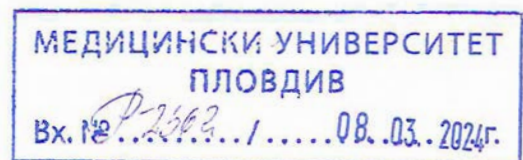


OPINION



By prof. Milena Georgieva Velizarova, MD, PhD

**Head of the Department of Clinical laboratory, Faculty of Medicine,
Medical University-Sofia**

Subject: PhD thesis of Dr. Boyan Nikolaev Delev, presented for obtaining a PhD degree
Professional field 7.1. Medicine, Doctoral program "Clinical Laboratory"

Author: Dr. Boyan Nikolaev Delev

Type of Doctoral training: independent training

Department: Clinical Laboratory, Faculty of Medicine, Medical University-Plovdiv

PhD thesis title: " 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."

Scientific supervisors: Professor Dr. Tanya Deneva, MD, Ph.D

Assoc. prof. Dr. Boyan Nonchev, MD, Ph.D

With Decree No. P-141/11.01.2024, issued by Prof. Dr. A. Uchikov, MD, Rector of the Medical University of Plovdiv, I was appointed as an external member of the scientific committee. At the first meeting of the committee, I was tasked with preparing an opinion on the dissertation work.

1. General presentation of the procedure and doctoral candidate

The submitted set of materials on electronic media complies with Article 70 (1) of Section I. Acquisition of the educational and scientific degree "Doctor" and the scientific degree "Doctor of Sciences" at the Medical University of Plovdiv; Regulation of the Medical University of Plovdiv dated January 28, 2021, and includes all documents required for the procedure.

The doctoral candidate has submitted 3 publications - 1 in a refereed Bulgarian journal indexed in Scopus, and 2 in non-refereed international journals.

Dr. Delev began his professional career in 2004 as a laboratory doctor in the Clinical Laboratory of University Hospital "St. George" EAD, and since 2016, he has been an assistant at the Medical University of Plovdiv with the same teaching practice. Dr. Delev has undergone training as an internal auditor at the Quality Center of the Technical University, Varna, and since 2011, he has a diploma in Health management from the University "Prof. Dr. Assen Zlatarov" in Burgas.

Dr. Delev was enrolled as a self-preparation doctoral student with Decree No. P-942/15.06.2021 in the Department of Clinical Laboratory on the topic of his dissertation work, completed all required exams for doctoral preparation, and was officially discharged with the right to defend his dissertation with Decree No. P-3593/06.12.2023.

2. Relevance of the topic

The topic of the dissertation work is extremely relevant. Currently, recommendations from various authoritative international societies and organizations advocate for the development and implementation of trimester-specific reference values for assessing thyroid status in pregnant women for each individual center, taking into account the characteristics of the local population.

2. Understanding of the problem

From the presented dissertation work, it is evident that Dr. Delev has a deep understanding of the issue. He provides a detailed scientific literature review, very well-structured and illustrated with graphs, describing the physiological characteristics of thyroid function during pregnancy and its significance for the normal development of fetal brain function. The published literature data on the risks to the normal course of pregnancy in conditions of hypo- and hyperthyroidism are thoroughly and critically examined, as well as the need for clear criteria for assessing thyroid dysfunction during different stages of the gestational period.

4. Methodology of the Study

There are analytical methods for assessing thyroid function, which are characterized by varying sensitivity, specificity, and clinical/routine utility. Some of them currently hold historical significance (spectrophotometric analysis), while others have increasingly limited use due to their harmful effects (radioimmunoassay, RIA), and others (ELISA) are associated with manual techniques. Chromatographic methods such as HPLC typically exhibit high sensitivity, but they are not routinely applied in routine practice due to their high cost, labor-intensiveness, and the need for highly qualified staff. Nowadays, the chemiluminescent immunoassay (CLIA) is one of the most commonly used techniques in automated immunoassay systems, providing high medical reliability of results.

5. Evaluation of the Dissertation Work and Contributions

The dissertation work is very well-structured and comprises 114 pages, including abbreviations (2 pages), literature review (30 pages), objectives (1 page), materials and methods with study design (10 pages), results and discussion (32 pages), conclusions (1 page), contributions (2 pages), and references (21 pages). The results are illustrated with 4 figures, 11 histograms, and summarized in 13 tables.

The presented design, results, discussion, and conclusions are original, reliable, informative, and demonstrate a systematic and thorough approach by the doctoral candidate. Dr. Delev's efforts are focused on studying thyroid status and establishing population-specific reference intervals for TSH and fT4 for the first, second, and third trimesters of pregnancy in accordance with the recommendations of the International Federation of Clinical Chemistry (IFCC) and the Clinical and Laboratory Standards Institute (CLSI).

The references are from 263 literary sources and mainly include published results from leading researchers in thyroid function over the past 10 years.

The literature review is comprehensive, detailed, with a critical analysis by the dissertation author, and presents some unresolved problems. A logical review of physiological changes in thyroid status, thyroid dysfunction, and risks for pregnant women, the course of pregnancy and the fetus wellbeing in cases with maternal hypo- and hyperthyroidism, has been made. Results from various published studies on complications resulting from thyroid hypofunction are contradictory, focusing mainly on preeclampsia and gestational hypertension, and do not find a link between other

pregnancy complications and increased TSH concentration. Untreated maternal hypothyroidism is associated with various degrees of impairment in the nervous-psychological and neuro-cognitive development of the child. The review also addresses the prevalence and impact of thyroid autoantibodies, iodine deficiency, thyroid nodules, and other thyroid pathologies in pregnant women.

The doctoral candidate provides a broad overview of the reference intervals used in the scientific community for assessing thyroid function in pregnant women, with a focus on center-specific and trimester-specific reference intervals. Differences may be partly attributed to variations in iodine status among different populations, method-dependent reference ranges, body mass index, intake of certain medications, multifetal pregnancy, application of assisted reproductive techniques, racial, geographic, and ethnic backgrounds.

The aim of the study is clear and well defined, and the four objectives outlined correspond to the stated goal and lead to its achievement.

Materials and methods: The study design, protocol-driven examinations and investigations conducted, as well as the inclusion and exclusion criteria, are comprehensively described. An adequate number of pregnant women (120 in each trimester of pregnancy) were included in order to establish reference ranges. All requirements of the International Federation of Clinical Chemistry (IFCC) and the Clinical and Laboratory Standards Institute (CLSI) regarding the selection of the reference group and the creation of reference conditions for the study were met. The study received approval from the Ethics Committee at MU-Plovdiv (protocol No. P-172/21.01.2020) for compliance with planned scientific research standards and criteria for scientific rigor and accuracy.

Highly reliable analytical methods based on chemiluminescent immunoassay were used to determine thyroid status markers, along with appropriate and contemporary statistical methods for analyzing the obtained results. Analytical reliability of the studies was ensured through daily intra-laboratory quality control and participation in external quality assessment.

The results, presented in detail and logically, are illustrated with appropriate tables, figures, and histograms. When establishing reference ranges, demographic factors (age, height, pre-pregnancy and during pregnancy weight), medical history (family history, thyroid pathology, infertility, spontaneous abortions), and smoking were taken into account. The parametric method was used to calculate the reference intervals for TSH and fT4 for each trimester of pregnancy, with the following approaches applied in case of deviation from normal distribution: data transformation through natural logarithm.

Dr. Delev presents both textual and graphical changes in thyroid parameters in pregnant women with negative or positive titers of thyroid antibodies.

The results of the analysis of functional thyroid parameters in healthy pregnant women are also presented, depending on the morphological characteristics of the thyroid gland, assessed by measurement of thyroid volumes, and the physiological changes in thyroid function at different stages of pregnancy.

The statistical analysis is systematic and detailed. It would be beneficial, when determining the relationship between variables, statistical dependence, and correlation, to indicate whether they are directly proportional or inversely proportional.

The discussion is structured according to the tasks set for completion, with the obtained results compared to data published in the literature. Findings that differ from them or from the methodically defined reference ranges of the reagent manufacturer are noted. At the end of the dissertation, six conclusions are drawn, based on the obtained results, confirming the stated aim.

The doctoral candidate has identified six contributions of original and confirmatory nature, with promising scientific and practical applications.

6. Evaluation of the publications and the personal contribution of the doctoral candidate

Regarding the dissertation work, 3 publications have been presented, reflecting and popularizing the research results. In all of them, Dr. Delev is the first author.

Dr. Delev has participated in 2 scientific forums in Bulgaria, where he presented the obtained research results to the scientific community.

One university project involving the participation of doctoral candidate has been presented, in which part of the research for the dissertation work was conducted.

7. Abstract

The abstract contains 48 pages and accurately summarizes the dissertation work.

CONCLUSION

The proposed dissertation by Dr. Boyan Nikolaev Delev reflects his personal involvement and dedication in the conducted research, which is well-theoretically and methodically substantiated. Dr. Delev demonstrates focus in achieving his goals, critical thinking, and the ability to interpret and summarize, which are exceptional indicators for assessing his personal and professional qualities and skills for independent scientific research.

The dissertation contains *original, scientific and practical results, which represent an innovative contribution to science and meet the requirements* of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulation for the Implementation of LDASRB, and the Regulation of MU - Plovdiv. The materials and dissertation results presented fully comply with the specific requirements adopted in connection with the Regulation of MU - Plovdiv for the implementation of LDASRB.

Based on the above, I confidently give my positive assessment of the conducted research presented by the reviewed dissertation, abstract, achieved results, and contributions.

I propose to the esteemed academic jury to award the educational and scientific degree of 'Doctor' to Dr. Boyan Nikolaev Delev in the doctoral program in Clinical Laboratory.

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

05.03.2024

Prepared the opinion: 

(Prof. Milena Velizarova, MD, PhD)