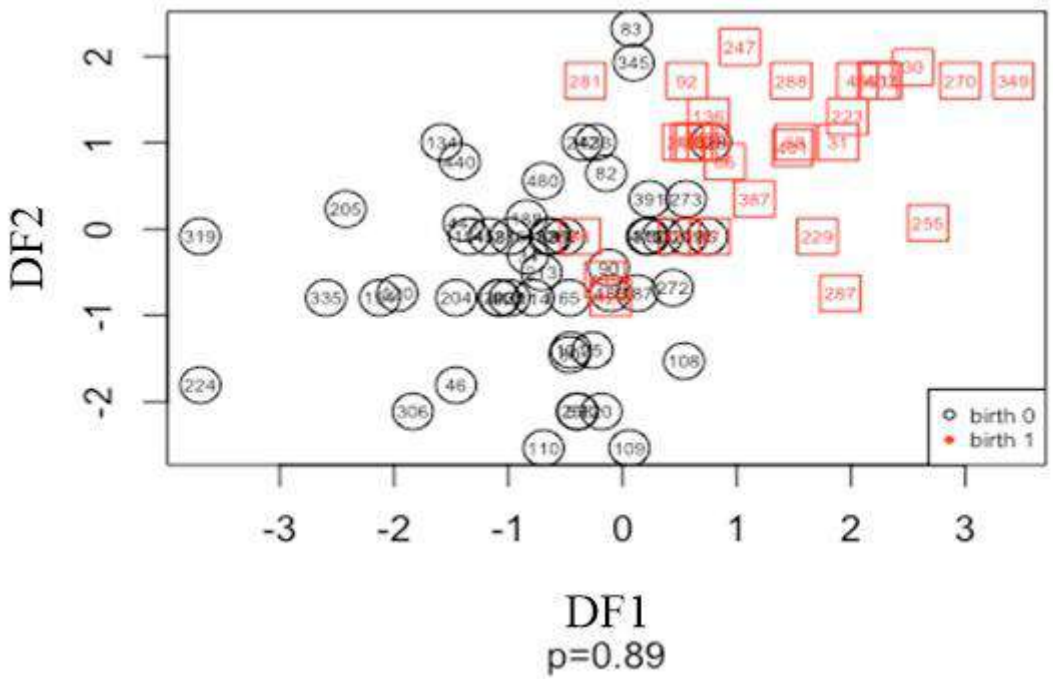


Figure 6
Distribution of IVF program outcomes (deliveries) depending on the presence of different factors (discriminative functions indicated in the Table above)

Thus, uterine fibroids and genital endometriosis are independent factors in reducing the efficiency of IVF (IVF+ICSI) programs. The efficiency of IVF (IVF+ICSI) programs in women with uterine fibroids is 35.1%, in severe EGE - 31.8%, in combination of uterine myoma and genital endometriosis - 30.9%, which is significantly lower as compared to women without proliferative diseases, comparable in age and history - 45.8% ($p<0.05$).

In women operated for severe forms of external genital endometriosis, the decrease in the IVF (IVF+ICSI) program efficiency in terms of clinical pregnancy rate is determined by the decrease in the ovarian reserve indices - decrease in the AMH level in comparison with women without proliferative diseases (1.3±0.24 and 2.64±0.2, respectively) and the number of antral follicles (7.18±0.51 and 10.54±0.29, respectively), ($p<0.05$), as women with EGE had a 1.8-fold decrease in the number of oocytes obtained during superovulation stimulation in IVF protocols (IVF+ICSI), in comparison with women without proliferative disease (4.8 and 8.6, respectively ($p<0.005$), whereas the efficiency of fertilization and embryo culturing is not affected, the number of embryos of optimal quality on day 4 is sufficient (4.4 and 5.2, respectively ($p>0.05$). The decrease in the IVF (IVF+ICSI) program

efficiency determined by the frequency of clinical pregnancy is probably due to the posttransfer interaction between blastocytes and the endometrium.

3.2. Findings of Comparative Clinical Anamnestic, Ultrasound and Doppler Study of the Myometrium and the Endometrium in Women with Uterine Fibroids and Combined Uterine Fibroids and Adenomyosis

87 women who subsequently underwent surgical intervention were examined.

General examination included clinical and anamnestic study, pelvic ultrasound before surgical intervention, and histologic examination of surgical material.

Prior to surgical treatment, for the purpose of complex comparative characterization of the state of the myometrium and endometrium in women with uterine fibroids and in combination of uterine myoma with adenomyosis, the uterine artery blood flow was assessed.

Inclusion criteria:

- US examination of pelvic organs before surgery;
- Doppler ultrasound of the uterine artery blood flow before the surgery;
- verified uterine myoma and uterine myoma in combination with diffuse adenomyosis according to histologic study of surgical material;
- absence of signs of myoma nutrition disorder;
- absence of signs of acute inflammatory process;
- consent for the study.

Exclusion criteria:

- focal adenomyosis;
- ovarian tumors and tumor-like formations;
- malignant diseases of any localization.

Indications for surgical treatment: size of myomas, marked clinical manifestations, submucosal myomas, pregnancy planning, impaired reproductive function, chronic pelvic pain syndrome.

The study included patients whose uterine volume (measured on day 3-5 of the m.c.) did not exceed 160 cm3. The diagnosis of uterine fibroids and adenomyosis before surgical intervention was based on ultrasound examination data.

Women, in whom no other uterine hyperplastic processes other than uterine myoma were detected during the complex examination, made up the main group (n=47); women with a combination of uterine myoma and adenomyosis were allocated to the comparison group (n=40).

The control group consisted of 10 healthy women of reproductive age with a regular menstrual cycle in the absence of gynecologic diseases in the anamnesis and in the process of preventive examination.

The age of the examined patients was within 24-45 years (mean 37.5±4.7 years); in the main group, the mean age was 39.8±4.3 years, in the comparison group – 36.9±4.8 years; the age of the control group women also did not differ significantly and amounted to 33.4±2.3 years ($p \geq 0.05$). There were also no differences in the age of menarche between all compared groups: 13.3±0.1 in the main group, 13.4±0.4 in the comparison group and 12.9±0.6 in the control group ($p \geq 0.05$).

Analysis of menstrual cycle characteristics revealed significant differences between the groups in the rate of menstrual cycle disorders – abnormal uterine bleeding was significantly more frequent in the comparison group ($p > 0.05$) (Table 31). There were no significant differences between the groups in the characteristics of gynecologic history and the number of pregnancies.

Table 31

Age characteristics, parity, and gynecologic history in women with uterine fibroids and in the combination of uterine myoma with adenomyosis, $\chi 2$ or Fisher's two-sided test was used

	Main group	Comparison group
n	47	40
Regular m.c., %	83	47.5*
Abnormal uterine bleeding, %	7	52.5*
Mean age of the first signs of the disease, years	36.8±1.1	36.2±0.9
Infertility, %	17.7	22.3
Primary infertility, %	10.5	10.8
Secondary infertility, %	7.3	6.1
Childbirth history, %	74.5	72.5
Conservative myomectomy history, number of women	2	4

Hormonal therapy history, %	18.5	28.8
Chronic tubo-ovarian abscess, %	31.9	35
Cervical diseases	27.2	43.9

*p <0.005 vs the main group

In a comparative analysis of gynecologic anamnesis parameters, a significant increase in the abnormal uterine bleeding rate in women with a combination of uterine myoma and adenomyosis is noteworthy.

Among the transferred and concomitant extragenital diseases, gastrointestinal diseases (37% and 34%), endocrine system and metabolic pathology (15% and 19%), and cardiovascular diseases (7% and 5%) prevailed, respectively. Appendectomy was previously performed in 4 women in the main group and in 3 women in the comparison group; cholecystectomy was previously performed on 1 woman in the comparison group.

The anemia rate was significantly higher in the comparison group. The indications for surgery in the main group were rapid growth of uterine myoma, abnormal uterine bleeding, pregnancy planning, submucosal myomas; the most frequent indications for surgery in the comparison group were pregnancy planning, abnormal uterine bleeding, combination of uterine myoma and adenomyosis.

3.2.1. Findings of Pelvic Ultrasound in Examined Women prior to Surgery

All examined women underwent ultrasound and Doppler ultrasound of the uterine artery blood flow on days 3-5 of the menstrual cycle and on days 20-23 of the menstrual cycle in the case of a preserved menstrual cycle before surgical intervention.

Ultrasound characteristics of diffuse adenomyosis included: uterine wall asymmetry, hypoechogenic areas in the myometrium, linear striation, hyperechogenic inclusions in the myometrium and changes in the connective zone between the myometrium and the endometrium (increased thickness up to 3-4mm), inhomogeneous thickness and structure.

For the subsequent IHC study, the composition of the compared groups was changed based on the results of surgical intervention. The main group included 4

additional women from the comparison group, in whom macroscopic examination and histologic examination did not confirm the signs of adenomyosis identified by ultrasound.

The majority of the examined women from the main group and from the comparison group had multiple uterine myomas: 68% of women from the main group and 80% of women from the comparison group had multiple uterine myomas (with the number of myomas ranging from 2 to 11). Uterine intramural myomas were detected in 44 women from the main group and 38 women from the comparison group. Subserosal myomas were detected in 9 women from the main group and 4 women from the comparison group; submucosal localization of myomas was noted in 3 and 1 cases, respectively.

Table 32 shows the results of biometric ultrasound examination of the uterus of women from the main group and from the comparison group, as well as the results obtained from healthy women.

Table 32

Comparative characteristics of uterine and endometrial biometric indices in women with uterine fibroids and a combination of uterine myoma and adenomyosis on day 3-5 of m.c. according to US study data

	Uterine sizes, cm			Uterine volume, cm^3	Endometrial thickness, cm
	Length	Anteroposterior	Transverse		
Control group (n=10)	4.5 ± 0.1	3.7 ± 0.1	4.2 ± 0.1	32.6 ± 3.2	0.53 ± 0.05
Main group (n=47)	6.9± 2.9	4.9 ± 1.1	7.3 ± 0.8*	115.9 ± 8.7*	0.51 ± 0.06
Comparison group (n=40)	7.7± 3.4	4.2 ± 1.5	6.4 ± 0.5*	104.7± 10.4*	0.55 ± 0.07

*$p<0.01$ vs the control group

Uterine volume in the studied groups of patients exceeded considerably the same index in women from the control group. Endometrial thickness in the early follicular phase of the menstrual cycle was comparable in all groups and did not exceed 0.6 cm, which made it possible to exclude the presence of hyperplastic processes of the endometrium and to continue the study during the current menstrual cycle.

The ovarian sizes determined on days 3-5 of the menstrual cycle in healthy women did not differ significantly from the reference population values (Bulanov M.N., 2022) [2]. The mean volume of the right ovary comprised 5.4±0.2cm^3, of the

left ovary – 5.1±0.3cm^3. In the structure of the ovaries in the early follicular phase, cavity formations (follicles) with a diameter of no more than 8-10mm were detected.

3.2.2. Findings of Doppler Velocimetry of the Uterine Artery Blood Flow in Women with Uterine Fibroids and Combined Uterine Fibroids and Adenomyosis

Doppler ultrasound of the uterine artery blood flow prior to surgical intervention was performed on all examined women on days 3-5 of the menstrual cycle and on days 20-23 of the cycle in the case of the preserved menstrual cycle using the previously described procedure [35].

We found no significant differences in the right and left uterine artery blood flow indices in all the studied groups. Below, mean values of the right and left uterine artery blood flow indices are provided.

The study of the uterine artery blood flow in the early follicular phase of the menstrual cycle revealed that in women with uterine fibroids, as well as with a combination of uterine myoma with adenomyosis, there is a decrease in all vascular resistance indices as compared to healthy women (Table 33). No significant differences in the studied parameters between the women from the main group and from the comparison group were revealed.

Table 33

Comparative characteristics of the Doppler blood flow indices in uterine arteries in women with uterine fibroids and with a combination of uterine myoma and adenomyosis on day 3-5 of the m.c.

	PI	RI	SDR
Control group (n=10)	2.8 ± 0.2	0.85 ± 0.01	7.9 ± 0.8
Main group (n=47)	1.70 ± 0.1*	0.74 ± 0.03*	5.21 ± 0.28**
Comparison group (n=40)	1.61± 0.4**	0.77 ± 0.05	5.11 ± 0.6*

*p<0.01 vs the control group

**p<0.05 vs the control group

In the study of the blood flow in the spiral arteries on days 3-5 of the m.c., visualization was possible only in 24 out of 47 women from the main group and in 17 out of 40 women from the comparison group (Table 34).

Table 34

Comparative characteristics of the Doppler blood flow indices in spiral arteries in women with uterine fibroids and with a combination of uterine myoma and adenomyosis on day 3-5 of the m.c.

	PI	RI	SDR
Control group (n=9)	0.63 ± 0.03	0.42 ± 0.02	1.7 ± 0.05
Main group (n=21)	0.49± 0.04*	0.41 ± 0.07	1.3 ± 0.04**
Comparison group (n=17)	0.51± 0.04*	0.52 ± 0.06	1.4± 0.07*

*p<0.05 vs the control group

**p<0.01 vs the control group

Visualization of spiral arteries in the control group was possible in 9 women, whereas in the main group and the comparison group, the same rate was significantly lower (51.1% and 42.5% of cases, respectively, p=0.05).

The indices of vascular resistance in spiral arteries in women with uterine fibroids were lower as compared to similar indices in healthy women (PI and SDR were significantly reduced); the same was true for the combination of uterine myoma and adenomyosis.

As a result of hormonal and ultrasound examination, in 41 women from group I and 29 women from group II, a full-fledged ovulatory menstrual cycle was verified: when observing the dynamics of the menstrual cycle on days 11-13 of the menstrual cycle, a dominant follicle was visualized; the mean diameter of the dominant follicle comprised 1.97±0.09cm. At the ultrasound examination of the ovary at the place of the dominant follicle performed on days 20-23 of the menstrual cycle, a hollow formation with thickened, often irregular contours with variable echogenicity – the corpus luteum – was visualized; the size of the corpus luteum averaged 2.1±0.1cm. During the hormone study, the level of progesterone in the blood on days 20-23 of the menstrual cycle reached 46.9±3.7nmol/l.

Doppler velocimetry was performed in the uterine artery basin on day 20-23 of the ovulatory menstrual cycle (Table 35).

Table 35

Comparative characteristics of the Doppler blood flow indices in uterine arteries in women with uterine fibroids and with a combination of uterine myoma and adenomyosis n the ovulatory cycle dynamics (on days 3-5 and 20-23 of the m.c.)

	PI		RI		SDR	
	m.c. day 3-5	m.c. day 20-23	m.c. day 3-5	m.c. day 20-23	m.c. day 3-5	m.c. day 20-23
Control group (n=10)	2.8 ± 0.2	2.1 ± 0.1	0.85 ± 0.01	0.79 ± 0.01	7.9 ± 0.8	5.4 ± 0.3

Main group (n=41)	1.72 ± 0.1*	1.53 ± 0.04*	0.79 ± 0.02	0.72 ± 0.03	5.3 ± 0.5	4.50 ± 0.19
Comparison group (n=29)	1.61 ± 0.3*	1.44 ± 0.12*	0.81 ± 0.04	0.73 ± 0.06	5.2± 0.4	4.6 ± 0.5

*p<0,01 vs the control group

The evaluation of vascular resistance indices in uterine arteries revealed that in the ovulatory menstrual cycle dynamics in women from the control group there was a significant unidirectional decrease in blood flow resistance relative to the value of the index in the follicular phase of the cycle: PI 2.8±0.2 and 2.1±0.1, respectively (p<0.01); at the same time, in the dynamics of unidirectional change the blood flow resistance indices in women with uterine fibroids and with a combination of myoma with adenomyosis had no significant differences: 1.72±0.1 and 1.53±0.04 in the group with uterine fibroids (p=0.08) and 1.61±0.3 and 1.44±0.12 (p=0.6) in the group with uterine fibroids in combination with adenomyosis (Table 35).

Visualization of the blood flow in the spiral arteries during the menstrual cycle was available in 9 women from the control group, 21 women from the main group and 14 women from the comparison group. We identified significantly lower SDR values on day 20-23 of the menstrual cycle in the main group and the comparison group as compared to the control group (Table 36).

Table 36

Comparative characteristics of the Doppler blood flow indices in spiral arteries in women with uterine fibroids and with a combination of uterine myoma and adenomyosis n the ovulatory cycle dynamics (on days 3-5 and 20-23 of the m.c.)

	PI		RI		SDR	
	m.c. day 3-5	m.c. day 20-23	m.c. day 3-5	m.c. day 20-23	m.c. day 3-5	m.c. day 20-23
Control group (n=9)	0.63 ± 0.03	0.48 ±0.01	0.42±0.02	0.37±0.01	1.7±0.05	1.51 ± 0.03
Main group (n=21)	0.49± 0.04*	0.44±0.03	0.41±0.05	0.36±0.02	1.3±0.05*	1.28± 0.04*
Comparison group (n=14)	0.51± 0.04**	0.45±0.02	0.52±0.06	0.45±0.04	1.4±0.04*	1.3± 0.04*

*p<0.01 vs the control group

**p<0.05 vs the control group

The evaluation of vascular resistance indices in the endometrial arteries revealed a significant decrease in all studied indices on day 20-23 of the menstrual cycle as compared to the early follicular phase in the control group (p<0.05 for all studied indices) [35]; at the same time, the decrease of vascular resistance indices during the luteal phase of the cycle as compared to the early follicular phase was not significant in uterine fibroids. In the comparison group, there was also no significant decrease in vascular resistance in the ovulatory menstrual cycle dynamics (Table

38). The results demonstrate a decreased ability of the endometrial spiral arteries to cyclic variability of blood flow resistance in uterine fibroids and in the combination of uterine myoma with adenomyosis corresponding to the luteal phase.

Blood flow in uterine myomas in the main group and the comparison group in the early follicular phase of the menstrual cycle was evaluated. Minimal or moderately expressed peripheral blood flow was observed in uterine myomas. In the central zone of the myoma, color signals were detected with a frequency not exceeding 40% (Table 37).

Table 37

Doppler blood flow indices in peripheral arteries of uterine myomas in women with uterine fibroids and with a combination of uterine myoma with adenomyosis on day 3-5 of m.c.

	PI	RI	SDR
Main group (n=40)	1.59± 0.06*	0.64 ± 0.07*	5.3 ± 0.04*
Comparison group (n=47)	1.51± 0.04*	0.60 ± 0.06*	4.9± 0.07*

*p>0.05 when comparing between the groups

Vascular resistance indices in intramural myomas in women with uterine fibroids and with a combination with adenomyosis were similar (p>0.05).

Moderate vascularization with low values of resistance indices (RI 0.55±0.07; 0.63 to 0.82) was noted in myometrial sites corresponding to ultrasound characteristics of adenomyosis.

Doppler indices of blood flow in peripheral arteries of uterine myomas do not change when uterine myoma is combined with adenomyosis.

Thus, in women with uterine fibroids during the spontaneous cycle, the indices of vascular resistance to blood flow in uterine and spiral arteries are significantly lower than in women without uterine fibroids, and the phase cyclicity of the decrease in the indices in ovulatory cycles is reduced. When myoma and adenomyosis are combined, the indices of vascular resistance to blood flow in uterine and spiral arteries are unequivocally comparable.

3.3. Findings of Doppler Velocimetry of the Uterine Artery Blood Flow during Multifollicular Ovarian Stimulation within the IVF (IVF+ICSI) Program in Women with Uterine Fibroids and EGE

Doppler ultrasound of the uterine artery blood flow was performed on 131 women who underwent IVF (IVF+ICSI) infertility treatment with the background of superovulation stimulation with gonadotropin preparations. Among them, 44 women with uterine fibroids and 48 women with EGE: 29 women with stage 1-2 EGE and 19 women with stage 3-4 EGE.

The control group consisted of 39 women, a complex examination of whom allowed us to exclude the presence of uterine myoma and EGE.

All women underwent standard IVF or IVF with intracytoplasmic sperm injection (ICSI) protocol with the use of gonadotropin-releasing hormone antagonists.

The mean age of women in the reported clinical groups was not significantly different (Table 38). Analysis of menstrual cycle characteristics revealed no significant differences between the groups in terms of such parameters as the age of menarche onset and the presence of a regular menstrual cycle. The number of pregnancies and their outcome, the structure of primary and secondary infertility in the selected clinical groups were comparable. However, among women with severe EGE the frequency of births in anamnesis was the lowest; the history of spontaneous abortions was predominantly observed among women with uterine fibroids in combination with genital endometriosis (Table 38).

Table 38

Age characteristics, parity and gynecologic history of women with uterine fibroids and external genital endometriosis

	Control group	Women with uterine fibroids	Women with EGE
n	39	44	48
Age, years ±m	33.4±0.27	35.6±0.46	33.7±0.75
Regular m.c., %	87.2%	93.2%	95.8%
Abnormal uterine bleeding, %	2.6%	6.8%	4.2%
Infertility duration, years	7.11±0.34	8.1±0.49	6.96±0.61
Primary infertility, %	56.4%	40.9%	58.3%

Secondary infertility, %	43.6%	59.1%	41.7%
Delivery, %	12.8%	9.1%	8.3%
Undeveloped pregnancies, %	7.7%	9.1%	6.25%
Spontaneous abortions, %	12.8%	9.1%	8.3%
Ectopic pregnancy, %	20.5%	20.45%	20.8%

Uterine sizes in women from the control group and with EGE were not significantly different (Table 39) on day 2-3 of the menstrual cycle at the start of superovulation stimulation within the IVF program (IVF+ICSI). In women with uterine fibroids, intramural myomas with a diameter ranging from 0.8 to 3.5cm were identified. The distance from the M-echo border to the myoma capsule was at least 1.0cm. The size of M-echo was determined to be not more than 4mm in all groups, the structure was homogeneous and hyperechogenic. After measuring the ovarian size, the volume of each ovary was calculated. In the control group, the mean volume of the right and left ovaries was determined as 6.87±0.54cm^3 and 7.12±0.64cm^3, respectively; in women with uterine fibroids – 7.1±0.48cm^3 and 5.98±0.67cm^3; in women with EGE – 5.98±0.57cm^3 and 6.45±0.77cm^3; no significant differences between the groups were obtained.

Table 39

Comparative characteristics of uterine body biometrics in women with uterine fibroids and in women with adenomyosis on day 2-3 of the m.c. according to US study data

	Uterine sizes, cm		
	Length	Anteroposterior	Transverse
Control group (n=39)	4.63 ± 0.6	3.81 ± 0.6	4.52 ± 0.7
Women with uterine fibroids (n=44)	7.1± 1.0*	5.4 ± 1.6	7.5 ± 1.3*
Women with EGE (n=48)	4.51± 0.4	4.1 ± 0.3	4.45 ± 0.3

*p<0.05 vs the control group

Doppler ultrasound of the uterine artery blood flow was performed during the IVF (IVF+ICSI) program in all examined women (n=131) during the following periods:

- on day 2-3 of the menstrual cycle, at the start of the IVF (IVF+ICSI) protocol;
- on the day of insertion of the final oocyte maturation trigger;
- on the day of embryo transfer.

Visualization of the spiral arteries on day 2-3 of the menstrual cycle was available in 15 (38.5%) women from the control group; in 18 (40.9%) women with uterine fibroids and in 18 (37.5%) women with EGE (Table 40).

Table 40

Comparative characteristics of the results of Doppler ultrasound in uterine and spiral arteries of women with uterine fibroids, EGE and from the control group on the 2-3 day of m.c. within the IVF (IVF+ICSI) program

		PI	RI	SDR
Control group				
Uterine arteries (n=39)		2.9 ± 0.05	0.88 ± 0.02	7.9 ± 0.7
Spiral arteries (n=15)		0.83 ± 0.03	0.59 ± 0.06	2.4 ± 0.08
Women with uterine fibroids				
Uterine arteries (n=44)		1.70 ± 0.1*	0.71 ± 0.03*	5.21 ± 0.28*
Spiral arteries (n=18)		0.59± 0.07**	0.39 ± 0.05**	1.3 ± 0.06**
Women with EGE				
Uterine arteries (n=48)		2.8± 0.09▪	0.87 ± 0.05▪	7.57 ± 0.6▪
Spiral arteries (n=18)		0.79 ± 0.04▪▪	0.57 ± 0.05	2.3 ± 0.07▪▪

*p<0.05 when comparing the studied indices in uterine arteries of women with uterine fibroids and women from the control group

** p<0.05 when comparing the studied indices in spiral arteries of women with uterine fibroids and women from the control group

▪ p<0.05 when comparing the studied indices in uterine arteries of women with EGE and women with uterine fibroids

▪▪ p<0.05 when comparing the studied indices in spiral arteries of women with EGE and women with uterine fibroids

Indices of blood flow resistance in uterine and spiral arteries of women with uterine fibroids were significantly lower than those of women with EGE and women from the control group. There were no significant differences in the blood flow resistance indices between women with EGE and from the control group.

On the day of administration of the final oocyte maturation trigger, the M-echo value was 9.3±0.21mm in the control group, 9.5±0.32mm in women with uterine fibroids and 8.9±0.19mm in women with EGE and did not differ significantly between the groups. In terms of structure, the endometrium was described as three-layered in all women, and an increase in echogenicity of the peripheral parts of the endometrium was determined in a number of women (26% in the control group, 51% in women with uterine fibroids and 47% in women with EGE).

Visualization of the spiral arteries was available in 30 (76.9%) women from the control group, in 34 (77.3%) women with uterine fibroids and in 36 (75%) women with EGE.

It was found that on the day of ovulation trigger administration, the blood flow resistance indices in uterine and spiral arteries of women with uterine fibroids were significantly lower than those of women with EGE and from the control group (Table 41).

Table 41

Comparative characteristics of the results of Doppler ultrasound in uterine and in spiral arteries of women with uterine fibroids, with EGE and from the control group on the day of final oocyte maturation trigger administration within the IVF (IVF+ICSI) program

	PI	RI	SDR
Control group			
Uterine arteries (n=39)	2,15±0,06	0,84±0,02	5,87±0,18
Spiral arteries (n=30)	0,70±0,02	0,44±0,02	1,81±0,04
Women with uterine fibroids			
Uterine arteries (n=44)	1,51 ± 0,07*	0,61 ± 0,03*	4,81 ± 0,15 *
Spiral arteries (n=34)	0,53± 0,05**	0,34 ± 0,03**	1,45 ± 0,04**
Women with EGE			
Uterine arteries (n=39)	2,2± 0,07▪	0,77 ± 0,06▪	6,98± 0,5▪
Spiral arteries (n=36)	0,68 ± 0,02▪▪	0,47 ± 0,03	1,8 ± 0,07▪▪

*p<0.05 when comparing the studied indices in uterine arteries of women with uterine fibroids and women from the control group,

** p<0.05 when comparing the studied indices in spiral arteries of women with uterine fibroids and women from the control group

▪ p<0.05 when comparing the studied indices in uterine arteries of women with EGE and women with uterine fibroids

▪▪ p<0.05 when comparing the studied indices in spiral arteries of women with EGE and women with uterine fibroids

On the day of embryo transfer, endometrial thickness was 9.44±0.17cm in the control group, 9.62±0.16cm in the group with uterine fibroids and 9.34±0.19cm in women with EGE (p>0.01). Signs of complete secretory transformation were determined in 57.5% of women from the control group, 42.7% of women with uterine fibroids and 44.8% of women with EGE. Visualization of spiral arteries on the day of embryo transfer was possible in 32 (82.1%) women from the control group; in 35 (79.5%) women with uterine fibroids and in 38 (79.1%) women with EGE.

The analysis of the results of Doppler velocimetry in uterine and spiral arteries on the day of embryo transfer into the uterine cavity showed that in women with uterine fibroids all indices of vascular resistance were significantly lower as compared to women with EGE and from the control group. Thus, the peculiarities of blood flow vascular resistance indices revealed at the start of IVF (IVF+ICSI) protocol on the day of embryo transfer persist (Table 42).

Table 42

Comparative characteristics of Doppler indices in uterine and in spiral arteries of women with uterine fibroids, with EGE and from the control group on the day of embryo transfer within the IVF (IVF+ICSI) program

	PI	RI	SDR
Control group			
Uterine arteries (n=39)	1.99±0.04	0.81±0.01	5.56±0.20
Spiral arteries (n=32)	0.65±0.03	0.43±0.01	1.77±0.04
Women with uterine fibroids			
Uterine arteries (n=44)	1.50 ± 0.08*	0.59 ± 0.05*	4.85 ± 0.4*
Spiral arteries (n=35)	0.55± 0.04**	0.3 ± 0.02**	1.38 ± 0.05**
Women with EGE			
Uterine arteries (n=48)	2.2± 0.08▪	0.75 ± 0.05▪	6.11 ± 0.6▪
Spiral arteries (n=38)	0.66 ± 0.02▪▪	0.47 ± 0.05	1.71 ± 0.08▪▪

*$p<0.05$ when comparing the studied indices in uterine arteries of women with uterine fibroids and women from the control group,

** $p<0.05$ when comparing the studied indices in spiral arteries of women with uterine fibroids and women from the control group,

▪ $p<0.05$ when comparing the studied indices in uterine arteries of women with EGE and women with uterine fibroids

▪▪ $p<0.05$ when comparing the studied indices in spiral arteries of women with EGE and women with uterine fibroids

The IVF(IVF+ICSI) program resulted in clinically verified pregnancy in 52 women out of 131: in 21 women (53.8%) from the control group, in 15 women with uterine fibroids (34%), in 16 women with EGE (33.3%).

Comparative analysis between the identified indices of uterine artery blood flow and the results of the IVF program made it possible to clarify the nature of these indices' conjugation in women with uterine fibroids, in women with EGE and from the control group (Table 43).

Table 43

Features of the IVF (IVF+ICSI) program outcomes in women with uterine fibroids, with EGE and from the control group depending on the value of Doppler indices in uterine and in spiral arteries on the 2-3 day of m.c. at the start of the IVF (IVF+ICSI) program

	PI		RI		SDR	
Control group						
	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
Uterine arteries	2.91 ± 0.08	2.84± 0.08	0.85±0.02	0.89 ± 0.05	7.7 ± 0.5	8.1 ± 0.6
Spiral arteries	0.84±0.01	0.82±0.03	0.59±0.02	0.60±0.03	2.3 ± 0.15	2.5 ± 0.3
Women with uterine fibroids						
	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
Uterine arteries	1.68±0.3	1.71±0.09	0.7±0.03	0.72±0.07	5.19±0.3	5.3±0.4
Spiral arteries	0.59±0.03	0.58± 0.08	0.39±0.03	0.42±0.07	1.3±0.05	1.24±0.1
Women with EGE						
	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
Uterine arteries	2.7±0.08	2.91±0.05	0.85±0.05	0.88±0.03	7.21 ± 0.2	7.66 ± 0.1
Spiral arteries	0.78±0.04	0.83±0.02	0.48±0.09	0.53±0.02	2.0 ± 0.2	2.2 ± 0.1

At the start of the IVF (IVF+ICSI) program, no significant differences between women with different program outcomes were found in any of the groups.

A similar comparative analysis was performed between the results of the IVF (IVF+ICSI) program and the value of blood flow resistance in uterine arteries on the day of ovulation trigger administration in women with uterine fibroids, with EGE and from the control group (Table 44).

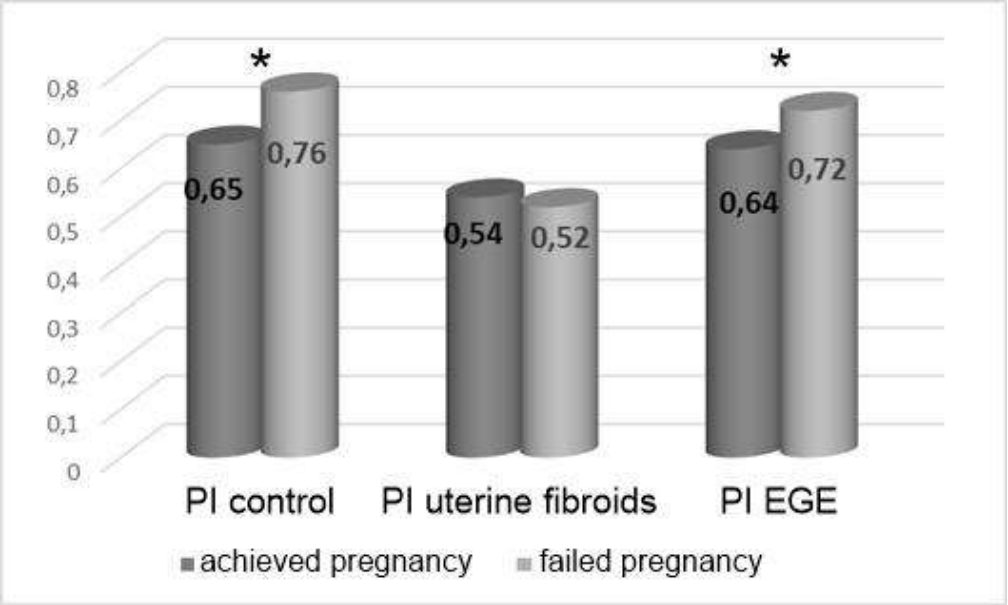
Table 44

Features of the IVF (IVF+ICSI) program outcomes in women with uterine fibroids, with EGE and from the control group depending on the value of Doppler indices in uterine arteries on the day of final oocyte maturation trigger administration within the IVF (IVF+ICSI) program

PI		RI		SDR	
Control group					
Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
2.1 ± 0.1	2.2± 0.1	0.84±0.02	0.83 ± 0.03	5.85 ± 0.1	6.1 ± 0.2
Women with uterine fibroids					
Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
1.5±0.04	1.52±0.09	0.61±0.03	0.52±0.06	4.9±0.3	4.7 ±0.3
Women with EGE					
Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
2.5±0.1	2.72±0.06	0.81±0.05	0.85±0.03	6.51 ± 0.7	6.8 ± 0.8

No significant differences in the studied indices in uterine arteries depending on the result of the IVF (IVF+ICSI) program were revealed in any of the examined groups.

Comparison of blood flow resistance indices in spiral arteries on the day of final oocyte maturation trigger administration revealed that pregnancy onset in women from the control group and in women with EGE occurs with lower PI indices as compared to women with failed IVF (IVF+ICSI) programs (Figure 7).



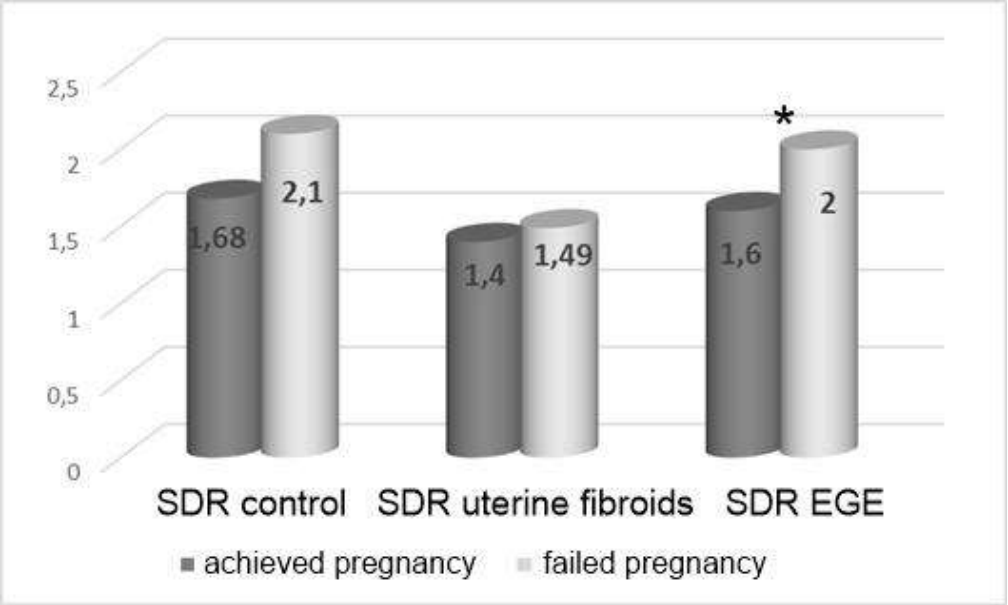
*p<0.02

Figure 7

PI values in spiral arteries on the day of final oocyte maturation trigger administration depending on the onset of pregnancy

Analysis of RI values did not reveal any significant differences.

In women with EGE, significant differences were also obtained in terms of SDR value (Figure 8).



*p<0.02

Figure 8

SDR value in spiral arteries on the day of final oocyte maturation trigger administration depending on the onset of pregnancy

In women with uterine fibroids, a similar comparative analysis of PI, RI and SDR in spiral arteries showed no significant differences depending on the IVF (IVF+ICSI) program outcomes. In women with uterine fibroids, on the day of the final oocyte maturation trigger, significantly lower values of all indicators were observed as compared to women from the control group and the group of women with EGE ($p<0.05$).

When constructing ROC curves using logistic regression methods for the studied blood flow resistance indices on the day of final oocyte maturation trigger administration, it was revealed that the control group had the highest value of the area under the curve – 0.73, which corresponds to high significance, in the group of women with EGE it comprised 0.59, whereas in women with uterine fibroids this indicator was 0.5, which determined the absence of significant dependence of the IVF (IVF+ICSI) program outcomes on blood flow resistance indices (Figure 9).

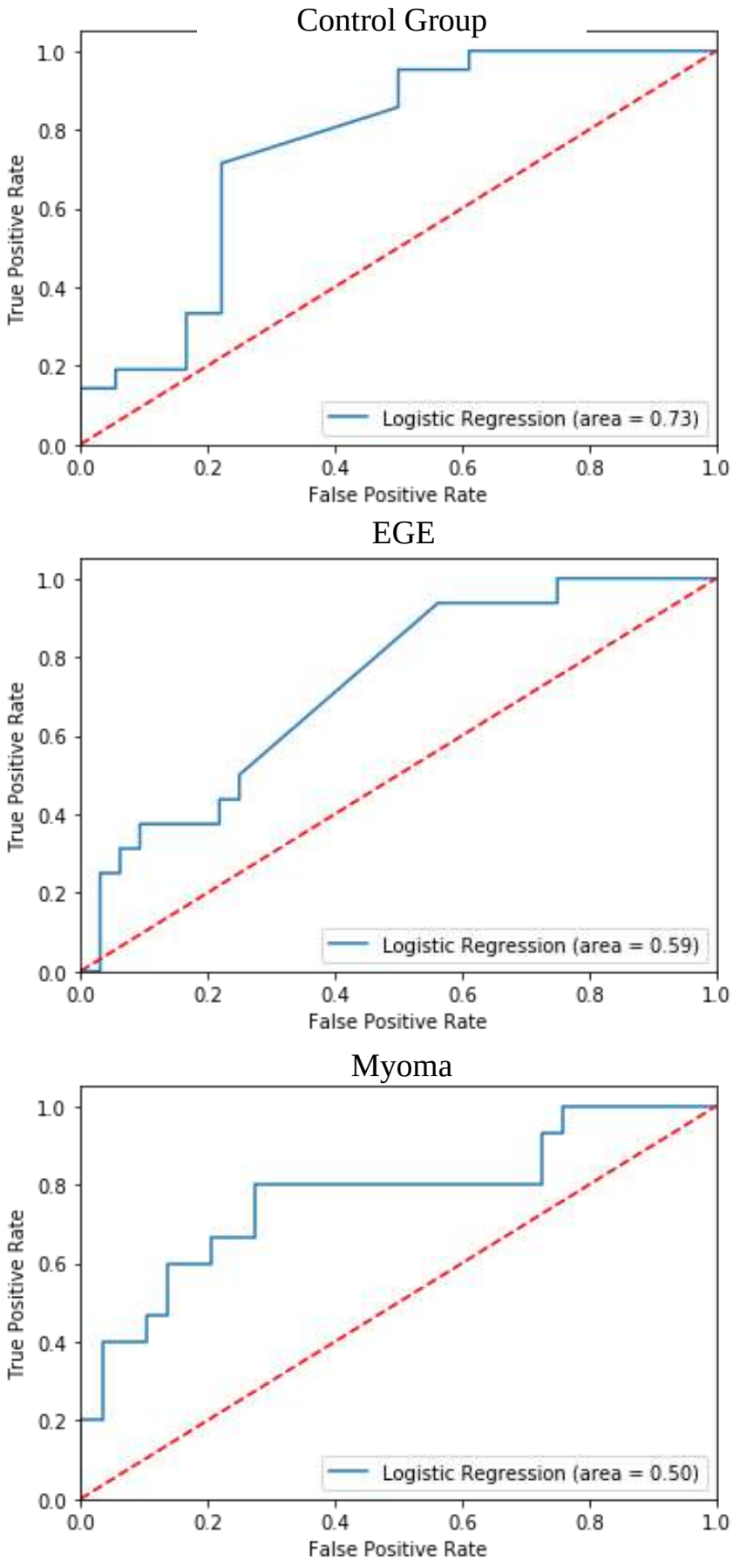


Figure 9

ROC curves to assess the dependence of the IVF (IVF+ICSI) program outcome on the Doppler velocimetry in spiral arteries on the day of final oocyte maturation trigger administration

A comparative analysis of blood flow resistance in uterine and spiral arteries on the day of embryo transfer depending on the outcome of the IVF (IVF+ICSI) program was performed. The results of the analysis of the indices in uterine arteries are provided in Table 45.

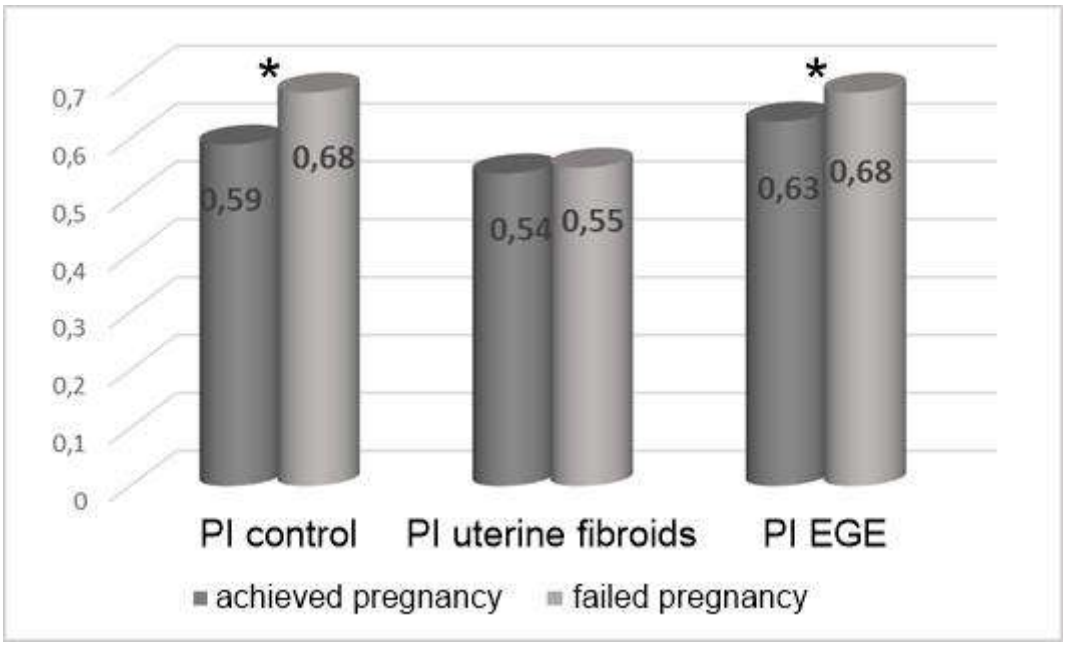
Table 45

Characteristics of the IVF (IVF+ICSI) program outcome in women with uterine fibroids, with EGE and from the control group depending on the value of Doppler velocimetry in uterine arteries on the day of embryo transfer within the IVF (IVF+ICSI) program

PI		RI		SDR	
Control group					
Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
1,9 ± 0,04	2,15± 0,1	0,79±0,05	0,82 ± 0,03	5,52 ± 0,3	5,61 ± 0,2
Women with uterine fibroids					
Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
1,51±0,04	1,5±0,09	0,59±0,03	0,59±0,05	4,88±0,4	4,75±0,3
Women with EGE					
Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
2,0±0,09	2,25±0,05	0,77±0,04	0,73±0,02	6,0 ± 0,2	6,3 ± 0,1

No significant differences in the studied indices in uterine arteries on the day of embryo transfer depending on the outcome of the IVF (IVF+ICSI) program were found.

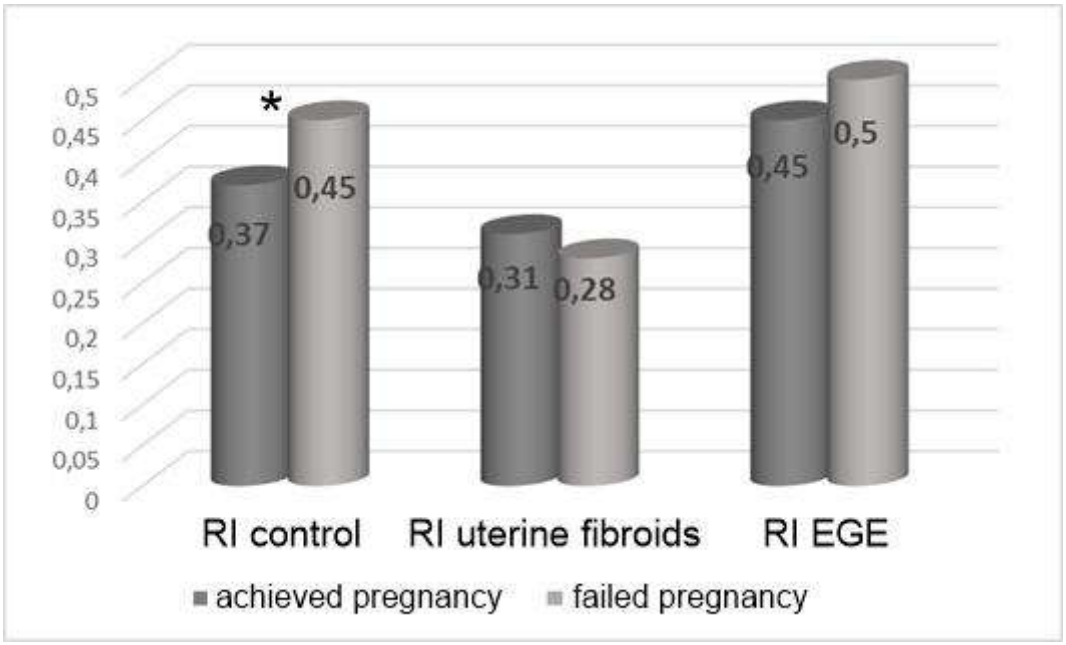
In women from the control group, reliable differences of all studied blood flow resistance indices in spiral arteries depending on the onset of pregnancy were revealed: in the case of successful completion of the IVF (IVF+ICSI) program, all indices were determined to be significantly lower as compared to women with an unsuccessful outcome of the program. Women with EGE had significantly lower PI and SDR at pregnancy onset (Figures 10, 11, 12).



*p<0.03

Figure 10

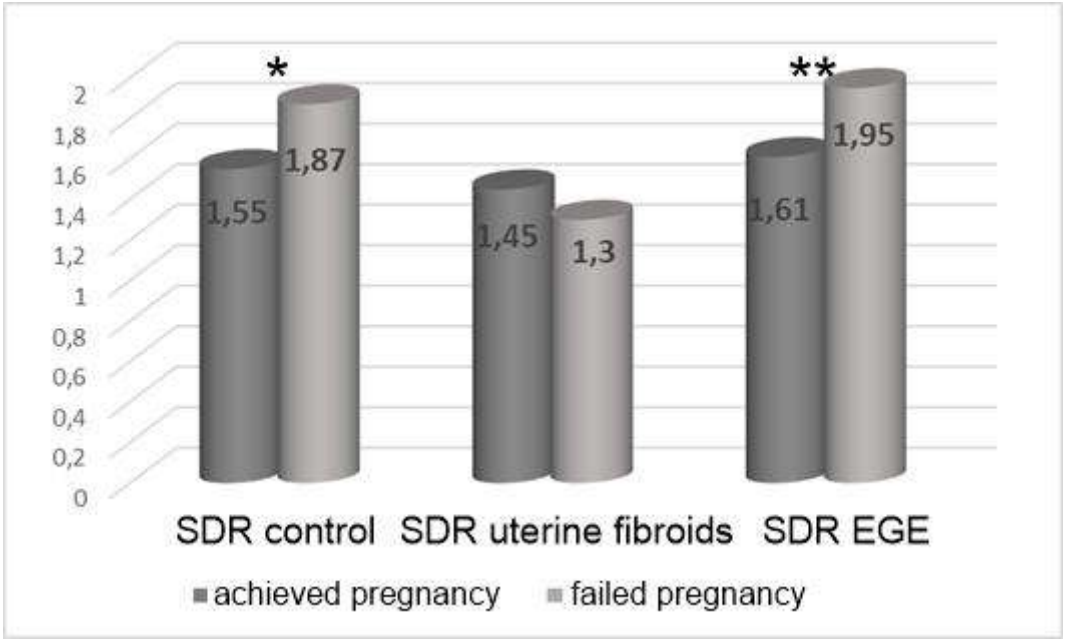
The value of PI in spiral arteries on the day of embryo transfer depending on the onset of pregnancy



*p<0.02

Figure 11

The value of RI in spiral arteries on the day of embryo transfer depending on the onset of pregnancy



*p<0.03
**p<0.005
Figure 12
The value of SDR in spiral arteries on the day of embryo transfer depending on the onset of pregnancy

In women with uterine fibroids, the indices of blood flow resistance (PI, RI, SDR) on the day of embryo transfer did not differ significantly either in uterine or spiral arteries at different outcomes of the IVF (IVF+ICSI) program.

ROC curves construction using logistic regression methods for the studied blood flow resistance indices on the day of embryo transfer revealed that in the control group and in the group of women with EGE, the area under the curve was 0.63 and 0.64, respectively, which indicates a high accuracy in predicting the outcome, whereas in uterine fibroids the area under the curve was 0.5 (Figure 13), which does not allow us to consider blood flow resistance indices as significant for predicting the onset of pregnancy.

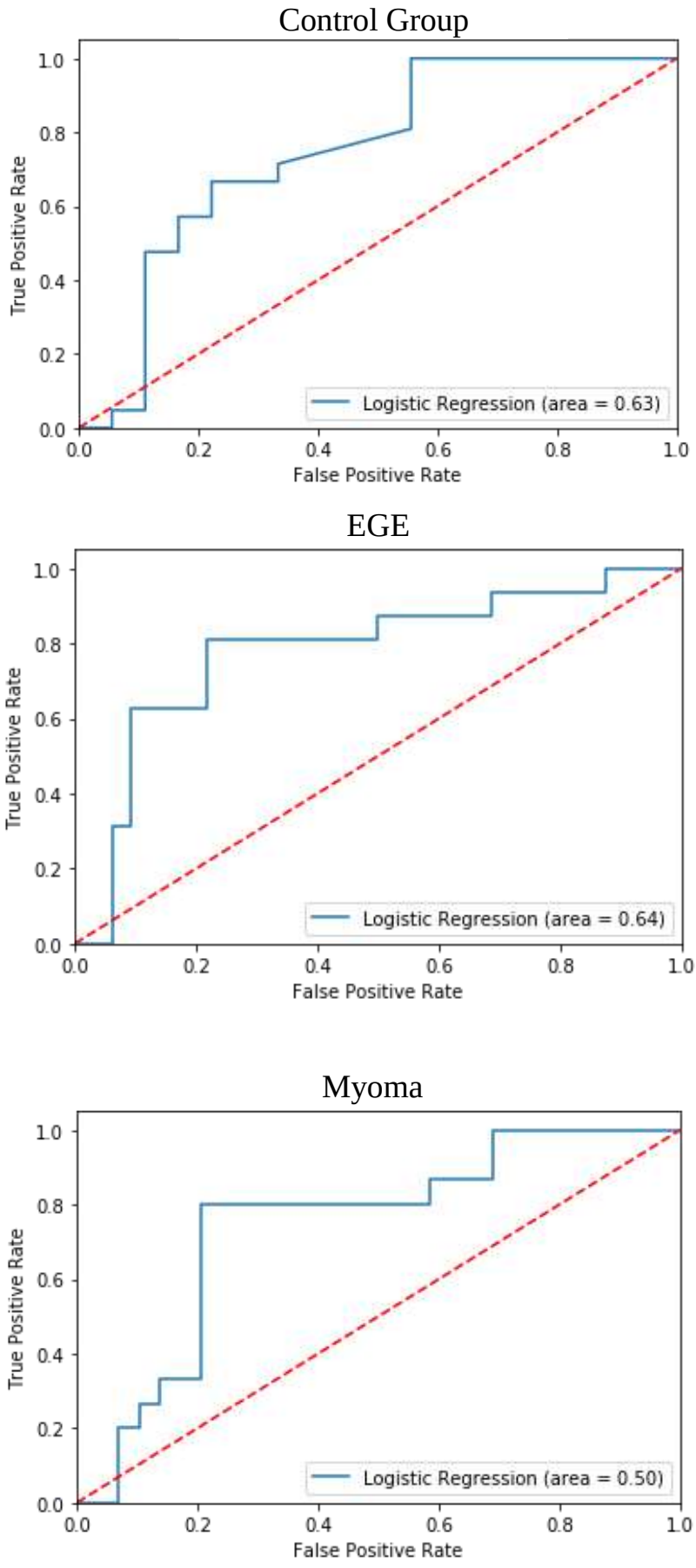


Figure 13

ROC curves for assessing the dependence of the IVF (IVF+ICSI) program outcome on Doppler velocimetry in spiral arteries on the day of final oocyte maturation trigger administration

Correlation analysis using the Spearman's rank correlation showed that in women from the control group, the incidence of clinical pregnancy had a moderate negative correlation with the blood flow resistance indices in spiral arteries on the day of ovulation trigger administration (for PI r=-0, 47, p=0.008, for SDR r=-0.36, p=0.049) and on the day of embryo transfer (for PI r=-0.4, p=0.022, for RI r=-0.44, p=0.01, for SDR r=-0.41, p=0.02). A similar significant correlation was also found between clinical pregnancy rate and PI, RI and SDR in women with EGE on the day of ovulation trigger administration (for PI r=-0.43, p=0.015, for SDR r=-0.46, p=0.009) and on the day of embryo transfer (for PI r=-0.36, p=0.02, for SDR r=-0.46, p=0.003). In women with uterine fibroids, no significant correlation between the clinical pregnancy rate and blood flow resistance indices in spiral arteries on the day of ovulation trigger administration was found.

A comparative evaluation of blood flow resistance indices in spiral arteries in the dynamics of the superovulation stimulation cycle within IVF (IVF+ICSI) programs in women with uterine fibroids, with EGE and from the control group was performed (Table 46).

Table 46

Results of Doppler velocimetry in spiral arteries in women with uterine fibroids, with EGE and in women from the control group in the dynamics of the IVF cycle (IVF+ICI) – on day 2-3 of the m.c. and on the day of final oocyte maturation trigger administration

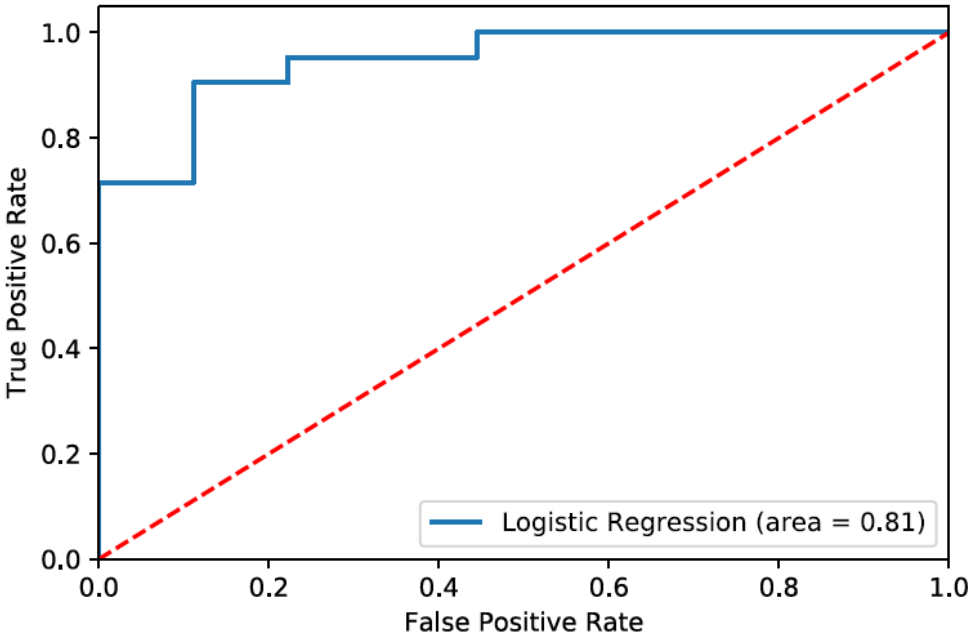
	PI		RI		SDR	
	m.c. day 2-3	ovulation trigger administration day	m.c. day 2-3	ovulation trigger administration day	m.c. day 2-3	ovulation trigger administration day
Control group	(n=15)	(n=30)	(n=15)	(n=30)	(n=15)	(n=30)
	0.83 ± 0.03	0.70±0.02*	0.59 ± 0.06	0.44±0.02*	2.4 ± 0.08	1.81±0.04
Women with uterine fibroids	(n=18)	(n=34)	(n=18)	(n=34)	(n=18)	(n=34)
	0.59± 0.07	0.53± 0.05	0.39 ± 0.05	0.34 ± 0.03	1.3 ± 0.06	1.45 ± 0.04
Women with EGE	(n=18)	(n=39)	(n=18)	(n=39)	(n=18)	(n=39)
	0.81 ± 0.04	0.68 ± 0.02*	0.57 ± 0.05	0.47 ± 0.03	2.3 ± 0.07	1.8 ± 0.07

* p<0.02 p<0.02 vs the corresponding indicators on day 2-3 of the m.c.

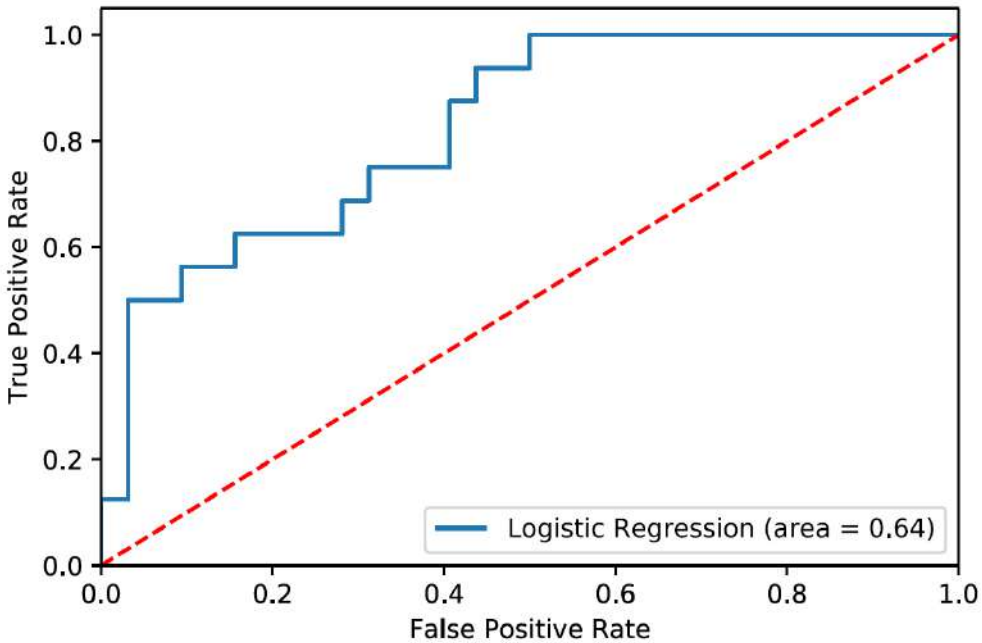
ROC curve construction using logistic regression methods revealed that Doppler indices had the highest predictive value in the control group: when all

indices are included in the analysis at all time points of Doppler velocimetry, the area under the curve comprises 0.81; in the group of women with EGE, the area under the curve is 0.64, which demonstrates moderate dependence, whereas in the group of women with uterine fibroids the area under the curve is 0.5 (Figure 14), which shows that there is no direct dependence of the program outcomes.

Control Group



EGE



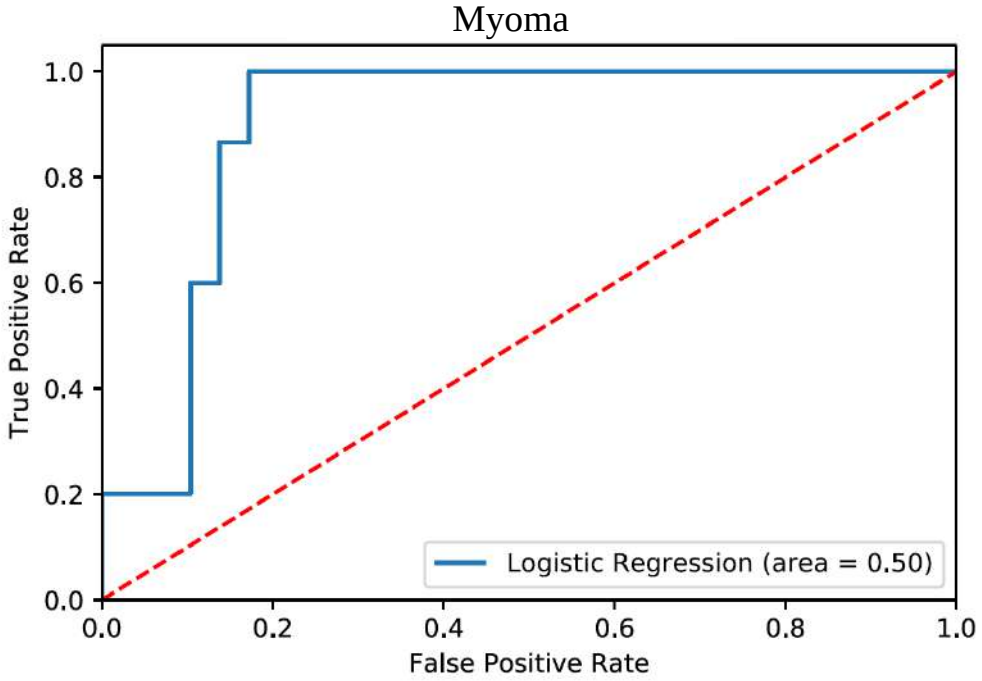


Figure 14

ROC curves for assessing the dependence of the IVF (IVF+ICSI) program outcome on Doppler velocimetry in uterine and spiral arteries throughout the cycle

Considering the high accuracy of prediction based on the ROC-curve, the threshold values of blood flow resistance in spiral arteries on the day of embryo transfer were defined for women from the comparison group: PI<0.61, RI <0.45, and SDR <1.9, which determine the probability of pregnancy.

Given the shown effect of diminished blood flow resistance in spiral arteries on the IVF (IVF+ICSI) program outcome, we analyzed the dependence of the program outcomes on the magnitude of diminished blood flow resistance in spiral arteries.

Control group women with pregnancy revealed significantly greater PI reduction in the dynamics of the IVF (IVF+ICSI) cycle as compared to women with negative results – both in the period up to the day of ovulation trigger administration and in the period up to the day of embryo transfer. In women with EGE, significant differences in PI reduction depending on the value of PI reduction were determined only when comparing the indicators at the start of the program and on the day of embryo transfer. In women with uterine fibroids, the value of PI reduction did not differ depending on the onset of pregnancy, and the value of the reduction was

significantly different from that of women from the control group (Table 47, Figures 15, 16).

Table 47

Characteristics of IVF (IVF+ICSI) program outcomes in women with uterine fibroids, with EGE and from the control group depending on the value of PI reduction in spiral arteries in the dynamics of the IVF (IVF+ICSI) program (Tukey test was used)

PI difference on day 2-3 of m.c. and on the day of final oocyte maturation trigger administration		p	PI difference on day 2-3 of m.c. and on the day of embryo transfer		p
Achieved pregnancy	Failed pregnancy		Achieved pregnancy	Failed pregnancy	
Control group					
0.18±0.02	-0.05±0.01	0.01	0.25±0.01	0.02±0.02	0.03
Women with uterine fibroids					
0.09±0.03	0.05±0.01	0.98	0.09±0.03	0.03±0.02	0.9
Women with EGE					
0.11±0.02	0.12±0.007	0.99	0.20±0.02	0.05±0.01	0.04

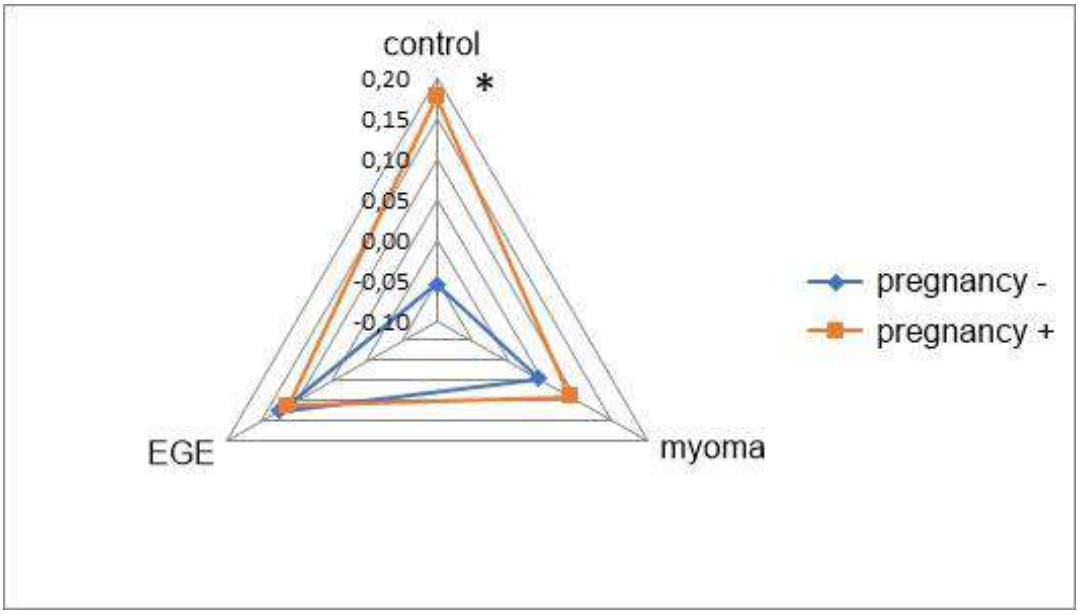


Figure 15

Characteristics of IVF (IVF+ICSI) program outcome depending on the value of PI reduction from day 2-3 of m.c. to the day of final oocyte maturation trigger administration in women with uterine fibroids, with EGE and from the control group

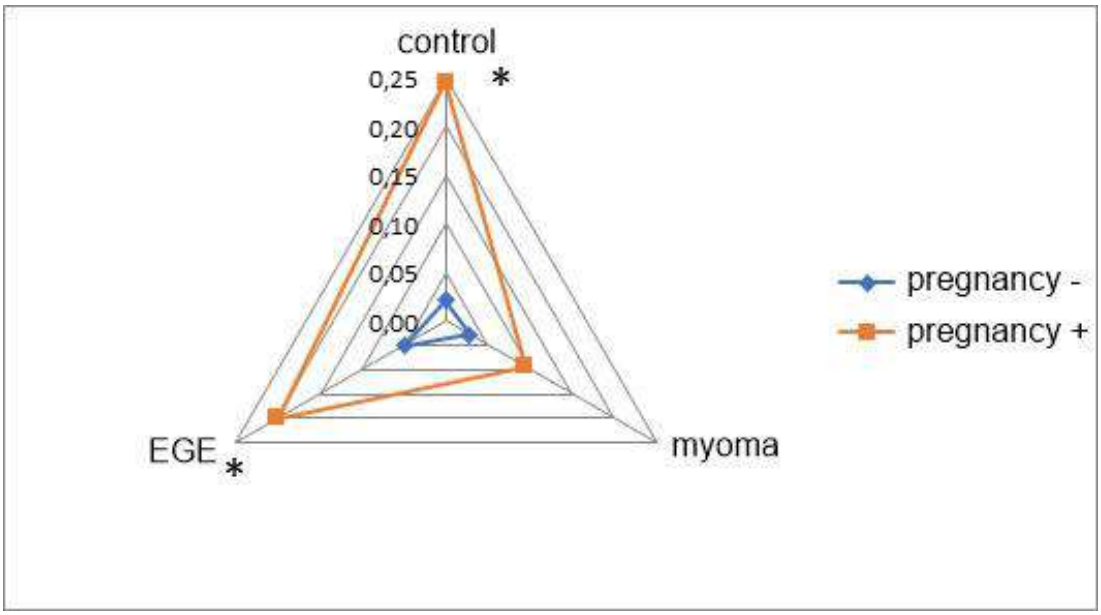


Figure 16

Characteristics of IVF (IVF+ICSI) program outcome depending on the value of PI reduction from day 2-3 of m.c. to the day of embryo transfer in women with uterine fibroids, with EGE and from the control group

The graphs (Figures 17, 18, 19) show the curves of changes in PI, RI and SDR in spiral arteries at the measurement points (1 – on the day of program start, 2 – on the day of ovulation trigger administration, 3 – on the day of embryo transfer) at different outcomes of IVF (IVF+ICSI) programs. The graphs clearly illustrate that in women from the control group and with EGE, pregnancy is achieved at higher values of the curve slope.

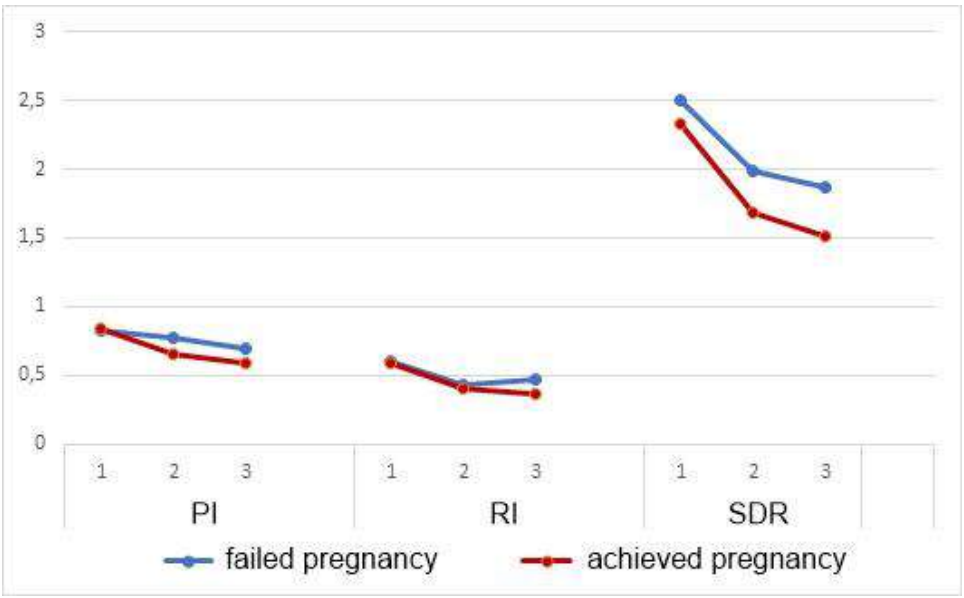


Figure 17

PI, RI, SDR curves during IVF (IVF+ICSI) programs in women with uterine fibroids depending on the onset of pregnancy

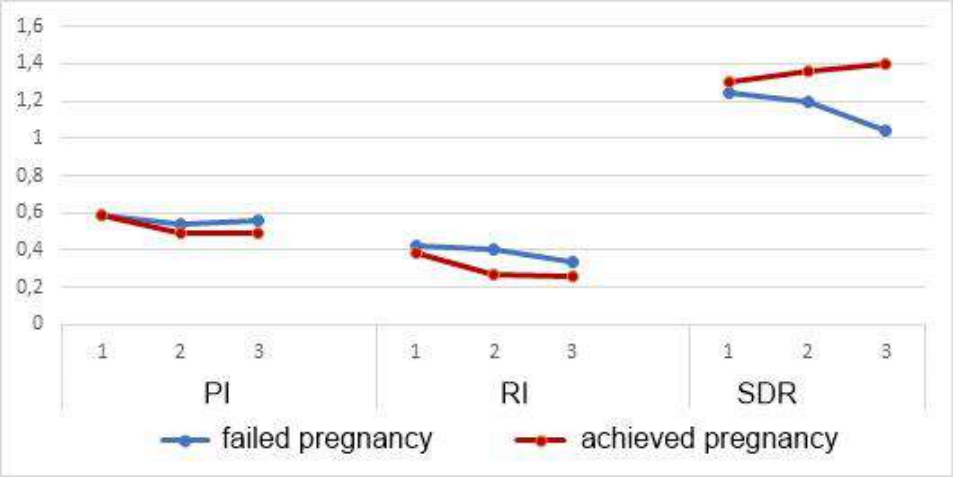


Figure 18

PI, RI, SDR curves during IVF (IVF+ICSI) programs in women with uterine fibroids depending on the onset of pregnancy

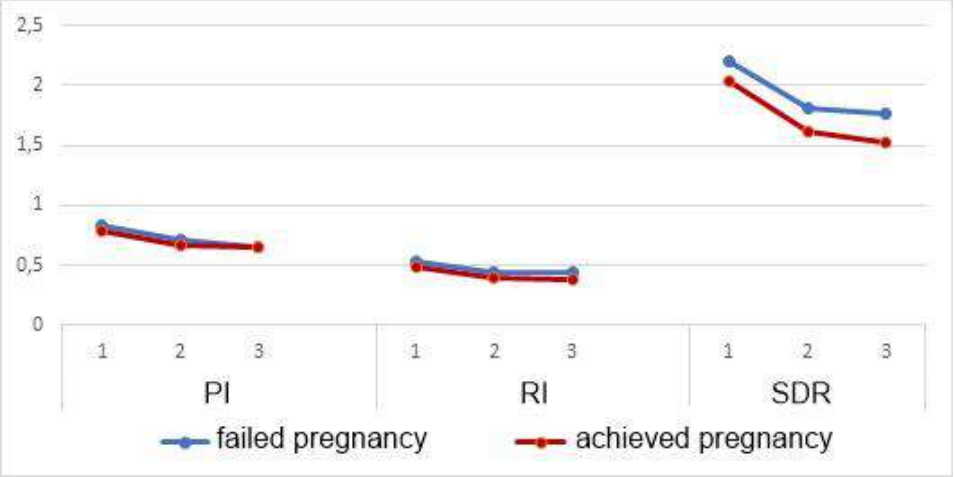


Figure 19

PI, RI, SDR curves during IVF (IVF+ICSI) programs in women with EGE depending on the onset of pregnancy

Using the logistic regression method, a significant value of RI reduction for pregnancy was found (p=0.037), with the ROC curve having a sensitivity of 56.5 with a specificity of 66.67 (Figure 20).

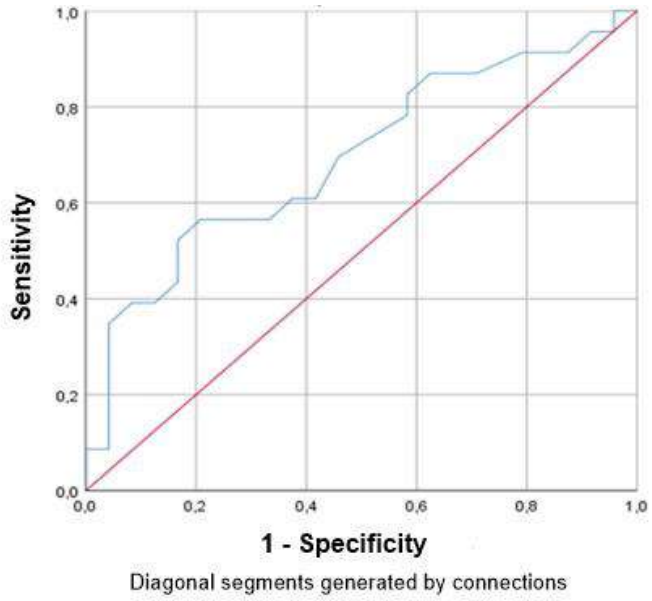


Figure 20

ROC curve for assessing the dependence of the IVF (IVF+ICSI) program outcome on the magnitude of RI reduction in the spiral arteries

To assess the significance of the value of RI reduction for pregnancy, we calculated the slope ratio, which represents the slope of the RI curve in dynamics for each woman, as follows:

$$\text{RIs} = \frac{\text{RI on the day of embryo transfer} - \text{RI on day } 2 - 3}{2}$$

Based on the calculated slope ration, the following formula for determining the probability of pregnancy (P) was derived, with a prediction acceptance value of 0.5:

$P = 1/(1 + e^{-z})$, where Z = -1.074-16.019*RIs

It was proved that the value of RIs was significantly higher in the case of pregnancy than in the case of failure (-0.075±0.047 and 0.05±0.04 respectively, p=0.022).

The borderline value of RIs was defined as -0.065. For example, when RIs=-0.68, z=0.015 and P=0.504, which shows the significance and reliability of decreasing blood flow resistance values for the onset of pregnancy.

Table 48 shows the values of the slope ration depending on the onset of pregnancy in the studied groups.

Table 48

Slope ratio depending on pregnancy onset in IVF (IVF+ICSI) programs in the control group and in women with uterine fibroids and EGE

	PI		RI		SDR	
Control group						
	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
Slope value (M±sd)	-0.12±0.026	-0.06±0.013	-0.11±0.034	-0.07±0.06	-0.41±0.214	-0.33±0.251
p	0.003		0.082		0.384	
Women with uterine fibroids						
	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
Slope value	-0.47±0.05	-0.01±0.04	-0.06±0.05	-0.04±0.03	-0.48±0.08	-0.1±0.08
p	0.02		0.18		0.06	
Women with EGE						
	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy	Achieved pregnancy	Failed pregnancy
Slope value	-0.067±0.02	-0.09±0.02	-0.52±0.04	-0.04±0.02	-0.26±0.07	-0.22±0.1
p	0.14		0.79		0.54	

The data above show that pregnancy rate in women from the control group is significantly affected by the value of PI reduction in spiral arteries during the IVF (IVF+ICSI) program, whereas in women with uterine fibroids significant PI reduction is not determined and is not associated with the pregnancy rate (Figures 10, 11, 12).

Thus, it is shown that in women from the control group, the highest pregnancy rate is associated with significantly lower indices of blood flow resistance indices in spiral arteries during the peri-implantation period. At the same time, a greater value of PI reduction in spiral arteries is determined in women with pregnancy. No significant differences in blood flow resistance in uterine arteries depending on the outcome of the IVF (IVF+ICSI) program were revealed. In women with uterine fibroids, no significant decrease in any of the indices of blood flow resistance in spiral arteries (PI, RI, SDR) during the cycle of superovulation stimulation was revealed. In women with EGE, the dynamics of blood flow indices in spiral arteries is similar to the dynamics of similar indices in women from the control group, and the pregnancy rate correlates with a decrease in resistance indices in spiral arteries.

It was revealed that in uterine fibroids, there is a stable decrease of blood flow resistance in uterine and spiral arteries, which can characterize an increased

endometrial vascularization during the stimulation cycle in IVF and ICSI programs and negatively affect the possibility of blastocyst implantation.

3.4. Morphological and Immunohistochemical Assessment of the Endometrium in Women with Uterine Fibroids and/or Genital Endometriosis, Who Entered IVF (IVF+ICSI) programs

A comparative analysis of clinical and anamnestic data, the results of morphological and immunohistochemical examination of the endometrium in addition to the outcome of the IVF (IVF+ICSI) protocol was performed in 232 women with uterine fibroids and/or genital endometriosis planning infertility treatment by ART methods in order to identify factors of the predicted efficiency of the IVF (IVF+ICSI) program.

Indications for endometrial biopsy for morphological and immunohistochemical study were taken into account in accordance with the Decree of the Ministry of Health of the Russian Federation No. 107n dated August 30, 2012 “On the Procedure for the Use of Assisted Reproductive Technologies, Contraindications and Restrictions to their Use”. If signs of endometrial hyperplasia were detected, hormone therapy was prescribed, an ART program was planned after the completion of treatment and biological material obtained from these women (n=8) was accordingly excluded from further study. Complex analysis of the endometrium was performed on samples obtained from 224 women.

Uterine fibroids occurred in 113 women (51.8%). Genital endometriosis was detected in 157 women (72.0%), including external genital endometriosis in 128 women and adenomyosis in 29 women. The combination of uterine myoma and genital endometriosis was found in 46 (21.1%) women. All women with adenomyosis had a combination with uterine fibroids. As a comparison group, 85 women entering IVF (IVF+ICSI) programs, in whom a targeted ultrasound and endoscopic examination made it possible to exclude the presence of uterine myoma and genital endometriosis, were included in the study.

Clinical and anamnestic characteristics of women with uterine fibroids and/or genital endometriosis who underwent histology and immunohistochemistry of the endometrium prior to the IVF (IVF+ICSI) program

According to the results of comparative analysis of reproductive function with respect to the indicators characterizing parity and peculiarities of menstrual function, there were no significant differences between the examined women in all clinical groups (Table 49).

Table 49

Comparative characteristics of obstetric and gynecologic history of women with uterine fibroids and/or genital endometriosis and women from the comparison group, entering IVF (IVF+ICSI) programs

	Comparison group	Women with uterine fibroids	Women with EGE	Women with a combination of uterine fibroids and GE	p, KW (Kruskall-Wallis)
	n=85	n=67	n=111	n=46	
Regular m.c., %	84	93	92	81	>0.05
Abnormal uterine bleeding, %,	16	7	8	19	>0.05
Infertility duration, years	5.78±0.75	8.11±0.91	8.23±0.59	6.65±0.43	>0.05
Primary infertility, %	55	40	63	59	>0.05
Secondary infertility, %	45	60	37	41%	>0.05
Induced abortion history, %	17.6	16.4	9.9	13.0	>0.05
Delivery, % of women	1.2	4.5	4.4	2.3	>0.05
Premature delivery, % of women	1.2	1.5	3.3	0.9	>0.05
Undeveloped pregnancy, %	3.4	6.7	7.8	4.14	>0.05
Spontaneous abortion, %	10.2	8.0	12.2	8.2	>0.05
Ectopic pregnancy, %	17.85	8.0	20.0	6.9	>0.05
Chronic endometritis, %	24.7	41.8	38.7	43.5	p_{1-2} <0.05

More than 80% of women in the comparison groups had regular menstrual cycles. Abnormal uterine bleeding in the comparison group amounted to 16%, in the other groups – from 7 to 19%. It should be noted that among all examined women with comparable rates of primary and secondary infertility, there was a rather high rate of reproductive losses due to ectopic pregnancies, spontaneous abortions and undeveloped pregnancies. Chronic endometritis was significantly more frequent in women with uterine fibroids (41.8%) as compared to women in the comparison group (24.7%), $p<0.05$.

The mean age in all groups was comparable, as was the frequency of representation of women in the age categories under 35 years and 35 years and older (Table 50).

Table 50

Comparative age characteristics of women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs

	Comparison group	Women with uterine fibroids	Women with EGE	Women with a combination of uterine fibroids and GE	p, KW (Kruskall-Wallis)
	n=85	n=67	n=111	n=46	
Mean age (M±m)	32.5±0.64	32.9±0.51	33.1±0.47	33.05±0.38	>0.05
Women younger than 35 y.o., %	72.9	61.2	66.7	64.3	>0.05
Women of 35 y.o., %	27.1	38.8	33.3	35.7	>0.05

The analysis of anamnesis data allows us to note that among all the examined women, 92 women received hormone therapy before the IVF program; 62 (67.4%) of them received GnRH agonists, 9 (9.8%) received combined hormonal contraceptives, and 21 women (22.8%) received gestagens. The indications for hormone therapy were external genital endometriosis and abnormal uterine bleeding. The period of hormone therapy ranged from 1 to 6 months. In the present study, control endometrial biopsy was performed between 3 and 18 months after completion of hormone therapy.

Results of morphological examination of the endometrium in women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs

The target characteristics of the transformation of the endometrium, according to the conditions set for endometrial biopsy in the spontaneous ovulatory menstrual cycle and in response to progesterone administration, were to correspond to the middle stage of the secretion phase. The highest occurrence of the middle stage of the secretion phase was found among women with uterine fibroids (70.1%), which was significantly more frequent than in women with genital endometriosis (p=0.048) (Table 51).

Table 51

Characteristics of the state of the endometrium in women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs (Fisher's exact test was used)

	Women with uterine fibroids	Women with EGE	Women with a combination of uterine fibroids and GE	p
	n=67	n=111	n=46	
Middle stage of the secretion phase, %	**70.1**	**55.0**	**47.8**	***0.048***
Early stage of the secretion phase, %	10.4	24.3	30.4	*0.178*
Late stage of the secretion phase, %	6.0	8.1	2.2	0.30
Lag in the development of the endometrial stroma, %	11.9	10.8	17.4	*0.67*

The dependence of the functional state of the endometrium on the presence of chronic inflammation is known; therefore, a comparative analysis of the frequency and severity of various signs of chronic inflammatory response was performed (Table 52).

Table 52

Comparative analysis of signs of chronic inflammatory reaction according to the results of histological study of the endometrium in women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs (Fisher's exact test was used)

	Comparison group	Women with uterine fibroids	Women with EGE	Women with a combination of uterine fibroids and GE	p
	n=85	n=67	n=111	n=46	
Edema of the endometrial stroma, %	4.3	6.4	4.1	7.3	*0.8*
Basal endometrial hyperplasia, %	2.17	6.4	4.1	9.75	*0.275*
Hypoplastic endometrium, %	4.3	6.4	0	7.3	*0.24*
Mononuclear infiltration of the endometrial stroma, %	8.7	12.9	7.3	19.5	*0.29*

There were no significant differences in the rate of detection of signs of chronic inflammatory reaction between the studied groups.

Along with the morphologic study of endometrium, in 103 samples of endometrium obtained among all examined women, an immunohistochemical (IHC) study was performed: 24 women with uterine fibroids, 33 with external genital endometriosis, 21 with a combination of uterine myoma with genital endometriosis and 25 women from the comparison group.

The analysis included determination of estrogen and progesterone receptor expression indices in the glands and stroma of the endometrium and evaluation of

signs of chronic endometritis using expression indices of immunocompetent markers: cytotoxic T-lymphocytes (CD8+), B-lymphocytes (CD20+), NK-cells (CD56+) and plasmacytes (CD138+). The figures show microphotographs of immunohistochemical study of estrogen receptors in the tissue of the endometrium of the examined women (Figures 21, 22, 23).

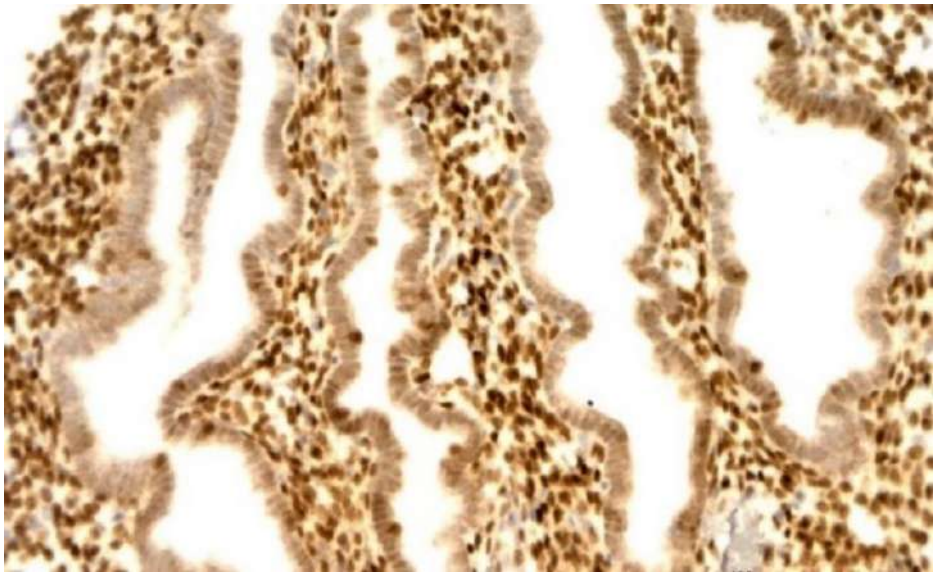


Figure 21
ER expression in endometrium, comparison group, IHC X 200

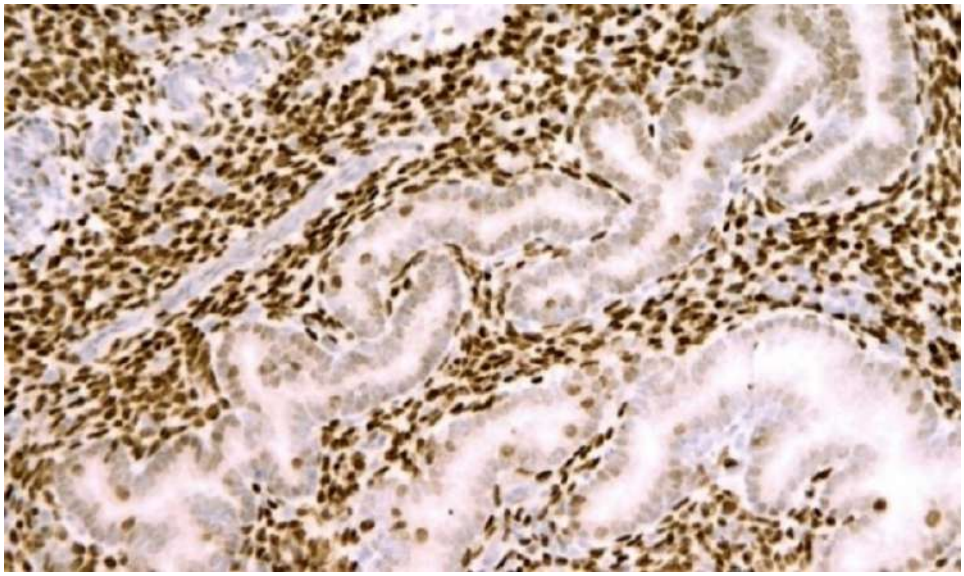


Figure 22
ER expression in the endometrium of a woman with uterine fibroids, IHC X 200

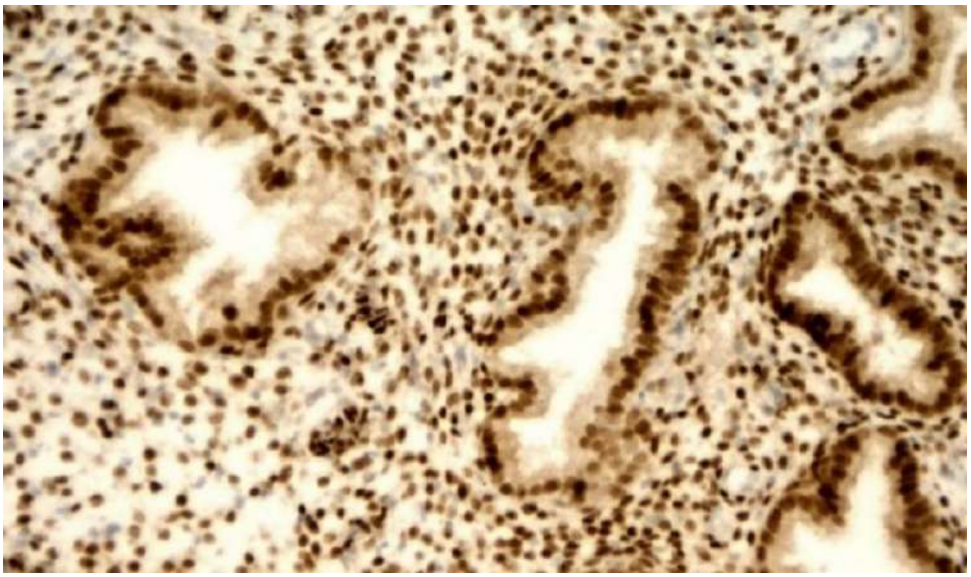


Figure 23
ER expression in the endometrium of a woman with EGE, IHC X 200

Fisher's exact test was used to analyze the results of the IHC study of endometrium. In the comparative intergroup analysis of the studied immunohistochemical parameters in the examined samples of the endometrium, significant differences were found only in the degree of estrogen receptor expression in the glands of the endometrium (Table 53).

Table 53
Comparative analysis of estrogen and progesterone receptor expression in the endometrium of women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs

	Comparison group n=25, M±m	Women with uterine fibroids n=24, M±m	Women with EGE n=33, M±m	Women with a combination of uterine fibroids and GE, n=21, M±m	p, KW (Kruskall-Wallis)
	1	2	3	4	
PR in the endometrial glands	142.8±13.4	126.9±13.7	127.3±11.7	113.1±16.6	0.619
PR in the endometrial stroma	158.9±7.5	168.8±4.7	150.5±6.8	137.2±11.6	0.275
ER in the endometrial glands	**151.7±10.5**	**94.4±8.0**	**110.5±9.8**	**147.8±14.3**	**0.006**
ER in the endometrial stroma	118.3±10.3	96.2±7.5	100.5±8.0	106.1±14.1	0.540

The lowest indicators of estrogen receptor expression in the glands of the endometrium were observed in women with uterine fibroids and genital endometriosis (94.4±39.4 and 110.5±56.1, respectively) as compared to the same

indicator in women from the comparison group (151.7±10.5), p=0.006. At the same time, the expression indices of estrogen receptors in the stroma of the endometrium, progesterone receptors in the glands and in the stroma of the endometrium in women in all clinical groups were comparable.

To assess the nature of the immune status of endometrium in women with uterine fibroids and/or genital endometriosis, the expression indices of proinflammatory markers were analyzed. The figures show microphotographs of immunohistochemical determination of proinflammatory markers' expression in the endometrial tissue of the examined women (Figures 24, 25, 26, 27).

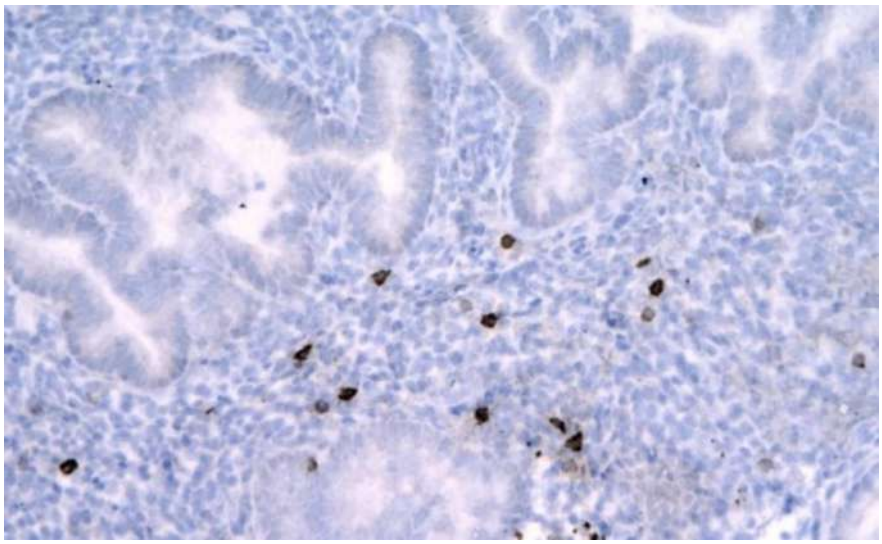


Figure 24

Expression of CD138+ plasmacytes in the endometrium of a woman with uterine fibroids, IHC X 200

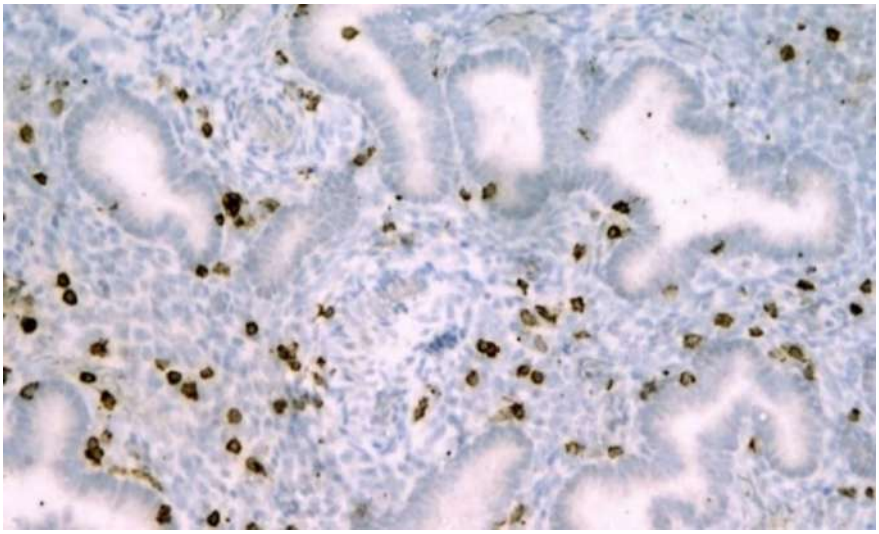


Figure 25

Expression of CD20+ B-lymphocytes in the endometrium of a woman with uterine fibroids, IHC X 200

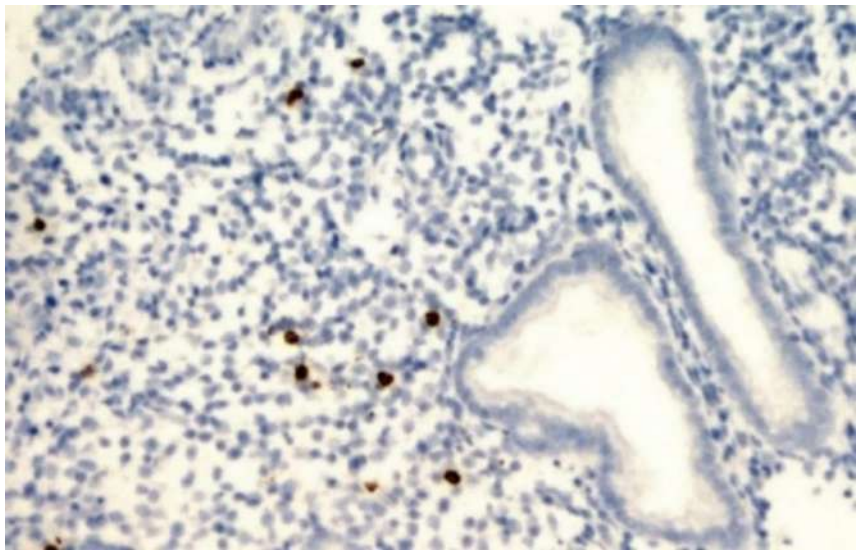


Figure 26
Expression of CD138+ plasmacytes in the endometrium of a woman with EGE, IHC X 200

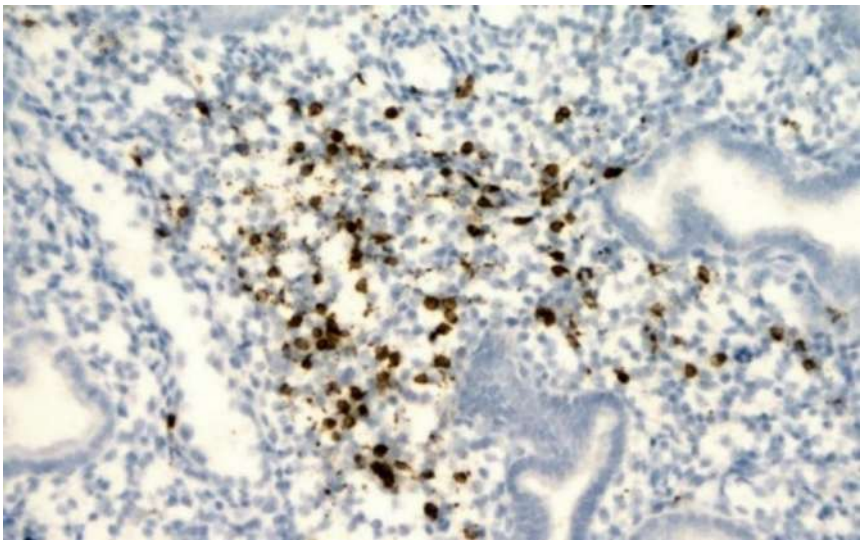


Figure 27
Expression of CD20+ B-lymphocytes in the endometrium of a woman with EGE, IHC X 200

Significant differences between women in the studied clinical groups were not revealed (Table 54).

Table 54
Comparative analysis of indices of expression of immunocompetent markers of the state of the endometrium in women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs

	Comparison group n=25 M±m	Women with uterine fibroids n=24 M±m	Women with EGE n=33 M±m	Women with a combination of uterine fibroids and GE n=21 M±m	p, KW (Kruskall-Wallis)
	1	2	3	4	
CD138+	7.3±6.0	2.3±1.0	1.9±0.5	1.8±0.4	0.465
CD20+	7.1±2.6	4.8±1.2	6.6±1.2	11.5±2.7	0.053

CD56+	9.9±7.0	3.8±0.4	2.5±0.4	2.1±0.4	0.147
CD8+	13.3±1.6	11.3±1.2	12.3±1.4	14.2±1.5	0.604

The absence of intergroup differences was confirmed when analyzing multiple comparisons of the studied indices.

According to the results of a complex morphological and immunohistochemical study of endometrium among all women in the compared clinical groups, signs of chronic endometritis prior to the IVF (IVF+ICSI) program were detected in 38 women (46.3%), including mild inflammation in 18 (47.3%), moderate inflammation in 17 (44.7%), and pronounced inflammation in 3 women (7.9%) (Tolibova G.H., 2017). According to the frequency of detection and severity of signs of chronic inflammatory response, the clinical groups under consideration were comparable (p>0.05) (Table 55).

Table 55

Comparative analysis of the incidence of chronic endometritis in women with uterine fibroids and/or genital endometriosis entering IVF (IVF+ICSI) programs (Fisher's exact test was used)

	Comparison group n=25	Women with uterine fibroids n=24	Women with GE n=78	Women with a combination of uterine fibroids and GE n=19	p
	1	2	3	4	
Chronic endometritis, %	36.0	41.7	39.7	57.9	*0.34*
Mild, %	66.7	40.0	41.9	45.5	*0.34*
Moderate, %	22.2	60.0	45.2	54.5	*0.55*
Severe, %	11.1	0	12.9	0	*0.68*

IVF+ICSI resulted in pregnancy in 33.5% of women with uterine fibroids and/or genital endometriosis, and in 37.6% of women without uterine fibroids and genital endometriosis (comparison group) (p=0.077).

To determine the factors associated with the outcome of the IVF (IVF+ICSI) program in women with uterine fibroids, with external genital endometriosis and with a combination of uterine myoma and genital endometriosis, a comparative analysis of the morphological characteristics of the endometrium depending on the outcome of the IVF (IVF+ICSI) program was performed. It was found that the achievement of clinical pregnancy was significantly more frequent in case the

morphologic picture of the endometrium corresponded to the peri-implantation period (p=0.031), in case of insufficient secretory transformation of the endometrium for the indicated period the frequency of clinical pregnancy was significantly lower (p=0.02) (Table 56).

Table 56

Comparative evaluation of IVF (IVF+ICSI) program efficiency in women with uterine fibroids and/or genital endometriosis considering the indicators of morphological state of the endometrium prior to the protocol

	Achieved pregnancy (n=75)	Failed pregnancy (n=149)
Middle stage of the secretion phase	**56.0% (42/75)**	**40.9% (61/149)**
Early stage of the secretion phase	**17.3% (13/75)**	**43.2% (64/149)**
Late stage of the secretion phase	9.3% (7/75)	8.0% (6/149)
Underdevelopment of the endometrial stroma	17.3% (13/75)	12.1% (18/149)

The middle stage of the secretion phase was significantly more frequently identified in women with a successful IVF (IVF+ICSI) program (42 of 75) compared to women with failed pregnancy (61 of 149), OR 1.84 (CI 1.05; 3.22), χ^2=4.56 (p<0.05). Early secretion phase was significantly more frequently detected in women with IVF (IVF+ICSI) program failure (64 of 149) as compared to women with pregnancy (13 of 75), OR 3.59 (CI 1.82; 7.09), χ^2=14.52 (p<0.05).

To assess the role of receptor expression indices of sex steroids in predicting the incidence of clinical pregnancy, we analyzed their expression indices depending on the outcome of the IVF program (IVF+ICSI) – no significant differences were found in the comparison between the groups with an achieved pregnancy and those with an unsuccessful outcome (Table 57).

Table 57

Comparative evaluation of IVF (IVF+ICSI) program efficiency in women with uterine fibroids and/or genital endometriosis considering estrogen and progesterone receptor expression in the endometrium prior to the protocol

	Achieved pregnancy (n=26), M±m	Failed pregnancy (n=52), M±m	p
PR in the endometrial glands	114.8±6.1	104.0±4.4	0.263
PR in the endometrial stroma	129.9±6.6	132.0±4.4	0.833
ER in the endometrial glands	151.1±4.3	152.3±3.6	0.878
ER in the endometrial stroma	130.6±6.9	121.1±5.9	0.435

According to the data of the analysis of the state of the endometrium prior to the IVF (IVF+ICSI) program, in women with uterine fibroids and/or genital endometriosis with confirmed clinical pregnancy, the rate of chronic inflammatory response was 41.8%, which is comparable to the same rate among women with IVF (IVF+ICSI) failure – 43.2% (p>0.05) (Table 58).

Table 58

Comparative evaluation of the IVF (IVF+ICSI) program in women with uterine fibroids and/or genital endometriosis considering the incidence of chronic endometritis prior to the protocol

	Achieved pregnancy (n=26)	Failed pregnancy (n=52)	p
Chronic endometritis, %	41.8	43.2	0.94
Mild, %	47.8	33.3	0.086
Moderate, %	30.4	44.4	0.15
Severe, %	8.7	5.56	0.89

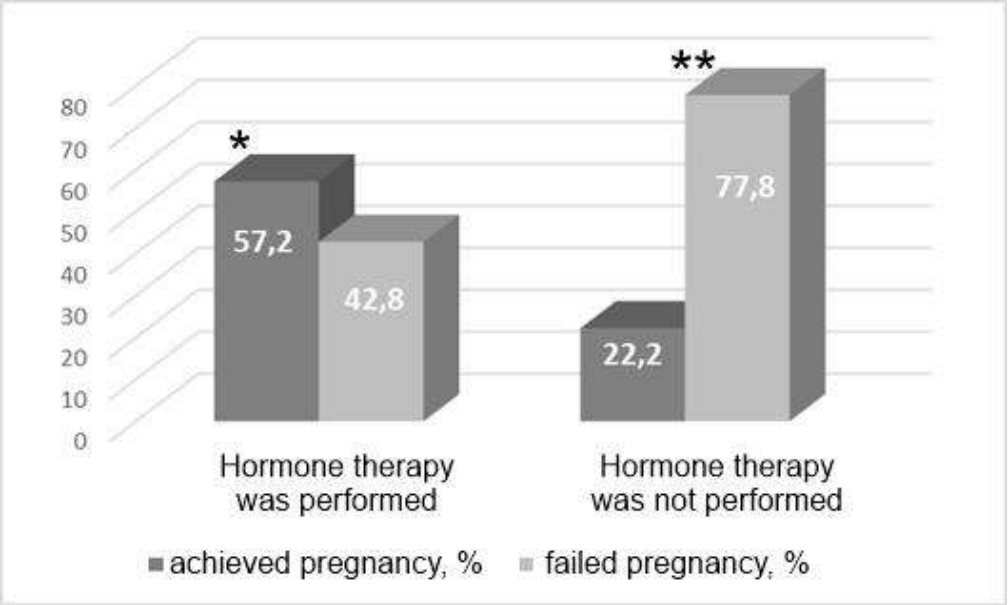
Analysis of the results of the expression of immunocompetent markers in the endometrium of women with failed IVF (IVF+ICSI) protocol showed higher expression of pro-inflammatory markers CD8+ and CD20+ as compared to women with clinical pregnancy (p<0.05) (Table 59).

Table 59

Comparative evaluation of the IVF program efficiency (IVF+ICSI) in women with uterine fibroids and/or genital endometriosis considering the expression of immunocompetent markers prior to the protocol

	Achieved pregnancy (n=26), M±m	Failed pregnancy (n=52), M±m	p, KW (Kruskall-Wallis)
CD8+	**13.2±0.9**	**17.9±1.1**	**0.027**
CD20+	**6.2±1.0**	**12.1±1.2**	**0.007**
CD56+	6.9±3.2	3.6±0.3	0.344
CD138+	4.8±2.6	3.3±0.5	0.565

When considering the effect of hormone therapy prior to the IVF (IVF+ICSI) protocol on its efficiency, significant differences were found: in the absence of hormone treatment with GnRHa and/or gestagens, pregnancy rate among all examined women with uterine fibroids and/or genital endometriosis was almost three times lower as compared to the same indicator in women who received hormone treatment prior to the IVF (IVF+ICSI) protocol (p=0.00001) (Figure 28).



*p=0.01
** p=0.00001
Figure 28
Pregnancy rate in women with uterine fibroids and/or genital endometriosis considering hormone therapy prior to IVF (IVF+ICSI) protocols

Pregnancy rate in women with a history of hormone therapy (57.2%) was found to be significantly higher as compared to women who did not receive hormone therapy (22.2%) – OR 4.68 (CI 2.47; 8.9), χ^2=24.12 ($p<0.05$).

The dependence of ART program performance on the duration of the period from the end of hormone therapy to the beginning of the program was also revealed – with the value of more than 12 months the ART rate was determined to be significantly lower as compared to women who received hormone therapy during the year closest to the IVF (IVF+ICSI) program, OR 0.25 (0.12; 0.5), χ^2=15.86 ($p<0.05$) (Table 60).

Table 60
Comparative evaluation of the IVF (IVF+ICSI) program in women with uterine fibroids and/or genital endometriosis considering the time interval of hormone therapy prior to the protocol

Index	Pregnancy rate
Time period from hormone therapy completion to IVF (IVF+ICSI) initiation more than 12 months, n=59	27.1%
Time period from hormone therapy completion to IVF (IVF+ICSI) initiation less than 12 months, n=93	60.2%
p	<0.01

Analysis of the IVF (IVF+ICSI) program efficiency depending on the duration of the period from the hormone therapy completion to the IVF (IVF+ICSI) program initiation revealed that the differences in the pregnancy rate were found to be significant when the period did not exceed 12 months. When the period exceeded 12 months and ranged from 12 to 18 months, no significant differences in the pregnancy rate were found – 32.8% and 34.7%, respectively (p=0.12).

The analysis of the state of the endometrium in clinically comparable groups of women with uterine fibroids, genital endometriosis and with the combination of uterine myoma and genital endometriosis entering the IVF protocol (IVF+ICSI) allowed to determine a reliable dependence of the IVF (IVF+ICSI) program outcome on the achievement of adequate secretory transformation of the endometrium. In women with a detected middle stage of the secretion phase of the endometrium in the cycle preceding the IVF (IVF+ICSI) protocol, the rate of clinical pregnancy was 54.5%, while in women with insufficient secretory transformation of the endometrium – only 40.7% (p=0.031).

The conducted studies showed that in women with uterine fibroids, the rate of detection of the middle stage of the secretion phase prior to the IVF (IVF+ICSI) program is significantly higher than in women with genital endometriosis; however, the pregnancy rate in women with uterine fibroids and genital endometriosis has no significant differences (34.7% and 32.2%, respectively, p>0.05), but is unequivocally lower than in women from the comparison group.

Thus, a significant positive effect of suppressive hormone therapy prior to the IVF (IVF+ICSI) program on the incidence of pregnancy in women with uterine fibroids and/or genital endometriosis was established, and the dependence of the realization of the target clinical effect on the time period between the end of therapy and the IVF (IVF+ICSI) program was proved.

The negative impact of increased expression of proinflammatory markers CD8+ and CD20+ on pregnancy onset among all examined women with uterine fibroids and/or genital endometriosis who entered the IVF (IVF+ICSI) program was shown.

Comparative analysis of the state of the endometrium in women with EGE planning infertility treatment within IVF (IVF+ICSI) programs

A comparative analysis of the results of morphologic and immunohistochemical study of endometrium in 111 women with EGE was performed, including 67 women with stage 1-2 EGE and 44 women with stage 3-4 EGE.

The mean age of the women was 33.1±0.38 years, the majority (63%) had primary infertility, 4.4% of women had a history of childbirth, and 20% of women had miscarriage.

Hormone treatment with GnRHa or dienogest in anamnesis was performed on 60 women for 3-6 months, but it was completed in the period from 12 to 3 months prior to the IVF (IVF+ICSI) program and not later than 2 months prior to the endometrial biopsy. There were 51 women with EGE who did not previously receive hormone treatment.

According to the results of morphologic study of the endometrium in women with EGE not earlier than 2 months after hormone treatment completion, the correspondence of the structure of the endometrium to a given average secretory phase of the menstrual cycle was observed significantly more often than in women who did not receive hormone treatment (39.2% and 48.3%, respectively, $p<0.05$), while the lag in the development of the stromal component of the endometrium is twice less frequent ($p<0.05$). There is a tendency for a significant endometrial hyperplasia rate (Table 61).

Table 61

Comparative analysis of the histological structure of the endometrium in women with EGE depending on hormone treatment prior to the IVF (IVF+ICSI) program

	No hormone therapy for EGE, n=51	Hormone therapy for EGE, n=60	p, KW (Kruskall-Wallis)
	%	%	>0,05
Middle stage of the secretion phase, %	**39,2**	**48,3**	**<0,05**
Early stage of the secretion phase, %	3,9	8,3	>0,05
Late stage of the secretion phase, %	35,2	30,0	>0,05
Underdevelopment of the endometrial stroma, %	**23,5**	**11,7**	**<0,05**
Basal endometrial hyperplasia, %	5,9	5,0	>0,05

Endometrial hyperplasia without atypia, %	13,7	10,0	>0,05
Hypoplastic endometrium, %	2,0	3,3	>0,05
Stromal edema, %	5,9	6,7	>0,05
Mononuclear infiltration of the endometrial stroma, %	9,8	11,7	>0,05

The results of immunohistochemical study of the endometrium showed that women who received hormone therapy for EGE with AGT-PH and/or gestagens had higher progesterone receptor expression in the stroma and glands of the endometrium as compared to women with EGE who did not receive hormone therapy (Table 62).

Table 62

Comparative analysis of estrogen and progesterone receptor expression indices in the endometrium of women with EGE depending on the hormone treatment prior to the IVF (IVF+ICSI) program

Index	No hormone therapy for EGE, n=51	Hormone therapy for EGE, n=60	p
ER in endometrial glands, M±m	133.1±6.6	126.7±8.2	0.647
ER in endometrial stroma, M±m	107.5±7.4	109.5±7.2	0.685
PR in endometrial glands, M±m	**132.7±7.7**	**161.1±8.4**	**0.049**
PR in endometrial stroma, M±m	**148.8±6.6**	**166.234±4.6**	**0.047**

It was established that the revealed changes in the indicators of the state of the endometrium in the examined women with genital endometriosis have a significant relation to the IVF (IVF+ICSI) protocol efficiency, especially when applied to the hormone-dependent component.

Comparative analysis of the studied indicators of the expression of markers of immunocompetent cells in the endometrium of women with EGE showed no evidence of dependence on the hormone treatment prior to the IVF (IVF+ICSI) program (Table 63).

Table 63

Comparative analysis of indices of immune competent cells marker expression in the endometrium of women with EGE depending on hormone treatment prior to the IVF (IVF+ICSI) program

Index	No hormone therapy for EGE, n=51	Hormone therapy for EGE, n=60	p
CD8+, M±m	2.1±0.07	2.7±0.1	0.159
CD20+, M±m	8.6±1.8	9.6±1.2	0.623
CD56+, M±m	0.98±0.08	1.3±0.09	0.323
CD138+, M±m	1.5±0.2	0.96±0.08	0.092

Evaluation of the receptor status in women with EGE who did not receive hormone treatment prior to the IVF (IVF+ICSI) protocol, as compared to women in the comparison group, regardless of the severity of EGE, revealed a significant decrease in progesterone receptor expression in the stroma of the endometrium, most pronounced in women with EGE of III-IV severity (p=0.021). There was also a clear tendency for a decrease in progesterone receptor expression in the endometrial glands of women with stage I-II EGE (Table 64). At the same time, the level of estrogen receptor expression in both the stroma and glands of the endometrium, regardless of the severity of EGE in women who did not receive hormone treatment, had no significant differences from the similar index in women from the comparison group.

Table 64

Comparative analysis of estrogen and progesterone receptor expression indices in the endometrium of women with EGE who did not receive hormone treatment, depending on the severity of EGE

	Comparison group, n=85	St. 1-2 EGE, n=33	St. 3-4 EGE, n=18	p, KW (Kruskall-Wallis)
	1	2	3	
Age (years), m±sd	32.9±4.2	32.6±3.3	32.9±3.9	p=0.9
ER in endometrial glands, M±m	137.2±6.2	135.8±8.3	113.7±13.8	p=0.13
ER in endometrial stroma, M±m	112.0±6.0	103.0±9.1	106.3±11.8	p=0.7
PR in endometrial glands, M±m	134.8±7.1	124.7±11.7	104.8±16.2	p=0.13
PR in endometrial stroma, M±m	**163.0±3.9***	**144.3±8.2**	**139.0±9.4***	**p=0.012**

Note: ***p_{1-3} =0.021**

Comparative evaluation of indices of immunocompetent cell marker expression in women with EGE who did not receive hormone treatment revealed a significant increase in the number of pro-inflammatory cells with markers CD8+, CD20+, CD138+ in combination with a decreased content of CD56+ cells (Table 65).

Table 65

Comparative analysis of the expression of immunocompetent cell markers in the endometrium of women with EGE who did not receive hormone therapy, depending on the severity of EGE

	Comparison group, n=85	St. 1-2 EGE, n=33	St. 3-4 EGE, n=18	p, KW (Kruskall-Wallis)
	1	2	3	

CD8+	**2.6±0.05**	**2.5±0.1**	**2.9±0.18**	**p_{2-3}=0.017**
CD20+	**8.5±1.4**	**8.1±1.7**	**15.0±3.3**	**p_{1-3} =0.047**
CD138+	**0.7±0.08**	**0.9±0.1**	**1.4±0.26**	**p_{1-3}=0 p_{2-3} =0.049**
CD56+	**1.5±0.08**	**1.0±0.1**	**1.1±0.17**	**p_{1-2}=0.006**

It was found that a significant reliable increase in the expression of markers of immunocompetent cells CD20+, CD138+ is determined in the endometrium of women with severe EGE who did not receive hormone therapy as compared to women from the comparison group (p=0.047 and p=0, respectively) and as compared to the expression of CD8+ in women with stage 1-2 EGE (p=0.017).

Analysis of variance of the whole array of the studied characteristics (age, presence of uterine myoma, adenomyosis, stage I-II EGE, stage III-IV EGE, treatment of EGE with GnRHa or gestagens, data of morphologic study of the endometrium, results of determination of ER expression in endometrial glands, ER in endometrial stroma, PR in endometrial glands, PR in endometrial stroma, CD8+, CD20+, CD56+, CD138+) in the group of women with EGE who did not receive hormone treatment, three indicators were identified: age, the level of progesterone receptor expression in endometrial stroma and the level of CD8+ expression, the presence of which significantly affects the outcome of the IVF program. Significant differences in these indicators, determined in women from the comparison group and in women with EGE who did not receive hormone treatment, were determined by the level of progesterone receptor expression in endometrial stroma (164.7 and 143.0; p=0.051). A similar significant difference was determined in the content of the CD8+ marker, but depending on the severity of the disease course (between EGE I-II stage and EGE III-IV stage groups (2.6 and 3.1; p=0.013, respectively) (Table 66).

Table 66

Results of variance analysis of signs revealing the state of the endometrium in women with EGE who did not receive hormone treatment

	Comparison group, n=44	St. I-II EGE, n=21	St. III-IV EGE, n=13	p, KW (Kruskall-Wallis)
	1	2	3	
Age, m±sd	33.3±4.1	32.6±3.4	31.8	p>0.05

PR in endometrial stroma, M±m	**164.7±4.6**	**143.0±9.9**	150.0±10.9	p_{1-2} =0.051
CD8+, M±m	**2.7±0.08**	**2.6±0.15**	**3.1±0.2**	p_{1-3} =0.054 p_{2-3} =0.013

In addition to the age characteristics of women with EGE entering the IVF (IVF+ICSI) protocol, we established unidirectional mutually aggravating risk factors for a negative outcome of the IVF (IVF+ICSI) protocol in women with EGE who did not previously receive hormone treatment, namely, progesterone receptor deficiency in the stroma and increased expression of CD8+ cells in the eutopic endometrium.

In women with EGE, in order to clarify approaches to differentiated management tactics and to build projective classifications for personalized prediction of pregnancy in IVF (IVF+ICSI) programs, we analyzed the studied indicators of the state of the endometrium depending on the different severity of the disease course.

Results of projective classifications for predicting clinical pregnancy in IVF(IVF/ICSI) protocols in women with genital endometriosis

To determine the prognostic factors of the IVF (IVF+ICSI) program success in women with genital endometriosis, an analysis with the identification of discriminant function coefficients was performed in relation to the diagnosis, taking into account the immunohistochemical indices of the state of endometrium and the fact of the performed hormonal treatment (Table 67).

Table 67
Discriminant function ratios
Metric indices:

Index	Discriminant function value
Age	-0.0983
ER in endometrial glands	-0.0049
ER in endometrial stroma	0.0115
PR in endometrial glands	-0.0056
PR in endometrial stroma	0.0059
CD8+	-0.0212
CD20+	-0.0256
CD56+	-0.0465
CD138+	-0.0275

Categorical indices:

Index	Discriminant function value
Uterine fibroids	-0.2865
Adenomyosis	-0.1170
1-2 EGE	-0.2653
3-4 EGE	-0.3273
EGE GnRHa or gestagen treatment	2.6969
Middle secretion phase	0.3810
Early secretion phase	-0.3886
Late secretion phase	0.4716
Basal endometrial hyperplasia	-0.6057
Endometrial hyperplasia without atypia	0.5755
Hypoplastic endometrium	-0.4999
Stromal edema	-0.9914

The cumulative division according to the results of the IVF program depending on the identified factors allowed us to make a scheme (Figure 29) with cases of a successful IVF (IVF+ICSI) program showing a satisfactory predictive result in the upper right corner.

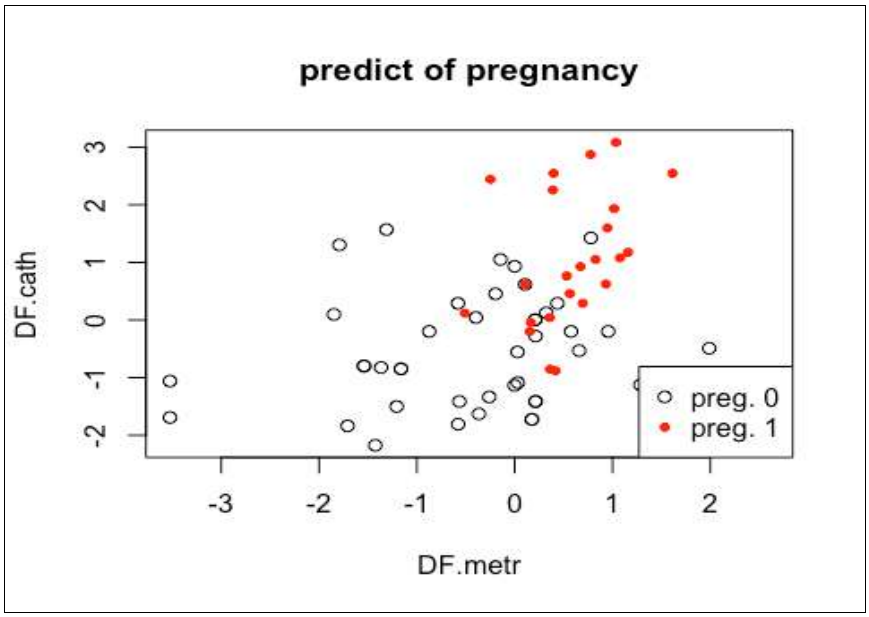


Figure 29

Cumulative distribution of discriminant functions by the onset of clinical pregnancy in women with EGE

The studied parameters related to diagnosis and hormone treatment in all examined women with genital endometriosis were used to perform multivariate symptom analysis using logistic regression. At the first stage, factors significant for clinical pregnancy were identified, and subsequently analyzed to identify a group of predictors of successful IVF (IVF/ICSI) program outcome.

The first combination of factors predicted clinical pregnancy with a high probability (66%) – these included:

- absence of adenomyosis;
- hormone treatment of genital endometriosis prior to the IVF (IVF/ICSI) protocol;
- middle phase of secretion in the endometrium on day 20-22 of the m.c.

Thus, in women who did not receive hormone treatment for genital endometriosis prior to the IVF(IVF/ICSI) program and/or in the absence of secretory transformation of the endometrium and the presence of adenomyosis, failure of the IVF(IVF/ICSI) protocol is predicted with 91% probability.

The second and third combinations of factors were negative prognosis factors.

The second combination of factors **negatively** predicting the outcome of the IVF(IVF/ICSI) protocol:

- absence of hormone treatment of genital endometriosis with GnRHa and/or gestagens
- early phase of secretion of the endometrium on day 20-22 of the m.c.

The presence and combination of these factors predicted clinical pregnancy in only 19% of women.

The third combination of factors negatively predicting the outcome of the IVF(IVF/ICSI) protocol:

- hormone treatment of genital endometriosis completed more than 12 months prior to the IVF(IVF/ICSI) protocol
- presence of EGE
- early phase of secretion on day 20-22 of the m.c.

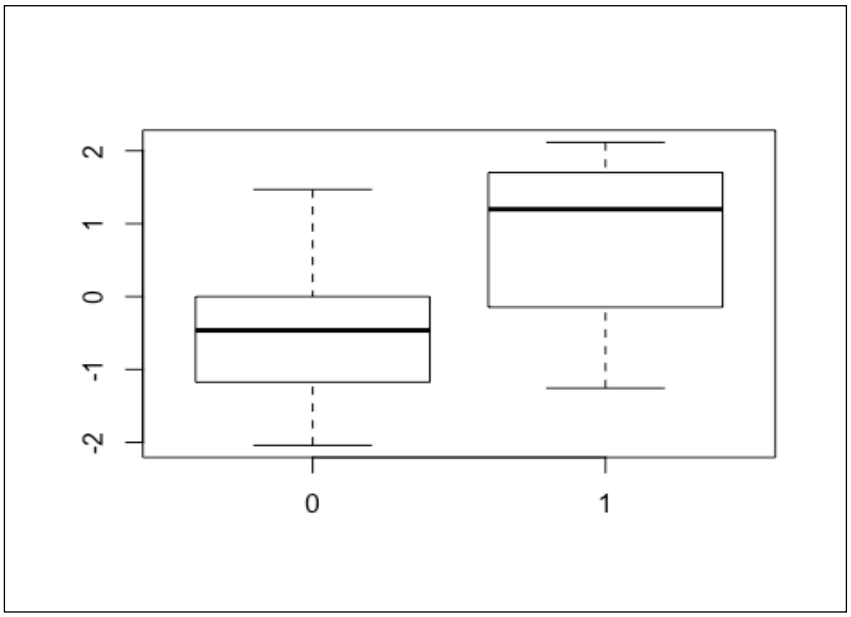
The presence and combination of these factors predicted clinical pregnancy in only 13% of women.

In the analysis based on clinical data, the combination of the presence of the first and absence of the second factors had the highest clinical pregnancy rate of 73.9%. In the presence of the first factor and the absence of the second and third factors, the clinical pregnancy rate was 60.8%.

Thus, as a result of the analysis, we can identify positive prognostic factors for the onset of clinical pregnancy in women with genital endometriosis:

- absence of adenomyosis;
- hormone treatment of EGE prior to the IVF (IVF/ICSI) protocol;
- middle phase of secretion in the endometrium on day 20-22 of the m.c.

To build a projective classification for predicting the onset of pregnancy in women with genital endometriosis, the entire array of studied parameters was analyzed; in all women, the predictive probability of the set of factors did not exceed 75%, whereas when analyzed with the selected factors, the predictive probability increased to 83% (Fig. 30, 31).



0 – failed clinical pregnancy
1 – achieved clinical pregnancy

Figure 30
Differences in discriminant factors depending on the onset of clinical pregnancy in women with genital endometriosis

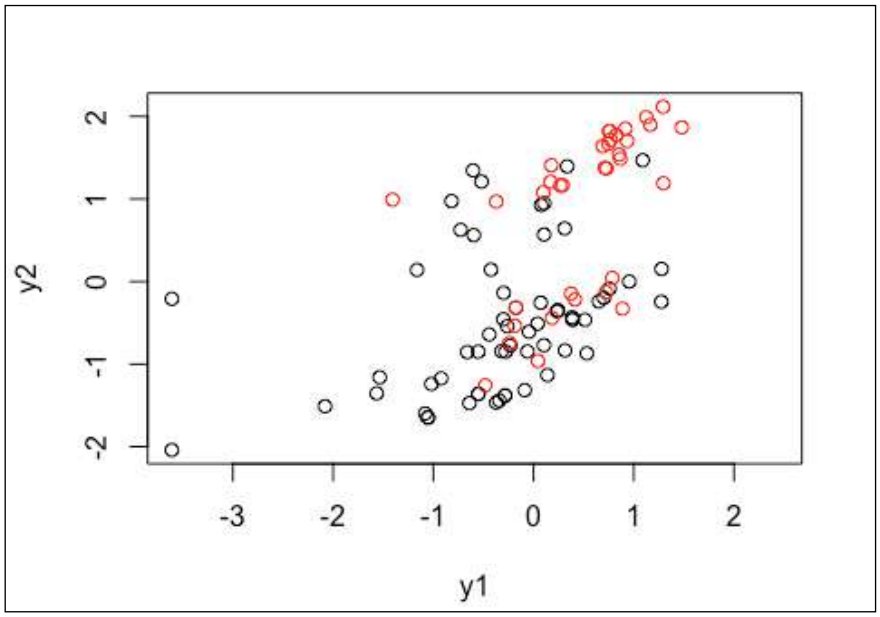


Figure 31

Cumulative distribution of discriminant functions by pregnancy onset in women with genital endometriosis

Multivariate analysis showed that the presence of adenomyosis, stage III-IV EGE and lack of hormone treatment, including for stage I-II EGE, are predictors of IVF (IVF/ICSI) protocol failure in women with genital endometriosis. Women with genital endometriosis in the absence of adenomyosis who received hormone treatment with GnRHa or gestagens and entered IVF (IVF+ICSI) programs within 12 months after hormone treatment completion have the highest chance of clinical pregnancy. At the same time, an increase in the clinical pregnancy rate was observed with low CD8+ and CD20+ expression in the endometrium.

Analysis of the results of the study of endometrium and construction of projective classifications to predict the onset of clinical pregnancy in women with uterine fibroids

With a view to highlight the factors affecting the IVF (IVF+ICSI) program outcomes, a comparative analysis of the results of morphological and immunohistochemical study of endometrium in 67 examined women with uterine fibroids was performed.

The mean age of women with uterine fibroids was 32.9±0.51 years; in most cases, secondary infertility was diagnosed (60%); 4.5% of women had a history of delivery, and 16.2% had a history of failed pregnancy.

A comparative analysis of the IVF (IVF+ICSI) program outcomes depending on the histological study of the endometrium in women with uterine fibroids allowed us to determine the correlation between the achievement of clinical pregnancy and the degree of secretory transformation of the endometrium (Table 68).

Table 68

Comparative evaluation of IVF (IVF+ICSI) program efficiency in women with uterine fibroids considering morphological characteristics of the endometrium prior to the IVF (IVF+ICSI) program

	Achieved pregnancy, n=23	Failed pregnancy, n=44	p	$\chi 2$ or Fisher's two-sided test
Secretory transformation	**78.3% (18/23)**	**40.9% (18/44)**	**0.005**	**8.48**
Early secretion phase	**8.7% (2/23)**	**36.4% (16/44)**	**0.02**	**5.88**
Late secretion phase	4.3% (1/23)	4.5% (2/44)	1.0	0.31
Underdeveloped stroma	4.3% (1/23)	11.4% (5/44)	0.7	0.91
Endometrial hyperplasia without atypia	4.3% (1/23)	6.8% (3/44)	1.0	0.16

It was established that clinically verified pregnancy occurs significantly more often in those cases when the study of the endometrium prior to the IVF (IVF+ICSI) program identifies the endometrium corresponding to the middle secretion phase stage, OR 5.2 (CI 1.6-16.6), χ^2=8.48 ($p<0.05$). When an early secretion phase stage was detected, pregnancy rate decreased, OR 0.17 (CI 0.03-0.81), χ^2=5.88($p<0.05$).

Considering the previously shown negative influence of signs of chronic inflammatory processes in the endometrium on the IVF (IVF+ICSI) program outcomes, we determined the frequency of chronic endometritis at different IVF (IVF+ICSI) program outcomes in women with uterine fibroids based on the results of morphological and immunohistochemical study of the endometrium (Table 69).

Table 69

Comparative evaluation of the IVF (IVF+ICSI) program efficiency in women with uterine fibroids considering the incidence of chronic endometritis prior to the IVF (IVF+ICSI) program

	Achieved clinical pregnancy, n=23	Failed pregnancy, n=44	p	$\chi 2$ or Fisher's two-sided test
Chronic endometritis	58.8% (14/23)	47.1% (21/44)	0.4	1.05
Mild	**50.0% (7/14)**	**14.3% (3/21)**	**0.02**	**5.25**
Moderate	**50.0% (7/14)**	**85.7% (18/21)**	**0.02**	**5.25**
Severe	0	0		

Examination of the endometrium of women with uterine fibroids prior to the IVF (IVF+ICSI) program that resulted in a clinical pregnancy revealed chronic endometritis in a mildly severe form (in 50%), p=0.02, whereas in women with failed IVF (IVF+ICSI) program there was a clear tendency for chronic endometritis to predominate with a moderately severe reaction (in 85.7%); OR 4.38 (CI 1.12-17.02), χ^2=5.01 (p<0.05).

In women with uterine fibroids, the factors identified on the basis of the dispersion analysis (Table 70) with regard to clinical data, hormone therapy, results of morphologic study of the endometrium, determination of ER and PR expression indices in the glands and stroma of the endometrium, CD8+, CD20+, CD56+, CD138+ are poorly predictive, with a probability of no more than 57%. Among the combinations of the identified factors of positive prognosis, there are secretory transformation of the endometrium, as well as hormone therapy with gestagens and/or GnRHa preparations in the period not more than 12 months prior to the IVF (IVF+ICSI) program. When the discriminant analysis included the indices of estrogen and progesterone receptor expression in the endometrium, the indices of CD 8+, CD 20+, CD 57 and CD 138+ markers in the endometrium, it was found that the factors of negative prognosis include increased expression of progesterone receptors both in endometrial stroma and in endometrial glands, as well as increased content of CD8+, CD56+ and CD138+ in the endometrium.

Table 70
Discriminant function ratios
Metric indices:

Index	Discriminant function value
ER in endometrial glands	0.016119557
ER in endometrial stroma	-0.024959762
PR in endometrial glands	-0.005173807
PR in endometrial stroma	-0.003610620
CD8+	-0.012736272
CD20+	0.008968583
CD56+	-0.011251534
CD138+	-0.013036052

Categorial indices:

Index	Discriminant function value
Treatment with GnRHa or gestagens	0.66021789
Middle secretion phase	1.33952910

Analysis with determination of discriminant function ratios for evaluation of prognostic factors of IVF (IVF+ICSI) program success in women with uterine fibroids did not allow to single out indicators with high prognostic reliability (analysis of immunohistochemical study parameters and women's anamnesis data was performed), the predictive probability of the aggregate of factors does not exceed 68.75% (Figure 32).

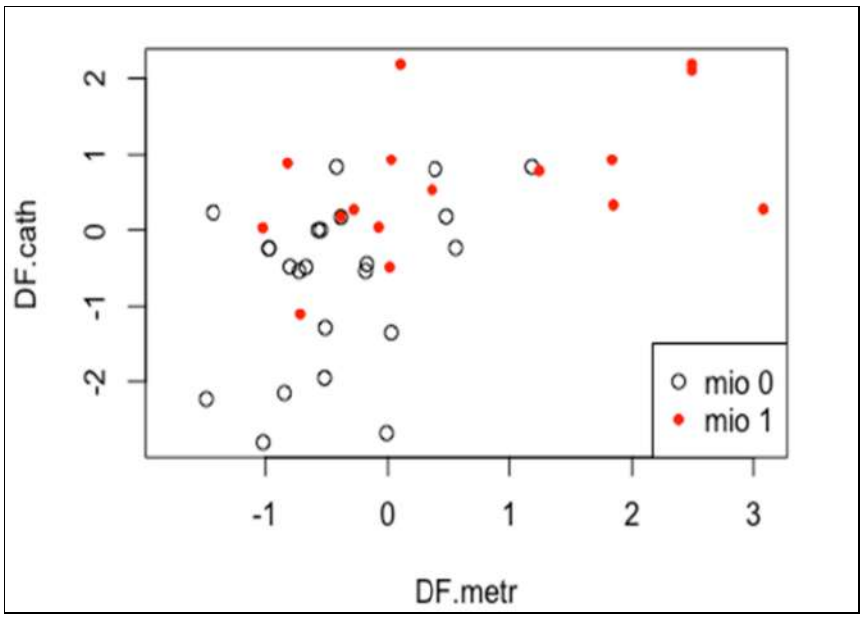


Figure 32

Cumulative distribution of discriminant functions by the onset of clinical pregnancy in women with uterine fibroids

Among all women examined prior to entering the IVF (IVF+ICSI) program, clinical, morphological and immunohistochemical signs of chronic inflammatory reaction in the endometrium are detected more frequently in infertility comorbidity with uterine fibroids and/or genital endometriosis as compared to women without proliferative diseases. Data analysis showed decreased estrogen receptor expression in endometrial glands of women planning IVF with uterine fibroids and genital endometriosis.

It was shown that women with EGE have lower rates of progesterone receptor expression in the endometrium as compared to women without EGE and are associated with an increased level of expression of the CD8+ immunocompetent cell marker, which may be a factor of the combined negative effect on the implantation ability of the eutopic endometrium within IVF (IVF+ICSI) programs. Progesterone

receptor expression in endometrial stroma and glands increases under the influence of EGE hormone therapy with gestagen or GnRHa preparations. The use of analysis of variance revealed the incomplete secretion phase in the cycle prior to entering the IVF (IVF+ICSI) program, the absence of EGE hormone therapy for more than 12 months prior to the IVF (IVF+ICSI) program, and the presence of adenomyosis as factors of negative prognosis.

Thereby, in women with uterine fibroids, the prognosis of IVF (IVF+ICSI) program efficiency does not depend on the structural and functional organization of the endometrium prior to entering the IVF (IVF+ICSI) protocol, which is shown by using the method of analysis of variance.

3.5. Comprehensive Analysis of the Results of the Endometrium Examination in Women with Uterine Fibroids and/or Genital Endometriosis after Failure of the IVF (IVF+ICSI) Program

To clarify the factors of negative prognosis of the IVF (IVF+ICSI) program, we analyzed the state of the endometrium after IVF (IVF+ICSI) program failure in 119 women who underwent endometrial biopsy in native cycles not earlier than three months after the protocol completion.

Clinical and anamnestic characteristics of women with uterine fibroids and genital endometriosis who underwent examination of the endometrium after IVF (IVF+ICSI) program failure

Uterine fibroids were detected in 26 women (21.8%), EGE – in 42 women (35.3%), uterine fibroids combined with adenomyosis and EGE – in 12 women (10.1%).

The mean age of the examined women was 35.8±1.1 years, with a significantly higher age ratio only in women with adenomyosis (38.25±1.57, $p<0.05$). Myomectomy in anamnesis was performed on three women (11.5%). Genital endometriosis in 37 women was diagnosed prior to the IVF (IVF+ICSI) program. In 17 women, it was first detected as a result of laparoscopic examination

after failure of the IVF (IVF+ICSI) protocol. Genital endometriosis history was treated in 14 cases (33.3%), of which 10 women (71.4%) received GnRHa, two women (4.8%) received CHC, and two women (4.8%) received gestagens.

The comparison group consisted of 39 women after a failed IVF(IVF/ICSI) program, in whom signs of uterine myoma and genital endometriosis were excluded (Table 71).

Table 71

Comparative characteristics of obstetric and gynecologic anamnesis in women with uterine fibroids and/or genital endometriosis after a failed IVF (IVF+ICSI) program

	Women without uterine fibroids and GE	Women with uterine fibroids	Women with EGE	Women with uterine fibroids and GE	p
	n=39	n=26	n=42	n=12	
Age, years±m	33.4±0.78	35.7±0.57	34.3±0.56	38.25±1.57	0.0047
Regular m.c., %	86	89	93	80	>0.05
Hyperpolymenorrhea, %	2.5	7.7	7.1	8.3	>0.05
Infertility duration, years	6.18±0.77	9.12±0.81	9.44±0.69	8.65±0.74	>0.05
Primary infertility, %	53.8	42.3	57.1	50	>0.05
Secondary infertility, %	46.2	57.7	42.9	50	>0.05
Number of abortions in history, %	0.27±0.09	0.41±0.11	0.21±0.07	0.23±0.14	>0.05
Delivery, % of women	2.5	11.5	9.5	8.3	>0.05
Undeveloped pregnancy, %	10.25	11.5	7.1	8.3	>0.05
Spontaneous abortion, %	10.25	7.7	11.9	16.7	>0.05
Ectopic pregnancy, %	15.4	11.5	16.7	8.3	>0.05

In the clinical groups under consideration, no significant differences were found in the comparative analysis of obstetric and gynecological history in terms of menstrual cycle characteristics, pregnancy rate and outcome.

Results of morphological and immunohistochemical study of endometrium in women with uterine fibroids and/or genital endometriosis after a failed IVF (IVF+ICSI) program

The results of the morphologic study of the endometrium after the considered failed IVF (IVF+ICSI) protocol showed that only 34 women (32.4%) achieved the target secretory transformation of the endometrium, 46 women (38.7%) showed delayed underdeveloped endometrium (early secretion phase), 5 women (4.2%) showed signs of premature development of the endometrium (late secretion phase),

28 women (23.5%) showed delayed development of the endometrial stroma; 5 women (4.2%) showed simple hyperplasia of the endometrium without atypia, and 1 woman (0.85%) had hypoplastic endometrium (Table 72).

Table 72

Comparative evaluation of the results of morphological study of the endometrium in women with uterine fibroids and/or genital endometriosis after a failed IVF (IVF+ICSI) program

	Women without uterine fibroids and GE	Women with uterine fibroids	Women with EGE	Women with uterine fibroids and GE	p
	n=39	n=26	n=42	n=12	
Middle secretion phase, %	25.6	34.6	28.6	25	0.85
Early secretion phase, %	38.5	46.2	35.7	33.3	0.94
Late secretion phase, %	5.1	3.8	4.8	0	0.12
Underdeveloped endometrial stroma, %	25.6	11.5	31	16.7	0.22
Endometrial hyperplasia without atypia, %	2.6	3.8	0	25	0.31
Hypoplastic endometrium, %	2.6	0	0	0	0

Comparison of the results of morphologic study of women from the control group and women with uterine fibroids and/or genital endometriosis revealed no significant differences. The detection rate of secretory transformation of the endometrium did not exceed 34.6%.

Morphologic signs of chronic inflammatory reaction in the endometrium: in 11 women (9.2%) – basal hyperplasia of the endometrium. We detected mononuclear infiltration of the stroma in 10 women (8.4%), edema of the endometrial stroma in 6 women (5.0%), and hypoplastic endometrium in 1 woman (0.8%).

After a failed IVF (IVF+ICSI) protocol, based on complex morphologic and immunohistochemical indices, signs of chronic endometritis were detected in 79 samples of the endometrium among all samples received (66.4%), including 20 women from the control group (in 51.3%), 16 women with uterine fibroids (in 61.5%), 35 women with genital endometriosis (in 83.3%) and 8 women with a combination of uterine myoma and genital endometriosis (in 66.7%) vs the incidence of chronic endometritis in the control group and in women with EGE p=0.051.

When applied to the outcome of the IVF (IVF+ICSI) program, in women with uterine fibroids and/or genital endometriosis in case of confirmed clinical pregnancy (the group previously considered in this study), the incidence of chronic inflammatory response before the protocol was 42.4%, which was significantly lower than this rate in women after the IVF (IVF+ICSI) program failure (p=0.001) (Table 73).

Table 73

Comparative evaluation of the IVF (IVF+ICSI) program efficiency in women with uterine fibroids and/or genital endometriosis considering the rate of chronic inflammatory response prior to an IVF (IVF+ICSI) protocol and after a failed protocol

Chronic endometritis	Endometrial biopsy prior to IVF (IVF/ICSI) program, achieved pregnancy, n=59	Endometrial biopsy after IVF (IVF+ICSI) program failure, n=80	p	$\chi 2$ or Fisher's two-sided test
Chronic endometritis	**42.4% (25/59)**	**73.85 (59/80)**	**0.001**	**13.98**
Mild, %	**52.0% (13/25)**	**20.3% (12/59)**	**0.006**	**8.42**
Moderate, %	**36.0 (9/25)**	**64.4% (38/59)**	**0.02**	**5.75**
Severe, %	12.0% (3/25)	15.3% (9/59)	0.8	0.15

It should be noted that significant differences were also revealed in the degree of severity of inflammatory reaction: in women with uterine fibroids with successful completion of an IVF (IVF+ICSI) program, a predominantly mildly expressed form of chronic endometritis was observed with frequency significantly higher than in women with IVF (IVF+ICSI) failure (p=0.006), and moderately expressed chronic endometritis was significantly more often detected in women with failure compared to women with pregnancy (p=0.02).

Thus, according to the results of a complex assessment of the state of the endometrium in women with uterine fibroids and genital endometriosis after the IVF (IVF+ICSI) program failure, in most cases the endometrium does not reach the target secretory transformation, and in more than 70% of cases it has signs of chronic inflammatory reaction.

After analyzing the results of all samples of endometrium obtained from women with uterine fibroids and genital endometriosis after a failed protocol, there was a need for a differentiated assessment of the factors directly affecting the

outcome of IVF (IVF+ICSI) programs depending on the presence of uterine myoma or the influence of genital endometriosis.

3.5.1. Results of the Endometrium Examination in Woment with External Genital Endometriosis after Failure of the IVF (IVF+ICSI) Program

Clinical and anamnestic characteristics of women with external genital endometriosis who underwent the study of endometrium after failure of the IVF (IVF+ICSI) program

To clarify the prognostic factors of the IVF (IVF+ICSI) program, morphological and immunohistochemical analysis of the state of the endometrium was performed in 93 women after the IVF (IVF+ICSI) program failure. Endometrial biopsy was performed on days 20-22 in native cycles not earlier than three months after the completion of the failed protocol.

The main group included 54 examined women with EGE, the comparison group consisted of 39 women after a failed IVF(IVF/ICSI) program, in whom complex examination did not reveal signs of external genital endometriosis.

The mean age of the examined women was 35.8±1.1 years. Genital endometriosis was diagnosed in 37 women before an IVF (IVF+ICSI) program. In 17 women, it was first detected as a result of laparoscopic examination after failure of IVF (IVF+ICSI) protocol. Treatment of genital endometriosis in history was performed in 14 cases (33.3%), of which 10 women (71.4%) received GnRHa preparations, two women (4.8%) received CHC preparations, and two women (4.8%) received gestagenic preparations.

A comparative analysis of the data of obstetric and gynecological history of women after a failed IVF (IVF+ICSI) program who underwent endometrial biopsy was performed (Table 74).

Table 74

Comparative characteristics of obstetric and gynecologic anamnesis in women with external genital endometriosis after a failed IVF (IVF+ICSI) program

	Comparison group, n=39	Women with EGE, n=54	p
Age, years±m	33.4±0.78	34.3±0.56	>0.05
Regular m.c., %	86	93	>0.05
Abnormal uterine bleeding, %,	2.5	7.1	>0.05
Infertility duration, years	6.18±0.77	9.44±0.69	>0.05
Primary infertility, %	53.8	57.1	>0.05
Secondary infertility, %	46.2	42.9	>0.05
Induced abortion history, %	15.4	9.2	>0.05
Delivery, % of women	2.5	9.5	>0.05
Undeveloped pregnancy, %	10.25	7.1	>0.05
Spontaneous abortion, %	10.25	11.9	>0.05
Ectopic pregnancy, %	15.4	16.7	>0.05

In the clinical groups under consideration, no significant differences were found in the comparative analysis of obstetric and gynecological history in terms of menstrual cycle characteristics, pregnancy rate and outcome.

54 women (58.1%) had a history of repeated IVF (IVF+ICSI) protocol failures.

Results of morphological and immunohistochemical study of endometrium in women with external genital endometriosis after a failed IVF (IVF+ICSI) program

According to the results of the morphologic study of endometrium in the long-term period after a failed IVF (IVF+ICSI) protocol, among all the examined women, only 16 women out of 54 (29.6%) had target secretory transformation of the endometrium in the native cycle, 19 women (35.2%) had underdeveloped endometrium (early phase of secretion), 2 (3.7%) had signs of premature development of the endometrium (late phase of secretion), 11 (20.4%) had underdeveloped endometrial stroma; hyperplasia of the endometrium without atypia was detected in 3 women (5.6%). In 5 women (9.3%), basal hyperplasia of the endometrium was detected. Mononuclear infiltration of the stroma was detected in 4 (7.4%) women.

In comparative intergroup analysis, significant differences in the condition of the endometrium were identified by the rate of basal hyperplasia of the

endometrium, which was significantly more frequent in women with EGE (Table 75).

Table 75

Results of the morphologic study of the endometrium in women with external genital endometriosis after a failed IVF (IVF+ICSI) program

	Comparison group, n=39	Women with EGE, n=54	p
Middle secretion phase, %	25.6	29.6	0.75
Early secretion phase, %	38.5	35.2	0.88
Late secretion phase, %	5.1	3.7	0.27
Underdeveloped endometrial stroma, %	25.6	20.4	0.15
Endometrial hyperplasia without atypia, %	2.6	5.6	0.08
Hypoplastic endometrium, %	2.6	0	0.23
Basal hyperplasia of the endometrium, %	2.6	9.3	0.04
Mononuclear infiltration of the endometrial stroma, %	7.7	7.4	0.44

Comparison with the previously obtained results of evaluation of the endometrium of women with EGE and successful outcome of the IVF (IVF+ICSI) program showed that target secretory transformation in women after a failed IVF (IVF+ICSI) program was detected significantly less frequently – by 1.8 times (53.8% and 29.6%, respectively, p=0.015) (Table 76).

Table 76

Comparative evaluation of the morphological state of the endometrium in women with external genital endometriosis prior to an IVF (IVF+ICSI) program ended in pregnancy and after a failed IVF (IVF+ICSI) program

	Endometrial biopsy prior to IVF (IVF/ICSI) program, achieved pregnancy, n=48	Endometrial biopsy after IVF (IVF+ICSI) program failure, n=54	p	$\chi 2$ or Fisher's two-sided test
Middle secretion phase, %	**54.2 (26/48)**	**29.6 (16/54)**	**0.015**	**6.32**
Early secretion phase, %	**16.7 (8/48)**	**35.2 (19/54)**	**0.04**	**4.48**
Late secretion phase, %	6.25 (3/48)	3.7 (2/54)	0.6	0.35
Underdeveloped endometrial stroma, %	22.9 (11/48)	20.4 (11/54)	0.8	0.1

According to a combination of morphologic and immunohistochemical parameters, signs of chronic endometritis were detected in 43 women (79.6%), of which 7 (16.3%) had a mild chronic inflammatory reaction, 26 (60.5%) had a moderate one, and 10 (23.3%) had a severe one.

There was a higher incidence of chronic endometritis among women with EGE (79.6%) as compared to that in the comparison group (51.3%), (Table 79);

analysis of the degree of severity of the inflammatory reaction showed that moderate manifestations were significantly more frequent in women with EGE, whereas mild manifestations were more frequent in the comparison group (Table 77).

Table 77

Detection rate and characteristics of the course of chronic endometritis in women with external genital endometriosis after a failed IVF (IVF+ICSI) protocol according to the results of a complex morphological and immunohistochemical study

	Comparison group, n=39	Women with EGE, n=54	p	$\chi 2$ or Fisher's two-sided test
Chronic endometritis	**51.3 (20/39)**	**79.6 (43/54)**	**0.005**	**8.33**
Mild, %	**38.5 (15/39)**	**12.9 (7/54)**	**0.006**	**8.15**
Moderate, %	**12.8 (5/39)**	**48.1 (26/54)**	**0.0004**	**12.72**
Severe, %	0	18.5 (10/54)	0.29	

In comparison with the previously obtained data on the state of the endometrium in women with successful outcome of the IVF (IVF+ICSI) program, chronic endometritis is detected significantly more often in women after a failed protocol (42.4% and 79.6%, respectively, p=0.014); thereby, in women after a failed protocol, chronic endometritis tends to be more often detected in a moderate form, whereas in women before a successful protocol, mild endometritis is detected significantly more often (Table 78).

Table 78

Comparative evaluation of the IVF (IVF+ICSI) program efficiency in women with external genital endometriosis considering the rate and characteristics of the course of chronic endometritis prior to an IVF (IVF+ICSI) protocol ended in pregnancy and after a failed IVF (IVF+ICSI) protocol

Chronic endometritis	Endometrial biopsy prior to IVF (IVF/ICSI) program, achieved pregnancy, n=59	Endometrial biopsy after IVF (IVF+ICSI) program failure, n=54	p	$\chi 2$ or Fisher's two-sided test
Chronic endometritis	**42.4% (25/59)**	**79.6% (43/54)**	**0.003**	**16.33**
Mild, %	**52.0% (13/25)**	**16.3% (7/43)**	**0.003**	**9.72**
Moderate, %	36.0 (9/25)	60.5% (26/43)	0.08	3.79
Severe, %	12.0% (3/25)	23.3 (10/43)	0.3	1.3

Analysis of the results of determining the expression of immunocompetent markers in the endometrium revealed a tendency to increase the expression of CD8+ and CD20+ in women with EGE as compared to women from the comparison group;

no differences between the compared groups were found in terms of CD138+ and CD56+ markers (Table 79).

Table 79

Characteristics of expression of immunocompetent markers of the state of the endometrium in women with external genital endometriosis after a failed IVF (IVF+ICSI) program

	Comparison group, n=24		Women with EGE, n=36		p, KW (Kruskal-Wallis)
	m	sd	m	sd	
CD8+	14.92	11.1	19.01	12.7	0.055
CD20+	8.25	12.8	14.62	7.0	0.063
CD56+	5.43	4.8	5.88	6.2	0.547
CD138+	3.01	5.2	5.43	7.4	0.604

Comparative analysis of estrogen and progesterone receptor expression indices in the endometrial stroma and glands among women with a failed IVF (IVF+ICSI) program did not reveal any significant differences (Table 80).

Table 80

Characteristics of estrogen and progesterone receptor expression in the endometrium of women with external genital endometriosis after a failed IVF (IVF+ICSI) program

	Comparison group, n=24		Women with EGE, n=36		p, KW (Kruskal-Wallis)
	m	sd	m	sd	
PR in endometrial glands	124.2	57.8	104.8	63.1	0.619
PR in endometrial stroma	149.75	41.1	126.9	42.0	0.275
ER in endometrial glands	139.0	37.8	120.7	47.9	0.276
ER in endometrial stroma	121.3	50.1	97.6	39.9	0.540

Thereby, the comparative analysis of estrogen and progesterone receptor expression indices in the endometrial stroma and glands determined in women prior to the IVF (IVF+ICSI) program that resulted in pregnancy and in women after a failed IVF also did not reveal any significant differences (Table 81).

Table 81

Comparative evaluation of IVF (IVF+ICSI) program efficiency in women with external genital endometriosis with regard to estrogen and progesterone receptor expression in the endometrium prior to an IVF (IVF+ICSI) protocol and after a failed protocol

	Endometrial biopsy prior to IVF (IVF/ICSI) program, achieved pregnancy, n=39		Endometrial biopsy after IVF (IVF+ICSI) program failure, n=36		p, KW (Kruskal-Wallis)
	m	sd	m	sd	
ER in endometrial stroma	121.658	48.265	83.854	61.9	0.276
ER in endometrial glands	118.756	54.565	138.754	40.2	0.315
PR in endometrial stroma	149.221	29.325	137.258	27.2	0.99
PR in endometrial glands	132.254	48.998	118.236	41.2	0.89

Thus, according to the results of morphological evaluation of endometrium in women with EGE after a failed IVF (IVF+ICSI) program, it was found that in most cases the endometrium does not reach the target secretory transformation and, in more than 75% of cases, has signs of chronic endometritis.

After a failed IVF (IVF+ICSI) program in women with EGE, a tendency to increased expression of CD8+ and CD20+ cells in the endometrium compared to women without proliferative diseases was determined, whereas no significant differences were found when analyzing the results of estrogen and progesterone receptor determination in the endometrial stroma and glands.

3.6. Comparative Evaluation of Effeciency of Recurrent IVF (IVF+ICSI) Programs in Women with Uterine Fibroids and Genital Endometriosis depending on Hormone Therapy Application

In order to evaluate the clinical effect of progestagens at the pregravid preparation stage, the results of IVF (IVF+ICSI) programs in 211 women with EGE were analyzed.

The following were defined as inclusion criteria:

- previous IVF program failed with a history of embryo transfer of satisfactory quality;
- verified EGE diagnosis;
- absence of contraindications to ART infertility treatment.

Exclusion criteria:

- therapy with GnRHant, gestagens, combined hormonal contraceptives, which ended less than 12 months before the start of this protocol;
- stage 3-4 adenomyosis (according to the “Clinical Guidelines: Endometriosis”, 2020);
- multiple uterine myomas.

Of all the women included in the study, 11 had a history of protocols that ended in delivery. On average, there was a history of 1.9 failed protocols (1 to 7).

The time interval from a previous IVF (IVF+ICSI) program that ended in failure averaged 11.3 months (6 to 36 months).

Stage 1-2 EGE was diagnosed in 111 patients, stage 3-4 EGE was diagnosed in 100 patients. 28 women (13.3%) had stage 1-2 adenomyosis, 53 women (25.2%) had a combination with uterine fibroids (type 4-7).

Primary infertility was determined in 116 women (54.98%), secondary infertility – in 95 women (45.02%). In the structure of infertility causes, the most frequent cause of infertility was genital endometriosis in 117 women (55.5%) and male factor in 96 women (45.5%); tubal factor infertility was noted in 83 women (39.3%), endocrine infertility in 14 (6.6%), and idiopathic infertility in 9 (4.3%).

The mean age of menarche was 12.5±1.1 years. Regular menstrual cycle was determined in 194 women (91.9%), and abnormal uterine bleeding in 17 cases (8.1%).

Diminished ovarian reserve was determined in 33 (15.6%) women during clinical and laboratory examination.

Pregnancy history was noted in 95 women (45.02%). Nineteen (20% of all pregnancies) ended in delivery; 15 (15.8% of all pregnancies) ended in abortion, 18 (18.9%) had a history of undeveloped pregnancies, 21 (22.1%) had spontaneous abortions, and 22 (23.15%) had ectopic pregnancies.

45 women were diagnosed with chronic endometritis and were treated accordingly before starting the IVF (IVF+ICSI) program (according to the recommendations in “Gynecology: National Guidelines,” 2019) [5]. The treatment was carried out in the period not more than 12 months prior to the start of the program.

By the beginning of the IVF (IVF+ICSI) program, all chronic somatic diseases in the examined women were in remission or medically compensated.

In all women, EGE was diagnosed by surgical laparoscopy with concomitant surgical treatment of endometriosis. Ovarian resection and cystectomy were performed on 35 women.

Previous hormonal treatment of genital endometriosis was performed on 55 women (26.07%). In 38 women, GnRHa preparations were used, in 5 – dienogest, in 12 – combined hormonal contraceptives; the therapy duration ranged from 3 to 6 months.

The main group consisted of 135 women who, if the inclusion criteria were met, underwent pregravid hormonal preparation for EGE with a gestagenic drug (dienogest). 3 women did not complete the course of treatment and refused to take the drug (due to the appearance of pronounced side effects) and were excluded from the study.

Dienogest was used at a dose of 2 mg daily for 3-6 months. The time period from the end of therapy to the start of the IVF (IVF+ICSI) program was not more than 8 weeks.

The control group consisted of 76 women with EGE, provided that they did not receive preimplantation hormonal preparation in the period of 12 months or less before the beginning of the IVF (IVF+ICSI) program.

In the main group, stage 1-2 EGE was detected in 72 women (53.3%) and stage 3-4 EGE – in 62 women (45.9%); of these, adenomyosis was diagnosed in 20 women (14.8%) and uterine fibroids – in 33 women (24.4%).

In the control group, stage 1-2 EGE was diagnosed in 43 women (56.6%), and stage 3-4 EGE was diagnosed in 33 women (43.4%). Adenomyosis was diagnosed in 8 women (10.5%); uterine fibroids – in 20 women (26.3%).

Women from the main and control groups were comparable in age (34.47±0.32 and 35.15±0.47 respectively, $p>0.05$). When comparing such indicators as infertility duration, pregnancy history, number of IVF (IVF+ICSI) programs and failed outcomes of such programs, no significant differences between the groups were revealed; a significantly higher rate of ectopic pregnancy history in the control group (19.3%) as compared to the comparison group (39.5%) was determined, $p=0.032$.

When comparing the mean values of gonadotropic hormone levels in plasma of women from the selected clinical groups, no significant differences were found; AMH levels and the number of antral follicles were also comparable (Table 82).

Table 82

Results of ovarian reserve evaluation among women with genital endomentriosis who did and did not receive preimplantation hormonal preparation prior to an IVF (IVF+ICSI) program

Index values	Main group (dienogest treatment), n=135	Control group (no hormonal preparation), n=76	p
FSH, mlU/ml	7.14±0.54	6.98±0.47	>0.05
LH, mlU/ml	5.11±0.34	4.79±0.42	>0.05
AMH, ng/ml	1.41±0.25	1.33±0.34	>0.05
Antral follicle count, n	8.45±0.39	7.13±0.64	>0.05

There were no significant intergroup differences in the rate of detection of women with diminished ovarian reserve (16.3% in the main group and 14.4% in the control group, p>0.05).

All women underwent the protocol of superovulation stimulation with the use of GnRHant.

Comparative characteristics of the IVF (IVF+ICSI) cycles in women with genital endomentriosis who did and did not receive preimplantation hormonal preparation prior to an IVF (IVF+ICSI) program

Analysis of the main parameters of IVF (IVF+ICSI) cycle – duration of superovulation stimulation, average total dose of rFSH preparations – did not reveal any significant intergroup differences (Table 83).

Table 83

Total dose of rFSH preparations per cycle and duration of superovulation stimulation in women with genital endomentriosis who did and did not receive preimplantation hormonal preparation prior to an IVF (IVF+ICSI) program

	Main group (dienogest treatment), n=135	Control group (no hormonal preparation), n=76	p
Total FSH dose (IU)	1952.3	2011.1	>0.05
Effective dose (IU)	237.3±51.1	260.5±47.7	>0.05
Stimulation duration (days)	8.8	9	>0.05
Cycle cancelation, number of women	9	7	

Follow-up evaluation of the efficiency of stimulation and embryologic stage was performed after excluding from the calculation women with canceled

transvaginal puncture, women in whom no oocytes were obtained by transvaginal puncture, or when immature or degenerated oocytes were obtained. Fertilization was performed on 126 women from the main group and 69 women from the comparison group (Table 84).

Table 84

Comparative characteristics of the efficiency of the superovulation stimulation stage in women with genital endomentriosis who did and did not receive preimplantation hormonal preparation prior to an IVF (IVF+ICSI) program

	Main group (dienogest treatment), n=126	Control group (no hormonal preparation), n=69	p
Number of follicles punctured	9.8	9.6	>0.05
Number of obtained oocytes	8.45	7.9	>0.05
Number of obtained MII stage oocytes	6.7	6.45	>0.05
Frequency of fertilization by IVF+ICSI method	51.85	47.4	>0.05
Number of bipronuclear zygotes	4.9	5.0	>0.05
Fertilization efficiency (number of 2p zygotes/ number of oocytes), %	58.1	59.1	>0.05
Number of embryos of optimal quality on day 4 of culturing	4.45	4.61	>0.05
Share of women with embryos of satisfactory quality, %	93.7	89.9	>0.05

Comparison of the average number of obtained oocytes also showed no significant differences between the main and control groups.

Transfer of one embryo was performed on 50 women (37.04%) from the main group, on 17 women (28.9%) from the control group, and in the remaining cases, 2 embryos were transferred. Embryos of satisfactory quality were transferred at the stage of fragmentation, morula and blastocyst in 118 cases (87.4%) in the main group and in 62 cases (82.6%) in the control group; the evaluation was performed according to the criteria of Ebner T., 2001, Tao J., 2002 and Gardner D., 1999.

Endometrial thickness and pregnancy rate were evaluated in cycles with embryo transfer of satisfactory quality. Endometrial thickness on the day of embryo transfer did not differ significantly among the compared groups – 9.44±0.37 in the main group and 9.58±0.19 in the control group, $p>0.01$.

Thus, comparison of clinical and anamnestic data and results of the IVF (IVF+ICSI) program in women with EGE who were treated with dienogest hormone

therapy in comparison with women who did not receive hormonal preparation during the year preceding the ART program did not reveal any significant differences. There were also no significant differences in the indicators of the embryological stage of IVF (IVF+ICSI) programs – fertilization efficiency, rate of obtaining embryos of satisfactory quality.

The IVF (IVF+ICSI) program resulted in pregnancy in 55 women from the main group and 20 women from the control group; the rate of clinically verified pregnancy was significantly higher in women from the main group (43.7%) as compared to women from the control group (28.9%), OR 1.9; CI 1.01-3.56, $p<0.05$. In women with EGE combined with uterine fibroids after dienogest therapy, pregnancy rates did not differ significantly from the control group women 32.5%, $p=0.754$.

Comparative analysis of women treated with EGE depending on the IVF (IVF+ICSI) program outcome revealed a tendency to failure depending on age (33.6±0.18 and 35.7±0.21 respectively, p=0,06). No significant differences in other studied parameters were revealed.

The increase in the clinical pregnancy rate in the main group was determined regardless of age – in women not older than 35 years, the clinical pregnancy rate was 48.1%, in women older than 35 years – 43.1% ($p>0.05$).

As a result of this study, it was proved that in women with EGE, hormonal therapy, the point of application of which is the eutopic state of the endometrium, is a factor affecting IVF (IVF+ICSI) program efficiency (a significantly significant decrease in progesterone receptor expression in endometrial stroma and an increase in the expression of proinflammatory cytokines in women who received hormonal therapy were revealed). The results showed that preimplantation preparation based on the gestagenic drug dienogest is indicated for women with EGE planning IVF (IVF+ICSI) programs. The condition for efficiency is represented by a period not exceeding 12 months before the start of the program.

3.7. Findings of Assessment of Polymorphism of Estrogen and Progesterone Receptor Genes, Catechol-O-Methyltransferase and CYP 19 in Women with Uterine Fibroids

We examined 104 women after surgical treatment for uterine myoma, aged 24 to 59 years, who made up the main group.

Inclusion criteria were the presence of morphologically verified uterine myoma and consent to the study. Exclusion criteria – genital endometriosis, malignant diseases.

Indications for surgical treatment: size of myomas, severe clinical manifestations, submucosal localization of myoma, pregnancy planning, impaired reproductive function, presence of combined uterine and ovarian pathology, recurrent uterine myoma, chronic pelvic pain syndrome. The examination included clinical and anamnestic study, pelvic ultrasound, histologic examination of surgical material.

Out of 104 women with uterine fibroids, solitary uterine myomas were diagnosed in 59 women during examination and surgical treatment, and multiple myomas (from 2 to 6) were diagnosed in 45 women. Subserosal myomas were the most frequent – in 72.2±0.1% of women.

Recurrent uterine myoma after earlier myomectomy (in the period from 1 to 11 years) was observed in 22 women.

Extirpation and supravaginal amputation of the uterus were performed on 12 women, which amounted to 22%; the rest of the women underwent conservative myomectomy.

The population control group included 106 women – a population sample of women of the same race, place of birth and residence, who were limited to one region. The age ranged from 24 to 61 years.

Inclusion criteria for the population control group for this study were:

1) age – older than 18 years;
2) sex – female;

3) race – Caucasian;

4) region of residence – northwest Russia;

5) voluntary participation in the study.

Results of estrogen and progesterone receptor gene polymorphism determination

The appearance of the *XbaI* restriction polymorphism is due to the replacement of adenine with guanine in the intronic region of the *ERα* gene (*dbSNP rs*9340799, ***IVS1-351A>G***). In the specialized literature, the normal allele **A* of the *ERα* gene is denoted by **x*, and the polymorphic allele **G* -**X* (Colin E., 2003). The appearance of an additional site for the restriction endonuclease PvuII results from a single nucleotide substitution of thymine for cytosine (*dbSNP rs*2234693, ***IVS1-397T>C***). The **T* allele was designated **p*, and the **C* allele was designated **P*.

Evaluation of the allele rate of the estrogen receptor and progesterone receptor genes revealed almost identical values in women with uterine fibroids and in population control groups (Table 85).

Table 85

ERα and *PGR* alelle rates in the group of women with uterine fibroids and in the population control group

Gene	Allele	Women with uterine fibroids		Population control group	
		n	h±S_h (%)	n	h±S_h (%)
Erα (Xba1)	X	78/216	72±4.3	135/206	65.5±3.3
	x	30/216	28±4.3	71/206	34.5±3.3
Erα (PvuII)	P	63/216	58±4.8	102/206	49.5±3.5
	p	45/216	42±4.8	104/206	50.5±3.5
PGR	T1	84/216	81±3.8	174/206	84.5±2.5
	T2	20/216	19±3.8	32/206	15.5±2.5

Comparative analysis of the frequencies of *Xba1* and *PvuII* polymorphisms of the *ERα* and *PGR* genes in the group of women with uterine fibroids and in the population control group revealed no statistically significant differences ($p>0.05$).

The distribution of genotype frequencies for *Xba1* and *PvuII* polymorphisms of the *ERα* gene was performed (Table 86).

Table 86

Distribution of *ERα* genotypes in the group of women with uterine fibroids and in the population control group

Gene	Genotype	Women with uterine fibroids		Population control group	
		n	h±S_h (%)	n	h±S_h (%)
ERα (Xba1)	xx	3/54	5.4±3.2	10/103	10±3.0
	XX	27/54	50.0±6.8	42/103	41±4.9
	Xx	24/54	44.4±6.8	51/103	49±4.9
ERα (PvuII)	pp	10/54	18.5±5.3	27/103	26±4.3
	PP	19/54	35.2±6.5	26/103	25±4.3
	Pp	25/54	46.3±6.8	50/103	49±4.9

Comparative analysis of genotype frequency distribution in the group of women with uterine fibroids and in the population sample also revealed no statistically significant differences (p>0.05) in the genotypes under study.

Analysis of the frequencies of combined genotypes for polymorphic restriction sites *Xba1* and *PvuII* did not identify the genotypes *XxPP*, *xxPP* and *xxPp* in any of the groups (Figure 33).

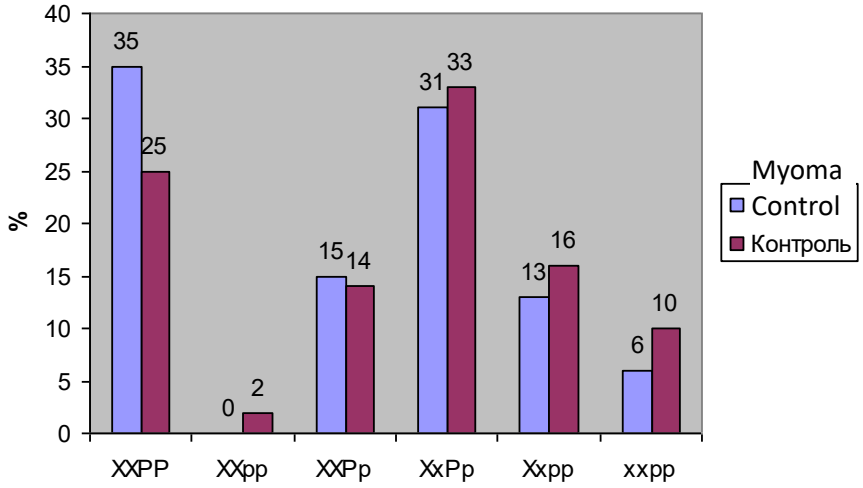


Figure 33

Distribution of genotypes for polymorphic restriction sites *PvuII* and *XbaI* of the estrogen receptor gene in women with uterine fibroids and in the population control group

The distribution of genotype frequencies did not differ significantly between the studied groups (p>0.05). However, there is a tendency to increase the frequency of the ‘mutant’ *XXPP* genotype in the group of women with uterine fibroids (35%) compared to women from the population control group (25%).

The frequency of the studied receptor genotypes depending on the presence of uterine myoma recurrences was evaluated (Table 87).

Table 87

Distribution of genotypes in the group of women with and without uterine myoma recurrence

Erα genotypes	XX		Xx		xx		Total
	n	%	n	%	n	%	
With recurrence	6	54.5	11	25	5	21.7	22
Without recurrence	5	45.5	44	75	18	78.3	67

p>0.05

In the absence of significant differences, there was a tendency to increase the frequency of detection of the *xx* estrogen receptor genotype in women without signs of uterine myoma recurrence as compared to women with recurrence.

The frequency of different variants of progesterone receptor gene polymorphism (*PGR*) in women with uterine fibroids was analyzed. The polymorphic variant of the progesterone receptor gene containing a 306 bp *Alu* insertion in intron *G* was named *Progins* (allele T2) [46] (Table 88).

Table 88

Distribution of genotypes in the group of women with uterine fibroids and in the population control group by *PGR* genes

Gene	Genotype	Women with uterine fibroids		Population control group	
		n	$h \pm S_h$ (%)	n	$h \pm S_h$ (%)
PGR	T1/ T1	35/54	65±6.5	72/103	70±4.5
	T1/T2	18/54	33±6.4	30/103	29±4.5
	T2/T2	1/54	2±1.9	1/103	1±1.0

(p>0,05)

The frequency of polymorphic alleles of the progesterone receptor gene did not differ significantly in the two studied groups. Comparative analysis revealed no statistically significant differences in the T1/T1, T1/T2 and T2/T2genotypes of the *PGR* gene in the group of women with uterine fibroids and in the population control group.

The distribution of progesterone receptor gene genotype frequencies was also analyzed in women with *XXPP* genotype at polymorphic loci *Xba1* and *PvuII* of the estrogen receptor gene in the group of women with uterine fibroids and in the population control group (Table 89).

Table 89

Distribution of genotypes for the progesterone receptor gene in the group of women with 'mutant' *XXPP* genotype for the estrogen receptor gene

	Women with uterine fibroids		Population control group	
	n	%	n	%
T1/T1	25	71.4	22	88
T1/T2	8	22.8	3	12
T2/T2	2	5.7	0	0
Всего	35	100	25	100

$p>0.05$

No significant differences in the distribution of genotype frequencies for the progesterone receptor gene were revealed. In women with the 'mutant' *XXPP* genotype of the estrogen receptor gene, there is a tendency for a higher total frequency of T2/T2 and T1/T2 genotypes carrying *Alu* insertion of the progesterone receptor gene in the group of women with uterine fibroids (more than 28%) compared to the population control group (12%).

Results of determining the polymorphism of the catechol-O-methyltransferase gene (*COMT*)

Transversion of G to A in the fourth exon of the *COMT* gene leads to the replacement of the amino acid valine by methionine in position 158 of the protein, thus determining the polymorphism of this gene, which is functionally significant – in the presence of the A/A genotype, the enzymatic activity of 2-methoxyestradiol is reduced almost 4-fold (Lotta T., 2005), whereas in the presence of G/G genotype catechol-O-methyltransferase converts 2-hydroxyestrogen into its methylated form more efficiently and faster and thus reduces the amount of anti-estrogen, creating a higher level of active forms of estrogen in tissues. To determine the frequency of *COMT* gene polymorphism, a comparative analysis was performed with the selection of 45 women with multiple uterine myoma (with the presence of 2-6 myomas of different localization) from the group of examined women.

The allele frequencies of polymorphic variant *A108G* of the *COMT* gene were analyzed in patients with uterine fibroids and women from the population control group (Table 90).

Table 90

Allele frequencies of the COMT gene in the group of women with uterine fibroids and in women from the population control group

	Women with uterine fibroids, n=208		Women with a solitary myoma, n=59		Women with multiple myomas, n=45		Population control group, n=59	
	abs.	%	abs.	%	abs.	%	abs.	%
Allele								
G	113	54.3	56	47.5*	57	63.3*	58	49.2
A	95	45.7	62	52.5	33	36.7	60	50.8
Genotype								
GG (Val/Val)	30	28.8	12	20.3**	18	40**	11	18.6**
GA (Val/Met)	53	51	32	54.2	21	46.7	36	61
AA (Met/Met)	21	20.2	15	25.5	6	13.3	12	20.4

*p=0.023

**p=0.028 when comparing groups of women with multiple myomas and with a solitary myoma; p=0.016 when comparing groups of women with multiple myomas with the population control group

It was revealed that the frequency of the G allele in the group of women with uterine fibroids and in the control group was 54.3% and 49.2%, respectively (p=0.369). At the same time, the frequency of the G allele in women with multiple myomas was 63.3% as compared to 47.5% in women with a single myoma (p=0.023) and 49.2% as compared to the population control group (p=0.042).

When comparing the frequency of the 'active' Val/Val variant, it was determined that this variant dominates in the group of women with multiple uterine myoma nodes as compared to the group of women with solitary myomas and women from the population control group (40.0%, 20.3% and 18.6%, respectively; p=0.028 and p=0.016).

The frequencies of polymorphisms of the *COMT* gene depending on the presence/absence of uterine myoma recurrence were compared (Table 91).

Table 91

Allele frequencies of the *COMT* gene in women with and without uterine myoma recurrence

COMT genotypes	GG		GA		AA	
	n	%	n	%	n	%
With recurrence	16	80*	5	25*	2	14.3*
Without recurrence	4	20	15	75	12	85.7
Total	20	100	20	100	14	100

*p=0.044 (GG/GA), p=0.031 (GA/AA)

In women with GG genotype, uterine myoma recurrence was found in 80% of cases, whereas in the case of GA and AA genotype variants, the disease recurrence was detected in 25% and 14.3% of cases, respectively.

Results of genotype frequency analysis for the *CYP19* gene

The frequency of *CYP19* genotypes was analyzed. It was revealed that in the group of women with uterine fibroids there was a tendency to increase the frequency of del/del genotype (11.1%) as compared to the population sample (3.9%). The number of patients with ins/ins genotype in the group of women with uterine fibroids amounted to 21 (38.9%), while in the population sample there were 59 patients (58%). The del/ins genotype was found at a frequency of 50% and 38.8% in the group of patients with uterine fibroids and in the population sample, respectively (Table 92).

Table 92

Frequencies of *CYP19* genotypes in the group of patients with uterine fibroids and in the population control group

Genotypes	Women with uterine fibroids		Population control group		p
	n	%	n	%	
del/del	6	11.1	4	3.9	0.06
del/ins	27	50	40	38.8	0.17
ins/ins	21	38.9	59	57.3	0.14

p=0.1334

Comparative analysis of the frequencies of genotypes for the *CYP19* gene in the group of patients with uterine fibroids and in the population control group did not reveal statistically significant differences.

Thus, no significant change in the frequency of polymorphisms of estrogen receptor genes (*Xbal* and *PvuII*) and progesterone receptor genes depending on the presence of uterine myoma was revealed; a tendency to increase the frequency of carrying the *XXPP* genotype of estrogen receptor in uterine fibroids compared to the population control group was revealed. The combination of uterine myoma with adenomyosis is also not associated with polymorphisms of progesterone receptor

genes, *PvuII* and *XbaI* polymorphisms of estrogen receptor gene, *COMT* gene and *CYP19* gene. The G/G polymorphism in the catechol-O-methyltransferase (*COMT*) gene associated with higher enzyme activity is significantly more frequently detected in women with multiple uterine myomas, determining the clinical significance of detecting this variant.

We analyzed the allele frequency of *COMT* and *CYP19* genes in the group of women with uterine fibroids depending on the IVF (IVF+ICSI) program outcomes.

In 34 women with uterine fibroids who had previously undergone the study of *COMT* and *CYP19* gene polymorphisms, pregnancy occurred in 9 women (26.5%). Analysis of the frequency of *COMT* and *CYP19* gene polymorphic variants depending on the IVF (IVF+ICSI) program outcome did not reveal any significant differences (Table 93).

Table 93

Frequencies of *COMT* and *CYP19* genotypes in the group of patients with uterine fibroids depending on the IVF (IVF+ICSI) program outcome

Genotypes	Achieved prgnancy (n=9)		Failed pregnancy (n=25)		p
	n	%	n	%	
COMT genotypes					
GG	5	55.6	11	44.0	>0.05
GA	3	33.3	8	32.0	>0.05
AA	1	11.1	6	24.0	>0.05
CYP19 genotypes					
del/del	1	11.1	4	16.0	>0.05
del/ins	4	44.4	10	40.0	>0.05
ins/ins	4	44.4	11	44.0	>0.05

The previously identified differences in the clinical course of uterine myoma in the GG genotype of the *COMT* gene were not accompanied by changes in the ART program efficiency.

Chapter 4. DISCUSSION

Improving the ART program efficiency, determining the factors predicting the results are topical areas of research in the field of reproductive health restoration, and the most efficient tactic is the formation of a personalized approach to pre-conception preparation [22]. Researchers' opinions on the significance of the influence of uterine myoma and genital endometriosis on ART program outcomes are contradictory. Uterine fibroids of submucosal localization are undoubtedly a factor in reducing both natural fertility and the efficiency of ART programs, whereas subserosal myomas, according to many researchers, do not affect pregnancy rates [345]. The idea of the negative role of intramural myomas in natural fertility and ART programs is debated. In previous years, a significant number of authors indicated that uterine intramural fibroids, which do not deform the uterine cavity, have no negative impact on the ART program efficiency [173, 374]; at the same time, in recent years, data on the presence of a negative impact of uterine intramural myoma on the pregnancy rate in IVF (IVF+ICSI) programs have been presented [110, 171, 294, 355]. Regarding EGE, there are also contradictory judgments about its effect on the ART program efficiency: Surrey E.S. et al. (2013), de Ziegler D. et al. (2018), found no negative effect [331, 365] at the same time, Muteshi C. M. et al. (2018), Zhang N. et al. (2022), Morcel K. et al. (2024), Alson S. et al. (2024), report a decreased pregnancy rate after IVF (IVF+ICSI) in genital endomentriosis [140, 305, 341, 381].

We have shown that the IVF (IVF+ICSI) program efficiency in women with uterine fibroids is 35.1%, in severe forms of genital endometriosis – 31.8%, in combination of uterine myoma and genital endometriosis – 30.9%, which is significantly lower as compared to women without proliferative diseases, comparable in age and history, pregnancy rate in which was determined as 45.8% ($p<0.05$). A significant decrease in pregnancy rate in IVF (IVF+ICSI) programs in women with uterine intramural fibroids (OR 0.53 (CI 0.31-0.93), $p<0.05$ and in adenomyosis (OR 0.2 (CI 0.04-0.91), $p<0.05$) was determined. In the discriminant

analysis, uterine fibroids of intramural localization and severe forms of genital endometriosis were identified as negative prognostic factors for pregnancy after an IVF (IVF+ICSI) program. Analysis of the negative impact of the combination of factors on IVF (IVF+ICSI) program outcomes highlighted the following combinations (at $p \leq 0.01$): multiple uterine fibroids and adenomyosis, multiple uterine fibroids and retrocervical endometriosis, adenomyosis and stage III EGE, multiple uterine fibroids and adenomyosis.

The impact of endometriosis on fertility is multifaceted; at the same time, the reasons for the reduced efficiency of IVF (IVF+ICSI) programs in endometriosis are debated. The need for surgical intervention, including that accompanied by thermal damage, devascularization of ovarian tissue in endometriomas determines the decrease in ovarian reserve; there is evidence that the presence of endometrioma regardless of surgical treatment is accompanied by a decrease in ovarian reserve indices (AMH level is reduced, FSH level is increased); it has been shown that in EGE the proportion of women with decreased AMH is significantly greater than in male factor infertility [342]. Due to a decrease in ovarian reserve, IVF programs (IVF+ICSI) in women with external genital endometriosis are accompanied by an increased rate of cycle cancellation associated with a lack of adequate response to ovarian stimulation. At the same time, the role of endometrioid ovarian lesions in the deterioration of oocyte quality and reduced efficiency of ART programs due to impaired embryo development is debated. There are published studies showing the negative impact of endometriomas on oocyte quality and fertilization outcomes [213, 257, 350]. On the other hand, Pacchiarotti A. et al. (2020) [319] showed that while the number of oocytes obtained from women with endometriosis decreased, the morphologic characteristics of embryos, implantation rate, and pregnancy rate were comparable in both groups, on the basis of which the authors suggested that in women with severe forms of endometriosis despite reduced ovarian reserve, the quality of embryos obtained does not suffer and pregnancy rate does not decrease. Similar results are demonstrated in a number of other clinical studies [104, 285, 351].

Our study shows that in women operated for severe forms of external genital endometriosis the decrease in the IVF (IVF+ICSI) program efficiency in terms of clinical pregnancy rate is determined by a decrease in ovarian reserve indices – decrease in AMH level as compared to women without proliferative diseases (1.3±0, 24 and 2.64±0.2, respectively) and the number of antral follicles (7.18±0.51 and 10.54±0.29, respectively), ($p<0.05$), which is confirmed by the data of correlation analysis – a positive correlation of AFC, the number of obtained oocytes, the number of dipronuclear zygotes, the number of embryos of satisfactory quality with the results of ART programs was revealed ($p<0.01$). At the same time, according to our data, despite the decrease in the quantitative indicators of ovulation stimulation, the quality of the embryos obtained from women with EGE does not suffer – we found that during ovulation stimulation in IVF protocols (IVF+ICSI) the number of oocytes was reduced by 1, 8 times as compared to women without proliferative diseases (4.8 and 8.6, respectively ($p<0.005$); at the same time, the efficiency of fertilization and embryo culturing, the number of embryos of optimal quality on day 4 is comparable (4.4 and 5.2, respectively ($p>0.05$). The decrease in the IVF (IVF+ICSI) program efficiency determined by the clinical pregnancy rate may be due to the posttransfer interaction between the blastocyst and the endometrium – with comparable embryo quality – largely determined by the state of the endometrium.

Sufficient endometrial blood supply in the middle of the secretion phase is one of the most important conditions for achieving pregnancy. In spontaneous ovulatory cycles in healthy women, there is a normal decrease in blood flow resistance indices in uterine arteries and their branches throughout the cycle (from the early follicular phase to the middle of the secretion phase) [17, 33], and an increase in blood flow resistance in the endometrial arteries is observed in women with habitual non-pregnancy [317]. Previously, we and other researchers have shown that a positive IVF program outcome is associated with a decrease in blood flow resistance throughout the cycle of superovulation stimulation [7, 61]. At the same time, it is known that women with uterine fibroids have a permanent decrease

in blood flow resistance indices in uterine arteries and their branches, including spiral arteries [31]. At the same time, Ng E.H. et al. found no differences in the blood supply indices of the endometrium in women with uterine fibroids and in the absence of myoma during IVF (IVF+ICSI) programs [130]. Kamel et al. showed that increased vascularization of the endometrium was detected in women with solitary intramural nodules, whereas no differences in uterine artery blood flow resistance indices (PI, RI) were found [120]. Increased expression of the TGF-β gene in women with uterine fibroids can be presented as one of the possible factors of increased blood flow activity in the endometrium in uterine fibroids [179]. We have shown that TGF-β secretion is significantly increased both in leiomyomas and in myometrium [10]. Overexpression of TGF-β3 is accompanied by excessive production of such extracellular matrix proteins as collagen-1, fibronectin, PAI-1, which enhances leiomyoma growth and is accompanied by impaired receptivity of the endometrium [59, 322, 334]. Blood flow parameters in the endometrium are also associated with the level of cytokines in the peri-implantation period and may influence the receptivity of the endometrium [56, 138]; cytokines are known to be involved in local angiogenesis during the formation of receptive of the endometrium [232]; we showed the association of high expression of angiogenesis factors and proliferation of VEGF, TGF-ß in the structures of the endometrium with the probability of pregnancy as compared to women who did not become pregnant ($p<0.01$) [9, 210].

Our evaluation of vascular resistance indices in the endometrial arteries showed a decrease in all studied indices on day 20-23 of the menstrual cycle as compared to the early follicular phase in the control group, which is consistent with the data of other studies [17, 317]. In women without uterine myoma, the highest pregnancy rate is associated with significantly lower indices of blood flow resistance indices in the spiral arteries during the peri-implantation period. At the same time, the greater value of PI reduction in the spiral arteries is determined in women with an achieved pregnancy. During a spontaneous cycle, women with uterine fibroids have significantly lower indices of vascular resistance to blood flow in uterine and

spiral arteries than women without uterine myoma (in the early follicular phase, PI in uterine arteries 1.70 ± 0.1 and 2.8 ± 0.2, respectively, $p<0.05$; PI in spiral arteries 0.49 ± 0.04 and 0.63 ± 0.03, respectively, $p<0.05$), and the ability to phase cyclic changes in ovulatory cycles was reduced. Despite the previously obtained data on the increase of vascular resistance indices in uterine arteries and their branches in women with adenomyosis [26], the study of these blood flow indices in the uterine artery basin in the combination of uterine myoma and adenomyosis revealed significantly lower indices as compared to the control group [20].

During ovulation stimulation cycles, women with uterine fibroids have no reliable dynamics of vascular resistance reduction in both uterine and spiral arteries (when comparing PI, RI, SDR measured on the day of stimulation start and on the day of oocyte final maturation trigger administration), and when comparing PI and RI with the indices of control group women and women with EGE – blood flow resistance indices in women with uterine fibroids are significantly lower (PI – 0.53±0.05, 0.70±0.02 and 0.68±0.02, respectively, $p<0.05$). There is no correlation between clinical pregnancy rate and spiral artery blood flow resistance indices on the day of ovulation trigger administration and on the day of embryo transfer in women with uterine fibroids, whereas in women without uterine myoma, blood flow indices in spiral arteries have a significant predictive value. In uterine fibroids, a stable decrease of blood flow resistance in uterine and spiral arteries was revealed, which may characterize increased endometrial vascularization during the stimulation cycle in IVF programs (IVF+ICSI) and negatively affect the possibility of blastocyst implantation [20].

Inflammation in EGE is considered a key mechanism associated with pain syndrome and with impaired receptivity of the endometrium [222, 227]. In our studies, the balance of growth factors in the embryo transfer cycle has been shown to be critical for pregnancy [32, 135]. The disorders associated with progesterone resistance in EGE concern changes in the expression of a significant number of receptivity markers of the endometrium, including growth factors and prostaglandins, integrins, cadherins, selectins, immunoglobulins, cytokines, LIF,

IL6, IL11, glycodelin A [208, 239, 240, 226], which in turn leads to a decrease in the expression of HOXA10 and HOXA11 genes involved in interaction with the blastocyst during the implantation window (normally, with adequate progesterone levels, the expression of these factors increases in the middle of the secretion phase). If there is a deficiency of progesterone action, the activity of the Wnt/b-catenin signaling pathway is disturbed [216]. Thus, markers of the endometrial receptivity demonstrate pronounced interrelations with proinflammatory and hormonal factors.

In our study, the results of determining the expression of immunocompetent cells associated with proinflammatory effects in the endometrium were included in the analysis: CD8+ is a marker of cytotoxic T-lymphocytes, the cytolytic activity of which under physiological conditions should decrease in the secretion phase, and at the onset of pregnancy should be significantly suppressed, determining the tolerance of the mother's body to the fetus [380]; increased expression of CD8+ cells in the secretion phase accompanies the state of chronic inflammatory reaction of any etiology; CD20+ is a marker of B-lymphocytes, which plays a significant role in the development of chronic inflammatory reaction in the endometrium. CD8+, CD20+ immunocompetent cells are known to have a negative effect on ER, PR expression in endometrial stroma. CD56+ is a marker of natural killer cells with high cytolytic potential, involved in the regulation of angiogenesis; their expression in the decidual membrane is significantly increased in habitual miscarriage [361]. CD138+ is a marker of plasmocytes and is used as a diagnostic marker of chronic endometritis [54, 70, 85, 96]. Increased CD138+ expression is associated with increased IL-6 expression and is associated with impaired implantation [258]. We found that in women with stage III-IV EGE the state of the endometrium is characterized by disorders of secretory transformation with decreased expression of progesterone receptors in endometrial stroma in comparison with women without proliferative diseases (139.0 and 163.0, respectively, $p=0.021$) and increased expression of proinflammatory cytokines (CD20+ – 15.0 and 8.5, respectively, $p=0.047$) and (CD138+ – 1.4 and 0.7, respectively, $p<0.005$). When hormone therapy for EGE was performed in the present study, an increase in progesterone receptor expression

from 148.8 to 166.2 was shown. The state of progesterone receptor deficiency in the endometrium of women with EGE determines a decrease in the efficacy of ART infertility treatment in such women, whereas after EGE hormonal therapy an increase in progesterone receptor expression and a higher pregnancy rate were determined. The endometrial receptivity disorders in endometriosis are largely associated with the inflammatory nature of the disease. Progesterone resistance leads to insufficient compensation of estrogen influence, additional increase in the activity of inflammatory reaction, inadequate differentiation of structures of the endometrium, which eventually disrupts the interaction with embryos. In EGE, signaling pathways associated with cell proliferation and survival are activated in the endometrium, whereas antiproliferative signaling pathways are deactivated. Thus, eutopic endometrium is a critical barrier to implantation in women with endometriosis.

Dienogest is a selective progestin of the 4th generation, a derivative of 19-norsteroiods, highly selective to progesterone receptors. Given long term daily administration of dienogest, a decrease in the production of prostaglandin E2, proinflammatory cytokines IL-6, IL-8, aromatase VEGF has been shown both in eutopic endometrium and in implants [100, 101]; few experimental data have shown an increase in the expression of progesterone A and B receptors, which may contribute to the compensation of progesterone resistance [97]. It is known that the use of dienogest causes significant effects from the point of view of endometriosis pathogenesis – decidualization and atrophy of endometrioid foci, anti-inflammatory effect, anti-angiogenic, antiproliferative effects; it is shown that against the background of the drug administration the number of natural killer cells infiltrating glandular structures of the endometrium increases, which causes a potential beneficial effect on the process of embryo implantation [40, 314]. At the same time, Reiter A. and co-authors [348], based on the results of their meta-analysis, concluded that further studies are required to evaluate the role of dienogest prescription in improving the effectiveness of IVF programs (no significant positive effect of long-

term dienogest prescription on the incidence of pregnancy and delivery after IVF was found).

The present study shows that women with stage III-IV EGE have a decreased level of progesterone receptor expression in endometrial stroma as compared to women from the control group; the results of a multivariate discriminant analysis identified hormone therapy for EGE for a period not exceeding 12 months prior to the start of the IVF (IVF+ICSI) program as a positive prognostic factor.

Our study shows that the formation of physiologic secretory transformation of the endometrium is an important aspect of predecidual changes in the formation of a receptive endometrium, ready not only for contact with the blastocyst, but also for appropriate differentiation in response to implantation [21, 37]. After pregravid preparation with the use of dienogest in women with EGE, we determined that the efficiency of the superovulation stimulation stage does not differ; at the same time, we showed the effect of this therapy on increasing the rate of clinical pregnancy up to 43.7% as compared to 28.9% (in women who did not receive the therapy) ($p=0.041$), OR 1.9; CI 1.01-3.56, $p<0.05$; in women with EGE combined with uterine fibroids after similar therapy with dienogest, pregnancy rate was not significantly different as compared to women with EGE without dienogest therapy (32.5%, $p=0.754$).

There are few studies of the morphological state of the endometrium in relation to ART program outcomes in women with uterine intramural fibroids. A number of studies showed that in the case of submucosal and intramural localization of myomas in the endometrium, there are signs of chronic inflammatory reaction, including reproductive dysfunction [25, 102]. It is noted that a significant role in the pathogenesis of an impaired functional state of the endometrium belongs to proangiogenic cytokines that determine endometrial blood supply. In particular, an increase in the expression of marker CD34 against the background of high frequency of chronic endometritis and hyperplasia of the endometrium [16, 86], disorders of progesterone and estrogen receptor expression [16], an increase in the number of immunocompetent markers CD8, CD20, CD138 [29] were shown. Studies of

endometrium in women with uterine fibroids in the peri-implantation period show both phase transformation disorders and changes in the expression of various cytokines affecting the factors responsible for the formation of endometrial receptivity [195].

In women with uterine fibroids, we found a tendency to increase the expression of CD8+, CD56+, CD138+, which may be associated with impaired regulation of angiogenesis in the secretion phase and hyperperfusion – increased endometrial blood flow (with a detected decrease in PI, RI) – and contribute to implantation failures.

In women with EGE and with uterine fibroids, the characteristics of the state of the endometrium associated with the IVF (IVF+ICSI) program efficiency were determined. In EGE, a reliable negative impact is shown for a decrease in the expression of progesterone receptors and an increase in the expression of proinflammatory cytokines; in uterine fibroids, a reliable negative impact on the result of the IVF program is determined by an increase in endometrial blood flow determined by a decrease in vascular resistance indices (PI, RI). Certain failure factors allow us to form a tactic of pregravid hormonal preparation that is efficient for EGE.

When planning fertility treatment for women with uterine fibroids, the ability to obtain objective indicators that predict the progression of the disease in relation to IVF protocol efficiency and maternal and fetal outcome is of great importance in determining the prognosis of efficacy. This is particularly true in the case of co-morbid, operated and recurrent forms. It is known that data on the genetic characteristics of the disease can shape the prognosis of the clinical course. The presence of associations between various *ERα* gene polymorphism variants and estrogen-related diseases, including adenomyosis, uterine myoma, etc., has been confirmed by genetic studies previously [271]. At the same time, data on the association of the *PvuII* polymorphic locus of the *ERα* gene with uterine fibroids are few and ambiguous [27, 50, 55, 73]. Our comparative analysis of the distribution of allele and genotype frequencies for the *PvuII* and *XbaI* polymorphic sites of the *ERα*

gene and the *Alu* insertion polymorphism of the *PGR* gene in the group of women with uterine fibroids and in the population control group revealed no statistically significant differences ($p>0.05$). At the same time, there was a tendency for a decrease in the frequency of homozygotes for the normal *pp* genotype (*PvuII* polymorphism) in women with uterine fibroids (19%) as compared to the population control group (26%) and an increase in the frequency of homozygotes for the 'mutant' allele **P* 35% and 25%, respectively. The same trend was observed when analyzing genotypes for the *Xba1* polymorphism. The frequency of homozygotes for the normal allele **x* in women with uterine fibroids corresponded to 6%, in the population control group -10%, and the frequency of homozygotes for the 'mutant' allele **X*- 50% and 42%, respectively. Catechol-O-methyl transferase (*COMT*) is involved in the catabolism of catecholamines (adrenaline, noradrenaline, dopamine) and catecholestrogens. In the presence of genotype A/A, enzymatic activity is reduced [231], whereas in the presence of genotype G/G catechol-O-methyltransferase is more active and provides a significant reduction of 2-hydroxyestrogen (2HONE2), which exhibits anti-estrogenic activity in tissues. The data on the frequency of associations of these genotypes with uterine fibroids are few and multidirectional – according to Denschlag D. Et al., (2006), polymorphic variant A/G is not associated with uterine fibroids [182]; the study by Heidari M. et al. (2019) showed the association of AA+GG genotypes with an increased risk of uterine myoma development (in contrast to GA genotype) [190]; the association of G/G genotype of SOMT with the size of uterine myomas was shown [337, 338].

According to our data, there were no differences in the content of G/G and A/A genotypes for the COMT gene between women with uterine fibroids and the population control group. However, the G/G genotype, which determines a higher concentration of active forms of estrogens in tissues, is significantly more frequent in women with multiple uterine myoma nodules compared to women with solitary nodules and the population control group. The identified differences in the frequency of different genotype variants depending on the presence of solitary or multiple uterine myoma nodules may apparently explain the contradictory results obtained

by researchers earlier. When analyzing the frequencies of COMT genotypes, we also found that the G/G variant was significantly more frequently detected in women with recurent uterine myoma as compared to women who did not have recurrent uterine myoma [18, 81, 82]. The analysis of CYP19 gene polymorphism can be recommended as a prognostic test to assess the risk of both uterine myoma recurrence and the formation of several myomas, which is of great importance for planning the time of reproductive function realization, since these clinical conditions are associated with an increased frequency of surgical interventions and, accordingly, an increased time to pregnancy. The previously performed comparative analysis of the genotype frequencies of the polymorphic variant of the CYP19 gene (del (TCT)) between the groups of women with adenomyosis and healthy subjects revealed statistically significant differences – the frequency of carrying the D allele in patients was determined to be significantly higher than in the control group [58]. Thereby, it is assumed that the risk of adenomyosis development increases 2.5-fold in the case of carrying del (TCT) in the CYP19 gene. At the same time, other authors show that the difference in aromatase gene polymorphisms between healthy women and women with myoma and endometriosis is not significant [182]. The present study revealed no data on the association of the studied polymorphism variants with the presence of a combination of uterine myoma and adenomyosis. The study of the frequency of CYP19 aromatase polymorphism variants in women with uterine fibroids as compared to the population control group did not reveal any significant differences. We found that in women with uterine fibroids, the genetic profile associated with the metabolism and receptivity of sex hormones has no specific differences: allele and genotype frequency distributions of the estrogen receptor α gene and progesterone receptor gene are comparable to those in the population control group ($p>0.05$). When uterine myoma and adenomyosis are combined, there are also no significant differences in the distribution of estrogen receptor gene, progesterone receptor gene, COMT and CYP19 genotype frequencies relative to the population control group ($p>0.05$) [19]. Thus, the presence of an unfavorable polymorphism of the COMT gene is a risk factor for both primary and repeated

surgical interventions for women with uterine fibroids; at the same time, considering the results of our study showing that conservative myomectomy is a factor of unfavorable prognosis of the IVF program, the detection of the G/G genotype is associated with an increased risk for the reproductive function realization.

Thus, uterine fibroids and genital endometriosis are independent factors in reducing the IVF (IVF+ICSI) program efficiency. Stable decrease of blood flow resistance in the endometrium with no significant dynamic fluctuations during the IVF (IVF+ICSI) cycle was determined as a factor in decreasing ART program efficiency in women with uterine fibroids. Despite the decrease in ovarian reserve indices in women with severe EGE entering ART programs, accompanied by a decrease in the quantitative results of superovulation stimulation, the efficiency of fertilization and embryo culturing is not disturbed; the decrease in pregnancy rate is due to changes in the state of the eutopic endometrium.

CONCLUSIONS

1. Uterine intramural myoma and severe forms of external genital endometriosis (stage III-IV), as well as the combination of uterine myoma and genital endometriosis are associated with a significantly lower rate of clinically verified pregnancy rate within IVF (IVF+ICSI) programs as compared to the pregnancy rate in women without uterine myoma and genital endometriosis (OR 0.64, CI 0.42-0.98, OR 0.55, CI 0.34-0.9, OR 0.53, CI 0.37-0.76, respectively, $p<0.05$).

2. In women with uterine intramural myoma and with stage III-IV EGE within IVF (IVF+ICSI) programs, the number of punctured follicles, obtained oocytes, bipronuclear zygotes, embryos of optimal quality were significantly lower as compared to the same indices in women without uterine myoma and genital endometriosis. A significant positive correlation ($p<0.05$) between the above indices and the efficiency of IVF (IVF+ICSI) programs was identified. The oocyte fertilization rate and the frequency of obtaining optimal quality embryos did not differ in comparison with the same indices in women without uterine myoma and genital endometriosis.

3. Women with a history of intramural myomectomy had a clinically verified pregnancy after IVF (IVF+ICSI) programs less frequently than women without myomectomy, OR 0.35 (0.16-0.77, $p=0.008$).

4. Doppler indices of blood flow resistance in spiral arteries (PI, RI, SDR) in women without uterine myoma and genital endometriosis, determined in the dynamics of IVF (IVF+ICSI) programs, are associated with the clinical pregnancy rate – a significant correlation of the above indices on the day of embryo transfer was revealed ($r=-0.47$ for PI, $r=-0.44$ for RI, $r=-0.41$ for SDR, $p<0.03$). In the cycles that ended with pregnancy, the dynamics of PI in the spiral arteries from the day of the stimulation initiation to embryo transfer was characterized by a significant decrease by an average of 0.25 ± 0.01. No association with the frequency of pregnancy was found in the uterine arteries.

5. Dynamic Doppler study of blood flow indices in the spiral arteries within an IVF (IVF+ICSI) program in women with EGE showed a significant correlation between PI (r=-0.36) and SDR (r=-0.46), which were determined on the day of embryo transfer, and the clinical pregnancy rate ($p<0.03$). In cycles that ended in pregnancy, PI significantly decreased from the day of stimulation initiation to embryo transfer by an average of 0.20 ± 0.02. No association with pregnancy rate was identified during the evolution of uterine artery indices.

6. In women with intramural uterine myoma, no significant relationship of Doppler indices of blood flow resistance (PI, RI, SDR) in uterine and spiral arteries with the pregnancy rate was established; no data on reliable dynamics of blood flow resistance indices during the IVF (IVF+ICSI) program were obtained. During the IVF (IVF+ICSI) cycle, all determined indices were steadily and significantly reduced ($p<0.05$) relative to the same indices in women without uterine myoma and genital endometriosis.

7. According to the immunohistochemical study on day 20-23 of the cycle prior to an IVF (IVF+ICSI) program, in women with uterine intramural myoma, the magnitude of estrogen and progesterone receptor expression in the glands and endometrial stroma and the expression of inflammatory response markers (CD8+, CD20+, CD56+, CD138+) have no significant differences as compared to the same indices in women without uterine myoma and genital endometriosis. The studied immunohistochemical indices of the endometrium state were not identified as predictors of clinical pregnancy based on multivariate analysis of variance.

8. According to the data of an immunohistochemical study of endometrium on day 20-23 of the cycle, a significant decrease of progesterone receptor expression in the endometrial stroma was found ($p=0,021$) in women with stage III-IV EGE; the content of inflammatory response markers CD20+ and CD138+ was increased ($p<0,005$) relative to similar indicators in women without uterine myoma and genital endometriosis. In stage I-II EGE, no significant differences were found in the expression of estrogen and progesterone receptors and inflammatory response

markers relative to the same indices in women without uterine myoma and genital endometriosis.

9. In women with EGE with a history of GnRHa therapy, a significantly higher frequency of secretory transformation of the endometrium (48.3% and 39.2%, respectively, $p<0.05$) and a significantly higher level of progesterone receptor expression in endometrial stroma (166.2 and 148.8, respectively, $p=0.047$) were determined as compared to women who did not receive similar therapy.

10. According to the results of the multiple discriminant analysis of the data of women with EGE who entered IVF (IVF+ICSI) programs, the following factors of positive prognosis regarding the pregnancy rate with a probability of 89% were determined: hormone therapy for EGE completed within 12 months prior to an IVF (IVF+ICSI) program and the presence of secretory transformation of the endometrium during the peri-implantation period.

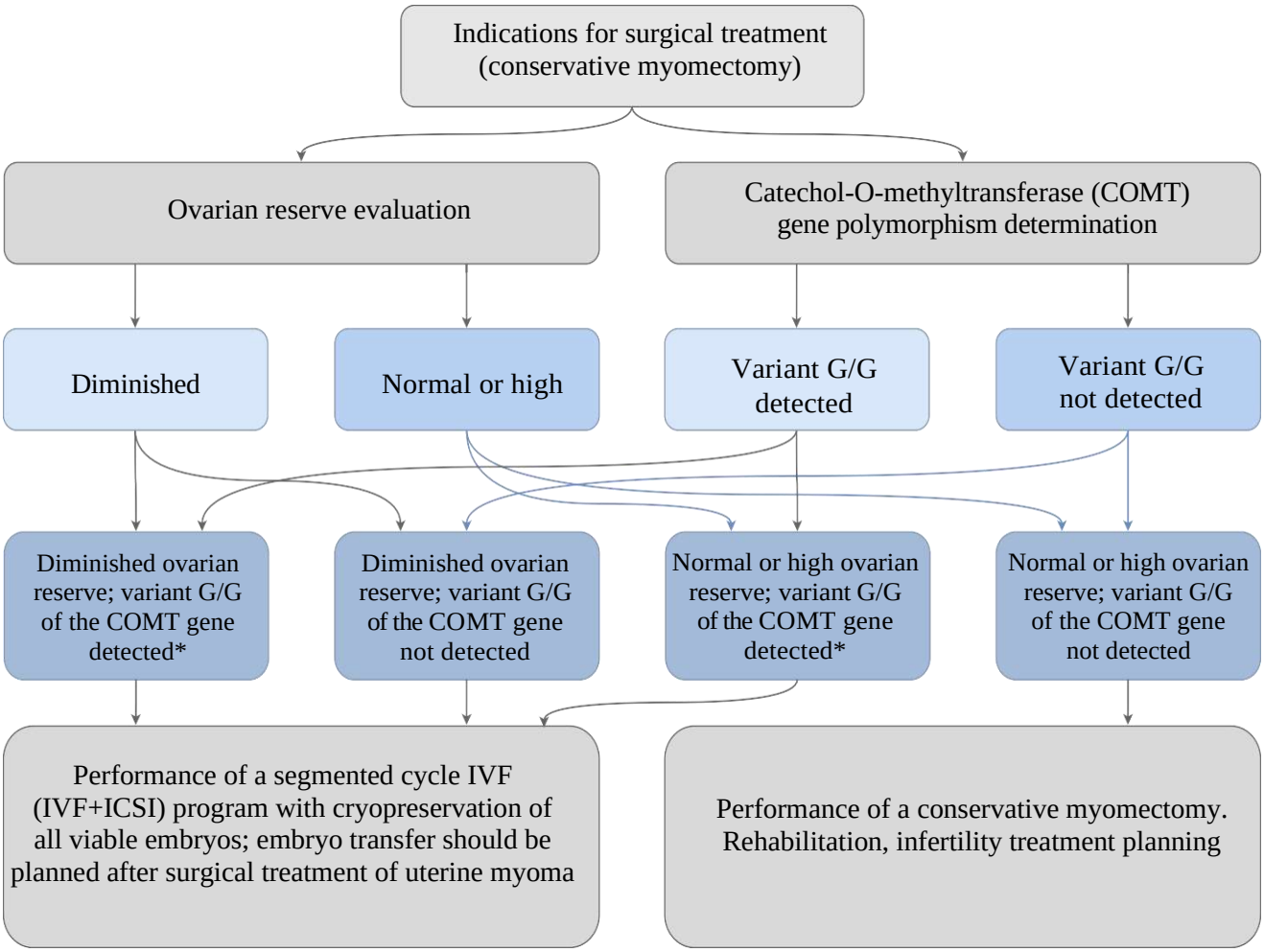
11. Preconception preparation with dienogest in women with EGE determines a higher clinical pregnancy rate within IVF (IVF+ICSI) programs as compared to women not treated with dienogest therapy, OR 1.9; CI 1.01-3.56, ($p<0.05$).

12. In women with multiple uterine myoma and recurrent course of the disease, a significantly higher frequency of polymorphism G/G of the catechol-O-methyltransferase gene (COMT) is determined. The efficiency of IVF (IVF+ICSI) programs in women with uterine myoma does not depend on the variant of COMT and CYP19 gene polymorphism.

PRACTICAL RECOMMENDATIONS

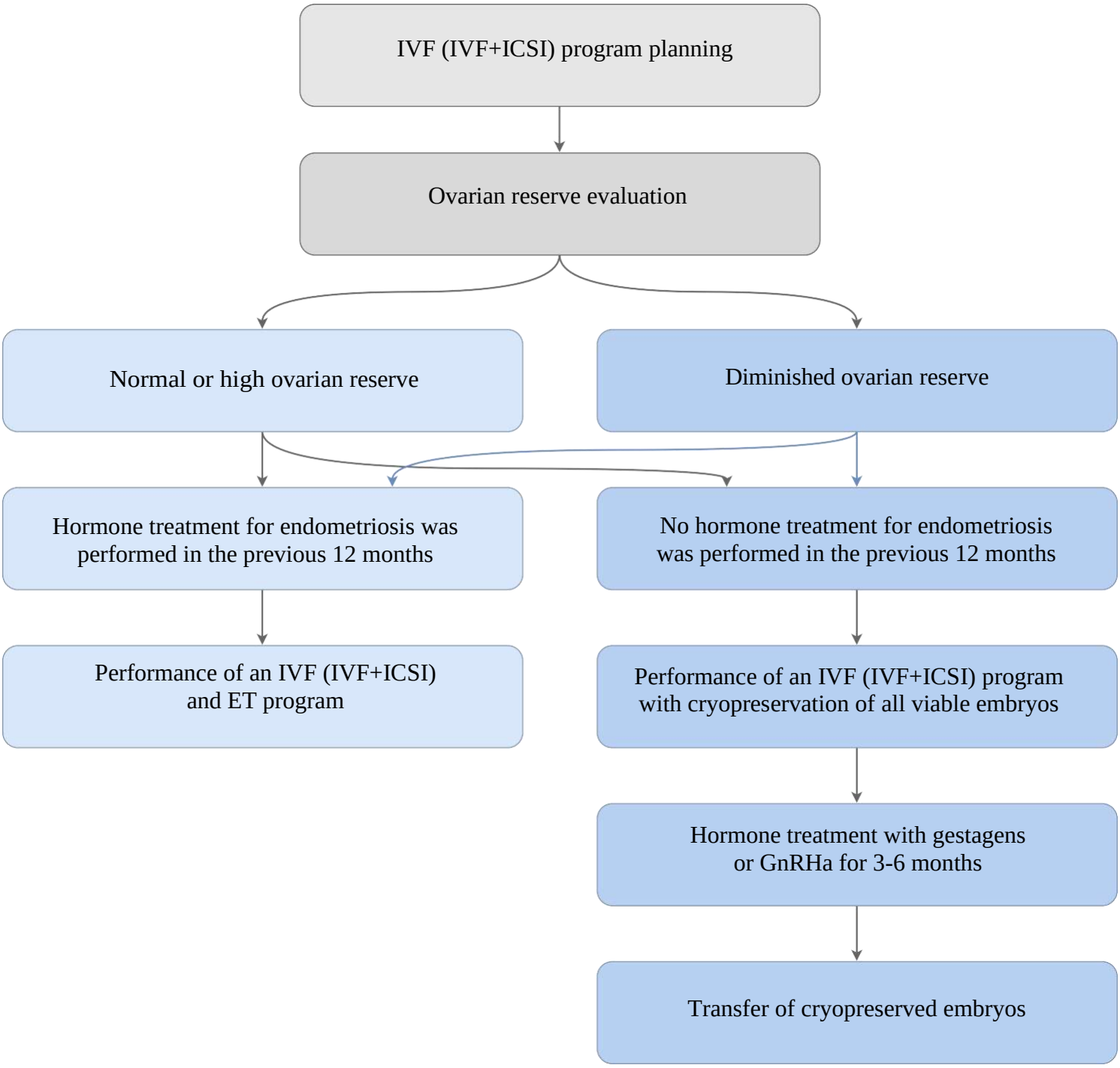
1. In the presence of indications for myomectomy in women of older reproductive age and with diminished ovarian reserve before myomectomy, an IVF (IVF+ICSI) program is indicated, followed by cryopreservation of all viable embryos with planning of embryo transfer after rehabilitation.
2. For women with multiple uterine myoma who are planning infertility treatment, determination of the polymorphism of the catechol-O-methyltransferase gene (COMT) is indicated; if the G/G variant is detected, it is necessary to inform about the high risk of recurrent course of the disease after surgical treatment with the recommendation to treat infertility by ART methods during the recurrence-free period.
3. In women with EGE, pre-conception planning for IVF (IVF+ICSI) programs should include 3-6 months of hormone treatment with gestagens or GnRHa if such treatment has not been performed within less than 12 months prior to the program.
4. Under conditions of a diminished ovarian reserve in women with EGE and/or older reproductive age, ART programs with cryopreservation of all obtained embryos are indicated, followed by the proposed pre-conception preparation.
5. If the values of blood flow resistance in the spiral arteries in women without uterine myoma on the day of embryo transfer are below the threshold values (PI<0.61, RI <0.45 and SDR <1.9), the probability of pregnancy is reduced, and discussion of the feasibility of embryo transfer in the given ART cycle is indicated.

Algorithm of preimplantation preparation in planning ART programs in women with uterine fibroids



***** - inform about the high risk of recurrent uterine myoma

Algorithm of preimplantation preparation for ART program in women with external genital endometriosis



LIST OF ABBREVIATIONS

GnRHa	gonadotrophin-releasing hormone agonist
AMH	anti-Müllerian hormone
GnRHant	gonadotrophin-releasing hormone antagonists
ART	assisted reproductive technologies
HSG	hysterosalpingography
GE	genital endometriosis
IHC	immunohistochemistry
ICSI	intracytoplasmic sperm injection
IL	interleukin
BMI	body mass index
RI	resistance index
AFC	antral follicle count
CHC	combined hormonal contraceptives
LH	luteinizing hormone
LIF	leukaemia inhibitory factor
mRNA	micro ribonucleic acid
MCP-1	monocyte chemotactic protein 1
EGE	external genital endometriosis
PGT	preimplantation genetic screening
PGT-A	preimplantation genetic screening of embrypos for aneuploidy
PI	pulsatility index
ET	embryo transfer into the uterine cavity
OHSS	ovarian hyperstimulation syndrome
PCOS	polycystic ovarian syndrome
VEGF	vascular endothelial growth factor
OR	transvaginal oocyte retrieval
TGF-β	transforming growth factor beta
US	ultrasound

NGF	nerve growth factor
FSH	follicle-stimulating hormone
CG	chorionic gonadotropin
CPR	clinical pregnancy rate
IVF	in vitro fertilisation
EGF	endothelial growth factor
3D US	three-dimensional ultrasound
BCL6	B-cell lymphoma 6
BMP	bone morphogenetic proteins
CD	cluster of differentiation
COMT	catechol-O-methyltransferase
ERα	estrogen receptors alpha
ERß	estrogen receptors beta
FI	flow index
Kras	gene encoding a RAS/MAPK signaling cascade protein
NK cells	natural killer cells
PAI-1	plasminogen activator inhibitor
VI	vascularization index
VFI	perfusion index
STAT	signal transducer and activator of transcription

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