MOLECULAR GENETIC ASPECTS OF PREDICTING EARLY PREGNANCY LOSS

Yusef OV[1], Ibragimov BR[2], Klimenko MP[1]✉, Gerasimova AA[3], Aimetdinova AB[1], Marnat EG[1], Abramov DD[4], Klimenko PA[1], Kurtser MA[1]

[1] Pirogov Russian National Research Medical University, Moscow, Russia
[2] Dagestan State Medical University, Makhachkala, Russia
[3] Patrice Lumumba Peoples' Friendship University of Russia, Moscow, Russia
[4] Institute of Immunology of the Federal Medical Biological Agency of Russia, Moscow, Russia

Missed abortion is one of the most prevalent forms of early pregnancy loss that remains a pressing issue of obstetrics and gynecology. Despite advances in reproductive medicine, the molecular mechanisms underlying the embryo development termination in early gestation are poorly understood. A comparative single-center study aimed to assess the expression of *TGF-β* and *MMP-9* genes in peripheral blood of women with physiological and missed abortion and assess their potential prognostic value for evaluation of the risk of early pregnancy loss. A total of 40 pregnant women were included in the study: 20 patients with the 9–11 week physiological pregnancy (control group) and 20 women diagnosed with missed abortion (index group). The *TGF-β* and *MMP-9* gene expression was determined by the real-time polymerase chain reaction method after the total RNA isolation from peripheral blood. The Mann–Whitney U-test and ROC analysis were used for statistical data processing. No significant differences in the *TGF-β* and *MMP-9* gene expression between the studied groups were revealed. At the same time, ROC analysis made it possible to determine the threshold values of the studied indicators having some diagnostic information content. As for *MMP-9*, the threshold value $Ct \leq 29$ ensuring the 80% sensitivity and 60% specificity turned out to be the most informative. As for *TGF-β*, the threshold value $Ct \leq 27.4$ was characterized by the 75% sensitivity and 70% specificity. The findings suggest the potential prognostic value of the studied genes for evaluation of the risk of missed abortion.

Keywords: expression of *TGF-β* and *MMP-9* genes, missed abortion, physiological pregnancy, prognosis of pregnancy course

Funding: the study was conducted as part of the Program for Basic Research in the Russian Federation for the Long Term (2021–2030) (No. 122030100170-5).

Author contribution: Yusef OV — clinical material collection, laboratory testing; Ibragimov BR — statistical processing, analysis of results; Klimenko MP — database creation; Gerasimova AA — ultrasound examination, clinical assessment of results; Aimetdinova AB — clinical and functional assessment of patients; Marnat EG — laboratory testing (PCR); Abramov DD — literature review, interpretation of results, manuscript writing; Klimenko PA — study design, clinical phase arrangement, interpretation of results; Kurtser MA — study concept and design, academic advising, manuscript approval.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Pirogov Russian National Research Medical University (protocol No. 258 dated February 16, 2026). All the surveyed individuals submitted the informed consent to take part in the study.

✉ **Correspondence should be addressed:** Pyotr A. Klimenko
Sevastopolsky prospekt, 24a, Moscow, 117209; pa.klimenko@mail.ru

Received: 24.06.2026 **Accepted:** 05.08.2026 **Published online:** 18.08.2026

DOI: 10.24075/brsmu.2026.043

МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКИЕ АСПЕКТЫ ПРОГНОЗИРОВАНИЯ РАННИХ РЕПРОДУКТИВНЫХ ПОТЕРЬ

О. В. Юсеф[1], Б. Р. Ибрагимов[2], М. П. Клименко[1]✉, А. А. Герасимова[3], А. Б. Айметдинова[1], Е. Г. Марнат[1], Д. Д. Абрамов[4], П. А. Клименко[1], М. А. Курцер[1]

[1] Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва, Россия
[2] Дагестанский государственный медицинский университет, Махачкала, Россия
[3] Российский университет дружбы народов имени Патриса Лумумбы, Москва, Россия
[4] Институт иммунологии Федерального медико-биологического агентства России, Москва, Россия

Замершая беременность относится к числу наиболее распространенных форм ранних репродуктивных потерь и остается актуальной проблемой акушерства и гинекологии. Несмотря на достижения в области репродуктивной медицины, молекулярные механизмы, лежащие в основе прекращения развития эмбриона на ранних сроках гестации, изучены недостаточно. Целью сравнительного одноцентрового исследования было оценить уровень экспрессии генов *TGF-β* и *MMP-9* в периферической крови женщин с физиологической и замершей беременностью и определить их потенциальную прогностическую значимость при оценке риска ранних репродуктивных потерь. В исследование были включены 40 беременных женщин: 20 пациенток с физиологически протекающей беременностью сроком 9–11 недель (контрольная группа) и 20 женщин с диагнозом замершей беременности (основная группа). Уровень экспрессии генов *TGF-β* и *MMP-9* определяли методом полимеразной цепной реакции в режиме реального времени после выделения тотальной РНК из периферической крови. Для статистической обработки результатов использовали критерий Манна–Уитни и ROC-анализ. Статистически значимых различий между исследуемыми группами по уровням экспрессии генов *TGF-β* и *MMP-9* выявлено не было. Вместе с тем ROC-анализ позволил определить пороговые значения исследуемых показателей, обладающие определенной диагностической информативностью. Для *MMP-9* наиболее информативным оказалось значение $Ct \leq 29$, обеспечивающее чувствительность 80% и специфичность 60%. Для *TGF-β* пороговое значение $Ct \leq 27{,}4$ характеризовалось чувствительностью 75% и специфичностью 70%. Полученные результаты свидетельствуют о потенциальной прогностической значимости исследуемых генов при оценке риска замершей беременности.

Ключевые слова: экспрессия генов *TGF-β* и *MMP-9*, физиологическая и замершая беременность, прогнозирование течения беременности

Финансирование: работа выполнена в рамках Программы фундаментальных научных исследований в Российской Федерации на долгосрочный период (2021–2030 гг.) (№ 122030100170-5).

Вклад авторов: О. В. Юсеф — сбор клинического материала, проведение лабораторных исследований; Б. Р. Ибрагимов — статистическая обработка, анализ результатов; М. П. Клименко — формирование базы данных; А. А. Герасимова — ультразвуковое исследование, клиническая оценка результатов; А. Б. Айметдинова — клинико-функциональное обследование пациентов; Е. Г. Марнат — проведение лабораторных исследований (ПЦР); Д. Д. Абрамов — анализ литературы, интерпретация результатов, подготовка текста рукописи; П. А. Клименко — дизайн исследования, организация клинического этапа, интерпретация результатов; М. А. Курцер — концепция и дизайн исследования, научное руководство, утверждение рукописи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом РНИМУ им. Н. И. Пирогова (протокол № 258 от 16 февраля 2026 г.). Все обследованные подписали добровольное информированное согласие на участие в исследовании.

✉ **Для корреспонденции:** Петр Афанасьевич Клименко
Севастопольский пр-т, д. 24а, г. Москва, 117209; pa.klimenko@mail.ru

Статья получена: 24.06.2026 **Статья принята к печати:** 05.08.2026 **Опубликована онлайн:** 18.08.2026

DOI: 10.24075/vrgmu.2026.043

Missed abortion is one of the most significant problems of modern reproductive medicine that occupies an important place in the structure of early pregnancy loss. Despite the improvement of the diagnosis and treatment methods, the prevalence of this disorder remains high. Abnormal embryo development in early gestation results from the combination of genetic, immune, endocrine, infectious, and vascular factors, the contribution of each of which can be different depending on the clinical situation.

The normal pregnancy course is ensured by the coherent interaction between the mother's body and the developing embryo. Successful implantation and subsequent formation of the placental complex require an adequate trophoblast invasion, extracellular matrix remodeling, vascular network formation, and immune tolerance maintenance. Violation of any of the above processes can result in pregnancy arrest.

The earlier studies revealed molecular features of the tissues collected from individuals with missed abortion. It has been found that early pregnancy loss is associated with changes in the ribosomal DNA content [1, 2], abnormal expression of a number of placenta-specific proteins of the PSG family [3, 4], as well as downregulation of the reticulon 4 (RTN4) protein involved in apoptosis and cell differentiation. The results obtained suggest that there are complex molecular abnormalities affecting various phases of embryo development and placenta formation [1–6]. At the same time, the immune regulation and tissue remodeling mechanisms in patients with miscarriage are poorly understood. In this regard, the transforming growth factor β (*TGF-β*) and matrix metalloproteinase 9 (*MMP-9*) genes play an important role in ensuring the immune tolerance, trophoblast invasion, and placental bed formation are of special interest.

MMP-9 is an enzyme involved in degradation of the extracellular matrix components. Its activity is important for the throphoblastic cell migration and invasion, endometrial tissue remodeling, and placental complex formation. The *MMP-9* regulation impairment can be associated with placentation defects and complicated pregnancy course [7–13].

Matrix metalloproteinase 9, also playing an important role in leukocyte migration, osteoclastic bone resorption, belongs to the M10A peptidase family; it functions as a growth factor regulating the cell differentiation, migration, and cell death, activates the signaling cascades via CD63 and ITGB1. According to the String data (Fig. 1), it is also involved in protein-protein interaction.

TGF-β belongs to the key regulators of cell proliferation, differentiation, and immune response. During pregnancy this cytokine is involved in developing the immune tolerance between the mother's body and the fetus, limiting the development of excess immune responses and contributing to continuation of pregnancy [14–25].

Despite a large number of studies focused on the role of TGF-β and MMP-9 in reproductive processes, the information about the specifics of their expression in patients with missed abortion is still limited and largely controversial. This determines the need for further study of these molecular markers.

According to the String data (Fig. 2), TGF-β is involved in protein-protein interaction in the following way.

The studied genes (proteomes) almost never interact with each other or together (Fig. 3).

The study aimed to assess the *TGF-β* and *MMP-9* gene expression in peripheral blood of women with physiological pregnancy and missed abortion, as well as to determine their

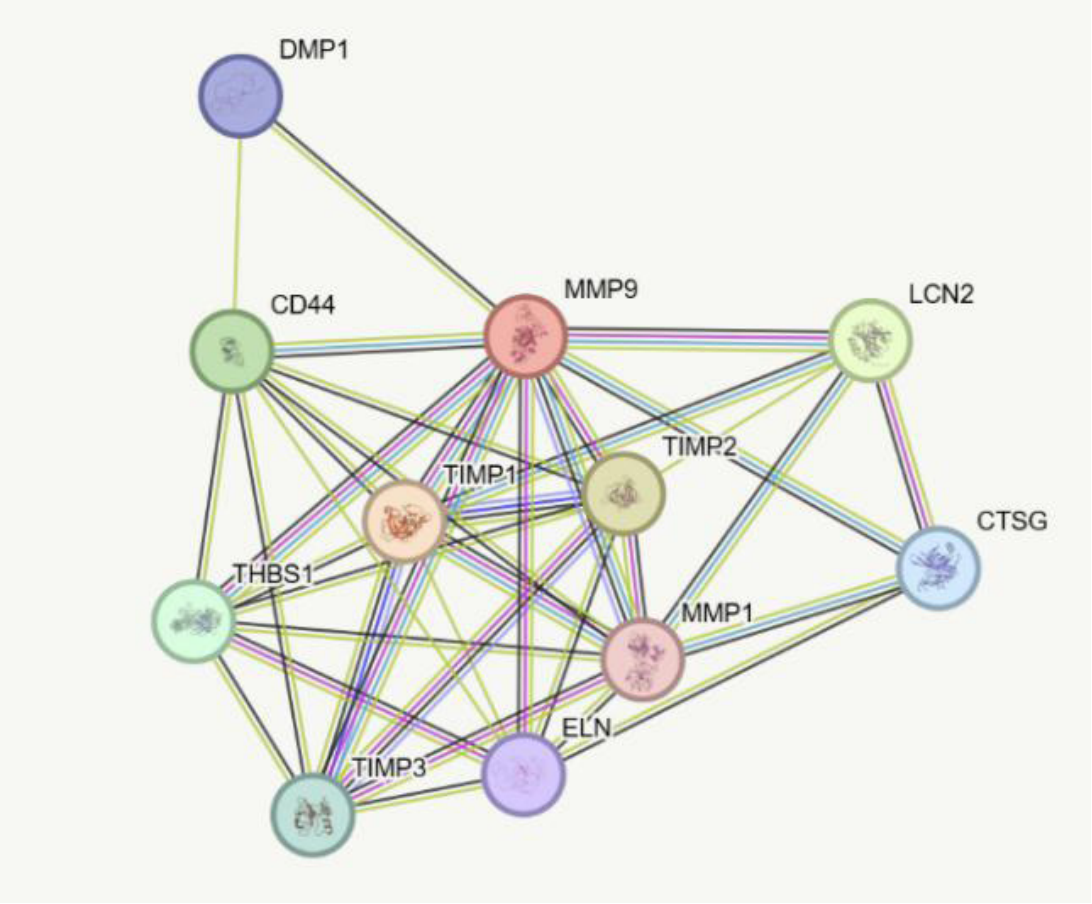

Fig. 1. Protein-protein interaction of MMP-9. Contribution of the MMP-9 biochemical interaction with other bioactive substances. The interaction network is constructed using the STRING resource (https://string-db.org)

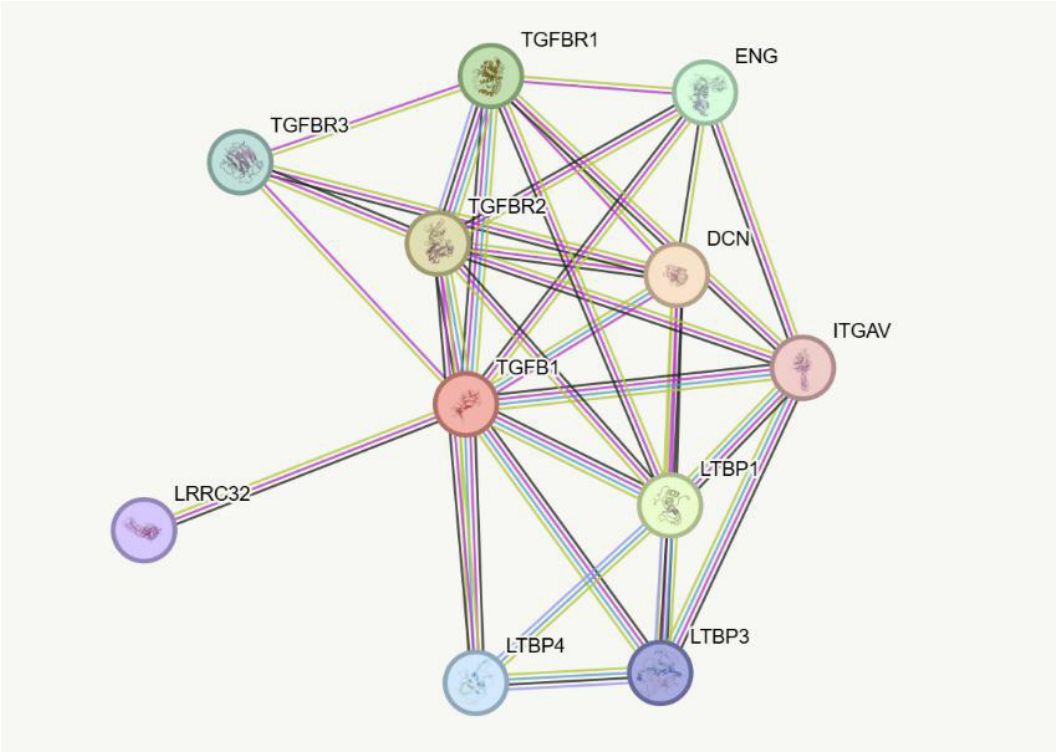

Fig. 2. Protein-protein interaction of TGF-β. Contribution of the TGF-β biochemical interaction with other bioactive substances. The interaction network is constructed using the STRING resource (https://string-db.org)

potential prognostic value for evaluation of the risk of early pregnancy loss.

METHODS

Research design. A comparative single-center study aimed at assessing the *TGF-β* and *MMP-9* gene expression in peripheral blood of women with physiological pregnancy and missed abortion was conducted.

Characteristics of surveyed patients

A total of 40 pregnant women were included in the study. The control group consisted of 20 patients with the 9–11-week physiological singleton pregnancy, who were through the first prenatal screening. The index group consisted of 20 women diagnosed with missed abortion. Missed abortion was detected during the scheduled visit and the ultrasound examination, and the pregnancy age was determined based on the medical history data and fetal ultrasound. In 13 patients, pregnancy arrest occurred at 6–9 weeks of gestation, and in 4 patients it occurred at 9–12 weeks. Furthermore, a mismatch between anthropometric measurements based on the ultrasound examination of dead embryos and the gestational age of 3–5 weeks. In 3 patients, pregnancy was terminated for medical reasons (teratogenic effects) after the genetic counseling and the consilium at 13–21 weeks. Fetal karyotypes were not determined in cases of developmental abnormalities. Inclusion criteria: age over 18 years; confirmed intrauterine pregnancy; signed informed consent to take part in the study. Exclusion criteria: multiple pregnancy.

Biomaterial collection

Peripheral venous blood collection from the cubital vein was performed in all patients prior to surgery and ultrasound examination. The main diagnosis was made after the embryo tissue assessment at the cytogenetic laboratory.

RNA isolation and cDNA synthesis

Whole venous blood was used to isolate total RNA. After lysis of cellular elements samples were centrifuged, and further RNA extraction was performed using the ExtractRNA kit (Evrogen, Russia) in accordance with the manufacturer's guidelines. The quality of the RNA obtained was controlled by electrophoresis. The nucleic acid concentration was determined by spectrophotometry using the Nano500 system (AllSheng, China). The BioMaster RNAscribe RT Plus kit (Biolabmix, Russia) was used to synthesize complementary DNA. A total of 1 μg of total RNA was added to the reverse transcription reaction. After the reaction was complete the resulting cDNA was diluted with nuclease-free water and used for further gene expression analysis.

Determination of gene expression

The expression of the *TGF-β* and *MMP-9* genes was determined by the real-time polymerase chain reaction method. Amplification was accomplished in the DT-96 cycler (DNA-Technology, Russia). All the samples were analyzed in two technical replicates. To increase the analysis specificity,

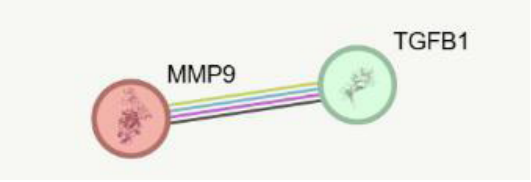

Fig. 3. Biological interaction of TGF-β and MMP9 between each other in the pregnant woman's body. The interaction network is constructed using the STRING resource (https://string-db.org)

Table. Comparative statistics of the *TGF-β* and *MMP-9* expression in blood of patients physiological pregnancy and missed abortion

Parameters	Group	Number of cases	Mean	Standard error (±)	Minimum	Maximum
Ct_TGFb	Missed abortion	20	27.15	0.3	24.7	30.8
Ct_TGFb	Control	20	28.205	0.33	26	32.7
Ct_MMP9	Missed abortion	20	27.805	0.42	25.4	32.1
Ct_MMP9	Control	20	29.31	0.37	26.2	32.4
Ct_B2M	Missed abortion	20	19.935	0.37	17.9	24.8
Ct_B2M	Control	20	20.5	0.28	18.4	23.7
Ct_GUSB	Missed abortion	20	28.265	0.37	25.9	33.4
Ct_GUSB	Control	20	29.47	0.37	26.2	33.1
Ctref	Missed abortion	20	24.1	0.36	22.3	29.1
Ctref	Control	20	24.985	0.31	23	28.4
ΔCt_TGFb	Missed abortion	20	3.05	0.21	1.2	4.9
ΔCt_TGFb	Control	20	3.22	0.2	2	6.1
ΔCt_MMP9	Missed abortion	20	3.705	0.23	2.35	6.15
ΔCt_MMP9	Control	20	4.325	0.26	2.8	8.3

Note: Ct_TGFb — *Ct* value of *TGF-β* gene amplification, Ct_MMP9 — *Ct* value of *MMP-9* gene amplification.

primer was placed on the exon–exon junction, which prevented amplification with the genomic DNA. *B2M* and *GUSB* were used as reference genes. Relative expression was calculated by the *ΔΔCt* method with subsequent mean reference gene normalization.

Statistical analysis

Statistical data processing was performed using the StatPlus 2007 software. The mean, standard error of the mean, median minimum and maximum values were calculated for quantitative indicators. Independent groups were compared using the nonparametric Mann–Whitney test. This method was selected due to small sample size and no need to assume the normal distribution of the studied traits. The differences were considered significant at $p < 0.05$. ROC analysis involving determination of optimal threshold values, sensitivity and specificity was used to assess the diagnostic informativity of the studied indicators. No adjustment for multiple comparisons was applied. The study was preliminary, since the cohort size was 20 individuals per group.

RESULTS

Comparative analysis of the *TGF-β* and *MMP-9* gene expression in peripheral blood of women with physiological

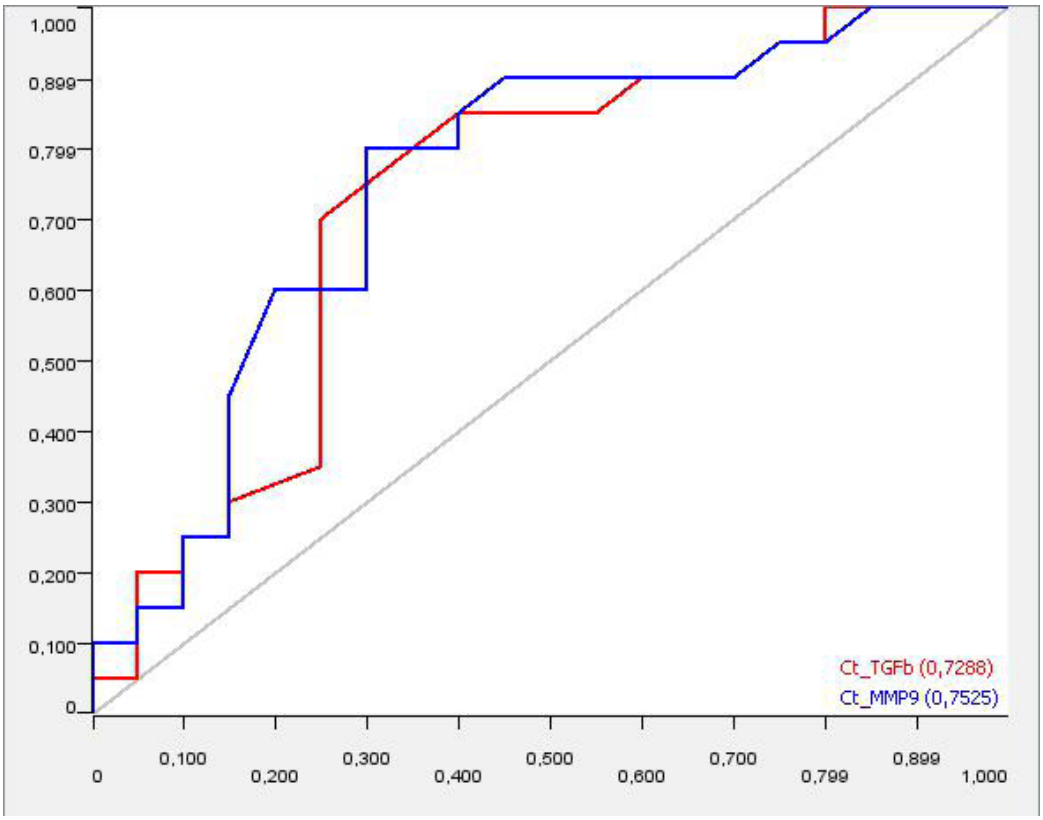

Fig. 4. ROC curves characterizing the Ct_TGFb and Ct_MMP9 expression sensitivity and specificity for the success of missed abortion prediction. X axis — False positive rate (specificity), Y axis — True positive rate (sensitivity)

pregnancy and missed abortion was conducted. The analysis of threshold amplification cycles revealed no significant intergroup differences (Table). The mean *Ct* value for *TGF-β* was 27.15 ± 0.30 in the group with missed abortion, while in the control group it was 28.21 ± 0.33. As for the *MMP-9* gene, the mean *Ct* values were 27.81 ± 0.42 and 29.31 ± 0.37, respectively.

Therefore, *TGFb* and *MMP-9* do not have a 100% diagnostic value for prediction of missed abortion, but in fact there are more data: for example, we accurately calculated the limits of intervals, based on which the subtle difference was found. Thus, the analysis of parameters for the risk of "missed abortion" (Fig. 4) showed the most significant differences for the Ct_TGFb and Ct_MMP9 parameters.

The value ≤ 29, at which sensitivity reaches 80% with the 60% specificity, is diagnostically important for Ct_MMP9 (Fig. 4). As for Ct_TGFb, such expression value is 27.4, at which sensitivity reaches 75% with the 70% specificity. Prediction of missed abortion based on the Ct_TGFb and Ct_MMP9 expression can yield the result of up to 80%/70%.

DISCUSSION

In this study the expression of the *TGF-β* and *MMP-9* genes in peripheral blood of women with physiological pregnancy and missed abortion was assessed. Despite the fact that there were no significant differences between the studied groups, the ROC analysis results showed that there were threshold values of the studied indicators having some prognostic informativity. The data obtained suggest that changes in the *TGF-β* and *MMP-9* expression cannot be considered as the only mechanism underlying the development of missed abortion. It is likely that the molecular alterations identified reflect only some links of a complex pathogenetic process including impaired placentation, immune adaptation, and cell-cell interactions at the maternal-fetal interface [14–25].

It is well known that successful implantation of the embryo and further pregnancy development require the adequate throphoblast invasion of the endometrium and development of the full-fledged maternal-placental blood flow. Matrix metalloproteinases ensuring the controlled extracellular matrix remodeling play an important role in these processes [7–13]. Among members of this family of special importance is MMP-9 involved in degradation of the basal membrane components, throphoblastic cell migration, and placental bed formation [7–13].

According to a number of studies, the MMP-9 activity is strongly associated with the throphoblast invasion and normal development of the placenta [7–13]. Abnormal metalloproteinase regulation can result in incomplete placentation at different fetus's gestational ages and the development of pregnancy complications [7–13]. The data on the MMP-9 potential prognostic value obtained in this study are in line with modern views of the role of this enzyme in early gestation.

An equally important component of the successful pregnancy is the formation of immunological tolerance between the mother's body and the fetus [15–25]. A central place in the regulation of this process is occupied by TGF-β having pronounced immunomodulatory properties [15–25]. This cytokine is involved in controlling the activity of T cells, natural killers, and other immunocompetent cells, it ensures maintenance of the immune balance essential for pregnancy continuation [14–25].

According to the literature, the decrease in activity of the TGF-β signaling pathways can be associated with violation of the maternal-fetal immune tolerance and the increased risk of miscarriage [15–25]. Our results revealed no significant intergroup differences due to insufficient number of measurements of the studied indicators at various embryogenesis and placentation terms. However, the fact that there is a diagnostically significant threshold value suggests the TGF-β involvement in the mechanisms associated with the risk of pregnancy arrest.

It should be taken into account that the missed abortion pathogenesis is multifactorial [7–25]. Genetic abnormalities in the embryo, endocrine disorders, infectious processes, hemostatic disorders, and immune alterations can be realized simultaneously to form various clinical variants of the disease. In this regard, the use of distinct molecular markers does not always ensure high diagnostic accuracy. Limitations of the study include the relatively small sample size and heterogeneity of pregnancy age in the group of patients with missed abortion. Furthermore, biomaterial was collected after making the diagnosis, which did not allow us to assess the dynamic changes in expression of the studied genes at various stages of the disease process.

Thus, the findings confirm that further investigation of *TGF-β* and *MMP-9* as the components of complex prognostic models for assessment of the risk of early pregnancy loss is promising [7–25]. To clarify clinical significance of the patterns identified, studies with the inclusion of a larger number of observations and the expanded range of molecular genetic indicators are necessary.

The study made it possible to assess the features of the *TGF-β* and *MMP-9* gene expression in peripheral blood of women with physiological pregnancy and missed abortion. No significant intergroup differences in expression of the studied genes were revealed. At the same time, the ROC analysis results showed that there were threshold values of the *TGF-β* and *MMP-9* indicators having some prognostic informativity when assessing the risk of missed abortion.

The data obtained suggest possible involvement of the studied genes in the molecular mechanisms ensuring the normal pregnancy course. However, the small sample size makes it impossible to consider the patterns revealed as the definitely proven ones. Further research should be focused on assessing the *TGF-β* and *MMP-9* expression in the larger and clinically homogeneous groups of patients, as well as on developing the complex prognostic models combining molecular genetic, laboratory, and clinical indicators.

CONCLUSIONS

There were no significant differences in the *TGF-β* and *MMP-9* gene expression in peripheral blood of women with physiological pregnancy and missed abortion. The threshold value *Ct* ≤ 29 enduring the 80% sensitivity and 60% specificity turned out to be of diagnostic value for the *MMP-9* gene. As for the *TGF-β* gene, the value *Ct* ≤ 27.4 with the 75% sensitivity and 70% specificity was the most informative. The findings suggest the potential prognostic value of these molecular markers and the need for further research aimed to confirm their clinical significance and ensure validation in the independent sample.

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