Immune modulation treatments—where is the evidence?

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While advances in assisted reproductive techniques have been substantial, failure of the apparently viable embryo to implant remains a source of distress and frustration to patients and specialists alike. The unique maternal immunological response to the embryo and the notion that defects in early placentation underlie the great complications of pregnancy have focused attention on the therapeutic potential of peri-implantation immunomodulation. On the face of it, the rationale for this approach is very attractive. However, as will be argued in this review, the clinical evidence base supporting the use of immunosuppressive treatments is weak and difficult to apply in practice and fails the needs of both doctors and their patients. This evidence gap is filled by justifications that are based largely on meeting patient expectations and commercial imperatives. However, this does not mean that immunomodulation treatments should be written off as ineffective. The literature in this field, while suffering the same challenges of heterogeneity, small studies, and publication bias as other areas of medicine, does hint at the way forward. Recurrent implantation failure and pregnancy loss are not diagnoses but clinical presentations that require appropriate phenotyping and etiological investigation. We are increasingly gaining the tools to make an "endometrial diagnosis," and these will allow us to design clinical studies of interventions that treat the underlying cause rather than the symptoms of implantation failure. The current evidence base does not support the clinical use of immunomodulation therapies in patients undergoing IVF. However, more discerning phenotyping may identify groups who could benefit. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

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Despite advances in assisted reproductive techniques (ART), the majority of IVF cycles still do not result in an ongoing pregnancy or live birth. The failure of apparently morphologically sound embryos to implant now represents the major limiting step to improving IVF outcomes. Depending on the definition used, up to 10% of couples undergoing IVF will experience recurrent implantation failure (RIF), and among those who do achieve implantation, many will face the disappointment of early pregnancy loss. Both represent a devastating occurrence for patients in whom serial transfers of high-quality embryos fail to result in a pregnancy. The pressures to "do something" to "improve implantation," which include assertive patient demand and the competitive commercial context in which IVF is increasingly practiced, continue to rise, and empirical treatments have come in to fill the gap between scientific rationale and clinical need (1, 2).

Particular interest has focused on modulating the maternal immune response to the implanting embryo. The premise for this would appear compelling, as much research has focused on understanding how the mother tolerates a genetically alien embryo and the mechanisms by which invasion of the maternal tissues by the embryo is permitted but limited. One of the paradigms to emerge has been the concept of a balance between pro- and anti-inflammatory states, characterized by a palette of cytokines and immune cells such as T-helper cells and natural killer (NK) cells, the relative populations of which are proposed to determine the fate of the implanting embryo. While it is becoming clear that such concepts risk oversimplification, the story is readily communicated and understood by the lay press and by patients, and an industry has grown at the interface of IVF and belief in the importance of the immunological determinants of implantation and their therapeutic modulation.

The drivers to implement new innovations into clinical practice are strong and numerous in IVF, and much of the progress made since the very early days of assisted conception has derived from the willingness of patients to try something new, as well as a measure of serendipity. However, the

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failure of our field to thus far effectively address the remaining challenges in implantation failure requires us to reassess the data supporting current treatment approaches and, more importantly, the established paradigms of human implantation.

There is a sizable literature relating to the use of immune modulation treatments in IVF. But the studies exploring the efficacy of different immunomodulation therapies, while numerous, are heterogeneous in design, method, intervention, and study population, making it difficult to interpret them and to design evidence-based rational therapy strategies. If we are to make progress in this challenging field, we need a greater understanding of the mechanisms and modulators of human implantation. In the meantime, immunomodulation therapies remain attractive to both patients and their doctors. This review aims to provide a brief overview of the current evidence supporting their use.

THE RATIONALE FOR USING IMMUNOMODULATORS

In order for successful implantation to occur, a high-quality embryo must engage with and breach the luminal surface of the endometrium before embedding in the decidualized endometrium. As the embryo differentiates, angiogenesis and remodeling of the spiral arteries are induced, establishing the maternal-fetal circulation. Immune cell populations have been shown to be key players in the maternal response to the embryo, and many studies have illustrated the importance of a balanced cytokine environment. A still prevailing paradigm describes the balance between T-helper 1 (Th1) and T-helper 2 (Th2) produced cytokines as determinants of implantation. A shift in the ratio towards Th1 cells leads to increased production of proinflammatory cytokines such as interferon gamma (IFN-γ), interleukin (IL) 2, and tumor necrosis factor alpha (TNF-α) that mediate a cytotoxic cell-mediated immune response and increase phagocytosis and inflammation. In contrast, Th2 cells produce a range of interleukins involved in the humeral immune response and inhibit several functions of phagocytosis, which together represent an anti-inflammatory response (3). This paradigm is supported by a number of observational studies reporting increased expression of proinflammatory cytokines in women with a history of recurrent pregnancy loss (4).

Disrupted population of peripheral and/or uterine NK (uNK) cells has also been implicated in implantation failure and early pregnancy. After ovulation, uNK cells become the dominant immune cells present in the decidualized endometrium, accounting for >30% of immune cells (5). In early gestation, the uNK cells expand in number and mass around the trophoblast cells in the decidualized endometrium (5). Here the uNK cells are thought to play an important role in the regulation of placentation by maintaining a balance between normal invasion of the trophoblast and excessive invasion. While peripheral blood NK cells play an important part in the innate immune system by recognizing foreign cells not representing HLA-class 1 molecules and early killing of viral pathogens, they are not thought to be key determinants of endometrial function (5). Furthermore they stimulate antigen-presenting cells and thereby promote activation of the adaptive immune system.

Another theory rests on the local balance between proinflammatory and anti-inflammatory cytokines in the receptive endometrium. The assumption that a pure anti-inflammatory milieu in the maternal fetal interface exists is an oversimplification (6–8). Studying the cytokine composition in endometrial secretions aspirated before ET in 210 women, our group demonstrated a positive association between IL-10 and TNF-α on implantation and clinical pregnancy, respectively. Conversely, a negative association was observed between secretions of monocyte chemoattractant protein-1 levels and IL-1β levels on implantation and clinical pregnancy, respectively. This study was the first to show a positive association between the proinflammatory cytokine TNF-α and clinical pregnancy (9).

The widely reported association between increased peripheral blood NK cells and an increased Th1/Th2 ratio (3,10–12) among women with recurrent miscarriage (RM) and RIF has fueled interest in testing peripheral NK cell counts, but these have been shown to bear little correlation to the NK cell populations present within the endometrium (5, 8). Some authors have reported a significantly higher count of uNK cells in the endometrium from women with RIF (13). Both peripheral blood sampling and endometrial biopsies interrogating NK cell counts and types have gained popularity with patients as intuitively attractive means of assessing the maternal factor in RIF and pregnancy loss. Such testing offers a means of diagnosing specific immune "defects" and a rationale for a variety of immune-modulating therapies. While a number of treatments are available, in general they derive from the premise that dampening the immune response to the embryo will improve outcomes.

GLUCOCORTICOIDS

Corticosteroid treatment presents a number of appealing characteristics in the context of IVF. The treatment is easy to take and cheap and occurs in short treatment regimens, considered to be safe. As a result they are widely prescribed, often as part of an immunomodulating package that includes other interventions such as aspirin or low molecular weight heparin (LMWH). But do they work? Our group has published a meta-analysis of randomized controlled trials (RCTs) in which the evidence for the efficacy of supplementary systemic administration of glucocorticoids in the peri-implantation period in women undergoing IVF or intracytoplasmic sperm injection (ICSI) was subject to systematic review (14). The analysis was restricted to women with a standard IVF or ICSI indication, and studies on men or women with autoantibodies were excluded. Thirteen studies were eligible for inclusion in the meta-analysis, involving a total number of 1,759 trial participants.

Within the three studies that reported the live-birth rate per couple, no significant difference was observed between the intervention and control group odds ratio (OR), 1.21, and 95% confidence interval (CI), 0.67–2.19 (15–17). The pregnancy rate per couple was reported in all the included