

## **ABSTRACT**

for the dissertation of Stanova Sayazhan Kenesovna  
on the topic "**A personalized approach to the diagnosis and treatment of  
chronic tonsillopharyngitis in pregnant**",  
submitted for the degree of Doctor of Philosophy (PhD) in the specialty  
6D110100 - "Medicine"

### **Relevance of the research topic**

The increase in the frequency of extragenital diseases in women of reproductive age in recent decades has necessitated a review of approaches to the diagnosis and treatment of inflammatory diseases in obstetric practice. Among them, a significant place is occupied by chronic tonsillopharyngitis (CTP), which is one of the leading forms of chronic ENT pathology accompanying pregnancy. The effect of chronic oropharyngeal inflammation on the course of the gestational process, birth outcomes, and newborn health has been confirmed by numerous clinical observations. However, existing methods of treatment and prevention do not take into account the characteristics of the immune, hormonal and microbiological status of pregnant women, which reduces the effectiveness of therapy and increases the risk of complications. The relevance of this study is determined by the need to introduce the principles of personalized and evidence-based medicine into the clinical practice of managing pregnant women with chronic inflammatory diseases of the oropharynx. The scientific and practical significance of the work lies in the development and justification of a new algorithm for the diagnosis and treatment of CTP, based on the consideration of individual clinical, immunological and microbiological characteristics of patients.

The results of the study are aimed at improving the effectiveness of medical care, reducing obstetric complications and improving reproductive outcomes, which corresponds to the strategic priorities of healthcare in the Republic of Kazakhstan in the field of maternal and child health.

### **The purpose of the dissertation research**

Improving the diagnosis and treatment of chronic tonsillopharyngitis in pregnant women based on a personalized approach, taking into account clinical, immunological, bacteriological, molecular biological and morphological characteristics.

### **Objectives of the dissertation research**

1. To conduct a systematic analysis of domestic and international literature on the problem of chronic tonsillopharyngitis in pregnant women with an emphasis on a personalized approach to therapy.
2. To evaluate the clinical and laboratory results and the level of endogenous intoxication in pregnant women with various forms of CTP.

3. To determine the immunological, bacteriological, virological and histological markers of chronic tonsillopharyngitis in pregnant women and their effect on the course and outcome of pregnancy.

4. To evaluate the dynamic effectiveness of the developed complex of therapeutic measures aimed at eliminating the clinical manifestations of CTP during pregnancy in comparison with traditional ones.

5. To develop a clinical protocol for the diagnosis and treatment of CTP in pregnant women, taking into account a personalized approach and predicting the course of pregnancy.

#### **Methods of dissertation research**

The study uses modern methods of evidence-based medicine, clinical epidemiology and personalized analysis. Clinical observations, microbiological studies with the identification of pathogens, immunological methods, including the determination of cytokine and immunoglobulin profiles, as well as morphological and cytological methods for assessing the condition of oropharyngeal tissues, were used.

For statistical data processing, methods of correlation, regression and factor analysis were used, providing an objective interpretation of the results obtained. The principles of reproducibility, biosafety and ethical verification are fully respected in accordance with the international standards of the GCP and the Helsinki Declaration.

#### **The object of the dissertation research**

Somatic and reproductive health of pregnant women suffering from chronic tonsillopharyngitis.

#### **The subject of the dissertation research**

Clinical, immunological, bacteriological, morphological features of chronic tonsillopharyngitis in pregnant women, its effect on the course of pregnancy, as well as the effectiveness of personalized therapy aimed at improving maternal and perinatal prognosis.

#### **The main provisions submitted for defense**

1. Chronic tonsillopharyngitis in pregnant women is a significant extragenital factor associated with a high level of somatic burden and a decrease in the body's adaptive reactivity during gestation.

2. Changes in clinical, immunological and laboratory parameters in pregnant women with CTP allow us to consider this pathology as an important prognostic marker of the complicated course of pregnancy.

3. A significant correlation was found between the severity of tonsillopharyngeal intoxication, the presence of pathogenic microflora and the risks of placental circulatory disorders.

4. A personalized approach to the treatment of CTiF, including an assessment of the immunological and histological status, makes it possible to increase the effectiveness and safety of therapy for mother and fetus.

5. The implementation of the proposed clinical protocol ensures an improvement in the quality of medical care for pregnant women with ENT pathology, promotes the preservation of reproductive health and improves perinatal outcomes.

The study established new relationships between the clinical manifestations of chronic tonsillopharyngitis and the features of pregnancy. It has been shown that the presence of a chronic focus of oropharyngeal inflammation is accompanied by systemic immune restructuring, impaired local microbiocenosis, and morphological changes in tissues that can affect the condition of the placenta and fetus.

A personalized algorithm for managing pregnant women with CTP has been scientifically substantiated and proposed, including risk stratification and the choice of treatment tactics based on individual immunomicrobiological characteristics. The clinical protocol was tested, confirming its effectiveness and safety.

The results obtained are of practical value, as they form the basis for the introduction of personalized standards for the diagnosis and treatment of infectious and inflammatory diseases of the oropharynx in pregnant women.

#### **Description of the main research results**

As a result of a comprehensive clinical and laboratory study of chronic tonsillopharyngitis (CTiF) in pregnant women, the following significant scientific and practical data were obtained:

1. The clinical and epidemiological features of chronic tonsillopharyngitis in pregnant women have been clarified.

It has been established that the disease is a widespread extragenital condition that has a systemic effect on the course of gestation. A high frequency of the form of CTP is shown - up to 76-82% of cases, characterized by erased symptoms, chronic intoxication and late medical treatment.

2. The microbiological characteristics of the disease have been studied and the spectrum of leading pathogens has been identified.

Pathogenic microflora was found in 20.6% of pregnant women, while polymicrobial associations were identified in 89% of cases. The main pathogens were *Staphylococcus aureus* (35.7%), *Streptococcus viridans* (22.9%), *Staphylococcus epidermidis*, *S. saprophyticus*, *Streptococcus pneumoniae*, etc. A connection has been established between the unregulated use of antibiotics before pregnancy and a violation of the oropharyngeal normobiota.

3. The key immunological mechanisms of CTP in pregnant women have been identified.

There was an increase in the level of pro-inflammatory cytokines (IL-1, IL-6, alpha-TNF, gamma-interferon), a decrease in the phagocytic activity of neutrophils and an imbalance of the T-cell immune system, which determines the persistence of infection and the development of endotoxemia. Immunological decompensation has been recorded in both mild and severe clinical forms of CTiF.

4. Clinically significant correlations between immune, microbiological and morphological parameters have been established.

It has been shown that the severity of microbial contamination, the age of patients and the nature of immune disorders are directly related to the data of pharyngoscopy, hematological tests and cytological studies.

5. The adverse effect of CTiF on the course of pregnancy and the condition of the fetoplacental complex has been proven.

Pregnant women in the main group were more often diagnosed with the threat of termination of pregnancy (on average, at  $6.2 \pm 0.6$  weeks versus  $8.9 \pm 1.8$  weeks;  $p < 0.05$ ). Histological studies of the placenta revealed deciduitis, membranitis, and focal inflammatory changes, which confirms the possible trans-systemic effects of oropharyngeal infection.

6. The effectiveness of a comprehensive therapeutic program, including hardware washing of palatine tonsil lacunae and immunocorrective effects, was evaluated.

A significant decrease in the level of endotoxemia, normalization of the immune status and improvement of clinical and laboratory parameters were shown, especially with a mild degree of severity of the process. In patients with moderate severity, stabilization was slower, up to 7 days.

7. A significant decrease in the frequency of relapses of the disease after treatment has been demonstrated.

Repeated episodes of CTP were detected in only 3.9% of pregnant women in the main group ( $p < 0.01$ ), which confirms the high therapeutic effectiveness of the developed therapeutic and diagnostic algorithm.

8. A personalized algorithm for managing pregnant women with CTP has been developed.

It includes identification of the pathogen, assessment of local and systemic immunity, monitoring of endotoxemia, and prediction of risks to the mother and fetus. The algorithm allows you to choose the optimal therapeutic tactics, taking into account the form of the disease, the immune status and the severity of the pathological process.

#### **Justification of scientific novelty**

1. For the first time, the effect of the severity of tonsillopharyngeal intoxication on the course of pregnancy was revealed based on the study of clinical, immunological and morphological features of chronic tonsillopharyngitis.

2. For the first time, the prognostic significance of CTP as an extragenital pathology in the structure of somatic diseases of pregnant women, which affects the course of the gestational process, has been proven.

3. New data have been obtained on markers of endotoxemia in pregnant women with CTP and their possible effect on the development of placental insufficiency and complicated pregnancy.

4. A personalized approach to the diagnosis and treatment of CTP in pregnant women has been developed and scientifically substantiated, which has improved the safety of therapy for mother and fetus.

5. For the first time, a clinical protocol for the diagnosis and treatment of CTP has been proposed, adapted to the characteristics of the gestational period, followed by its testing in practical healthcare.

6. A correlation was established between clinical, laboratory and histological data, which made it possible to identify risk groups and define criteria for predicting reproductive health.

7. An algorithm for a comprehensive examination of pregnant women with CTP with the inclusion of histological analysis of the placenta as a marker of chronicization of the inflammatory process is proposed.

#### **Practical significance of the results obtained**

The practical significance of this study is due to the possibility of introducing its results and developed practical recommendations into clinical practice in providing care to pregnant women with chronic tonsillopharyngitis (CTiF) both in primary health care (PHC) and in inpatient healthcare settings. Based on a comprehensive analysis of clinical, immunological, bacteriological, cytological, virological and histological data, as well as taking into account pathognomonic signs, an algorithm for early detection of extragenital pathology (CTiF) in pregnant women was scientifically substantiated and developed. The approach to choosing safe therapy has been rationalized, which has made it possible to achieve a reduction in treatment time, minimize the risk to mother and fetus, and establish correlations between the clinical and laboratory features of the disease and the factors determining the formation of risk groups for reproductive health disorders. This contributes to the timely start of preventive and therapeutic measures.

As part of the study, a new clinical protocol for the diagnosis and treatment of chronic tonsillopharyngitis in pregnant women was developed and scientifically substantiated, which expands the arsenal of practical healthcare in the management of this category of patients. Suggestions have been made to clarify the classification of diagnoses, taking into account the combined pathology of chronic tonsillopharyngitis and the characteristic clinical symptoms in pregnant women. Additionally, in order to better understand the effect of chronic tonsillopharyngitis on the course of pregnancy and the condition of the fetus, the expediency of including histological examination of the placenta in delivered women with CTP in a comprehensive assessment of the pathology has been substantiated. The data obtained make it possible to expand the understanding of indirect morphological markers associated with chronic

inflammation in the oropharynx and use them as an additional tool for retrospective analysis and clinical observation in the postpartum period. For the first time, a comparative assessment of the effectiveness of existing and proposed methods for the diagnosis of CTP in pregnant women is presented, on the basis of which an algorithm for diagnostic and therapeutic measures adapted to the characteristics of the gestational period is formulated and visualized.

The developed complex of conservative therapy is recognized as optimal from the standpoint of biosafety for pregnant women and the fetus. The choice of medicines was based on data on the condition of the oropharynx in combination with the clinical picture of the disease, which provided an individualized approach to treatment. The results of the study contribute to increasing women's awareness of the risks associated with CTP during pregnancy, and can be used in the prenatal counseling system for pregnancy planning and prevention of complications, which enhances the preventive potential of domestic medicine.

#### **Personal contribution of the doctoral student**

All stages of the scientific research were performed by Stanova Sayazhan Kenesovna under the scientific supervision of Doctor of Medicine, Professor, Academician of the National Academy of Sciences of the Republic of Kazakhstan, Academician of the Russian Academy of Medical Sciences, Academician of the Russian Academy of Medical Sciences V.N. Lokshin, foreign head, Doctor of Medicine, Professor of the Research Institute of Obstetrics, Gynecology and Reproductology. Otta (Russia) Savicheva A.M., scientific consultant, MD, Professor of the Faculty of Medicine and Public Health at Al-Farabi KazNU - Zhaisakova D.E.

Stanov S.K.:

1. conducted a comprehensive analysis of literary sources on the topic of the thesis;
2. carried out the selection and clinical and laboratory examination of pregnant women with chronic tonsillopharyngitis;
3. performed a complex of otorhinolaryngological, immunological, bacteriological, virological and histological studies;
4. conducted a comparative analysis of various treatment tactics, including an assessment of the effectiveness of the proposed personalized approach;
5. Developed and tested a clinical protocol, proposed an algorithm for predicting complications;
6. performed statistical data processing using modern biostatistics methods;
7. She prepared the results in the form of dissertations, scientific articles and reports at specialized scientific conferences.

#### **Conclusions**

1. In pregnant women with chronic tonsillopharyngitis, the development of endogenous intoxication syndrome and a systemic inflammatory response was established. The level of middle molecules in patients with chronic tonsillopharyngitis exceeded that of the control group by 1.8 times ( $p < 0.05$ ), indicating a pronounced intoxication syndrome even in clinically mild or paucisymptomatic forms of the disease.
2. Chronic tonsillopharyngitis in pregnant women is associated with an unfavorable course of the gestational process. The incidence of threatened miscarriage in patients with chronic tonsillopharyngitis was 36.7%, which was 4.4 times higher than in the control group (8.3%;  $p < 0.05$ ). Inflammatory morphological changes of the placenta (deciduitis, choriodecuiditis, membranitis) were diagnosed in 11.4% of cases, indicating involvement of the placental complex in the pathological inflammatory process.
3. Immunological and microbiological disturbances are key markers of chronic tonsillopharyngitis in pregnant women. Elevated levels of pro-inflammatory cytokines (IL-6, IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ ) were detected in 17.1% of patients, while IL-6 concentrations in some cases exceeded reference values by 2.1–9.9 times ( $p < 0.05$ ). In decompensated forms of chronic tonsillopharyngitis, microbial colonization of the oropharynx, predominantly *Staphylococcus aureus* (35.7%), *Streptococcus viridans* (22.9%), *Streptococcus pneumoniae* (5.7%), and *Enterococcus faecalis* (4.3%), reached  $>10^4$ – $10^5$  CFU, accompanied by marked cytological inflammatory infiltration (up to 50+ neutrophils and 60 lymphocytes per field of view).
4. The personalized approach to the treatment of chronic tonsillopharyngitis in pregnant women demonstrated a pronounced anti-inflammatory effect. Following treatment according to the proposed algorithm, levels of pro-inflammatory cytokines in blood and saliva decreased on average by 28% ( $p < 0.05$ ), the oropharyngeal microbial landscape normalized to reference values ( $10^2$ – $10^3$  CFU), and clinical manifestations of intoxication and local inflammation were resolved in a shorter time compared with standard therapy (10 days versus the control group).
5. Implementation of the developed personalized diagnostic and treatment algorithm for chronic tonsillopharyngitis in pregnant women resulted in a reduction in adverse pregnancy outcomes. In the main group receiving personalized treatment, no obstetric complications were recorded, whereas in the group receiving standard treatment the rates of spontaneous abortion and preterm delivery were 4.8% and 9.5%, respectively. The differences between the study groups were statistically significant (Pearson's chi-square test,  $p = 0.027$ ), reliably confirming the clinical effectiveness of the proposed algorithm. No cases of stillbirth or intrauterine infection of newborns were observed in either study group.

## **Approbation of the dissertation results**

The results of this dissertation research have been comprehensively tested in clinical and scientific practice, and have also been implemented in educational and professional programs.

- The practical application of the proposed approaches has demonstrated high clinical effectiveness, which are described in the article “Features of a personalized approach in the treatment of chronic tonsillopharyngitis in pregnant women” (S.K. Stanova et al., 2022), published in the journal Pharmacy of Kazakhstan.

- A clinical protocol developed as part of a dissertation study on the diagnosis and treatment of chronic tonsillopharyngitis in pregnant women at the examination stage at the Salidat Kairbekova National Scientific Center for Healthcare Development.

- The approach to individualized therapy has gained international recognition and was highlighted in the English-language publication “Patient-oriented approach to prevention, diagnosis and treatment of pregnant women with chronic tonsillopharyngitis” (Stanova S.K. et al., 2023), which substantiates the need for personalized stratification of patients.

- Pathogenetic and clinical and immunological features of the course of chronic tonsillitis during pregnancy are analyzed in the publications “Chronic tonsillitis during pregnancy” (S.K. Stanova, 2019) and “Features of the course of chronic tonsillitis during pregnancy” (V.N. Lokshin, D.E. Zhaisakova, S.K. Stanova, 2019).

- The results of histological, cytokine and microbiological analysis are reflected in the article “Ethiopathogenetic Orientation in the Diagnosis and Treatment of Chronic Tonsillopharyngitis in Pregnant Women” (Stanova S.K. et al., 2022), published in the Open Access Macedonian Journal of Medical Sciences.

- Special attention was paid to the study of the immune profile of pregnant women with CTiF: the report “Zhukti ayelderdegi sozylmaly tonsillopharyngitis kezinde ainalimdagy zhane zhergilikti cytokinderdi taldau”, presented at the III Congress of otorhinolaryngologists of Kazakhstan (Turkistan, October 13-14, 2023), and the article “Analysis of circulating cytokines in chronic tonsillopharyngitis in pregnant women”, published in the proceedings of the International Congress “Global Health” (Almaty, December 5-6, 2024).

- S.K. Stanova made an oral presentation “A personalized approach to the diagnosis and treatment of chronic tonsillopharyngitis in pregnant women” at the International Forum of Otorhinolaryngologists (Aktau, September 29-30, 2022), which became an important milestone in the testing of the presented scientific provisions on an international platform.

- The effectiveness of the proposed strategy for managing pregnant women with CTP in the long term is reviewed in the article “Long-term impact of Personalized Treatment of Chronic Tonsillopharyngitis in Pregnant Women and after

Childbirth on Maternal and Child Health" (Stanova S.K. et al., 2024), published in the Research Journal of Pharmacy and Technology.

As part of the approbation and scientific dissemination of the results of the dissertation research, 6 scientific articles were published, including:

1 article - in the international scientific journal with impact factor (Research Journal of Pharmacy and Technology);

3 articles are in publications recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 2 articles in other scientific publications;

additionally, 2 oral reports and 1 publication in the proceedings of the international conference.

### **Publications**

A sufficient number of scientific papers have been published on the topic of the dissertation, including articles in peer-reviewed journals indexed in the Scopus and Web of Science databases, as well as materials from international conferences. This confirms the high scientific level of the research and the recognition of its results by the scientific community.

Publications on the topic of the dissertation

1. S.K. Stanova, V.N. Lokshin, D.E. Zhaysakova, A.M. Savicheva, D.J. Batyrbayeva. Features of a personalized approach in the treatment of chronic tonsillopharyngitis in pregnant women // Pharmacy of Kazakhstan. – 2022. – No. 3. – p. 26.

2. Sayazhan K. Stanova, Vacheslav N. Lokshin, Dyamely Ye. Zhaisakova, Alevtina M. Savicheva, Dinara Zh. Batyrbayeva. Patient-oriented approach to prevention, diagnosis and treatment of pregnant women with chronic tonsillopharyngitis // Pharmacy of Kazakhstan. – 2023. – No. 3. – P. 226.

3. S.K. Stanova. Chronic tonsillitis during pregnancy// Reproductive medicine. – 2019. – № 1(38). – P. 44.

4. V.N. Lokshin, D.E. Zhaysakova, S.K. Stanova. Features of the course of chronic tonsillitis during pregnancy // Bulletin of the National Academy of Sciences of the Republic of Kazakhstan. – 2019. – No. 4. – p. 22.

5. Stanova S.K., Lokshin V.N., Zhaysakova D.E., Savicheva A.M., Medeulova A.R., Batyrbaeva D.Zh., Kulanchiyeva Zh.A. Ethio-pathogenetic Orientation in the Diagnosis and Treatment of Chronic Tonsillopharyngitis in Pregnant Women // Open Access Macedonian Journal of Medical Sciences. – 2022. – Vol. 10(B). – P. 1571-1575.

6. S.K. Stanova. Analysis of circulating cytokines in chronic tonsillopharyngitis in pregnant women // Materials of the International Congress "Global Health". – 2024. – P. 83.

7. Stanova S.K., Lokshin V.N., Zhaisakova D.E., Savicheva A.M. Long-term Impact of Personalized Treatment of Chronic Tonsillopharyngitis in Pregnant Women and after Childbirth on Maternal and Child Health // Research Journal of Pharmacy and Technology. – 2024. – Vol. 17, Iss. 9. – P. 4519–4527.

#### Presentations and reports

1. A personalized approach to the diagnosis and treatment of chronic tonsillopharyngitis in pregnant women – oral presentation at the International Forum of Otorhinolaryngologists (Aktau, September 29-30, 2022).

2. Zhukti ayelderdegi sozylmaly tonsillopharyngitis kezinde ainalimdagi zhane zhergilikti cytokinderdi taldau – oral report at the III Congress of Otorhinolaryngologists of Kazakhstan (Turkestan, October 13-14, 2023).

#### Patent

Method for Predicting Exacerbation of Chronic Tonsillopharyngitis in Pregnant Women in the Third Trimester.

Pre-patent for invention No. 2024/1056.1 dated 09 December 2024.

#### Copyright for the protected object

“Method for Predicting Exacerbation of Chronic Tonsillopharyngitis in Pregnant Women.”

According to the official notification of the Republican State Enterprise on the Right of Economic Management “Salidat Kairbekova National Scientific Center for Health Development” of the Ministry of Health of the Republic of Kazakhstan, based on the results of scientific expertise, the topic “Chronic Tonsillopharyngitis in Pregnant Women” has been included in the list of priority topics for the development of clinical protocols for diagnosis and treatment for 2025.

#### Acts of Implementation

Municipal State Enterprise on the Right of Economic Management “City Clinical Hospital No. 5”

(Act No. 2083 dated 12 October 2023):

Improvement of medical care for pregnant women with chronic tonsillopharyngitis.

Clinical monitoring of pregnant women with chronic tonsillopharyngitis (CTP).

A method for preventing complicated pregnancy outcomes in women with chronic tonsillopharyngitis through pregravid sanitation of the oropharynx in partners.

#### Scope and Structure of the Dissertation

The dissertation includes regulatory references, definitions, and a list of abbreviations and symbols, and consists of four chapters: Introduction, Materials and Methods, Results of Original Research, and Conclusion.

The dissertation is completed with a list of references and appendices.

The dissertation comprises 185 pages of typed text, includes 35 tables, 14 figures, and 2 appendices.

The reference list contains 165 sources, including 117 sources in Russian and 48 sources in foreign languages.