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Evaluation

Of the Dissertation for the title of Doctor of Medicine of mgr Beata Raczkowska

New insights into the pathophysiology and potential diagnosis of gestational diabetes mellitus

(Nowe spojrzenie na patofizjologię i diagnostykę cukrzycy ciążowej)

Supervised by prof. Michał Ciborowski, MD

Co-supervised by prof. Coral Barbas, MD

Beata Raczkowska, the PhD Candidate, provides detailed analysis of the pathophysiology and diagnostics of gestational diabetes mellitus (GDM), the most common metabolic complications affecting women in pregnancy. The pathophysiology of gestational hyperglycemia, despite long history of studies, are only partially understood. Moreover, its diagnostics remains in the center of a vivid debate among diabetologists and obstetricians. Hence, the problems which the Candidate attempts to address, regarding the metabolomic changes in women with GDM, dysregulation of carbohydrate metabolism (IGT vs IFG), as well as a possibility to replace the 75OGTT with analyses of novel early gestation predictional biomarkers for diagnosis of GDM, are very current.

In search for answers to these questions, the Candidate utilized metabolomics – a combination of mass spectrometry techniques (LC-MS, GC-MS, CE-MS), whose detailed technical explanations are covered in the *Materials and Methods* section of the dissertation. The techniques used throughout the study are consistent with the most up-to-date trends in the modern science. The statistical methods used for the data analysis are appropriately used. It is particularly interesting to analyze the data of GDM group with respect to iIFG and

iIGT subpopulations. Currently, for these conditions, only obstetric data have been analyzed, and these have not yielded conclusive answers about clinical relevance of impaired fasting and postprandial glycemia. Studies of different aspects of IFG and IGT in non-gestation patients indicating different mechanisms of their occurrence are also available. I agree that these two conditions are pathophysiologically different and, consequently, can be analyzed independently in GDM patients group. The selection of study groups is therefore proper. The only limitation in this aspect is an unclear and complex description of study groups, rendering it difficult to understand from the reader viewpoint. An overview figure of the study group composition would be helpful to follow the Author's analysis.

The results of the study are presented in a solid *Results* section (pp. 44-71) and include numerous tables and graphs, which in a concise and neat manner represent most important data, along with extensive commentary. The maturely written and well-backed by current and appropriately selected literature data (180 references) *Discussion* section follows. The scientifically mature critical section *The strengths and the limitations of the study with future directions* proves the capability and scientific level of the Candidate. I agree with all discussed *pros* and *cons* of the study. In fact, I believe that a particularly interesting continuation of the study would be the follow-up observation of the women in relation with the metabolic status from the first pregnancy trimester until late postnatal period. Early diagnosis and prevention of the disease is nowadays a top priority of modern medicine. Thus, finding specific prediction markers and introduction of targeted analytical methods, along with following prophylaxis would be a critical improvement of current treatment of GDM.

The Dissertation ends with 4 major conclusions, which are correctly drawn and backed by obtained results, and constitute the answer to the main hypotheses of the thesis. Metabolomic analyses allowed for identification of the differences in the pathophysiology of IGT and IFG, indicating that the main metabolic disorder of GDM is modulation of lipid metabolism. The conclusion of potential role of gut microbiota in developing carbohydrate disturbances during pregnancy is particularly interesting. This observation fits well into current "hot topic" of bacterial flora impact on various disease conditions.

Conclusions 3 and 4 are drawn from performed studies, however they need to be approached with reserve due to numerous limitations of the performed analyses. I am afraid that (despite the Candidate's justified optimism) metabolomic studies will not replace simple laboratory tests in the nearest future, as these enjoy well-established position in clinics for their simplicity and reliability. Metabolomic analyses require population-wise studies and extensive standardization, and are not (as the Candidate suggests) less demanding and time-consuming than current standard diagnostic methods quite yet. Formulation of conclusion 4 however indicates the Candidate's strong understanding of the importance of basic research in clinical studies, and this fact predisposes her well to the future research career.

To summarize, I would like to point out that the presented study, along with innovative and interesting approach to tackle the relatively poorly explored subject, deserves praise. Congratulations on the quality of presented research, mature results analysis and thoughtful considerations of the limitations of used methods, analyzed population and other, external factors capable of influencing the results. As a reviewer, I would like to express my enthusiastic support for continuation of this research in the future by the Candidate.

In my opinion, the Dissertation *"New insigths into the pathophysiology and potential diagnosis of gestational diabetes mellitus"* presented by Beata Raczkowska constitutes an independent and mature analysis and solution of a scientific problem, thus satisfying all requirements for the title of the Doctor of Medicine.

Given all above, I hereby recommend that the Dissertation of Beata Raczkowska is accepted for the further proceedings of the doctoral conferment by the Research Council of the Faculty of Medicine, English Division, of the University of Białystok. Moreover, I propose that the Dissertation is granted with distinction.

Katarzyna Cyprys

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