

REVIEW

from Assoc. Prof. Mitko Dimitrov Mitkov, MD, PhD

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Member of the Scientific Jury with Order No **P-141/11.01.2024** the Rector of MU-Plovdiv

subject: dissertation on the award of the educational and scientific degree of Doctor,
professional field 7.1. *Medicine*, doctoral program: "*Clinical Laboratory*"

Topic: „Study of thyroid function in healthy pregnant women from Plovdiv region and development of population-specific reference limits of thyroid stimulating hormone for each trimester of pregnancy “

Author: Boyan Nikolaev Delev, MD

Form of doctoral studies: PhD student of independent training

Department: Clinical Laboratory of the Faculty of Medicine at Medical University of Plovdiv

Research supervisor: Prof. Tanya Deneva, MD, PhD, Assoc. Prof. Boyan Nonchev, MD, PhD

1. General presentation of the procedure and the doctoral student

The presented set of materials in paper / electronic form is in accordance with the terms and conditions of LDASRB, ARLDASRB and RAD at MU-Plovdiv and includes:

1. Application to the Rector of MU-Plovdiv for Disclosure of the Dissertation Protection Procedure
2. CV in European format with signature of the doctoral student
3. Notarized copy of a higher education diploma
4. enrollment orders; for deduction with the right of defence
5. Order for conducting an exam from the individual plan and a relevant protocol for passed exam or doctoral student minimum in the specialty
6. Minutes of the Department Council for preliminary discussion of the doctoral work and the decisions taken for opening a procedure and for the composition of a scientific jury
7. dissertation
8. abstract
9. List of scientific publications on the topic of the dissertation
10. Copies of scientific publications
11. List of participations in scientific forums
12. List of participation in projects
13. Reference for compliance with minimum national requirements
14. other documents relating to the progress of the procedure

The examination of the documents shows that the deductibility procedure and the procedure for declaring a defence have been followed. The documents are prepared in accordance with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for its application, as well as the Regulations on the Terms and Conditions for acquiring a degree at the Medical University - Plovdiv

2. Brief biographical data about the PhD student

Boyan Nikolaev Delev, MD graduated in medicine in 1992 at the Medical University of Plovdiv. In 2003 he was enrolled for specialization in clinical laboratory at MU-Plovdiv, and since 2004 he works as a doctor in the Central Clinical Laboratory of the University Hospital "St. Georgi" Plovdiv. In 2007 he successfully acquired a specialty in clinical laboratory. Boyan Delev since 2016, after a successful competition, has held the position of Assistant Professor at the Department of Clinical Laboratory at MU-Plovdiv. Since 2021 he is a PhD student of independent training at the Department of Clinical Laboratory of MU-Plovdiv. Boyan Delev is a member of the Bulgarian Society of Clinical Laboratory.

3. Topicality of the topic and appropriateness of the objectives and tasks set

The topic is relevant for medical science and clinical practice as it presents valuable data on physiological changes in the thyroid gland in the population of pregnant women in the Plovdiv region. During pregnancy, thyroid function undergoes significant changes in the conditions of increased demands for hormone synthesis and unusual (but physiological) stimulating effects on the part of hCG. These processes are dynamic and are often associated with pronounced fluctuations in the values of thyroid hormones and TSH, which increases the risk of incorrect interpretation of laboratory results and often hyperdiagnosis of thyroid dysfunction. On the other hand, thyroid dysfunction is associated with significant risks for pregnancy and the fetus, and a correct assessment of hypo- or hyperthyroidism is of paramount importance to prevent pregnancy complications. At present, the measurement of serum TSH remains the main factor in assessing the condition of the mother's thyroid gland and is used in making decisions and determining treatment goals. Therefore, the construction and implementation of geolocation reference intervals would provide an optimal approach for estimating gestational thyroid function.

Proceeding from the above, I believe that the topic of Boyan Dele, MD is extremely applicable in clinical and laboratory practice. The PhD student focused on the population defined reference for TSH and fT4 in pregnant women from the Plovdiv region obtained from the analysis of healthy, thyroperoxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-Tg), lacking so far as applicability in the clinical laboratory modern medical practice, which determines the

scientifically applied and original contribution of the developed dissertation. In the dissertation presented Boyan Delev, MD also points out the advantages of using population defined reference values compared to fixed values and generally applied reference intervals.

4. Knowledge of the problem

The PhD student shows in-depth knowledge in the field of clinical-laboratory assessment of gestational thyroid function and application of the most commonly used serum biomarkers. It presents an in-depth analysis of the results of a number of studies on physiological processes determining the dynamics of TSH and thyroid hormones during pregnancy, the possibility of occurrence of specific complications and their prevention, as well as the risk of hyperdiagnosis. The need for laboratory assessment of gestational thyroid function to be performed on the basis of population-conditioned trimester specific reference intervals is also demonstrated. 263 literary sources were cited, of which 5 in Cyrillic and 258 in Latin. The review is divided into important theoretical and methodological guidelines on the topic: physiological features of thyroid function during pregnancy, thyroid dysfunction and risks for pregnancy and fetus, the prevalence and influence of thyroid autoantibodies in pregnant women, assessment of thyroid function during pregnancy, clinical laboratory assessment of thyroid function.

Particularly important is the presentation of the possibilities recommended by authoritative thyroid organizations for assessing gestational thyroid function as well as emphasizing the optimal approach. The PhD student manages to correctly use professional terminology, which he analyzes and systematizes in a very good way. The very focus on this topical topic shows knowledge of the problem and the challenges in analyzing and interpreting the data from studies in clinical practice.

Logically, from the literature review is derived the aim of the study to study the functional, morphological and immunological characteristics of the thyroid gland in healthy pregnant women and to develop population-specific reference intervals of TSH and fT4 for the different stages of pregnancy.

5. Methodology of the study

The methodology of the study is presented comprehensively and allows achieving the goal and the implementation of 4 clearly formulated tasks in the dissertation. The methods used are selected in detail and adequately. The object and units of observation are defined.

The clinical material included three groups of 120 pregnant women from each trimester of pregnancy over 18 years of age. All participants were selected using previously developed for the purposes of the study questionnaires, anamnesis, clinical examination by endocrinologist, ultrasound assessment of the thyroid gland and laboratory tests. The selection criteria are consistent

with the generally accepted recommendations of the International Federation of Clinical Chemistry (IFCC) and the Institute of Clinical and Laboratory Standards (CLSI).

The clinical-laboratory methods used are of high analytical reliability. With a detailed description of the analytical methodology. The reliability of the results is guaranteed by the use of modern statistical analyses.

6. Characterization and evaluation of the dissertation

The dissertation "Study of thyroid function in healthy pregnant women from Plovdiv region and development of population-specific reference limits of thyroid stimulating hormone for each trimester of pregnancy" is a well-planned, developed and implemented prospective scientific study. It is written on 114 standard pages and contains 14 tables, 11 histograms and 6 figures. The scientific study is structured as follows: introduction – 2 pages, literature review – 30 pages, purpose and tasks - 1 pages, material and methods – 10 pages, results – 24 pages, discussion – 8 pages, conclusions – 1 pages, contributions – 2 pages; Annexes – 6 pages, conclusion – 1 page, bibliography – 21 pages.

The introduction outlines the significance of the problem studied. The critical analysis of the literary data enables the doctoral student to correctly formulate the purpose of the study and to justify the individual tasks for its implementation.

The aim of the dissertation is clearly formulated and achieved. The tasks to be performed are specific and follow the set goal.

The results of the tasks are described in detail, graphically presented with tables and figures that emphasize the importance of the research. In the discussion section the skills of the doctoral student to interpret the results obtained with their own reasoning and comparison with the data from the international literature are visible.

The conclusions are properly reasoned and correspond to the set goal and the tasks performed. They synthesize the analysis of the review data and their own study.

7. Contributions and relevance of development to science and practice

The contributions are of an original, scientifically applied and confirmatory nature, which objectively reflect the importance of the results obtained scientifically and their applicability - actual clinical practice.

Contributions of an original nature prove that:

For the first time in Bulgaria, a prospective study providing valuable data on physiological changes in the thyroid gland during pregnancy in women in our population has been carried out.

For the first time in Bulgaria in the Plovdiv region, a prospective study and analysis of serum concentrations of TSH and fT4 in healthy pregnant women with negative thyroid antibody titres in the Ist, II and III trimesters of pregnancy was carried out.

For the first time in Bulgaria in the Plovdiv region, a prospective study and analysis of the changes in TSH and fT4 concentrations in healthy pregnant women with negative thyroid antibody titres in the Ist, II and III trimesters of pregnancy was carried out.

For the first time in Bulgaria in the Plovdiv region are developed population-specific reference intervals for the values of TSH and fT4 for the Ist, II and III trimesters of pregnancy in healthy pregnant women.

The scientifically applied and confirmatory contributions are:

A significant amount of literature on the topic has been analyzed, confirming the topicality of the problem and proving the need for the construction and implementation of population-specific reference intervals for TSH and fT4 for each trimester of pregnancy.

The informative value and diagnostic capabilities of population-specific reference intervals for TSH and fT4 in the gestational evaluation of thyroid function were analyzed.

The view is confirmed that the preparation and implementation of trimester specific intervals for TSH and fT4 could help to:

- Reducing the risk of incorrect interpretation of laboratory results and often hyperdiagnosis of thyroid dysfunction, which in turn is associated with significant risks for pregnancy and fetus.

- Correct assessment of the conditions of hypo- or hyperthyroidism, which is of paramount importance to prevent complications of pregnancy.

- Limitation of the application of fixed reference values of TSH for each trimester of pregnancy proposed in the consensus opinions of some authoritative thyroid organizations whose main disadvantage is the overdiagnosis of thyroid insufficiency.

The obtained results can serve as an information base for optimizing the diagnostic process in thyroid dysfunction.

8. Assessment of publications on the dissertation

In connection with the dissertation Boyan Delev, MD presents 3 publications as a first author, referenced and indexed in Scopus and Web of Science, 2 participations in scientific forums and 1 participation in research projects, which meets the minimum national requirements of the LDASRB and the quantitative criteria placed in RAD in MU-Plovdiv.

9. Personal participation of the doctoral student

In the proposed dissertation, the doctoral student has a purely personal participation and all the conclusions, contributions and results obtained are his personal merit.

10. Abstract

The autoreferent has been developed in a standardized way. The following is the logical statement of the dissertation, the purpose and tasks, the methodology of the study, as well as the significant results and conclusions are presented. No further remarks regarding structure and content.

11. Critical remarks and recommendations

The PhD student has complied with the recommendations made in the earlier stages of the dissertation.


It is advisable to promote the results in order to reach the target group that is also the subject of this work. It would be good in his future work for the author to pay more attention to his publication activities in specialized periodicals indexed in international bibliographic databases and to participate more actively in international, national and even regional scientific forums.

CONCLUSION

The dissertation *paper contains scientific, scientific, applied and applied results, which represent an original contribution to science* and **meet all** the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria (LDASRB), the Rules for the Implementation of the Law on the Implementation of the Law on Academic Staff in the Republic of Bulgaria, and the Rules of the Medical University - Plovdiv. The presented materials and dissertation results fully correspond to the specific requirements adopted in connection with the Rules of the Medical University – Plovdiv for the application of the LDASRB.

The dissertation shows that the PhD student Boyan Nikolaev Delev, MD **has** in-depth theoretical knowledge and professional skills in the scientific specialty of the Clinical Laboratory, **demonstrating** qualities and skills for independent scientific research.

Due to the above, I confidently give my *positive assessment* of the conducted research, presented by the above-reviewed dissertation, autoreferreat, achieved results and contributions, and *I propose to the honorable scientific jury to award the educational and scientific degree 'Doctor'* to Boyan Nikolaev Delev, MD in the doctoral program in Clinical Laboratory.



Заличено на основание
Чл.5 §1, 6. "В" Регламент (ЕС)2016/679

05.03.2024

Plovdiv

Reviewer: Assoc. Prof. Mitko Mitkov, PhD

