

Endometrial proteomics: A promising path toward personalized reproductive medicine

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To the Editor,

I read with great interest the article titled “Investigation of the effect of protocol changes in IVF treatment on pregnancy outcomes: A retrospective analysis” published recently in *Zeynep Kamil Medical Journal*, Vol. 56, Issue 3, (2025), (127–132). In this retrospective study on infertility, patients who had previously failed IVF treatment and underwent a second IVF attempt using the same protocol, as well as those who followed a different protocol, were evaluated in terms of treatment effectiveness. In this context, data from 60 patients, in whom traditional biochemical parameters and imaging techniques were used in their treatment processes, were compiled. Patients with normal TSH and prolactin levels were included in the study, while patients with systemic or endocrine diseases were excluded. Unexplained infertility and endometriosis were part of the IVF indications included in the study. In the conclusion section, the researchers reported that there was no significant difference in pregnancy success between the groups with and without protocol changes. As emphasized in the study, the first step in infertility treatment is to identify the causes of infertility. However, infertility, in general, represents a truly challenging clinical situation due to its multifactorial nature and the presence of causes that remain unexplained in today’s context.^[1]

The fact that the effectiveness of treatment approaches may differ between patients adds complexity to the development of accurate diagnostic and treatment strategies. One of the most significant challenges for fertility clinics is identifying the embryo with the best developmental potential, both genetically and metabolically. Although significant progress has been made over the years employing various technologies, present practices for evaluating embryo developmental adequacy remain limited. While rates vary, the transfer of non-viable embryos is one of the most common reasons for the failure of a significant number of IVF treatments.^[2,3] However, successful implantation requires not only a healthy, functional blastocyst but also a suitable and receptive endometrium and a synchronized molecular interaction between the maternal and embryonic tissues. Therefore, many independent or interrelated factors, such as molecular regulation of maternal hormones, cellular disorders, genetic factors, and various pathological formations in the uterine wall, can play a role in the development of infertility.^[4] These clinical data highlight the necessity for new methods to clarify the unresolved aspects of infertility. In addition to imaging methods, genetic tests, and a limited number of biochemical parameters, which are indispensable for clinical research, I believe that high-throughput proteomic data from relevant tissues will make a strong contribution to understanding the unique characteristics of the disease. Having a dynamic and high-resolution molecular understanding of cellular activity can help explain many unexplained failures, from the selection of the correct embryo to molecular events affecting endometrial receptivity. Beyond their physical effects considered to be

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associated with infertility, fibroids can significantly influence the protein profile of the endometrial structure through molecular mechanisms.^[5] In some conditions, dynamic changes in the protein profile of tissues that cannot be detected by traditional biochemical tests and that have a morphologically expected appearance can strongly influence cellular functions. Recent studies examining the protein profiling of endometrial tissues have revealed dysregulation of numerous proteins and signalling networks associated with repeated implantation failure (RIF). Several proteins, including TPPP3, S100A13, HSD17B2, AZGP1, claudin-4, p38 kinase, PRKAB, IKB- β , myosin-2, PKG2, ANT3, CBG, and FETUA, have been identified as potential markers of impaired endometrial receptivity.^[6–8] In addition, extracellular vesicles released from endometrial epithelial cells contain collagens, integrins, laminins, annexins, mucins, and other adhesion-related proteins involved in extracellular matrix organization. Among these, FN1, ITGAV, VTN, ANXA2, and PFN1 have been proposed as novel biomarkers of implantation success.^[9] Furthermore, alterations in metabolic enzymes such as ENO1 and PKM indicate that lipid structure and energy metabolism, which have essential roles in successful implantation, are disrupted.^[6,10] Collectively, these findings highlight a complex network of signaling, structural, and metabolic proteins underlying defective endometrial receptivity in RIF.

In conclusion, next-generation mass spectrometry-based proteomics, which yields thousands of proteins from a small sample with a single analysis, has a much stronger potential than traditional methods in redefining diseases with higher resolution and monitoring their course. The thousands of proteins identified in each sample through quantitative analysis essentially mean that researchers can build their own protein library from patient samples. Establishing a large-scale database, on the other hand, requires an institutional framework, as in the case of the Human Fertilisation and Embryology Authority (HFEA). Comparing the data in these and similar databases with proteomics data obtained by clinicians from their own patients can enable an in-depth molecular characterization of implantation-related pathways in the endometrium and the in vitro culture environment. In this way, proteomics can help improve the effectiveness of IVF treatment by generating important data on both the state of maternal tissues and conditions and the metabolic activity and developmental potential of the embryo. By supporting an increase in the pregnancy rate per transfer, it can provide direct or indirect benefits in terms of treatment effectiveness, treatment-related costs, and patient comfort. In this context, it is clear that proteomics technologies can be used as an effective way to more strongly elucidate the multifactorial nature of infertility in research related to infertility. I believe that the increasing interest of health professionals, particularly fertility

specialists, in next-generation molecular technologies such as mass spectrometry-based proteomics, and their possession of strong and precise molecular approaches in specific areas such as infertility, will offer significant opportunities in advancing personalized treatment strategies and increasing treatment success rates.

Statement

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