

DOI: <https://doi.org/10.17816/JOWD62675>

# Regulation of the functional activity of peripheral B lymphocytes in pregnant women with a history of recurrent miscarriage

© Anna I. Malyshkina, Natalya Yu. Sotnikova, Dmitry N. Voronin, Alyona V. Kust

Ivanovo Research Institute of Maternity and Childhood named after V.N. Gorodkov, Ivanovo, Russia

**BACKGROUND:** The frequency of recurrent miscarriage is up to 5 % of all desired pregnancies and is mainly due to immunological disorders. Dysfunction in the regulation of the functional activity of B lymphocytes is the pathogenetic link in multiple obstetric complications, including habitual miscarriage.

**AIM:** The aim of this study was to characterize the regulation of the functional activity of peripheral B lymphocytes in pregnant women with threatened spontaneous miscarriage and a history of habitual miscarriage.

**MATERIALS AND METHODS:** We examined 88 women aged 18-40 years at a gestation period of 5-12 weeks. The main group consisted of 36 patients with threatened spontaneous miscarriage at the time of examination and a history of habitual miscarriage. The control group included 28 women with uncomplicated pregnancy. The comparison group consisted of 24 primary pregnant patients with threatened spontaneous abortion at the time of examination. BAFF and APRIL levels in the blood serum were determined by enzyme immunoassay. The content of CD19<sup>+</sup>BAFFR<sup>+</sup> B lymphocytes in the lymphocyte gate was evaluated in the peripheral blood by flow cytometry using monoclonal antibodies. Akt mRNA expression was assessed using real-time reverse-transcription quantitative polymerase chain reaction. CD19<sup>+</sup> B lymphocytes were isolated by direct magnetic separation.

**RESULTS:** In the main group, there was an increase in expression of BAFF receptors on peripheral CD19<sup>+</sup> B lymphocytes and a decrease in the serum BAFF concentration compared to the parameters in the other study groups. We also found a pronounced trend towards a decrease in the serum APRIL level in the main and comparison groups of patients compared to healthy pregnant women. Besides, Akt mRNA expression in peripheral CD19<sup>+</sup> B lymphocytes was increased in the main group.

**CONCLUSIONS:** Threatened habitual abortion is associated with the deficit of the regulatory influence of BAFF and APRIL, which is expressed in the disruption of B cell homeostasis and the weakening of humoral effector mechanisms.

**Keywords:** B-lymphocytes; recurrent miscarriage; threatened abortion; CD19<sup>+</sup>; BAFF; APRIL; Akt.

## To cite this article:

Malyshkina AI, Sotnikova NYu, Voronin DN, Kust AV. Regulation of the functional activity of peripheral B lymphocytes in pregnant women with a history of recurrent miscarriage. *Journal of Obstetrics and Women's Diseases*. 2021;70(4):73-79. DOI: <https://doi.org/10.17816/JOWD62675>

УДК 618.39-021.3-039.41

DOI: <https://doi.org/10.17816/JOWD62675>

# Особенности регуляции функциональной активности периферических В-лимфоцитов у беременных с привычным невынашиванием беременности в анамнезе

© А.И. Малышкина, Н.Ю. Сотникова, Д.Н. Воронин, А.В. Куст

Ивановский научно-исследовательский институт материнства и детства им. В.Н. Городкова, Иваново, Россия

**Обоснование.** Частота привычного невынашивания беременности составляет до 5 % среди всех желанных беременностей и обусловлена в основном иммунологическими нарушениями. Дисфункция в регуляции функциональной активности В-лимфоцитов является патогенетическим звеном многих акушерских осложнений, в том числе привычного невынашивания.

**Цель** — выявить особенности регуляции функциональной активности периферических В-лимфоцитов у женщин с угрожающим самопроизвольным выкидышем и привычным невынашиванием беременности в анамнезе.

**Материалы и методы.** Обследованы 88 женщин в возрасте 18–40 лет на сроке 5–12 недель беременности. Основную группу составили 36 пациенток с угрожающим самопроизвольным выкидышем на момент обследования и привычным невынашиванием беременности в анамнезе, в контрольную группу вошли 28 женщин с неосложненным течением беременности, в группу сравнения — 24 первобеременные пациентки с угрожающим самопроизвольным выкидышем на момент обследования. В сыворотке крови методом иммуноферментного анализа определяли содержание BAFF и APRIL. Методом проточной цитофлуориметрии с помощью моноклональных антител в периферической крови оценивали содержание CD19<sup>+</sup>BAFFR<sup>+</sup> В-лимфоцитов в лимфоцитарном гейте. Экспрессию мРНК Akt исследовали методом обратнo-транскрипционной количественной полимеразной цепной реакции в режиме реального времени. CD19<sup>+</sup> В-лимфоциты выделяли методом прямой магнитной сепарации.

**Результаты.** В основной группе отмечено увеличение количества рецепторов к BAFF на периферических CD19<sup>+</sup> В-лимфоцитах и снижение сывороточной концентрации BAFF по сравнению с показателями в остальных группах. Наблюдалась также выраженная тенденция к снижению сывороточного уровня APRIL у пациенток в основной группе и группе сравнения относительно таковой у здоровых беременных. При анализе экспрессии мРНК Akt в периферических CD19<sup>+</sup> В-лимфоцитах выявлена его повышенная экспрессия у пациенток основной группы.

**Заключение.** Угрожающий привычный выкидыш ассоциирован с недостатком регулирующего влияния BAFF и APRIL, что выражается в нарушении В-клеточного гомеостаза и ослаблении гуморальных эффекторных механизмов.

**Ключевые слова:** В-лимфоциты; привычное невынашивание беременности; угроза прерывания беременности; CD19<sup>+</sup>; BAFF; APRIL; Akt.

## Как цитировать:

Малышкина А.И., Сотникова Н.Ю., Воронин Д.Н., Куст А.В. Особенности регуляции функциональной активности периферических В-лимфоцитов у беременных с привычным невынашиванием беременности в анамнезе // Журнал акушерства и женских болезней. 2021. Т. 70. № 4. С. 73–79. DOI: <https://doi.org/10.17816/JOWD62675>

## BACKGROUND

Miscarriage remains an urgent problem until the present time, with an incidence that varies from 10% to 25% [1]. Concurrently, approximately 2%–5% of married couples repeatedly lose pregnancy, which is called recurrent miscarriage [2]. In recent years, the attention of scientists was attracted by the immunological aspects of recurrent miscarriage, which are detected in various parts of the immune system and rank first in the etiology of unexplained reproductive losses [3]. B-lymphocytes are significant in uncomplicated pregnancy through humoral immune responses and antibody production. In addition, B cells can cause various obstetric complications, such as spontaneous miscarriage, preeclampsia, intrauterine growth retardation, stillbirth, and preterm birth due to the production of autoantibodies [4].

Member 13 of the tumor necrosis factor superfamily (TNFSF) includes two soluble ligands that are involved in the development of B-lymphocytes, the B-cell-activating factor ([BAFF] or TNFSF13B) and the proliferation-inducing ligand ([APRIL] or TNFSF13). These two ligands signal through three receptors, namely the specific BAFF receptor (BAFF-R) and receptors that recognize both BAFF and APRIL, transmembrane activator-1 and calcium modulator and cyclophilin ligand interacting with CD267 (TACI), and B-cell maturation antigen ([BCMA], CD269) [5].

All three BAFF-R are predominantly expressed on B-lymphocytes, whereas TACI is present on both B cells and activated T lymphocytes. BAFF-R can be found on regulatory and activated T lymphocytes. By binding to these receptors, BAFF mediates the activation of the canonical nuclear factor- $\kappa$ B, which is an amplifier of the light chain of activated B cells (NF- $\kappa$ B), non-canonical NF- $\kappa$ B, N-terminal kinase c-Jun, extracellular signal of the regulated kinase (ERK), and phosphoinositide 3-kinase (PI3K), namely signaling protein kinase B (Akt) [5].

After binding to BAFF-R, BAFF activates Akt and ERK depending on I $\kappa$ B kinase (IKK)-1 in the primary B cells. Thereby promoting B-cell survival [6] and affecting the physiological activation of T cells by activating the PI3K–Akt signaling pathway, which reflects one of the pathological mechanisms of T lymphocyte-mediated autoimmune diseases [5].

BAFF maintains the homeostasis of the B-cell link of immunity, acting as a survival and adaptation factor for B-lymphocytes, starting from the transitional stage of development. Whereas, APRIL acts at a later stage, modulating the function and survival of B cells after an antigen contact and participates in the creation and survival of long-lived plasma cells in the bone marrow [7]. Both cytokines contribute to the formation of humoral effector mechanisms.

Increased levels of BAFF and APRIL in the blood serum are associated with autoimmune diseases and correlate with their severity and levels of pathogenic autoantibodies [7]. Thus, an increased level of BAFF and APRIL was noted in patients with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus [8], systemic sclerosis, etc. [9].

Currently, only a few data are available regarding the BAFF content in recurrent pregnancy loss, such as in patients with repeated spontaneous miscarriage. Its level in the decidual membrane and trophoblast was significantly reduced compared to healthy pregnant women [10]. In a pregnancy complicated by fetal growth retardation, the serum BAFF level was also reduced [11]. Currently, no literature data is available regarding the APRIL content during pregnancy.

**This work aimed** to identify the aspects of functional activity regulation of the peripheral B-lymphocytes in women at 5–12 weeks of gestation with a threatened spontaneous miscarriage and a history of recurrent miscarriage.

## MATERIALS AND METHODS

In the V.N. Gorodkov Ivanovo Research Institute of Motherhood and Childhood, 88 women aged 18–40 years, with a gestational age of 5–12 weeks, were examined. The main group consisted of 36 patients with threatened spontaneous miscarriage during the examination and a history of recurrent miscarriage, the control group included 28 female patients with an uncomplicated pregnancy, and the comparison group consisted of 24 primigravidae with threatened spontaneous miscarriage at the time of examination. Exclusion criteria include chromosomal rearrangements of spouses' karyotypes established at the pregravid stage, autoimmune diseases, severe allergic reactions, chronic disease exacerbations, and acute inflammatory diseases, and severe extragenital pathology. The peripheral venous blood was collected upon hospital admission, before the start of conservation therapy. BAFF and APRIL levels in the blood serum were determined by enzyme immunoassay, and CD19<sup>+</sup>BAFFR<sup>+</sup> B-lymphocytes levels in the lymphocyte gate were determined by flow cytometry using monoclonal antibodies.

A concentrated population of CD19<sup>+</sup> B-lymphocytes was obtained by direct magnetic separation using DETACHABEAD CD19 magnetic particles (Invitrogen). Total RNA was isolated from CD19<sup>+</sup> B-lymphocytes by the standard phenol method, and then RNA was converted into complementary DNA using a commercial kit manufactured by Fractal Bio (St. Petersburg, Russia). The obtained samples determined the expression level of Akt mRNA using the reverse transcriptional quantitative real-time polymerase chain reaction. All expression results of the studied genes were

presented as the number of copies of pairs of a specific gene in the sample of  $\times 10^4/\mu\text{l}$ , normalized to the level of mRNA expression of the housekeeping gene ( $\beta_2$ -microglobulin).

Informed voluntary consent for study participation was obtained from all participants. The study was approved at a meeting of the local ethical committee of the V.N. Gorodkov Ivanovo Research Institute of Motherhood and Childhood on November 21, 2018.

Statistical processing of the obtained data was performed using licensed applied programs Microsoft Office 2010, Statistica for Windows 13.0. Data on normal distribution were tested using the Kolmogorov and Shapiro–Wilk tests. Quantitative description of the values was made as mean and the standard error of the mean ( $M \pm m$ ). Statistically significant differences were assessed using the Student's and the Mann–Whitney tests; differences were considered statistically significant at a  $p$ -value of  $<0.05$ .

## STUDY RESULTS

The women who were examined were comparable in age, extra genital pathology, and menstrual function formation. Women with a threatened spontaneous miscarriage and recurrent miscarriage in the anamnesis in the range of extra genital pathology more often had thyroid diseases and anemia and were also married to an older spouse ( $p < 0.05$ ) compared to the rest of the patients. No significant differences were revealed when analyzing the childhood diseases of surgical (extra genital and genital) interventions and allergic reactions in the history of women in the studied groups. Female patients of the main group had a history of chronic endometritis, sexually transmitted infections, uterine cavity curettage, non-developing pregnancies, and spontaneous miscarriages ( $p < 0.05$ ) in all cases compared with the rest of the patients. Women with a history of threatened sporadic miscarriage had primary and secondary infertility more often than the rest of the patients. The clinical manifestations of a threatened spontaneous miscarriage

were more pronounced in primigravidae, thus the frequency of spotting was 8.5% among the participants of the main group and 70.8% in the comparison group ( $p < 0.05$ ). In addition, signs of ovum detachment, according to ultrasound examination of the pelvic organs were noted in 18.2% of cases in the main group and 50% in the comparison group. Expansion of the internal os of the cervical canal was recorded only among women in the comparison group (13.04% of cases).

The immunological examination data analysis showed that women with a threatened spontaneous miscarriage at the time of examination and a history of recurrent miscarriage had an increased level of BAFF-R on peripheral CD19<sup>+</sup> B-lymphocytes compared to patients in the control group and primigravidae with the threat of pregnancy termination (Table). Contrarily, the serum BAFF level was lower in the main group compared to that of healthy pregnant women and primigravidae with threatened sporadic miscarriages. The difference in serum BAFF concentration between the comparison and the control groups was statistically significant. No significant differences were found in the APRIL content in the peripheral blood of the study groups but a pronounced tendency toward a decreased APRIL level in the main and comparison groups relative to the indicator of healthy pregnant women in all cases.

The expression analysis of Akt mRNA in the peripheral CD19<sup>+</sup> B-lymphocytes found that women with a history of recurrent miscarriage and threatened spontaneous miscarriage at the time of examination are characterized by its increased level compared to healthy pregnant women and primigravidae with threatened pregnancy termination.

## DISCUSSION

Isolated data recently appeared that B-lymphocytes can play a direct role in the pathogenesis of recurrent miscarriages [12]. BAFF is actively involved in the homeostasis of the entire pool of B-lymphocytes under physiological

**Table.** Characteristics of indicators of the functional activity of B-lymphocytes in women with threatened spontaneous miscarriage and history of recurrent miscarriage

Indicator	Control group ( $n = 28$ )	Main group ( $n = 36$ )	Comparison group ( $n = 24$ )
BAFF-R, %	$95.3 \pm 0.5$	$97.89 \pm 0.30$ $p_1 = 0.0001$	$95.41 \pm 0.94$ $p_2 = 0.02$
BAFF, ng/ml	$1.5 \pm 0.1$	$1.3 \pm 0.05$ $p_1 = 0.03$	$1.9 \pm 0.21$ $p_2 = 0.01$
APRIL	$1.2 \pm 0.8$	$0.34 \pm 0.06$	$0.31 \pm 0.43$
mPHK Akt	$0.10 \pm 0.06$	$1.39 \pm 0.92$ $p_1 < 0.05$	$0.24 \pm 0.06$ $p_2 < 0.05$

Note:  $p_1$  — level of statistical significance of differences between the main and control groups;  $p_2$  — level of statistical significance of differences between the comparison and the control groups.

conditions by promoting the survival and maturation of B cells. In addition, data presented that increased B-cell activation leads to excessive formation of plasma cells and potentiation of humoral reactions, which may contribute to the development of autoimmune diseases [13]. Moreover, the BAFF/BAFF-R interaction activates the PI3K-Akt signaling pathway, which leads to increased viability and activation of T lymphocytes, showing a direct involvement in the mechanisms of recurrent miscarriages. Thus, BAFF is not only involved in maintaining the homeostasis of the B-cell link of immunity but is also an important factor in the pathogenesis of recurrent miscarriages.

An increased level of BAFF-R in women with threatened spontaneous miscarriages and recurrent miscarriages may indicate increased readiness for B-lymphocyte differentiation, and a simultaneously decreased serum BAFF concentration may indicate either accelerated binding of the ligand to the receptor or impaired homeostasis of both the B- and T-cell link of immunity. Decreased serum APRIL level in women with threatened pregnancy loss (both in primiparous women and in the group of recurrent miscarriage) probably indicates a reduced survival rate of mature high-efficiency forms of B-lymphocytes.

The PI3K/AKT pathway has recently attracted increasing attention from researchers, as it plays a critical role in the regulation of various cellular functions, including metabolism, growth, proliferation, survival, transcription, and protein synthesis [14]. A successful pregnancy is known to be associated with a sufficient level of relaxin produced by the corpus luteum, uterus, decidual tissue, and placenta. Insufficiency of this hormone is associated with the threat

of termination of both the first and repeated pregnancies due to necrosis and apoptosis of the cytotrophoblast [15]. The registered increased expression of Akt mRNA in the peripheral CD19<sup>+</sup> B-lymphocytes in women with recurrent miscarriages may indicate increased functional activity of B cells associated with a response to fetal antigens entering the mother's bloodstream. Similarly, however, less pronounced changes occurred during a threatened miscarriage in primigravidae.

In addition, hormone-mediated B-cell lymphopenia was described in normal pregnancy, which was accompanied by a lower amount of BAFF-R and, accordingly, an increased level of circulating BAFF, which is necessary to differentiate immature transitional B cells into naive mature ones [16]. According to our data, B-cell lymphocytosis was detected in women with threatened sporadic and recurrent miscarriage, along with a pronounced decreased proportion of mature naive B-lymphocytes, indicating an increased expression of BAFF-R and decreased serum BAFF concentration. Mature naive B cells give rise to highly efficient subpopulations, memory cells, and plasma cells. A possible deficiency of plasma cells as the main producers of antibodies may be due, among other things, to a deficiency of APRIL and, probably, leads to insufficient provision of the immune tolerance of the maternal organism in response to a semi-allogeneic fetus.

Therefore, a recurrent threatened miscarriage in women with a history of recurrent miscarriage is associated with an impaired regulatory influence of BAFF and APRIL, which is expressed in a change in B-cell homeostasis and a weakened regulation of humoral effector mechanisms.

## REFERENCES

1. Komilzhanova DK. The role of antiphospholipid syndrome in the prevention of miscarriage. *Biology and Integrative Medicine*. 2017;(5):21–27. (In Russ.)
2. Dobrokhotova YuE, Gankovskaya LV, Bakhareva IV, et al. Role of immune mechanisms in the pathogenesis of miscarriage. *Obstetrics and Gynecology*. 2016;(7):5–10. (In Russ.). DOI: 10.18565/aig.2016.7.5-10
3. Batrak NV, Malyshkina AI, Sotnikova NYU, et al. The role of cd178<sup>+</sup> mononuclear cells in the development of threatened late abortion in women with first-trimester threatened pregnancy interruption and a history of recurrent miscarriage. *Obstetrics and Gynecology*. 2020;(5):70–77. (In Russ.). DOI: 10.18565/aig.2020.5.70-77
4. Lima J., Cambridge G., Vilas-Boas A. et al. Serum markers of B-cell activation in pregnancy during late gestation, delivery, and the postpartum period. *Am J Reprod Immunol*. 2019;81(3):e13090. DOI: 10.1111/aji.13090
5. Hu S, Wang R, Zhang M, et al. BAFF promotes T cell activation through the BAFF-BAFF-R-PI3K-Akt signaling pathway. *Biomed Pharmacother*. 2019;114:108796. DOI: 10.1016/j.biopha.2019.108796
6. Zheng N, Wang D, Ming H, et al. BAFF promotes proliferation of human mesangial cells through interaction with BAFF-R. *BMC Nephrol*. 2015;16:72. DOI: 10.1186/s12882-015-0064-y
7. Samy E, Wax S, Huard B, et al. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases. *Int Rev Immunol*. 2017;36(1):3–19. DOI: 10.1080/08830185.2016.1276903
8. Matsuda Y, Haneda M, Kadomatsu K, Kobayashi T. A proliferation-inducing ligand sustains the proliferation of human naive (CD27<sup>-</sup>) B cells and mediates their differentiation into long-lived plasma cells *in vitro* via transmembrane activator and calcium modulator and cyclophilin ligand interactor and B-cell mature antigen. *Cell Immunol*. 2015;295(2):127–136. DOI: 10.1016/j.cellimm.2015.02.011
9. Xu J, Luo X, Qu S, et al. B cell activation factor (BAFF) induces inflammation in the human fallopian tube leading to tubal pregnancy. *BMC Pregnancy Childbirth*. 2019;19(1):169. DOI: 10.1186/s12884-019-2324-5
10. Guo WJ, Qu X, Yang MX, et al. Expression of BAFF in the trophoblast and decidua of normal early pregnant women and patients with recurrent spontaneous miscarriage. *Chin Med J (Engl)*. 2008;121(4):309–315.



11. Frolova MV. The character of baff production and reception during pregnancy complicated intrauterine growth retardation. *Russian journal of immunology*. 2016;19(2(1)):215–216. (In Russ.)
12. Danaï S, Ghorbani F, Ahmadi M, et al. IL-10-producing B cells play important role in the pathogenesis of recurrent pregnancy loss. *Int Immunopharmacol*. 2020;87:106806. DOI: 10.1016/j.intimp.2020.106806
13. Chan CT, Lieu M, Sobey CG, et al. Diagnosing and treating hypertensive disorders of pregnancy? The answer may now be less BAFF-ling. *Hypertension*. 2017;70(5):884–886. DOI: 10.1161/HYPERTENSIONAHA.117.09849
14. Jiang N, Dai Q, Su X, et al. Role of PI3K/AKT pathway in cancer: the framework of malignant behavior. *Mol Biol Rep*. 2020;47(6):4587–4629. DOI: 10.1007/s11033-020-05435-1
15. Ogunleye O, Campo B, Herrera D, et al. Relaxin confers cytotrophoblast protection from hypoxia-reoxygenation injury through the phosphatidylinositol 3-kinase-Akt/protein kinase B cell survival pathway. *Am J Physiol Regul Integr Comp Physiol*. 2017;312(4):R559–R568. DOI: 10.1152/ajpregu.00306.2016
16. Lima J, Cambridge G, Vilas-Boas A, et al. Serum markers of B-cell activation in pregnancy during late gestation, delivery, and the postpartum period. *Am J Reprod Immunol*. 2019;81(3):e13090. DOI: 10.1111/aji.13090

## СПИСОК ЛИТЕРАТУРЫ

1. Комилжанова Д.К. Роль антифосфолипидного синдрома в профилактике невынашивания беременности // Биология и интегративная медицина. 2017. № 5. С. 21–27.
2. Доброхотова Ю.Э., Ганковская Л.В., Бахарева И.В. и др. Роль иммунных механизмов в патогенезе привычного невынашивания беременности // Акушерство и гинекология. 2016. № 7. С. 5–10. DOI: 10.18565/aig.2016.7.5-10
3. Батрак Н.В., Малышкина А.И., Сотникова Н.Ю. и др. Роль CD178<sup>+</sup> мононуклеарных клеток в развитии угрожающего позднего выкидыша у женщин с угрозой прерывания беременности в I триместре и привычным невынашиванием в анамнезе // Акушерство и гинекология. 2020. № 5. С. 70–77. DOI: 10.18565/aig.2020.5.70-77
4. Lima J, Cambridge G, Vilas-Boas A, et al. Serum markers of B-cell activation in pregnancy during late gestation, delivery, and the postpartum period // *Am. J. Reprod. Immunol*. 2019. Vol. 81. No. 3. P. e13090. DOI: 10.1111/aji.13090
5. Hu S, Wang R, Zhang M, et al. BAFF promotes T cell activation through the BAFF-BAFF-R-PI3K-Akt signaling pathway // *Biomed. Pharmacother*. 2019. Vol. 114. P. 108796. DOI: 10.1016/j.biopha.2019.108796
6. Zheng N, Wang D, Ming H, et al. BAFF promotes proliferation of human mesangial cells through interaction with BAFF-R // *BMC Nephrol*. 2015. Vol. 16. P. 72. DOI: 10.1186/s12882-015-0064-y
7. Samy E, Wax S, Huard B, et al. Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases // *Int. Rev. Immunol*. 2017. Vol. 36. No. 1. P. 3–19. DOI: 10.1080/08830185.2016.1276903
8. Matsuda Y, Haneda M, Kadomatsu K, Kobayashi T. A proliferation-inducing ligand sustains the proliferation of human naive (CD27<sup>-</sup>) B cells and mediates their differentiation into long-lived plasma cells *in vitro* via transmembrane activator and calcium modulator and cyclophilin ligand interactor and B-cell mature antigen // *Cell. Immunol*. 2015. Vol. 295. No. 2. P. 127–136. DOI: 10.1016/j.cellimm.2015.02.011
9. Xu J, Luo X, Qu S, et al. B cell activation factor (BAFF) induces inflammation in the human fallopian tube leading to tubal pregnancy // *BMC Pregnancy Childbirth*. 2019. Vol. 19. No. 1. P. 169. DOI: 10.1186/s12884-019-2324-5
10. Guo W.J., Qu X., Yang M.X. et al. Expression of BAFF in the trophoblast and decidua of normal early pregnant women and patients with recurrent spontaneous miscarriage // *Chin. Med. J. (Engl)*. 2008. Vol. 121. No. 4. P. 309–315.
11. Фролова М.В. Особенности продукции и рецепции BAFF при беременности, осложненной задержкой роста плода // Российский иммунологический журнал. 2016. Т. 19. № 2 (1). С. 215–216.
12. Danaï S, Ghorbani F, Ahmadi M, et al. IL-10-producing B cells play important role in the pathogenesis of recurrent pregnancy loss // *Int. Immunopharmacol*. 2020. Vol. 87. P. 106806. DOI: 10.1016/j.intimp.2020.106806
13. Chan C.T., Lieu M., Sobey C.G. et al. Diagnosing and treating hypertensive disorders of pregnancy? The answer may now be less BAFF-ling // *Hypertension*. 2017. Vol. 70. No. 5. P. 884–886. DOI: 10.1161/HYPERTENSIONAHA.117.09849
14. Jiang N, Dai Q, Su X, et al. Role of PI3K/AKT pathway in cancer: the framework of malignant behavior // *Mol. Biol. Rep*. 2020. Vol. 47. No. 6. P. 4587–4629. DOI: 10.1007/s11033-020-05435-1
15. Ogunleye O., Campo B., Herrera D. et al. Relaxin confers cytotrophoblast protection from hypoxia-reoxygenation injury through the phosphatidylinositol 3-kinase-Akt/protein kinase B cell survival pathway // *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 2017. Vol. 312. No. 4. P. R559–R568. DOI: 10.1152/ajpregu.00306.2016
16. Lima J., Cambridge G., Vilas-Boas A. et al. Serum markers of B-cell activation in pregnancy during late gestation, delivery, and the postpartum period // *Am. J. Reprod. Immunol*. 2019. Vol. 81. No. 3. P. e13090. DOI: 10.1111/aji.13090

## AUTHORS INFO

**Anna I. Malyshkina**, MD, Dr. Sci. (Med.), Professor;  
ORCID: <https://orcid.org/0000-0002-1145-0563>;  
e-mail: [anna\\_im@mail.ru](mailto:anna_im@mail.ru)

**Natalya Yu. Sotnikova**, MD, Dr. Sci. (Med.), Professor;  
ORCID: <https://orcid.org/0000-0002-0608-0692>;  
e-mail: [niimid.immune@mail.ru](mailto:niimid.immune@mail.ru)

## ОБ АВТОРАХ

**Анна Ивановна Малышкина**, д-р мед. наук, профессор;  
ORCID: <https://orcid.org/0000-0002-1145-0563>;  
e-mail: [anna\\_im@mail.ru](mailto:anna_im@mail.ru)

**Наталья Юрьевна Сотникова**, д-р мед. наук, профессор;  
ORCID: <https://orcid.org/0000-0002-0608-0692>;  
e-mail: [niimid.immune@mail.ru](mailto:niimid.immune@mail.ru)

**Dmitry N. Voronin**, Cand. Sci. (Biol.);  
ORCID: <https://orcid.org/0000-0003-2836-8694>;  
e-mail: niimid.immune@mail.ru

**\*Alyona V. Kust**;  
address: 20 Pobedy Str., Ivanovo, 153045, Russia;  
ORCID: <https://orcid.org/0000-0002-1355-7225>;  
e-mail: avkMD@yandex.ru

**Дмитрий Николаевич Воронин**, канд. биол. наук;  
ORCID: <https://orcid.org/0000-0003-2836-8694>;  
e-mail: niimid.immune@mail.ru

**\*Алена Валерьевна Куст**;  
адрес: Россия, 153045, Иваново, ул. Победы, д. 20;  
ORCID: <https://orcid.org/0000-0002-1355-7225>;  
e-mail: avkMD@yandex.ru