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РЕСПУБЛИКИ КАЗАХСТАН

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ENDOMETRIOSIS GENITALIS EXTERNA, IMMUNOHISTOCHEMICAL DIAGNOSIS OF ENDOMETRIUM IMPLANTATION RECEPTIVITY

Abstract. The lack of implantation in cycles of in vitro fertilization (IVF) is one of the main problems of modern reproductive medicine. Implantation is a multifactorial process, it is difficult to imagine the existence of a single criterion, with which it is possible to determine the receptivity of the endometrium. However, the possibility of accurate diagnosis of the state of endometrium receptivity cannot be overestimated in terms of clinical relevance. Endometrial biopsy today remains the most common method to diagnose pathological conditions that lead to a significant reduction or loss of the ability of endometrial implantation.

Important one is the ability to predict the onset of implantation, since the detection of violations make it possible to avoid unnecessary emotional stress, not to carry out the support of the luteal phase and the hopeless refrain from embryo transfer, preserving them for the delayed transfer. We evaluated the possibility of using the immunohistochemical study with the assessment of key biological molecules involved in the formation of implantation window (LIF, ER, PR, Integrin, TGF-β1, VEGF), for prognosis and diagnosis of disorders of the endometrium implantation receptivity in patients with external genital endometriosis. As a result of studies there have been verified informative immunohistochemical markers that have been used to create the IVF treatment outcome prediction algorithm. With the help of the developed model it is possible to predict the group with poor outcome of treatment that can reasonably plan the tactics of treatment measures and enhances the effectiveness of IVF treatment.

Key words: IVF, endometrium implantation receptivity, receptivity, "implantation window", LIF, VEGF, Integrin αVβ3, TGFβ1, ER, PR.

Infertile couple is an important medical, social and economic problem. According to WHO, its frequency is 10-15%, and has no tendency to decrease. Lack of efficiency of restoration methods of natural human fertility has stimulated the development of new assisted reproductive technologies such as in vitro fertilization (IVF), the effectiveness of which varies from 28.5% to 32.5% [1]. Optimizing the efficiency of IVF is directly related to the decision of the key issues of reproductive medicine - the identification of the receptivity period (implantation receptivity of the endometrium) to determine the operational readiness of the endometrium to the blastocyst implantation [2]. Endometrium implantation receptivity is a complex of structural and functional characteristics of the endometrium with clear time constants that define the ability of the endometrium to provide implantation of the embryo. Implementation of endometrium receptivity is performed through genetic and molecular reactions that lead to the expression of large amounts of biologically active molecules such as cytokines, growth factors, adhesion molecules, etc. Traditionally assessment of the endometrium receptivity is performed by biopsy, allowing to identify the lack of the luteal phase [3]. However, this method does not allow to get complete information on the receptivity of the endometrium. So, the researchers admit that at the histological visualization it is not possible to identify functional subliminal disturbances of implantation susceptibility.

Determination by immunohistochemistry of signaling molecules ensuring the endometrium implantation ability enables for the evaluation of operational readiness of the endometrium for implantation.

Disorder of the functional activity of the endometrium is also probable in the normal morphological state that manifests with a change in the balance of regulatory molecules, providing endometrium receptivity. Based on the detection of violations in receptivity it is possible ещ appoint the complex therapy for women with reserved ovulatory cycles promoting trophic and metabolic processes in the endometrium.

The aim of this study was verifying the most specific and significant immunohistochemical markers of endometrium receptivity for the development of IVF treatment outcome prediction algorithm at external genital endometriosis of the I-II degree.

Material and Methods: The study material amounted to 95 cases of endometrial biopsy of women treated by IVF and following transferring the embryo into the uterus, on the basis of FSBSI "Ott RI OGR". To study the following groups were formed. Group I included 25 women with EGE of I-II degree and a positive outcome of the treatment program (pregnancy is confirmed echografically), II group consisted of 30 women with EGE of I-II degree, whose pregnancy has not occurred. Group III, the control group, included 40 women who were treated due to male factor of infertility, and the positive outcome of the program. The study included women with infertility in age from 24 to 35 years old, the level of follicle-stimulating hormone in the blood, defined on 3-5 days of the menstrual cycle (d.m.c.) of all surveyed women did not exceed 11 IU / L, at ultrasound investigation on 3-5 d.m.c determined from 7 to 12 antral follicles in the ovaries maximum echographic cut. All women received standard protocol IVF or IVF with intracytoplasmic sperm injection (ICSI) with the use of gonadotropin-releasing hormone antagonists. In order to support the luteal phase of the cycle the micronized progesterone was used. It was conducted transfer of only morphological qualitative embryos on the fourth or fifth day of cultivation. The average dose of recombinant gonadotropins, the number of obtained oocytes and the transferred embryos did not differ in clinical study groups. Pregnancy diagnostics was performed by determination of human chorionic gonadotropin in the blood on the 14 day after embryo transfer into the uterine cavity and ultrasonically on the 21 day. Forming a study group, we standardized as much as possible all the indicators, so that would be the only variable in the study was the endometrium implantation receptivity.

Endometrial biopsy was performed in the period of the intended implantation window on 7-9 day after ovulation in the cycle, prior to IVF cycle, using Pipelle de Cornier suction curette ("Jiangsu Suyun Medical Materials Co., Ltd.). Ovulation was confirmed by ultrasound and by determining the peak of luteinizing hormone in urine. The resulting endometrial samples were teated according to standard procedure to obtain the paraffin blocks. Histologic examination was conducted according to the criteria proposed by Mazur and Kurman [5], on the basis of which it was selected the samples containing middle stage secretion phase endometrium no evidence of inflammation and fibrosis. In case of doubt, the additional color on the Van Gieson method was used to identify chronic inflammation, leukocyte subpopulations CD20, CD138 were determined by immunohistochemistry.

Immunohistochemistry (IHC) was performed on deparaffinized and dehydrated sections of 4-6 um of thick with an avidin-biotin immunoperoxidase method. Expression levels were determined: leukemia of inhibiting factor (LIF) (Anti-LIF, Abcam (ab135629), 1:100); vascular endothelial growth factor type A (VEGF-A) (Anti-VEGF-A, Abcam (ab28775), 1:50); transforming growth factor beta 1 (TGF-β1) (Anti-TGF-β1, Novocastra, 1:40); estrogen receptor type alpha (ER) (Anti-ER, DAKO (1D5), 1:35); progesterone receptor, type A (PR) (Anti-PR, DAKO (636), 1:35); integrin alpha five beta three (Integrin αVβ3) (Anti- Integrin αVβ3, Abcam (ab7166), 1:250).

To quantify the immunohistochemical reaction there were obtained images using a Nikon DXM 1200 camera and "AST 1" software, version 2.12, fixing of the image was carried out on the x40 magnification. To evaluate the results of immunohistochemical staining it was performed morphometric study of micrographs using the system of computer analysis of microscopic images of Morphology 5.2. (VideoTest, Russia). In each case, all of the material was analyzed, except the field of vision, containing dyeing defects and artifacts.

The results of the reactions to the antigens having nuclear localization (ER, PR), was evaluated by counting system «histochemical score» (HS). The maximum value of HS is 300 points.

The intensity of reactions with antigens, localized in the cytoplasm and on cell membranes (LIF, VEGF-A, Integrin αVβ3, TGF-b1) was evaluated by two parameters - the relative area of expression and the optical density. The relative area of expression was calculated as the ratio of the area occupied by the immunopositive cells to the total cell area in the field of vision and expressed in percentage. The optical density of expression of the identified products was measured in arbitrary units. The first component reflects the expression of the test marker in cell population and the second - in the individual cells. Evaluation of immunohistochemical reaction was carried out in two histological endometrial structures - glands and stroma.

Statistical processing of the obtained data was performed using the «Microsoft Excel» standard package and the «Statistica for Windows» application package, version 6.0, StatSoft Inc. (USA) using parametric and non-parametric statistical methods.

Descriptive statistics included calculation of the mean (M), standard error of the mean (m). Evaluation of intergroup differences in characteristic values was carried out using Student's t-test and the Mann-Whitney rank-U-test. Differences were considered statistically significant at $p<0.05$ (95% -level of significance) and $p<0.01$ (99% -level of significance).

Prediction of IVF outcome was carried out with the help of discriminant analysis and classification trees. The list of potential predictors included variables (a predetermined pairing with the onset of pregnancy) with significance level of $p<0.05$.

Results

Status of the receptor apparatus of the endometrium in terms of ART is extremely important. This makes the choice of stimulation circuit, and may indicate a lack of sensitivity even to strong hormonal stimuli. Preparation of the endometrium to the blastocyst nidation is impossible without exposure to progesterone and estradiol by reaction with the appropriate steroid receptors.

The results for ER and PR receptors expression in the studied groups are shown in Table 1.

Table 1 - Expression of estrogen and progesterone receptors in the stromal and glandular component of the endometrium in the studied groups

Group	ER stromal, points	ER glandular, points	PR stromal, points	PR glandular, points
I	45,2±4,9	70,3±7,6	150,7±16,4	84,5±9,2
II	92,2±10,0*,**	75,2 ±8,2**	100,0±10,9*,**	73,2±8,0**
III	75,5±8,2	47,4±5,2	167,7±18,2	95,4±10,3
*- the differences in the two groups at the outcome are significant at $p<0.05$. ** - the differences in the two groups with the control are significant at $p<0.05$.				

The data on the expression of ER in the stromal and glandular components show an increase of indicators in the subgroup with a negative outcome ($p<0.005$), but lower levels of ER in the positive outcome group also differ from the control.

PR expression was high in the group of EGE and of positive outcome, as well as in control and was within normal "implantation window". A subgroup with negative outcome has a significant reduction in the level of PR both in stromal and glandular components.

LIF expression was observed predominantly in the luminal epithelia and glands, expression was in the stromal component was detected in women with histologically and immunohistochemically confirmed chronic inflammation in the endometrium, so those women were excluded from the study.

During apposition and adhesion of the blastocyst phase LIF is an intermediary in the interaction between maternal decidual leukocytes and implement trophoblast [6].

The results obtained for the LIF expression in the studied groups are presented in Table 2.

Table 2 - LIF Expression in the endometrial glandular component in the studied groups

Factor	Relative area of expression (RAE), %		Optical density (OD), c.u	
	«-»outcome	«+»outcome	«-»outcome	«+»outcome
Control	-	27,7±1,3	-	0,230±0,13
EGE	8,3±1,6*,**	14,5±1,6	0,176±0,04*,**	0,228±0,06
*- the differences in the compared groups at the outcome are significant at $p<0.05$. ** - the differences in the compared groups with the control are significant at $p<0.05$.				

Considering these results, we observed the LIF expression maximum values in the control group. The groups of women with EGE values are reduced relative to control and fluctuate within 14-10% in the subgroup with a positive outcome, and show a sharp decline as in the relative area of less than 10% and in optical density below 0,200 c.u. in subgroups with a negative outcome.

Integrin αVβ3 is involved in the initial attachment of the blastocyst and regulates intercellular interactions. Its expression is observed in the stromal and glandular component of the endometrium [6]. Results of the integrin αVβ3 expression in the endometrium of women of the study groups are presented in Tables 3 and 4.

Table 3 - Integrin αVβ3 expression in the stromal component of the endometrium in the studied groups

Factor	Relative area of expression (RAE), %		Optical density (OD), c.u	
	«-»outcome	«+»outcome	«-»outcome	«+»outcome
Control	-	5,5±0,4	-	0,159±0,029
EGE	2,2±0,8**	2,4±0,7	0,076±0,03*,**	0,170±0,039
*- the differences in the compared groups at the outcome are significant at p<0.05. ** - the differences in the compared groups with the control are significant at p<0.05.				

In the group of women with external genital endometriosis expression indicators of integrin αVβ3 in terms of area and optical density were the lowest in comparison with the control. When comparing the subgroups differences were not found (p>0.05).

Table 4 - Expression of integrin αVβ3 in endometrial glandular component in the studied groups

Factor	Relative area of expression (RAE), %		Optical density (OD), c.u	
	«-»outcome	«+»outcome	«-»outcome	«+»outcome
Control	-	14,1±2,0	-	0,289±0,018
EGE	6,8±0,6*,**	8,4±0,8	0,186±0,014*,**	0,244±0,026
*- the differences in the compared groups at the outcome are significant at p<0.05. ** - the differences in the compared groups with the control are significant at p<0.05.				

The obtained data demonstrate a direct link of indicators expression of integrin αVβ3 with a positive outcome. In the subgroup of women with pregnancies the area figures ranged from 8 to 14% while in the subgroups with a negative outcome they were 6.8%. The optical density was also the highest in the control group and in the EGE group with the negative outcome of the program it was minimal.

Vascular endothelial growth factor is a major regulator of angiogenesis, mitogen for vascular endothelial cells. Expression of VEGF-A was observed only in the stromal component of the endometrium and was absent in the surface and glandular epithelium. Results of VEGF-A expression in the endometrium of women of the studied groups are shown in Table 5.

Table 5- VEGF-A expression in the stromal component of the endometrium

Factor	Relative area of expression (RAE), %		Optical density (OD), c.u	
	«-»outcome	«+»outcome	«-»outcome	«+»outcome
Control	-	8,7±1,9	-	0,201±0,07
EGE	11,2±1,8**	10,1±1,9	0,182±0,007*	0,230±0,04
*- the differences in the compared groups at the outcome are significant at p<0.05. ** - the differences in the compared groups with the control are significant at p<0.05.				

VEGF-A expression in the endometrial stroma in women with external genital endometriosis is not differ significantly in terms of the area within the group, however, the optical density in the subgroup with positive outcome is higher than in negative one. Compared with the control of women with EGE the VEGF expression parameters in the stroma are higher in two times in terms of the area expression (p<0.05).

TGFβ1 is representative of the growth factors, its expression is detected in all structures of the endometrium: stroma, glandular component and the luminal epithelium. Expression in the glandular component exceeds the expression in the stroma. Results of TGFβ1 expression in the endometrium of women of the studied groups are shown in Tables 6 and 7.

Table 6 - TGFβ1 expression in the stromal component

Factor	Relative area of expression (RAE), %		Optical density (OD), c.u	
	«-»outcome	«+»outcome	«-»outcome	«+»outcome
Control	-	4,4±0,8	-	0,240±0,017
EGE	2,1±0,3*,**	4,4±1,0	0,230±0,019*,**	0,208±0,005
*- the differences in the compared groups at the outcome are significant at p<0.05. **- the differences in the compared groups with the control are significant at p<0.05.				

When comparing between subgroups there are significantly higher rates of the relative area in the group with a positive outcome, and the optical density indicators of the negative subgroup. When comparing the control group, the subgroup with a negative outcome has lower values of the relative area ($p<0.05$), and between the subgroups with a positive outcome differences were not found.

Table 7 - TGFβ1 expression in the glandular component

Factor	Relative area of expression (RAE), %		Optical density (OD), c.u	
	«-»outcome	«+»outcome	«-»outcome	«+»outcome
Control	-	11,8±1,4	-	0,198±0,013
EGE	10,9±1,9	11,7±1,8	0,203±0,012	0,205±0,010
*- the differences in the compared groups at the outcome are significant at p<0.05. **- the differences in the compared groups with the control are significant at p<0.05.				

When comparing subgroups with each other and with control significant differences were not found.

The next stage of our work was to evaluate the informativeness of immunohistochemical markers to predict the outcome of in vitro fertilization in the group of women with external genital endometriosis. For this we used discriminant analysis method, which showed that the most informative at the outcome forecast of IVF in the group of women with external genital endometriosis: the relative area of LIF expression; relative expression area and optical density of integrin αVβ3 in the glandular and stromal components of the endometrium as well as the relative area of expression of TGFβ1 and VEGF-A growth factor in the endometrial stromal component.

Using a stepwise procedure for adding variables on the basis of Wilkes statistics enabled to calculate the discriminant functions:

$$P = 0,04 \cdot A + 126,0 \cdot B + 3,7 \cdot C - 23,5 \quad (6)$$

$$O = 0,09 \cdot A + 83,9 \cdot B + 1,9 \cdot C - 13,4, \quad (7)$$

where P – discriminant function of a positive outcome of IVF; O – discriminant function of a negative outcome of IVF; A - PR expression in the endometrial glandular component; B - the optical density of the LIF expression in the endometrial glandular component; C - relative area of TGFβ1 expression in the endometrial stromal component

All included in the discriminant function variables are significantly different from zero. Test the resulting model in the control group showed 89.1% of correct discrimination. Cross-checking in the training group showed a slightly lower, but also good results: 88.8% of correct answers.

Prediction algorithm of in vitro fertilization outcomes according to the expression of immunohistochemical markers was developed using classification trees - a method to relate objects to one class or another depending on the respective values of one or more independent (predictor) variables. Building a classification tree enabled to classify objects on the basis of decision rules. Choosing the best tree was conducted on the basis of the lowest rates (the proportion of misclassified cases). The forecast has been selected with the lowest percentage of incorrect classifications (Figure 1). Analysis of the classification tree showed that the most informative indicators in predicting the IVF outcome: the relative area of the TGFβ1 expression in the stromal component of the endometrium (rank - 100), relative area of the LIF expression in the glandular component of the endometrium (rank - 84) and optical density of the LIF expression in the glandular component of the endometrium (rank - 71).

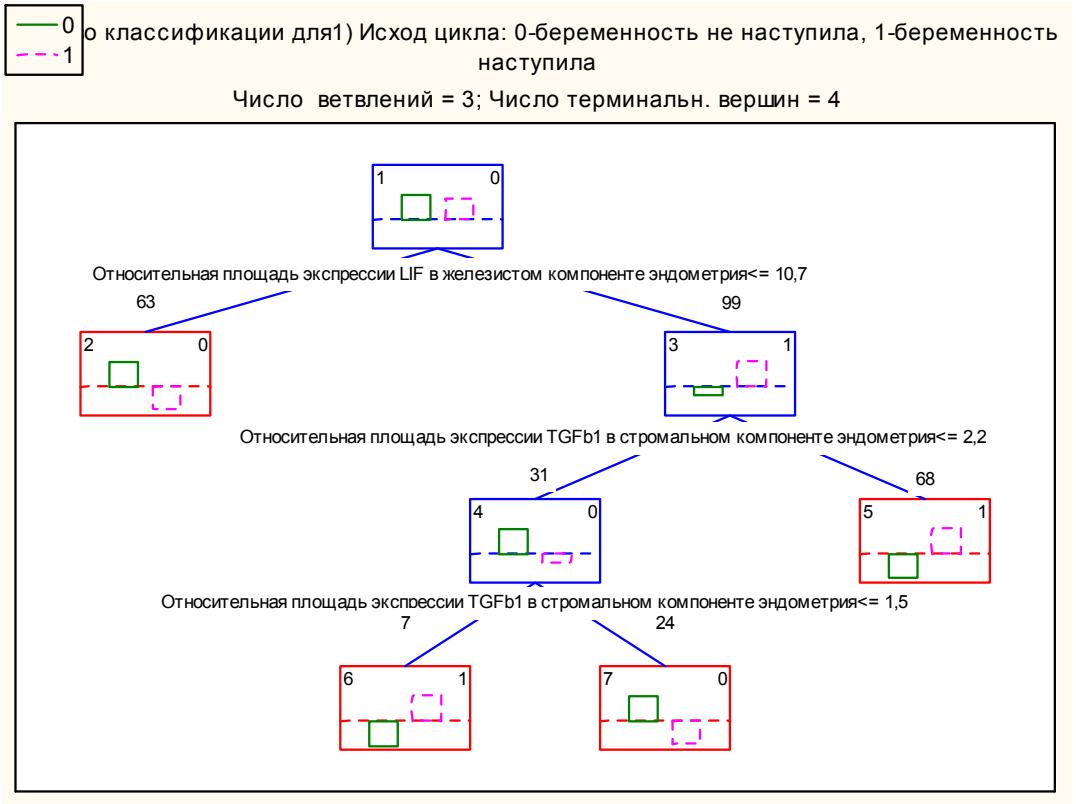

Figure 1 - Classification tree of decision-making

Note: The decision nodes are marked with boxes. In the boxes on the left side it is the node number, in the right - to which class (group) it belongs. Over the nodes there are indicated the number of cases occuring to this unit, under it - the condition of separation along the branches.

Terms of division of the examined are the following: if the value of the variable corresponds to or is equal to the condition laid down by the decision node, then select the left branch, otherwise - right. Thus, we move along the branches to the final node, which shows us the expected forecast of IVF treatment.

The discussion of the results:

The lack of implantation in IVF cycles is one of the main problems of modern reproductive medicine. Implantation is a multifactorial process, it is difficult to imagine the existence of a single criterion, with which it is possible to determine the receptivity of the endometrium. However, the possibility of accurate diagnosis of the state of receptivity of the endometrium cannot be overestimated in terms of clinical relevance. Endometrial biopsy today remains the most common method to diagnose pathological conditions that leads to a significant reduction or loss of the ability of endometrial implantation.

Important one is the ability to predict the onset of implantation, since the detection of violations make it possible to avoid unnecessary emotional stress, not to carry out the support of the luteal phase and the hopeless refrain from embryo transfer, preserving them for the delayed transfer.

Endometrial tissue obtained during the "implantation window" in the natural cycle, is able to reflect the receptivity of the endometrium during the cycle, despite the negative impact of ovulation stimulation. Endometrial receptivity is almost on the same level, from cycle to cycle, which provides a constant genomic profile [7]. Therefore, the use of immunohistochemistry studies of the endometrium in preparation for assisted procreation treatment is justified.

According to the studies we have verified the most significant and specific markers of endometrial receptivity, TGFβ1 and LIF that were used to develop a IVF treatment outcome prediction algorithm at external genital endometriosis of the I-II degree.

With the help of the developed model it is possible to predict the group with poor outcome of treatment that allows to take science-based solutions to improve the effectiveness of the remedial measures.

On the basis of the developed model it is proposed the following algorithm of prediction of adverse outcome:

1. When planning IVF treatment it is necessary to conduct a biopsy of the endometrium and histological examination.

2. The second step in the case of not revealing apparent reason preventing the formation of receptivity of the endometrium (hyperplasia, inflammatory changes) a comprehensive assessment of the functional state of the endometrium with immunohistochemistry is under way.

3. The third step is relating to each surveyed to the groups of "positive outcome" and "negative outcome" using a prediction algorithm.

Conclusion

It is becoming increasingly clear that the ideal biomarker for evaluating endometrial receptivity does not exist, as the complexity of the pathogenesis of any disease, leading to infertility, and physiological characteristics of each patient cannot be identified by a single biomarker.

Expansion of basic research on the molecular mechanisms of cell implantation will expand the understanding of the mechanisms underlying the formation of implantation and may be the basis for the development of drugs for the selective effect on the endometrium with impaired receptivity. It is necessary to conduct large studies on large cohorts of women with normal and impaired fertility, which will determine the range of the expression rate of different molecules, to standardize methods and will provide an opportunity in the future to use them for predictive diagnostics and correction of receptivity.

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СЫРТҚЫ ГЕНИТАЛДЫ ЭНДОМЕТРИОЗ, ЭНДОМЕТРИЯ ИМПЛАНТАЦИОНДЫ СЕЗГІШТІГІНІҢ ИММУНОГИСТОХИМИЯЛЫҚ ДИАГНОСТИКАСЫ

Аннотация. Экстрокорпоральді ұрықтандыруда (ЭКҰ) имплантацияның болмауы – заманауи репродуктологияның негізгі проблемаларының бірі. Имплантация көп факторлы үрдіс болып табылады, оның көмегімен эндометрияның рецептивтілігін анықтау мүмкін болатын біріңғай өлшемнің болуын елестету қиын. Алайда, эндометрийның рецептивтілігінің жағдайының сенімді диагностикасының мүмкіндігін клиникалық маңыздылық жағынан алып қарағанда әсіре бағалау қиын. Эндометрияның биопсиясы бүгінгі таңда оның имплантациялық қабілетінің айтарлықтау төмендеуіне немесе жоғалуына алып келетін патологиялық жағдайын диагностикалауға мүмкіндік беретін ең кең тараған әдіс болып қала береді.

Ақауларды анықтау барысында артық эмоциялық жүктемені болдырмауға, лютеин фазасын қуаттауды болдырмауға және эмбриондарды кейінге ауыстыру үшін сақтай отырып, оларды перспективсіз ауыстырудан тыюға болатындықтан, имплантацияның басталуын болжау мүмкіндігі маңызды болып табылады. Сыртқы генитальді эндометриозы бар емделушілердегі эндометрияның имлантациялық сезгіштігінің ақауларын болжау және диагностикалау үшін имплантациялық терезенің түзілуіне қатысатын маңызды биологиялық молекулаларды (LIF, ER, PR, Integrin, TGF-β1, VEGF) бағалай отырып, иммуногистохимиялық зерттеуді қолдану мүмкіндігін бағалау жүргізілді. Зерттеу нәтижесінде ЭКҰ әдісімен емдеу соңын болжайтын

алгоритмді жасау үшін қолданылған ақпараттық иммуногистохимиялық маркерлер анықталды. Жасалынған модельдің көмегімен емдеу нәтижесі жағымсызз топтарды болжауға болады, ол емдеу іс-шараларын жүргізу тәсілін дәлелдемемен жоспарлауға мүмкіндік береді және ЭКҰ әдісімен емделу тиімділігінің көтерілуіне себеп болады.

Тірек сөздер: ЭКҰ, эндотермияның имплантациялық сезгіштігі, рецептивтілік, «имплантация терезесі», LIF, VEGF, Integrin αVβ3, TGFβ1, ER, PR.

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НАРУЖНЫЙ ГЕНИТАЛЬНЫЙ ЭНДОМЕТРИОЗ, ИММУНОГИСТОХИМИЧЕСКАЯ ДИАГНОСТИКА ИМПЛАНТАЦИОННОЙ ВОСПРИИМЧИВОСТИ ЭНДОМЕТРИЯ

Резюме: Отсутствие имплантации в циклах экстракорпорального оплодотворения (ЭКО) – одна из основных проблем современной репродуктологии. Имплантация является многофакторным процессом, трудно представить себе наличие единого критерия, с помощью которого возможно определить рецептивность эндометрия. Однако, возможность достоверной диагностики состояния рецептивности эндометрия трудно переоценить с точки зрения клинической значимости. Биопсия эндометрия на сегодняшний день остается наиболее распространенным методом, позволяющим диагностировать патологические состояния, приводящие к существенному снижению или утрате имплантационной способности эндометрия.

Важной представляется возможность прогнозировать наступление имплантации, так как при выявлении нарушений можно избежать лишней эмоциональной нагрузки, не проводить поддержку лютеиновой фазы и воздержаться от бесперспективного переноса эмбрионов, сохранив их для отсроченного переноса. Нами проведена оценка возможности использования иммуногистохимического исследования с оценкой ключевых биологических молекул участвующих в формировании имплантационного окна (LIF,ER,PR,Integrin, TGF-β1,VEGF), для прогноза и диагностики нарушения имплантационной восприимчивости эндометрия, у пациенток с наружным генитальным эндометриозом. В результате исследований были верифицированны информативные иммуногистохимические маркеры, которые были использованы для создания алгоритма прогноза исхода лечения методом ЭКО. С помощью разработанной модели возможно прогнозирование группы с неблагоприятным исходом лечения, что позволяет обоснованно планировать тактику ведения лечебных мероприятий и способствует повышению эффективности лечения методами ЭКО.

Ключевые слова: ЭКО, имплантационная восприимчивость эндометрия, рецептивность, «окно имплантации», LIF, VEGF, Integrin αVβ3, TGFβ1, ER, PR.

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