What is the Mechanism of Poor Endometrial Proliferation in Patients with Unexplained Infertility After Clomiphene Citrate Treatment?

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Infertility is defined as an absence of conception despite 12 months of regular unprotected intercourse. It is a very common condition and estimated to affect 10-15% of couples worldwide. In some cases, there are specific underlying etiologies such as anovulation, endometriosis, adenomyosis, low ovarian reserve, poor sperm quality, or ovarian and uterine tract pathology; however, in ~10% to 30% of infertility cases, etiology remains unknown. Unexplained infertility is a diagnosis of exclusion, which requires a detailed and comprehensive evaluation to exclude other possible underlying pathologies. (1) The prevalence of unexplained infertility varies based on which criteria are used by clinicians for diagnosis. It is likely to be higher in countries with limited resources due to restricted access to diagnostic tools.

In recent years, clinicians have been using various therapies, including expectant observation, ovarian stimulation with oral agents or gonadotropins, intrauterine insemination (IUI), and IVF with and without intracytoplasmic sperm injection (ICSI) to treat unexplained infertility. However, all of these approaches are empirical since there are no identifiable treatable causes for unexplained infertility. One of the most widely used treatment options for ovarian stimulation is clomiphene citrate which acts as a selective estrogen receptor modulator. It has been used widely as a first-line oral treatment option to induce ovulation for more than 40 years with minimal side effects. (2)

A critical estrogen level is essential in regulating uterine receptivity, and inadequate estrogen action may lead to implantation failure. Clomiphene citrate has anti-estrogenic effects on the endometrium, which may cause decreased endometrial proliferation and delayed glandular growth. Since adherence of the embryo is one of the most critical steps in fertility, failure in the adherence may lead to poor pregnancy rates among those cases. (3) To avoid this adverse effect of clomiphene citrate, physicians considered using alternative treatments such as letrozole, an aromatase inhibitor that has no estrogen receptor antagonism nor antiestrogenic effects, such as thin endometrium and poor cervical mucus. However, there is still limited clinical evidence showing its superiority to clomiphene in those patients with suboptimal endometrial thickness. (4)

Furthermore, Von Wolff et al. showed an association between lower pregnancy rates and thin endometrium among women undergoing unstimulated cycles for the first time. This study suggested considering thin endometrium as an independent prognostic factor for pregnancy success. They indicated that there might be structural differences in these women’s endometrium, and those changes may contribute to suboptimal endometrial thickness. (5)

Although implantation failure is known to result from a thin endometrium, the mechanism that leads to a thin endometrium has not been clarified yet. In this issue, Bressler et al. investigated whether poor endometrial proliferation is related to inadequate or aberrant estrogen signaling mechanisms caused by altered estrogen receptor expression or post-receptor responses. This is the first study investigating underlying mechanisms in endometrium tissue of patients diagnosed with unexplained infertility and poor endometrial proliferation treated with clomiphene citrate. The study included
infertile women ages 18-45 who have received clomiphene citrate treatment (100 mg on cycle days 3-7) for unexplained infertility. Ultrasound examination was performed between stimulation cycle days 12-14, which divided the sample into two groups based on their endometrial thickness, “optimal” controls whose endometrial thickness is ≥ 8mm (N=7), and “suboptimal” subjects whose endometrial thickness is < 6 mm (N=6) (6). Even though the optimal endometrial thickness remains controversial among physicians, in general, endometrial thickness less than 7 mm is regarded as suboptimal thickness.

Previously Yuan et al. showed a decrease in the expression of ER-α in thin endometrium compared to normal endometrium in randomly selected patients, and they suggested that these findings may be associated with the unknown etiological thin endometrium. (7) Interestingly, Bressler et al. confirmed these results and showed that women with poor endometrial growth after clomiphene had decreased ERα and increased ERβ gene expression at the transcriptional and protein levels. This study contributes insightful mechanistic analysis of endometrial tissue in women who suffer poor endometrial proliferation after clomiphene exposure. The endometrium of those women generally exhibited reduced biomarkers of proliferation and angiogenesis, increased markers of inflammation, and aberrant estrogen receptor expression. Altered estrogen receptor subtype presence and activity suggest that poor growth might be caused by an intrinsic endometrial mechanism for the altered action of estrogen with clomiphene (6). This study provides a novel insight to understand the underlying mechanism of suboptimal thickness after clomiphene treatment and possibly a distinct cause of infertility among patients currently diagnosed with “unexplained” infertility. Further investigations are needed to explore these findings in unstimulated cycles using a larger sample size. If endometrium thickness is one of the possible causes of unexplained infertility, even in unstimulated cycles, the possibility of new therapeutic approaches addressing this element would be warranted.

In conclusion, suboptimal endometrial thickness remains a common challenge for physicians in clinical settings. Unfortunately, there is currently no effective treatment to treat this common encounter among infertile patients. Therefore, in depth understanding of the mechanisms of thin endometrium and the factors contributing to it, is an essential step forward to develop novel therapeutic modalities.

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