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Biography

Ana Maria Mihoci, MD, is a physician and doctoral researcher at the “Grigore T. Popa” University of Medicine and Pharmacy, Iași, Romania, affiliated with the Clinical Hospital of Obstetrics and Gynecology “Elena Doamna”. Her research focuses on reproductive medicine, infertility, chronic endometritis, endometrial receptivity, reproductive immunology, and assisted reproductive technologies, with particular interests in diagnostic biomarkers, evidence synthesis, and personalized approaches to infertility care.

Endometrial BCL6 as a Potential Triage Biomarker before Embryo Transfer: Bridging Recurrent Implantation Failure and Occult Endometriosis

Abstract

Background: Despite remarkable advances in assisted reproductive technologies, recurrent implantation failure and unexplained infertility remain major clinical challenges. Many women undergo repeated embryo transfers despite apparently good-quality embryos and the absence of an identifiable cause of implantation failure. Increasing evidence suggests that occult endometriosis and subtle endometrial dysfunction may contribute to these poor reproductive outcomes. Endometrial B-cell lymphoma 6 (BCL6), a marker associated with progesterone resistance and inflammatory signaling, has emerged as a promising biomarker of endometrial dysfunction. Rather than functioning as a stand-alone diagnostic test, BCL6 may help identify women who could benefit from further evaluation for underlying endometriosis before additional unsuccessful embryo transfer attempts. This systematic review aimed to evaluate the current evidence supporting the potential clinical role of endometrial BCL6 as a triage biomarker in infertility care.

Methods: A systematic review was conducted according to PRISMA 2020 guidelines following a prospectively registered PROSPERO protocol. Eligible studies evaluated endometrial BCL6 expression on endometrial biopsy in infertile women and reported reproductive outcomes or clinically relevant comparative data. Two predefined questions were addressed: whether abnormal BCL6 expression was associated with poorer reproductive outcomes than normal expression and whether pre-transfer treatment improved reproductive outcomes in BCL6-positive women. Owing to substantial clinical and methodological heterogeneity, findings were synthesized narratively, considering infertility phenotype, embryo-transfer setting, biopsy timing, hormonal preparation, BCL6 assessment methods, intervention strategies, and comparator structure.

Results: Thirteen studies met the inclusion criteria. Overall, abnormal endometrial BCL6 expression was associated with poorer reproductive outcomes in selected infertility populations, particularly among women with unexplained infertility

undergoing in vitro fertilization. Earlier studies generally demonstrated lower clinical pregnancy and live birth rates in women with elevated BCL6 expression, whereas more recent investigations in highly selected euploid embryo transfer cohorts did not reproduce these findings consistently. Studies evaluating pre-transfer interventions suggested that medical suppression or laparoscopic treatment may improve implantation, clinical pregnancy, and live birth in selected BCL6-positive women, supporting the concept that BCL6 identifies a potentially modifiable inflammatory or endometriosis-associated endometrial phenotype. However, interpretation of the available evidence remains limited by observational study designs, heterogeneous patient populations, variable biopsy protocols, differences in hormonal preparation, and inconsistent reporting of reproductive outcomes.

Conclusions: Current evidence does not support the routine use of endometrial BCL6 as an isolated diagnostic or treatment-guiding test. Nevertheless, BCL6 appears to be a clinically relevant triage biomarker that may help identify infertile women in whom occult endometriosis or inflammatory endometrial dysfunction should be considered before repeated embryo transfer attempts. By linking molecular evidence of endometrial dysfunction with more individualized patient selection for further investigation, BCL6 has the potential to support a more personalized approach to infertility care. Well-designed prospective studies using standardized testing protocols and harmonized reproductive outcome reporting are required before BCL6-guided management strategies can be routinely recommended.