СИСТЕМА CSF-1/CSF1R КАК ПРЕДИКТОР ЖИВОРОЖДЕНИЯ ПОСЛЕ ИНДУЦИРОВАННОЙ БЕРЕМЕННОСТИ

Лапштаева А.В.[1], Сычев И.В.[2], Адамчик А.И.[3]

[1] ФГБОУ ВО «Национальный исследовательский Мордовский государственный университет имени Н.П. Огарева», г. Саранск, Республика Мордовия, Россия
[2] ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения РФ, Москва, Россия
[3] ГБУЗ Республики Мордовия «Мордовская республиканская центральная клиническая больница», г. Саранск, Республика Мордовия, Россия

Резюме. Эффективность процедуры ЭКО оценивается не только показателями наступления клинической беременности, но и долей живорождений, поскольку около трети беременностей завершаются прерыванием, что безусловно, определяется многими факторами. Колониестимулирующие факторы можно рассматривать как потенциальные прогностические маркеры развития индуцированной беременности и последующего живорождения. Цель исследования – оценить прогностическую значимость системы CSF-1 (сывороточной концентрации CSF-1 и носительство полиморфизмов гена *CSF1R*) в рамках завершения ЭКО-индуцированной беременности родами у женщин с трубно-перитонеальным бесплодием. 88 пациенток, проходящих процедуру ЭКО, в возрасте от 25 до 40 лет были разделены на группы: I группа (n = 32) – пациентки, беременность после процедуры ЭКО у которых завершилась родами в срок от 24 недели и более, II группа (n = 52) – пациентки, у которых беременность не наступила или закончилась самопроизвольным выкидышем. Методом иммуноферментного анализа двукратно было определено содержание CSF-1: на 3-4-й день менструального цикла, предшествующего процедуре ЭКО, и на 15-й день после переноса эмбрионов. Генотипирование по полиморфным маркерам rs3216780 и rs386693509 гена *CSF1R* было проведено методом полимеразной цепной реакции с секвенированием по Сенгеру. Содержание CSF-1 увеличилось на 15-й день после переноса эмбриона (в 3,9 раза для I группы и в 1,8 раза для II группы) и у пациенток, беременность из группы II, содержание CSF-1 было достоверно выше, чем в группе сравнения (p = 0,0017). Наибольший процент женщин, беременность которых закончилась родами, были носителями генотипа *del/G* rs3216780 и *TG/CA* rs386693509 гена *CSF1R*. При однофакторном анализе были выявлены следующие предикторы завершения индуцированной беременности родами – уровни CSF-1 в периферической крови от 121,3 до 314,8 пг/мл на преконцептивном этапе и от 963,3 до 1682,8 пг/мл – на 15-й день после переноса эмбрионов, а также носительство генотипов *del/G* rs3216780 и *TG/CA* rs386693509 гена *CSF1R*. В сочетании данные предикторы отмечались у 66,7% женщин из I группы и у 7,7% из II группы. Система CSF-1 играет важную роль в реализации репродуктивной функции женщины и вы-

Адрес для переписки:

Лапштаева Анна Васильевна
ФГБОУ ВО «Мордовский государственный университет имени Н.П. Огарева»
430005, Россия, Республика Мордовия,
г. Саранск, ул. Большевистская, 68.
Тел.: 8 (927) 177-35-55.
E-mail: av_lapshtaeva@mail.ru

Address for correspondence:

Anna V. Lapshtaeva
National Research Ogarev Mordovia State University
68 Bolshevistskaya St
Saransk, Republic of Mordovia
430005 Russian Federation
Phone: +7 (927) 177-35-55.
E-mail: av_lapshtaeva@mail.ru

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явленные прогностические показатели – сывороточная концентрация CSF-1 на преконцептивном этапе и на 15-й день после переноса эмбрионов, а также носительство генотипов *del/G* rs3216780 и *TG/CA* rs386693509 гена *CSF1R,* могут быть использованы в качестве предикторов завершения индуцированной беременности родами.

Ключевые слова: экстракорпоральное оплодотворение, роды, индуцированная беременность, цитокины, колониестимулирующий фактор-1, макрофагальный колониестимулирующий фактор, CSF1, полиморфизм CSF1R, rs3216780, rs386693509

CSF-1/CSF1R SYSTEM AS PREDICTOR OF LIVE BIRTH AFTER INDUCED PREGNANCY

Lapshtaeva A.V.[a], Sychev I.V.[b], Adamchik A.I.[c]

[a] *National Research Ogarev Mordovia State University, Saransk, Republic of Mordovia, Russian Federation*
[b] *Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation*
[c] *Mordovia Republican Central Clinical Hospital, Saransk, Republic of Mordovia, Russian Federation*

Abstract. Efficiency of the IVF procedure is assessed not only by the indexes of clinical pregnancy onset but also by the proportion of live births, since about a third of pregnancies end in termination, which certainly depends on many factors. Colony-stimulating factors may be considered potential predictive markers of the induced pregnancy development and resulting into live birth. To evaluate the predictive value of the CSF-1 system (serum CSF-1 concentration and carriage of *CSF1R* gene polymorphisms) in the setting of live birth after IVF-induced pregnancy in women with tubo-peritoneal infertility. 88 patients undergoing IVF aged between 25 and 40 years were assigned to the following groups: Group I (n = 32): patients whose post-IVF pregnancies resulted in live births at Week 24 or later; and Group II (n = 52) which included patients whose pregnancies did not occur or resulted in spontaneous miscarriages. ELISA testing determined the CSF-1 levels twice: on pre-IVF menstrual cycle (Days 3-4), and on post-embryo-transfer (Day 15). Genotyping of the *CSF1R* gene rs3216780 and rs38669350 polymorphic markers was performed by PCR with subsequent Sanger sequencing. CSF-1 levels rised to post-embryo-transfer Day 15 (3.9-fold in Group I and 1.8-fold in Group II); the appropriate values in pregnant women of Group II were reliably higher than in comparison group (p = 0.0017). Most women whose pregnancy resulted in live births carried the *del/G* rs3216780 and *TG/CA* rs386693509 genotypes of *CSF1R* gene. Univariate analysis identified the following predictors for completion of induced pregnancy by delivery: (1) CSF-1 levels in peripheral blood from 121.3 to 314.8 pg/mL at the preconceptional stage, and 963.3 to 1682.8 pg/mL on Day 15 after embryo transfer; (2) harboring the *del/G* rs3216780 genotypes and *TG/CA* rs386693509 gene *CSF1R*. In combination. These predictors were observed in 66.7% of women from group I and in 7.7% from group II. The CSF-1 system plays an important role in performance of female reproductive function and the revealed prognostic indicators, i.e., pre-conception and post-ET Day 15 serum CSF-1 concentrations, and carriage of the following *CSF1R* gene variants: *del/G* rs3216780 and *TG/CA* rs386693509 genotypes which can be used as predictors of the completion of induced pregnancy by childbirth.

Keywords: in vitro fertilization, live birth, induced pregnancy, cytokines, colony-stimulating factor-1, CSF1, CSF1R polymorphism, rs3216780, rs386693509

Introduction

In vitro fertilization (IVF) is one of the most popular infertility treatment method. However, when assessing its effectiveness, on average, about a third of the protocols lead to pregnancy, and of these, about 70% result in live births [5]. This problem stimulates researchers to identify new informative factors influencing the success of IVF. As the factors of the immune system are directly involved in the realization of reproductive functions, its components can be considered potential predictive markers of the induced pregnancy development and resulting live birth [3, 11].

Colony-stimulating factors form a family of cytokines that regulate the differentiation and proliferation of hematopoietic progenitor cells. Thus, colony-stimulating factor-1 (CSF-1) regulates the proliferation, differentiation, and survival of macrophages; supports the growth and proliferation of extravillous trophoblastic cells; plays an important role in embryo implantation in the uterus and subsequent placental growth [1, 12, 14]. A reduced number of cells or poor development of trophoblast can induce alterations in the placental structure and nutrient transport function – these lead to pregnancy loss or disturbed development [1]. In addition, CSF-1 is an embryotrophic factor: it favors the development of the

blastocyst by increasing the number of blast cells and gene expression [2]. The CSF-1's biologic effects are implemented via its binding with the specific CSF1R receptor; this leads to its dimerization, activation of the tyrosine kinase and signaling cascade [4, 8, 12, 13]. Trophoblast expresses CSF and CSF1R more than any other non-macrophage-derived cell types do. The placental development depends upon the CSF signaling, as CSF stimulates the proliferation of the placental cells, the differentiation of the cytotrophoblastic cells, and regulates the pre-implantation division of the blastocystic cells. The total role of CSF in the development of the induced pregnancy is under study, yet [1].

The objective of this study is to evaluate the predictive value of the CSF-1 system (serum CSF-1 concentration and carriage of *CSF1R* gene polymorphisms) components in the setting of live birth after IVF-induced pregnancy in women with tuboperitoneal infertility.

Materials and methods

Ethical considerations

The Institutional Review Board at a large public university approved the research. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants involved in the study. The study was approved by the local ethics committee of Federal State Budgetary Educational Institution of Higher Education "National Research Ogarev Mordovia State University" protocol No. 68 of 31.03.2015.

Study population

Based on the inclusion, non-inclusion, and exclusion criteria, this study involved 88 women with tuboperitoneal infertility aged 25 to 35 years, with an average age of 28.7±2.9 years, who were treated from June 2022 to December 2023 at the Department of Assisted Reproductive Technologies of the Perinatal Center of the State Budgetary Healthcare Institution of the Republic of Mordovia "Mordovia Republican Central Clinical Hospital" (Saransk). Criteria for inclusion were: signed informed consent for enrollment; current tuboperitoneal infertility factor; normal ovarian reserve; regular menstrual cycle; normal karyotype of both spouses; fertile semen in partner/husband; and transfer of only-good-quality embryos. Criteria for non-inclusion were: patients with other forms of infertility, acute genital or extragenital diseases, as well as exacerbated chronic diseases. Criteria for exclusion were: voluntary withdrawal of patient from study at any stage.

All the patients received the "short-protocol" superovulation stimulation, which involved using the recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonists. All the patients had only-good-quality fresh embryos transferred into the uterine cavity under ultrasonic control on Days 5-6 of cultivation. Diagnosis of pregnancy was based on determining the serum concentration of the human chorionic gonadotropin β-subunit on post-embryo-transfer (ET) into uterine cavity Day 15 and ultrasounding on Day 21 to assess for the presence of one or two fetal eggs in the uterine cavity. Live birth was defined as the child born alive after 24 weeks of pregnancy and having survived more than 1 month. The facts of live birth were to be confirmed by personal observation and data from the clinical records of the postpartum women. Miscarriage was defined as the loss of pregnancy before 28 weeks.

Depending on the outcomes the patients were assigned to two groups. Group I consisted of the 36 women whose pregnancies resulted in live births, mean age 28.6±3.1 years. Group II consisted of the 52 patients whose pregnancies did not occur or resulted in spontaneous miscarriages, mean age 29.3±2.7 years. The study groups were comparable in terms of age, reproductive function and past gynecological diseases ($p > 0.05$).

Serological testing

To study the serum concentration of cytokines, venous blood was collected aseptically by venipuncture from the cubital vein in the morning on an empty stomach in a volume of 10 mL, obtained using a VACUETTE® vacuum system (GreinerBio-One, Austria) into tubes with a coagulation activator. The blood was centrifuged for 15 minutes at 2000 g, the supernatant liquid was collected into Eppendorf tubes and frozen at a temperature of -30 °C. Storage at a temperature of -40-60 °C in the refrigerator for up to 6 months. The samples were not thawed and re-frozen.

Blood from the peripheral vein was sampled twice during the IVF procedure. The first sampling was performed on pre-IVF menstrual cycle Days 3-4 (pre-conception stage), while the second sample was taken on post-embryo-transfer (ET) into uterine cavity Day 15. Serum CSF-1 concentration was determined by ELISA using kits from R&D Systems (USA) with a Personal Lab (Adaltis, Italy) immunoassay analyzer.

Sequence-based genotyping

The material for the genetic study was venous blood in a volume of 5 mL, obtained using a VACUETTE® vacuum system (GreinerBio-One, Austria) into tubes with EDTA (ethylenediaminetetraacetate). Storage of whole blood -80 °C, transportation at -20 °C.

Genomic DNA was isolated from whole blood with the help of a QIAamp DNA Mini Kit at a QIAcube automated nucleic acid isolation station (QIAGEN, Germany). The rs3216780 and rs386693509 dinucleotide polymorphisms in the *CSF1R* gene UTR-3 region were examined with Sanger sequencing. The primers for the *CSF1R* gene amplification were selected using the Primer-BLAST Internet resource (http://www.ncbi.nlm.nih.gov/tools/primer-blast) and the NG_012303.1 reference nucleotide sequence from the NCBI Database (http://www.ncbi.nlm.nih.

gov/nuccore/NG_012303.1). The sequencing of the purified PCR products used an ABI PRISM 3500 analyzer (Thermo Fisher Scientific, USA) with a Big Dye™ Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, USA). The nucleotide sequences were analyzed using the Sequence Scanner v. 1.0. Peak Trace, Vector NTI Advance 10, and Chromas Lite 2.1.1 software packages.

Statistical analysis

The statistical analysis of the findings used the Stat Soft Statistica 12.0 (USA) application software package. The distribution of quantitative data corresponded to the normal distribution, and therefore were expressed as the arithmetic mean with the standard deviation, and the Student's t-test was used to analyze the differences between groups. The qualitative values are presented as the absolute values (n) and percentages. To assess the associations of the factors with the procedure outcome, the Pearson's χ^2 test and the odds ratio (OR) with a 95% confidence interval (CI) were used. The significance level of the revealed differences and correlations in all the types of analysis was assumed to be $p < 0.05$. The distribution of the allele frequencies and genotypes of polymorphic variants complied with the Hardy–Weinberg equilibrium.

Results and discussion

The pre-conception CSF-1 levels did not significantly differ between the groups ($p = 0.730$); nevertheless, the over-time CSF-1 assessment found that on post-ET Day 15 women in both groups showed a reliably higher CSF-1 (3.9-fold in Group I ($p < 0.0001$) and 1.8-fold in Group II ($p = 0.012$), while the Group I patients had a reliably higher CSF-1 than those of the comparison group ($p < 0.0001$).

To assess the possible effects of the serum CSF-1 level on the post-IVF live births, an interquartile analysis was performed. Table 1 shows the isolated CSF-1 quartiles (Me ($Q_{0.25}$-$Q_{0.75}$)). The CSF-1 concentrations corresponding to the 1st and 2nd pre-conception quartiles and the 3rd and 4th post-ET Day 15 quartiles associated with the maximal numbers of the post-IVF live births.

To evaluate the predictive value of the CSF-1 concentrations, the odds ratio with a 95% confidence interval was calculated, and the sensitivities and specificities of the identified predictors of live births were determined. Patients with 121.3 to 314.8 pg/mL pre-conception peripheral blood CSF-1 had 6.18-fold higher odds of live birth at induced pregnancy (95% CI = 2.386-15.990, $p < 0.001$, sensitivity: 75%, specificity: 67.3%). Post-ET Day 15 CSF-1 963.3 to 1682.8 pg/mL supposes 71.4-fold higher odds of post-IVF live birth (95% CI = 14.646-348.073, $p < 0.05$, Complies with Fisher's exact test, sensitivity: 94.4%, specificity: 80.8%).

In the setting of the analysis of the gene *CSF1R* rs3216780 (*del/G*) and rs386693509 (*TG/CA*) polymorphisms, the distribution of genotypes was assessed for compliance with the Hardy–Weinberg equilibrium – no abnormalities were detected. Taking into account the findings, the multiplicative and general inheritance models were applied to these polymorphisms to identify the post-IVF live birth predictor.

The analysis of the *CSF1R* gene polymorphism alleles and genotypes distribution showed that 53.4% of the examined women carried the del allele, while 46.6% carried the *G* allele. The *G* allele and the *del/G* genotype were predominant in the favorable outcome group of women. Therefore, the carriage of the *CSF1R* gene *del/G* rs3216780 genotype acts as a predictor of live birth after induced pregnancy (OR = 11.18, 95% CI = 4.09-30.58, sensitivity: 75%, specificity: 78.8%) (Table 2).

The analysis of the *CSF1R* gene rs386693509 polymorphism distribution showed that 73.3% carried the *TG* allele, while 26.7% carried the *CA* allele. The *TG* allele was predominant in both groups. In Group I, the *TG/CA* was predominant (75%), versus 15.4% in Group II women. Therefore, the carriage of the *CSF1R* gene *TG/CA* rs386693509 genotype acts as a predictor of post-IVF live births (OR = 16.5, 95% CI = 5.68-47.92, sensitivity: 75%, specificity: 84.6%) (Table 2).

Therefore, the univariate analysis has identified the following predictors of the live births at induced pregnancy: 121.3 to 314.8 pg/mL pre-conception CSF-1 in peripheral blood and 963.3 to 1682.8 pg/mL post-ET Day 15 CSF-1, as well as the carriage of the *CSF1R* gene *del/G* rs3216780 and *TG/CA* genotypes. Combinations of these predictors were reported in 66.7% of Group I and 7.7% of Group II women.

Evaluating the IVF procedure's effectiveness implies not only the development of pregnancy but also its live-birth outcome, as about a third of pregnancies end in losses; these are, certainly, determined by multiple factors. Embryo implantation and subsequent placentation depend on the consistent embryo/endometrium interaction regulated by multiple neurohumoral factors. CSF1 is a major regulator of the macrophage-phagocytic system development and homeostasis and, accordingly, a key factor in the control of trophoblastic cells development and homeostasis [1, 12]. Earlier studies in women with tuboperitoneal infertility revealed a relationship between the CSF-1 concentration and the post-IVF pregnancy onset [6]. Literature sources show, however, only not numerous studies that have assessed the association between the CSF-1 system and post-IVF pregnancies resulting in live births.

This is consistent with the findings of other study showing an association between the grown CSF-1 levels and the higher probability of pregnancy [4]. Patients with recurrent miscarriage are also known to have inhibited endometrial CSF-1 production [9]. Hence, the CSF-1 expression can be a potential factor improving the IVF outcomes.

TABLE 1. CSF-1-LEVEL-DEPENDENT NUMBERS OF LIVE BIRTHS IN EXAMINED WOMEN

Factor	Pre-conception CSF-1, pg/mL			
	1st quartile 121.3-257.5 (n = 22)	2nd quartile 257.6-314.8 (n = 22)	3rd quartile 314.9-422.1 (n = 22)	4th quartile 422.2-725.7 (n = 22)
Live births, n (%)	11 (50%)	16 (72.7%)	5 (22.7%)	4 (18.2%)
Spontaneous miscarriages, n (%)	11 (50%)	6 (27.3%)	17 (77.3%)	18 (81.8%)
Factor	Post-ET Day 15 CSF-1, pg/mL			
	1st quartile 205.9-691.2 (n = 22)	2nd quartile 691.3-963.2 (n = 22)	3rd quartile 963.3-1251.4 (n = 22)	4th quartile 1251.4-1682.8 (n = 22)
Live births, n (%)	–	2 (9%)	14 (63.6%)	20 (91%)
Spontaneous miscarriages, n (%)	22 (100%)	20 (91%)	8 (36.4%)	2 (9%)

TABLE 2. MULTIPLICATIVE GENERAL MODELS OF INHERITANCE OF CSF1R **GENE rs3216780 (*del*/G) AND RS386693509 POLYMORPHISMS**

CSF1R gene	Allele/ genotype	Group I (n = 36)	Group II (n = 52)	χ^2	p	OR	
						Value	95% CI
rs3216780 (*del/G*)	*G*	0.597	0.375	8.44	0.004	2.47	1.33-4.58
	del	0.403	0.625			0.40	0.22-0.75
	del/del	0.028	0.519	–	< 0.05*	0.03	0.00-0.21
	del/G	0.750	0.212	25.139	< 0.001	11.18	4.09-30.58
	G/G	0.222	0.269	0.251	0.617	0.78	0.29-2.10
rs386693509 (*TG/CA*)	*TG*	0.597	0.827	11.47	0.0007	0.31	0.16-0.62
	CA	0.403	0.173			3.22	1.61-6.44
	TG/TG	0.222	0.750	23.81	< 0.001	0.10	0.03-0.26
	TG/CA	0.750	0.154	31.562	< 0.001	16.50	5.68-47.92
	CA/CA	0.028	0.096	–	> 0.05*	0.27	0.03-2.40

Note. *, complies with Fisher's exact test.

The mechanism by which CSF-1 influences the rates of implantation and placentation is not understood so far. It is known, however, that adding CSF-1 to a culture of human trophoblastic cells leads to their differentiation into syncytiotrophoblastic cells and stimulates the production of the placental lactogen. Moreover, adding CSF-1 to a culture of murine blastocystic cells causes the growth of the trophoblast [7]. It is worth noting that in experimental work using osteopetrotic mutant mice that lacked CSF-1, it was shown that the fetus can synthesize its own CSF-1, compensating for its lack in the mother [10].

We believe that the identified predictive value of the CSF-1 system can be due to the *CSF1R* gene polymorphism, which ensures its sensitivity and the implementation of the cytokine's biologic functions. An additional explanation is the longer CSF1R expression on the cell surface at the *del/G* and *TG/CA* variants – this favors the stimulation of trophoblastic cell growth, angioprotective effect, and faster placental vascularization.

Conclusions

The results of our study allow for the conclusion that CSF-1 plays a major role in the implementation of the female reproductive function. The pre-conception and post-ET Day 15 serum CSF-1 concentrations and the carriage of the *CSF1R* gene *del/G* rs3216780 and *TG/CA* rs386693509 genotypes are of predictive value in the setting of the post-IVF live births. The findings are of interest from the point of view of completing the data on the contributions of both cytokines and gene polymorphisms in the induced pregnancy development. A more accurate assessment requires further research and analysis of the other factors that may have an effect on the expression of the genes involved in the embryo/endometrium interaction and on the live births.

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Авторы:

Лапштаева А.В. *— доцент кафедры иммунологии, микробиологии и вирусологии с курсом клинической иммунологии и аллергологии Медицинского института ФГБОУ ВО «Национальный исследовательский Мордовский государственный университет имени Н.П. Огарева», г. Саранск, Республика Мордовия, Россия*

Сычев И.В. *— младший научный сотрудник Научно-исследовательского института молекулярной и персонализированной медицины ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения РФ, Москва, Россия*

Адамчик А.И. *— заведующая отделением вспомогательных репродуктивных технологий ГБУЗ Республики Мордовия «Мордовская республиканская центральная клиническая больница», г. Саранск, Республика Мордовия, Россия*

Authors:

Lapshtaeva A.V., *Associate Professor, Department of Immunology, Microbiology and Virology with Course of Clinical Immunology and Allergology, Medical Institute, National Research Ogarev Mordovia State University, Saransk, Republic of Mordovia, Russian Federation*

Sychev I.V., *Junior Researcher, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation*

Adamchik A.I., *Head, Department of Assisted Reproductive Technologies, Mordovia Republican Central Clinical Hospital, Saransk, Republic of Mordovia, Russian Federation*

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