Novel approach to recurrent implantation failure: short-term copper intrauterine device placement

Repeated implantation failure (RIF) remains one of the most enigmatic areas of assisted reproductive technology and while there have been many efforts to investigate etiology and treatment, we presently have no definitive solution. Given that RIF is associated with high emotional and physical tolls that lead to drop out of care, novel treatments are urgently needed.

A brief glimpse into the history of therapeutic endeavors for treatment of RIF has included evaluation and treatment of uterine cavity structural abnormalities, altering preparation of the endometrial lining, evaluation and subsequent treatment for endometrial infection, alternative medicine including acupuncture, diagnostic hysteroscopy, controlled endometrial injury and immune modulation (1, 2). As with many biologically plausible treatment options with little potential harm, many of these treatment options have been widely implemented with high hopes. Controlled endometrial injury, known as 'endometrial scratch', by use of endometrial biopsy pipelle or hysteroscopically under direct visualization, has been proposed to increase vascularity and lead to increased sustained implantation. However, inconsistencies in the literature remain and there is a lack of robust evidence (3). Along the same lines, diagnostic hysteroscopy has been hypothesized to alter the existing uterine milieu with expansion and lavage, but was recently evaluated by a multi-center randomized controlled trial in RIF patients, and fell short of a definitive therapeutic effect (4). Difficulties in accurately diagnosing pathologic endometrial states has further plagued directed therapies focused on endometritis. And newer treatments, aimed at altering the local receptive environment, including systemic and local infusion of immune modulators are under investigation, but again lack vigorous data and have been subject to vast heterogeneity (2). Overall, many attempts have been made to alter the endometrial environment to improve reproductive outcomes, but all have failed to demonstrate marked effects with rigorous evaluation.

In this issue of *Fertility and Sterility*, Mao et al. (5) evaluates the novel placement of a copper intrauterine device (IUD) for two cycles following hysteroscopy in patients with RIF. The authors hope to replicate a murine model that demonstrated alteration of the inflammatory cytokine profile of the endometrium by the placement of a short-term copper IUD. They hypothesized this could improve reproductive outcomes, akin to the theorized benefit from endometrial scratch or diagnostic hysteroscopy alone. The concept, much like the postulated effect of endometrial disruption during a dilation and curettage on abnormal uterine bleeding, hinges on a persistent altered endometrial environment after discontinuation of the foreign body for subsequent cycles.

In this retrospective analysis of 440 women with a history of at least two failed embryo transfers with good quality embryos, all patients underwent initial diagnostic hysteroscopy, treatment of uterine pathology identified, and then 382 patients opted to receive a short-term copper IUD and 58 patients did not. Those opting for IUD placement had the device removed two months later followed by repeat diagnostic and, if needed, therapeutic hysteroscopy, followed by frozen embryo transfer cycle. The IUD and non-IUD groups were compared and reproductive outcomes reviewed.

Notably, the authors report a significant increase in biochemical pregnancy, implantation and clinical pregnancy rates (12%, 9%, and 19%, respectively) in the IUD group. The significant increase in chemical pregnancy rates remained when accounting for multiple confounding variables including age and body mass index. The authors do not note if this held true for implantation or clinical pregnancy rates.

The IUD group had higher rates of uterine pathology at initial hysteroscopy including polyps, polypoid proliferation and endometritis, no difference in adhesions, and there was no association of these pathologies or their subsequent treatment with clinical pregnancy rate.

It is interesting to note that a significant percentage of patients in the study (>1/3) had some form of uterine pathology at time of initial hysteroscopy. While it is routine practice in most centers to perform some sort of cavity evaluation prior to transfer with removal of identified pathology, it is unclear if these represent new or recurrent cases of intrauterine pathology. In this study, there was more noted in the IUD treatment arm than the controls. Hence, hysteroscopic treatment of uterine pathology may be a possible confounding factor contributing to the IUD treatment effect. In addition, if there was initial pathology, the treatment arm underwent a second diagnostic or operative hysteroscopy, either confirming successful removal or readdressing recurrent pathology whereas the control group did not.

In addition to altering the intra-uterine milieu, IUDs also provide a physical barrier between raw uterine surfaces, which has been theorized to assist in the prevention of future adhesions. Although severe adhesive disease was excluded and the control group did not have a second look hysteroscopy, this is another possible mechanism for improvement in cases where adhesions were treated. It is worth noting that the shape of the IUD used in this study (heart-shaped) is not commercially available within the United States and many other parts of the world. Although this somewhat limits the generalizability, this treatment may be worth investigating as an adhesion prevention method in the future.

As evidenced by the large percentage of RIF patients in this study who opted for an experimental treatment that would delay future fertility care, patients are desperate for additional treatment options. It is imperative, however, to determine which specific subset of patients might benefit from these and other novel therapies. Future research aimed at development of tools to allow for identification of eligible patients will help strengthen demonstrable therapeutic effect and allow for personalized treatment to maximize reproductive success.

While Mao et al. (5) should be commended for the innovative concept and thoughtful execution of this study, readers

should take note of the sample size, selection bias and retrospective design. Questions remain as to how much disruption of the endometrial environment would lead to a beneficial change in the receptivity, and at what risk? The duration, form of foreign body and microscopic evaluation of endometrial tissue following application have also been largely unexplored. This study brings to light that new treatment options for recurrent implantation failure may be on the horizon and more investigation is warranted.

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