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**Review of the Doctoral dissertation  
of Beata Raczowska, MSc  
entitled: "New insights into pathophysiology and potential diagnosis  
of gestational diabetes mellitus"**

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Gestational diabetes is one of the most important metabolic disorders which occurs during pregnancy and which can lead to serious disorders in the mother and the developing fetus, and then in the child in the subsequent stages of its individual development. The correct diagnosis of gestational diabetes and the appropriate treatment of pregnant women seem to be the most important issue. Difficulties in the accurate epidemiological estimation of this important clinical problem in particular countries are largely due to the lack of uniform diagnostic standards for the diagnosis of gestational diabetes. An additional aspect is still insufficient knowledge of pathological mechanisms leading to insulin resistance and insufficient insulin secretion, which are clinical signs of gestational diabetes.

Beata Raczowska's PhD thesis is a part of this very important aspect of the study of gestational diabetes. At the beginning it should be noted that the thesis was written in English, which proves that the Doctoral student has a good knowledge of this language and allows for direct publication of the results obtained in English-speaking scientific journals.

The doctoral dissertation submitted to me for review is 104 pages long and has a typical layout. After the table of contents, the doctoral thesis includes a list of abbreviations, followed by the Introduction, the Aim of the study, Materials and

methods, Results, Discussion, Conclusions, a list of tables, a list of figures, a summary in Polish and English, and the References.

The Introduction chapter includes 19 pages. In the Introduction, the Doctoral student justifies the need to undertake research on gestational diabetes and in the following subsections presents the definition and epidemiology, followed by etiology, pathophysiology and risk factors of gestational diabetes, demonstrating great knowledge in this area. Next, the Author chronologically discusses changes in the approach to screening and diagnosis of gestational diabetes, enriching it additionally with a scheme of "milestones" of diagnostic management in this form of diabetes. In this section, the Author also takes into account dietary management and insulin therapy conducted in the patients with gestational diabetes. This part of Introduction ends with a detailed description of possible complications of gestational diabetes for the mother and her child.

The second part of the Introduction chapter is devoted to the description of the development of metabolomics as a new and dynamically growing field of the science, with a description of the particular techniques and analytical platforms used in metabolomics, in an interesting way introducing the reader to this difficult issue.

In the next chapter entitled Aim of the study the Doctoral student presents the goals of her work in an understandable and objective manner. It should be emphasized that the Doctoral student presented both the general and specific objectives, in response to which it was more easy to group the results in the following chapters of the dissertation and to define the conclusions from this work.

The next chapter entitled Methods has 13 pages. It begins with the information that the Bioethics Commission of the Medical University of Białystok has obtained permission to conduct the research (R-I-002/369//2014).

In the next section this chapter is dedicated to the characteristics of the recruited patients. The Doctoral student presents in detail the criteria for the enrollment of patients in the study and their classification to particular groups: experimental and validation ones as well as the samples collection. In the next part of this chapter the Author presents a methodology used in the study, with a precise description of both the non-targeted analysis, i.e. "metabolic fingerprinting", as well as the targeted analysis of the selected metabolites. This chapter ends with a detailed description of the statistical methods.



In the next chapter entitled Results (28 pages) the Doctoral student presents in detail the results of the research including 11 colorful figures and 12 tables.

Out of the many interesting results, I think it is particularly important and worth emphasizing:

1. To observe the significant differences in the level of metabolites in the group of patients with "iIGT" compared to the control group, indicating the most statistically significant increase in the medium- and long-chain fatty acids and organic acids.
2. To demonstrate on the basis of ROC curve analysis the usefulness of these metabolites as potential biomarkers of gestational diabetes.
3. To conclude, based on the ROC curve analysis, that the model consisted of three metabolites, i.e.  $\alpha$ -hydroxybutyric acid,  $\beta$ -hydroxybutyric acid and myristic acid, is the most useful for the identification of patients with "iIGT" in the second trimester of pregnancy and in the first trimester of pregnancy or at risk of "iIGT" in the second trimester of pregnancy.

It seems that an interesting addition to this chapter could also be the assessment of possible relationships between selected metabolites and clinical parameters of gestational diabetes, such as HOMA index.

In the next chapter entitled Discussion including 11 pages, the Author comprehensively describes the world reports on insulin resistance and lipid disorders found in patients with gestational diabetes against the background of the presented results from the studied groups. Then, referring to the obtained results of metabolic studies and selected biomarkers, the Doctoral student presents her own interpretation of them, analyzing them in detail against the background of reports from other authors. The wording of this chapter indicates a comprehensive knowledge of literature and the ability to logically and rationally support the research hypothesis. A valuable and interesting summary of the Discussion is a subchapter concerning both the strengths and limitations of the research, together with an indication for further investigation. All of these prove the high scientific maturity of the Doctoral student.

The results presented in the dissertation allowed to formulate 4 conclusions. They are transparent and correspond to the objectives of the dissertation in a substantial

way. References include 180 English-language publications, most of which have been published in recent years.

Concluding, I believe that this dissertation concerns a very important aspect of the pathophysiology of gestational diabetes and is an innovative approach to a potential complement to the diagnosis of this form of diabetes in the Caucasian population. The Doctoral student undertook the realization of this difficult topic with the use of modern research methods, obtaining very interesting results, which in the future may find their application in clinical practice. Validation of the obtained results on a larger cohort of patients from different ethnic groups can fully realize these expectations.

The PhD thesis is carefully written and its editorial form does not raise any objections. Minor comments do not affect its overall assessment.

I fully appreciate Beata Raczkowska's doctoral dissertation. The Doctoral student showed great theoretical knowledge and the ability to solve a scientific problem on her own.

Taking into account the entire doctoral dissertation, I conclude that it meets the conditions set out in Article 13 of the Act of 14 March 2003 on Academic Degrees and Academic Title and Degrees and Title in Art (Journal of Laws 2016, item 882, as amended). Based on the opinion presented above, I have the honour to ask the High Council of the Faculty of Medicine of the Medical University of Białystok to accept this doctoral dissertation and to admit Ms Beata Raczkowska to further stages of the doctoral thesis.

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