Predicting implantation failure: to BCL6 or not to BCL6

The endometrium coordinates multiple exceedingly complex and dynamic functions, including the vital process of implantation. Identifying well-validated clinical tools for diagnosis and management of implantation disorders within the endometrium has long proven to be challenging. In the article by Klimczak et al. (1) in this issue of *Fertility and Sterility*, the investigators comment that "as providers we are often quick to implement any tests proposed to explain prior failures or improve outcomes in the future." Certainly, clinicians' desire to use available clinical tests to guide management and optimize outcomes for their patients with infertility is understandable, especially for those experiencing the frustration of an implantation disorder. It is worth remembering, however, that luteal phase endometrial histologies were once widely used in the field until well-designed clinical trials demonstrated these were neither reliable nor predictive (2).

Clinical endometrial tests that have become available in recent years include histologic tests of B-cell lymphoma 6 (BCL6) protein expression and microarray-based assays of gene expression during the window of receptivity. B-cell lymphoma 6 protein emerged as a potential candidate marker for endometrial receptivity after studies suggested significant overexpression in patients with endometriosis (3) and in those with unexplained infertility (UI) (4). The latter study concluded that a high BCL6 expression level is a proxy marker for endometriosis in a population with UI because 98% of study patients with a high BCL6 expression level were found to have endometriosis on diagnostic laparoscopy (4). This study also linked BCL6 to impairment of implantation through correlating endometrial overexpression of BCL6 with diminished live birth rates in the population with UI undergoing in vitro fertilization (IVF). However, the purported role of BCL6 in endometrial dysfunction is unclear. There is evidence to support a role for BCL6 in progesterone resistance pathways that may impair implantation. Alternatively, BCL6 may have a role primarily as a marker of endometriosis and/or endometrial inflammation and not as a direct cause of endometrial dysfunction.

Klimczak et al. (1) examine the broader application of BCL6 testing to a general population with infertility. In their case-control study, the investigators found no significant difference in live birth outcomes after transfer of rewarmed single euploid embryos among patients with an elevated endometrial BCL6 expression level (in biopsies performed during their stimulated cycles) compared with patients with normal levels of BCL6 expression. The investigators offer several hypotheses to reconcile the differences between their findings and prior data. Most notably, the study population was different from prior published studies in that it comprised a general population with infertility not specifically evaluated for endometriosis. The study's reported prevalence of BCL6 overexpression in 30% of endometrial samples could be interpreted as concordant with the historically reported rates of laparoscopically confirmed endometriosis in a general population with infertility.

Regardless of a possible correlation between BCL6 and endometriosis, outcomes were not different, and thus, BCL6 expression did not seem to be clinically relevant. Indeed, the investigators conclude that routine BCL6 endometrial screening before first embryo transfer has limited utility in predicting IVF outcomes in a general infertility population. This finding is particularly interesting in the context of a study published recently in this journal showing that endometriosis did not impact live birth rates in frozen embryo transfers of euploid blastocysts (5). Compared with fresh embryo transfers, frozen embryo transfer cycles may confer more control over the endometrial synchrony and embryo quality, both issues that may have confounded earlier studies. It is also worth noting that none of the limited studies investigating treatment of BCL6 overexpression, either through prolonged GnRH-a suppression or surgical ablation of endometriosis, have attempted to correlate outcomes with histologic normalization of BCL6 expression.

In our view, the findings of this study call into question the role of BCL6 overexpression not only as a predictor of outcomes in a general IVF population but also as a clinical marker of impaired implantation and IVF outcomes in any population. Endometrial tests such as those for BCL6 expression have biologic plausibility and hold promise, but large well-designed trials are lacking. These tests come at a not insignificant cost of time and money to patients and necessitate, by their nature, a biopsy to access the tissue. Further studies are needed to unlock the black box of implantation disorders and validate which endometrial tools are helpful and for which group of patients.

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