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Original Article

The importance of assessing nucleotide polymorphisms of the *TP53* signaling pathway genes in uterine infertility factor diagnosis

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ABSTRACT

INTRODUCTION: The WHO reported a 30% frequency of female infertility, which does not tend to decrease. Concurrently, the uterine factor occupies one of the most important places in infertility structure, reaching 50%. Improvement of assisted reproductive technology methods can successfully overcome many causes of infertility, but the possibilities of the method are limited in the uterine factor of infertility.

AIM: To assess the presence of nucleotide polymorphisms of the *TP53* signaling pathway genes (*LIF* rs41281637, c.256G>A; *LIF* rs929271, n.397-2854T>G; *MDM2* rs2279744, c.14+309T>G; *MDM4* rs1563828, c.558+572A>G; *TP53* rs1042522, c.215C>G) in the endometrium in patients with primary and secondary infertility.

MATERIALS AND METHODS: In 2018–2021, the V.F. Snegirev Clinic of Obstetrics and Gynecology examined and treated 54 patients aged 26 to 48 years with primary or secondary infertility, including a genetic endometrial sample examination. The first group consisted of 28 patients with primary infertility aged 26 to 42 years. The 2nd group included 26 patients aged 29 to 48 years with secondary infertility.

RESULTS: The study evaluated the expression of nucleotide polymorphisms of the *TP53* signaling pathway genes in patients with primary and secondary infertility. Study results, data were obtained indicating various variants of nucleotide polymorphisms *LIF, MDM2, MDM4, and TP53* in primary and secondary infertility, as well as the identity of a marker, such as *LIF* rs41281637 (G/A) in patients of both groups.

CONCLUSION: The experimental data obtained indicate an important contribution of genetic polymorphisms in the genes of the *TP53*, *LIF* and *MDM4* signaling pathway to the development of primary and *MDM2* — secondary infertility in women.

Keywords: infertility; endometrial receptivity; gene polymorphism.

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Оригинальное исследование

Значение оценки нуклеотидных полиморфизмов генов сигнального пути *TP53* в диагностике маточного фактора бесплодия

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АННОТАЦИЯ

Введение. По данным ВОЗ, частота женского бесплодия может достигать 30% и не имеет тенденции к снижению. При этом маточный фактор занимает одно из важнейших мест в структуре бесплодия, достигая 50%. Совершенствование методов вспомогательных репродуктивных технологий позволяет успешно преодолеть многие причины бесплодия, но в отношении маточного фактора бесплодия возможности метода ограничены.

Целью данной работы стала оценка наличия нуклеотидных полиморфизмов генов сигнального пути *TP53* (*LIF* rs41281637, c.256G>A; *LIF* rs929271, n.397-2854T>G; *MDM2* rs2279744, c.14+309T>G; *MDM4* rs1563828, c.558+572A>G; *TP53* rs1042522, c.215C>G) в эндометрии у пациенток с первичным и вторичным бесплодием.

Материалы и методы. В Клинике акушерства и гинекологии им. В.Ф. Снегирёва в 2018–2021 гг. проведено обследование и лечение 54 пациенток в возрасте от 26 до 48 лет с первичным или вторичным бесплодием, включающее генетическое исследование образцов эндометрия. Первую группу составили 28 пациенток с первичным бесплодием в возрасте от 26 до 42 лет. Во 2-ю группу вошли 26 пациенток в возрасте от 29 до 48 лет со вторичным бесплодием.

Результаты и обсуждение. В работе оценена экспрессия нуклеотидных полиморфизмов генов сигнального пути *TP53* у пациенток с первичным и вторичным бесплодием. В результате исследования получены данные, свидетельствующие о различных вариантах нуклеотидных полиморфизмов *LIF, MDM2, MDM4, TP53* при первичном и вторичном бесплодии, а также об идентичности такого маркера, как *LIF* rs41281637 (G/A) у пациенток обеих групп.

Заключение. Полученные экспериментальные данные свидетельствуют о важном вкладе генетических полиморфизмов в генах сигнального пути *TP53*, *LIF* и *MDM4* в развитие первичного, а *MDM2* — вторичного бесплодия у женщин.

Ключевые слова: бесплодие; рецептивность эндометрия; полиморфизм генов.

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ЭКО•ВЕКТОР

INTRODUCTION

According to WHO, the incidence of female infertility has reached 30% and is continuously increasing. Uterine factor is one of the most important aspects in the infertility structure and accounts for 50%. The influence of obesity on the implementation of reproductive function has recently grown [1, 2]. Excess free fatty acids can be toxic to reproductive tissues, leading to cell damage and chronic or mild inflammation. Various markers, including C-reactive protein, interleukin-6, tumor necrosis factor alpha, and plasminogen activator inhibitor 1, have a detrimental effect on the reproductive cycle of obese patients [3].

The combination of various infertility factors and the ambiguous interpretation of examination results lead to difficulties in diagnosing the major causes of infertility. Even after complete clinical and laboratory examination, the cause of infertility remains unidentified, and the couple is considered healthy. In the diagnosis of infertility of unknown origin, the further management of an infertile couple presents significant difficulties because of the lack of single algorithm of action for this situation. Expectant management or assisted reproductive technology (ART) can be offered to the couple. Additional methods for assessing the endometrium state could also facilitate the prediction of reproductive success in a female patient.

Although the improved ART methods have successfully addressed many infertility causes, the possibilities of these techniques are limited in relation to the uterine factor of infertility [4–7].

One of the key points for a successful pregnancy is embryo implantation, which largely depends on the quality of the embryo itself and the morphofunctional state of the endometrium. The markers of endometrial receptivity include the morphological changes in the endometrium, expression of certain immunohistochemical markers, blood plasma level of progesterone, and state of pinopods at a certain time to form a full-fledged "implantation window" [8].

Leukemia inhibitory factor (*LIF*) plays a key role in the preparation of endometrium for implantation and the subsequent development of the embryo [9, 10]. *LIF* belongs to the interleukin-6 family of pro-inflammatory cytokines and binds to its individual receptor (LIF-R) on the cell surface to form the glycoprotein 130 (gp130) complex. Different from other cytokines of the same family, the largest amount of *LIF* is secreted precisely when the blastocyst has attached to the endometrium, i.e., in the "implantation window," to provide the expression of adhesion molecules necessary for the subsequent fixation of blastocyst. When *LIF* production by the endometrium is insufficient, the implantation of blastocyst does not occur. In the endometrium of healthy women, the *TP53* signaling pathway genes are expressed throughout the entire menstrual cycle, and the peak of expression falls on the "implantation window." Meanwhile, the endometrium of infertile women expresses significantly less *LIF* during the implantation period [11].

This work aimed to assess the nucleotide polymorphisms of the *TP53* signaling pathway genes, namely, *LIF* rs41281637 (c.256G>A), *LIF* rs929271 (n.397–2854T>G), *MDM2* rs2279744 (c.14+309T>G), *MDM4* rs1563828 (c.558+572A>G), and *TP53* rs1042522 (c.215C>G) in the endometrium of patients with primary and secondary infertility.

MATERIALS AND METHODS

From 2018 to 2021, 54 female patients aged 26–48 years (mean age of 35.0±4.2 years) with complaints of the absence of pregnancy with regular sexual activity without contraception and signs of intrauterine pathology at the time of treatment were examined and treated in the V.F. Snegirev Clinic of Obstetrics and Gynecology, Moscow, Russia. All the patients were admitted to the gynecology department for surgical treatment.

Group 1 consisted of 28 patients aged 26–42 years (mean age 32.8 years) with primary infertility. Group 2 included 26 patients aged 29–48 years (mean age 37.1±4.4 years) with secondary infertility.

Kolmogorov–Smirnov analysis of the anamnesis data of both groups showed that their age and anthropometric data obeyed the normal distribution law (p >0.05). Owing to the small sample size for each group, nonparametric calculation methods were used.

Mann–Whitney test did not reveal statistically significant differences in age and menstrual function (age of menarche, duration of the menstrual cycle, and duration of menstruation) between the two groups. The main indicator with statistically significant difference was BMI above 25 kg/m^2, and the number of patients with such BMI was higher in group 2 than in group 1 (Table 1).

Most of the patients in group 1 (with primary infertility) were admitted to the clinic with a diagnosis of endometrial polyp, and those in group 2 were diagnosed with hyperplasia and endometrial polyp, intrauterine synechia, and chronic endometritis.

Prior to surgical treatment, all the patients underwent clinical and laboratory examination as part of treatment preparation in accordance with the Order of the Ministry of Health of October 20, 2020 No. 1130n "On Approval of the Procedure for Providing Medical Care in Obstetrics and Gynecology". Special research methods included the ultrasound (US) examination of the pelvic organs with dopplerometry, office hysteroscopy, and hysterosalpingography according to indications. The US of the pelvic organs was performed on day 5–7 of the menstrual cycle and included the assessment of the size of the uterus, the thickness and structure of the endometrium, the size and structure of the ovaries, and the structure of the myometrium. Close attention was paid to the assessment of the median uterine echo (M-echo), which is the reflection from the endometrium and the walls of the uterine cavity. The procedure was performed on an

Table 1. Clinical and anamnestic characteristics of patients

Analyzed indicator	Group 1, primary infertility (*n*=28)	Group 2, secondary infertility (*n*=26)
Age of menarche, years	13.3±1.6	12.7±1.4
Menstrual cycle, days	26–35	27–35
Duration of menstruation, days	4–6	3–6
Body mass index up to 25 kg/m^2	22	15
Body mass index > 25 kg/m^2	6	11
Endometrial polyp	16	10
Endometrial hyperplasia	6	8
Uterine fibroids	6	5
Endometriosis	4	3
Chronic salpingo-oophoritis	5	0
Intrauterine synechia, chronic endometritis	2	11
History of IVF* attempts	6	8

*In vitro fertilization.

US machine with convex transabdominal and transvaginal sensors at a frequency of 4.5–8 MHz.

According to their pathology, the female patients underwent surgical treatment in the following volumes: hysteroscopy, separate diagnostic curettage; hysteroscopy, laser polypectomy; hysteroscopy, destruction of intrauterine synechia, followed by endometrial biopsy for histological examination and genomic DNA isolation.

Histological examination of tissues. Endometrial samples obtained during the surgery were studied in the pathomorphology laboratory of the I.M. Sechenov First Moscow State Medical University. Endocervix tissues were fixed in formalin alcohol, buffered 10% neutral formalin, processed using the kit for tissue histological processing manufactured by Pool Scientific Instruments (Switzerland), and embedded in paraffin. The total time of material fixation, processing, and paraffin embedding did not exceed 24 hours. For morphological study, at least 10 stepped sections were obtained from each block. Deparaffinized sections of 5 μm thickness were stained with hematoxylin and eosin and picrofuchsin according to the method of Van Gieson. The hyperplastically altered endocervix was assessed in accordance with WHO classification.

Isolation of genomic DNA. The endometrial tissues were applied as biological material for genomic DNA isolation using a spin column diaGene (Dia-m, RF), a kit that can isolate DNA from a wide range of biological samples. The purity of the isolated DNA was tested on a NanoDrop OneC spectrophotometer with the A260/280 ratio ranging from 1.8 to 1.91 and the A260/230 ratio ranging from 1.62 to 2.28. DNA concentration was measured using a dsDNA BR kit on a Qubit Flex fluorimeter. The concentration ranged from 15 ng/μL to 300 ng/μL. The concentration of all DNA samples was adjusted to 2 ng/μL.

DNA genotyping in the region of the studied polymorphic markers was performed using the Sanger sequencing method. Primer design was obtained from Primer-Blast (https://www.ncbi.nlm.nih.gov/tools/primer-blast/).

Sequencing. BigDye Terminator v3.1 Cycle Sequencing Kit was used for the sequencing reaction on a 3500 genetic analyzer (Thermo FS).

Statistical analysis. Fisher's exact two-sided test and chi-square test were used to calculate the statistical significance of the difference in the incidence. Statistical calculations were performed according to the dominant model (identification of the risk allele) and the recessive model (identification of the risk genotype). For the groups with significant differences, odds ratio (OR), 95% confidence interval, and statistical significance *p* were calculated. For the convenience of calculating the difference, the patients were grouped according to their polymorphism, namely, the group of female patients with primary infertility and the group of female patients with secondary infertility. Statistical analysis was performed using the SNPStats software.

This study was approved by the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University (minutes No. 01-18 dated January 17, 2018). All the patients signed informed consent to participate in the study and publish their medical data.

RESULTS AND DISCUSSION

Clinical and anamnestic evaluation revealed the absence of statistically significant differences in menstrual and reproductive function (age of menarche, duration of menstruation, and duration of the entire menstrual cycle) between the two groups. Overweight and obesity were more common in group 2 (11 people) than in group 1 (6 people). Most of the patients with primary infertility were admitted to the clinic with a diagnosis of endometrial polyp, and those with secondary infertility were admitted to the clinic with a diagnosis of endometrial hyperplasia and/or polyp, intrauterine synechia, and chronic endometritis (Table 2).

After the intervention, the patients stayed in the hospital for 1–2 bed-days and were then discharged in a satisfactory condition to continue the prescribed therapy on an outpatient basis.

A complex anti-inflammatory, angioprotective, and antihypoxic therapy was prescribed to all the patients in the postoperative period. In case of certain indications, antibacterial and hormonal therapy was also prescribed.

Histological examination confirmed the diagnosis of endometrial polyp in all patients. No pathology of the endometrium was found in three patients with primary infertility and seven patients with secondary infertility. This finding

Table 2. Results of histological examination of endometrial tissues

Histological conclusion	Group 1, primary infertility (*n*=28)	Group 2, secondary infertility (*n*=26)
Glandular-fibrous polyp	11	10
Glandular polyp	9	5
Endometrial hyperplasia without atypia	3	2
Proliferation phase endometrium	3	7
Histological signs of chronic endometritis, fibrous tissue (synechia)	2	2

corresponded to the phase of the menstrual cycle and may indirectly indicate the dysfunction of the endometrium with a normal histological structure.

Endometrium receptivity is the ability of the endometrium to accept the invading blastocyst. The transfer of an embryo without genetic abnormalities after preimplantation genetic screening does not result in pregnancy in many cases, and this phenomenon may indicate a uterine factor of infertility due to impaired endometrial receptivity [12].

Genetic markers, particularly the genes of the *TP53* signaling pathway, can play a certain role in the readiness of endometrium for blastocyst implantation [13].

A genetic study was conducted on the endometrial samples from the patients in both groups (Table 3).

Analysis of genetic polymorphic variants showed the statistically significant association of primary infertility with two genetic variants, namely, rs929271 in the *LIF* gene (a homozygous genotype for the minor allele G/G [OR=7.76; *p*=0.0047]) and rs1563828 in the *MDM4* gene (a homozygous genotype for the minor allele G/G [OR=5.75; *p*=0.0083]).

The gene for *LIF*, which plays a key role in implantation, is the target gene for the p53 protein. The p53 protein regulates basal and inducible *LIF* transcription by directly binding to specific DNA sequences and activating transcription. The variant G of rs929271 polymorphism in the 3'UTR of the *LIF* gene is associated with impaired blastocyst implantation. The occurrence of the G allele is high in women with idiopathic infertility under the age of 35 years but not older [14]. These data were confirmed in the present study i.e., the minor allele G/G *LIF* rs41281637 (G/A) was detected in the endometrial samples from all 54 women with infertility.

The *MDM4* gene encodes a nuclear protein containing a p53-binding domain at its N-terminus and a RING finger domain at its C-terminus. The MDM4 protein shows structural similarity to the p53 binding protein MDM2, and both proteins bind to p53 (tumor suppressor protein) and inhibit its activity. Both genes (*MDM4* and *MDM2*) are overexpressed in various human malignant tumors. Different from MDM2, which degrades p53, the MDM4 protein inhibits p53 by binding to its transcriptional activation domain. MDM4 also interacts with MDM2 through the RING finger domain and inhibits the degradation of the latter [15]. Thus, MDM4 can disrupt MDM2-induced degradation of p53, but retain the suppression of p53-induced transactivation and apoptotic functions. Transcriptional variants resulting from the alternative splicing of this gene encode several forms of the MDM4 protein.

The presence of the A allele in the rs1563828 polymorphism of the *MDM4* gene increases the expression of the p53 suppressor protein encoded by this gene. In turn, p53 inhibition decreases the amount of *LIF* and the probability of implantation [16].

The present results indicated that for *MDM2* gene polymorphism, the T/G variant was associated with primary infertility and the T/T variant was associated with secondary

Table 3. Results of genetic analysis of endometrial samples

Nucleotide gene polymorphisms	Group 1 primary infertility (*n*=28)	Group 2, secondary infertility (*n*=26)
LIF rs41281637 (G/A)		
G/G	28	26
LIF rs9292271 (T/G)		
T/T	10	15
T/G	5	9
G/G	11	2
MDM2 rs2279744 (T/G)		
T/T	7	14
T/G	16	11
G/G	3	1
MDM4 rs1563828 (A/G)		
A/A	6	14
A/G	9	9
G/G	11	3
TP53 rs1042522 (G/C)		
G/G	14	8
G/C	9	13
C/C	3	5

infertility. For the *MDM4* gene polymorphism, the G/G variant was associated with primary infertility and the A/A variant was associated with secondary infertility.

Analysis of the *TP53* gene polymorphism revealed that the G/G allele was associated with primary infertility and the G/C allele was associated with secondary infertility.

The obtained experimental data confirmed the findings in literature and indicated the important contribution of genetic polymorphisms in *TP53, LIF*, and *MDM4* signaling pathway genes to the development of primary infertility and in *MDM2* genes to the development of secondary infertility in women [17–20].

CONCLUSION

This study evaluated the expression of nucleotide polymorphisms of the *TP53* signaling pathway genes in patients with primary and secondary infertility. Results indicated the different variants of nucleotide polymorphisms *LIF* rs41281637 (c.256G>A), *LIF* rs929271 (n.397–2854T>G), *MDM2* rs2279744 (c.14+309T>G), and *MDM4* rs1563828 (c.558+572A>G), *TP53* rs1042522 (c.215C>G) detected in primary and secondary infertility. The detection of *LIF* rs41281637 was identical in the patients of both groups.

ADDITIONAL INFO

Author contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

REFERENCES

1. Fichman V, Costa RSSD, Miglioli TC, Marinheiro LPF. Association of obesity and anovulatory infertility. *Einstein* (Sao Paulo). 2020;18:eAO5150. doi: 10.31744/einstein_journal/2020AO5150
2. Gambineri A, Laudisio D, Marocco C, et al.; Obesity Programs of nutrition, Education, Research and Assessment (OPERA) group. Female infertility: which role for obesity? *Int J Obes Suppl.* 2019;9(1):65–72. doi: 10.1038/s41367-019-0009-1
3. Brouillet S, Boursier G, Anav M, et al. C-reactive protein and ART outcomes: a systematic review. *Hum Reprod Update*. 2020;26(5):753–773. doi: 10.1093/humupd/dmaa012
4. Tohma YA, Onalan G, Esin S, et al. Are There Any Predictors of Endometrial Premalignancy/Malignancy within Endometrial Polyps in Infertile Patients? *Gynecol Obstet Invest.* 2019;84(5):512–518. doi: 10.1159/000501682
5. Tanos V, Berry KE, Seikkula J, et al. The management of polyps in female reproductive organs. *Int J Surg.* 2017;43:7–16. doi: 10.1016/j.ijsu.2017.05.012
6. Knyazeva EA, Kuznetsova MV, Shubina ES, et al. Features of methylation of the noha10 and noha11 genes in patients with tubal-peritoneal factor of infertility and unsuccessful attempts of in vitro fertilization in the anamnesis. *Obstet Gynecol.* 2020;4:140–147. (In Russ). doi: 10.18565/aig.2020.4.140-147
7. Miroshkina MI, Korneeva IE, Burmenskaya OV, Mishina ND. The effectiveness of cryopreservation programs depending on the transcriptional «portrait» of endometrial receptivity genes. *Obstet Gynecol.* 2020;(11):85–92. (In Russ). doi: 10.18565/aig.2020.11.85-92
8. Hur C, Rehmer J, Flyckt R, Falcone T. Uterine Factor Infertility: A Clinical Review. *Clin Obstet Gynecol*. 2019;62(2):257–270. doi: 10.1097/GRF.0000000000000448
9. Turocy JM, Rackow BW. Uterine factor in recurrent pregnancy loss. *Semin Perinatol.* 2019;43(2):74–79. doi: 10.1053/j.semperi.2018.12.003
10. Santos LL, Ling CK, Dimitriadis E. Tripeptidyl peptidase I promotes human endometrial epithelial cell adhesive capacity implying a role in receptivity. *Reprod Biol Endocrinol.* 2020;18(1):124. doi: 10.1186/s12958-020-00682-0
11. Craciunas L, Gallos I, Chu J, et al. Conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis. *Hum Reprod Update*. 2019;25(2):202–223. doi: 10.1093/humupd/dmy044
12. Nag S, Qin J, Srivenugopal KS, Wang M, Zhang R. The MDM2-p53 pathway revisited. *J Biomed Res.* 2013;27(4):254–271. doi: 10.7555/JBR.27.20130030
13. Hu W. The role of p53 gene family in reproduction. *Cold Spring Harb Perspect Biol.* 2009;1(6):a001073. doi: 10.1101/cshperspect.a001073
14. Bosteels J, van Wessel S, Weyers S, et al. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database Syst Rev.* 2018;12(12):CD009461. doi: 10.1002/14651858.CD009461.pub4
15. Demirdag E, Guler I, Cevher Akdulum MF, et al. Subsequent IVF outcomes following antibiotic therapy for chronic endometritis in patients with recurrent implantation failure. *J Obstet Gynaecol Res.* 2021;47(12):4350–4356. doi: 10.1111/jog.15037
16. Vagnini LD, Renzi A, Petersen B, et al. Association between estrogen receptor 1 (ESR1) and leukemia inhibitory factor (LIF) polymorphisms can help in the prediction of recurrent implantation failure. *Fertil Steril.* 2019;111(3):527–534. doi: 10.1016/j.fertnstert.2018.11.016
17. Krasnopol'skaia KV, Nazarenko TA, Ershova IYu. Modern approaches to endometrial receptivity assessment (a review). *Russian Journal of Human Reproduction.* 2016;22(5):61–69. (In Russ). doi: 10.17116/repro201622561-69
18. Grishkina AA, Chistjakova GN, Remizova II, Melkozerova OA. Endometrial receptivity and expression of apoptosis and proliferation factors in the endometrium of women with hyperplasia

and infertility. *Journal of Volgograd State Medical University*. 2019;(4):37–39. (In Russ).
doi: 10.19163/1994-9480-2019-4(72)-37-39

19. Kibanov MV. The search for the ideal marker for assessing endometrial receptivity: from histology to modern molecular genetic approaches. *Almanac of Clinical Medicine*. 2019;47(1):12–25. (In Russ). doi: 10.18786/2072-0505-2019-47-005

20. Paramonova NB, Kogan EA, Kolotovkina AV, Burmenskaja OV. Morphological and molecular biological signs of endometrial receptivity disorders in infertility of women suffering from external genital endometriosis. *Archive of Pathology*. 2018;80(3):11–18. (In Russ). doi: 10.17116/patol201880311-18

СПИСОК ЛИТЕРАТУРЫ

1. Fichman V., Costa R.S.S.D., Miglioli T.C., Marinheiro L.P.F. Association of obesity and anovulatory infertility // Einstein (Sao Paulo). 2020. Vol. 18. P. eAO5150.
doi: 10.31744/einstein_journal/2020AO5150

2. Gambineri A., Laudisio D., Marocco C., et al.; Obesity Programs of nutrition, Education, Research and Assessment (OPERA) group. Female infertility: which role for obesity? // Int J Obes Suppl. 2019. Vol. 9, N 1. P. 65–72. doi: 10.1038/s41367-019-0009-1

3. Brouillet S., Boursier G., Anav M., et al. C-reactive protein and ART outcomes: a systematic review // Hum Reprod Update. 2020. Vol. 26, N 5. P. 753–773. doi: 10.1093/humupd/dmaa012

4. Tohma Y.A., Onalan G., Esin S., et al. Are There Any Predictors of Endometrial Premalignancy/Malignancy within Endometrial Polyps in Infertile Patients? // Gynecol Obstet Invest. 2019. Vol. 84, N 5. P. 512–518. doi: 10.1159/000501682

5. Tanos V., Berry K.E., Seikkula J., et al. The management of polyps in female reproductive organs // Int J Surg. 2017. Vol. 43. P. 7–16.
doi: 10.1016/j.ijsu.2017.05.012

6. Князева Е.А., Кузнецова М.В., Шубина Е.С., и др. Особенности метилирования генов hoxa10 и hoxa11 у пациенток с трубно-перитонеальным фактором бесплодия и неудачными попытками экстракорпорального оплодотворения в анамнезе // Акушерство и гинекология. 2020. Т. 4. С. 140–147. doi: 10.18565/aig.2020.4.140-147

7. Мирошкина М.И., Корнеева И.Е., Бурменская О.В., Мишина Н.Д. Эффективность программ криопереноса в зависимости от транскрипционного «портрета» генов рецептивности эндометрия // Акушерство и гинекология. 2020. № 11. С. 85–92. doi: 10.18565/aig.2020.11.85-92

8. Hur C., Rehmer J., Flyckt R., Falcone T. Uterine factor infertility: a clinical review // Clin Obstet Gynecol. 2019. Vol. 62, N 2. P. 257–270. doi: 10.1097/GRF.0000000000000448

9. Turocy J.M., Rackow B.W. Uterine factor in recurrent pregnancy loss // Semin Perinatol. 2019. Vol. 43, N 2. P. 74–79.
doi: 10.1053/j.semperi.2018.12.003

10. Santos L.L., Ling C.K., Dimitriadis E. Tripeptidyl peptidase I promotes human endometrial epithelial cell adhesive capacity implying a role in receptivity // Reprod Biol Endocrinol. 2020. Vol. 18, N 1. P. 124.
doi: 10.1186/s12958-020-00682-0

11. Craciunas L., Gallos I., Chu J., et al. Conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis // Hum Reprod Update. 2019. Vol. 25, N 2. P. 202–223. doi: 10.1093/humupd/dmy044

12. Nag S., Qin J., Srivenugopal K.S., Wang M., Zhang R. The MDM2-p53 pathway revisited // J Biomed Res. 2013. Vol. 27, N 4. P. 254–271. doi: 10.7555/JBR.27.20130030

13. Hu W. The role of p53 gene family in reproduction // Cold Spring Harb Perspect Biol. 2009. Vol. 1, N 6. P. a001073.
doi: 10.1101/cshperspect.a001073

14. Bosteels J., van Wessel S., Weyers S., et al. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities // Cochrane Database Syst Rev. 2018. Vol. 12, N 12. P. CD009461.
doi: 10.1002/14651858.CD009461.pub4

15. Demirdag E., Guler I., Cevher Akdulum M.F., et al. Subsequent IVF outcomes following antibiotic therapy for chronic endometritis in patients with recurrent implantation failure // J Obstet Gynaecol Res. 2021. Vol. 47, N 12. P. 4350–4356. doi: 10.1111/jog.15037

16. Vagnini L.D., Renzi A., Petersen B., et al. Association between estrogen receptor 1 (ESR1) and leukemia inhibitory factor (LIF) polymorphisms can help in the prediction of recurrent implantation failure // Fertil Steril. 2019. Vol. 111, N 3. P. 527–534. doi: 10.1016/j.fertnstert.2018.11.016

17. Краснопольская К.В., Назаренко Т.А., Ершова И.Ю. Современные подходы к оценке рецептивности эндометрия (обзор литературы) // Проблемы репродукции. 2016. Т. 22, № 5. С. 61–69. doi: 10.17116/repro201622561-69

18. Гришкина А.А., Чистякова Г.Н., Ремизова И.И., Мелкозерова О.А. Рецептивность эндометрия и экспрессия факторов апоптоза и пролиферации в эндометрии женщин с гиперплазией и бесплодием // Вестник Волгоградского государственного медицинского университета. 2019. № 4 (72). С. 37–39. doi: 10.19163/1994-9480-2019-4(72)-37-39

19. Кибанов М.В. Поиск идеального маркера для оценки рецептивности эндометрия: от гистологии до современных молекулярно-генетических подходов // Альманах клинической медицины. 2019. Т. 47, № 1. С. 12–25.
doi: 10.18786/2072-0505-2019-47-005

20. Парамонова Н.Б., Коган Е.А., Колотовкина А.В., Бурменская О.В. Морфологические и молекулярно-биологические признаки нарушения рецептивности эндометрия при бесплодии женщин, страдающих наружным генитальным эндометриозом // Архив патологии. 2018. Т. 80, № 3. С. 11–18. doi: 10.17116/patol201880311-18

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