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The thin endometrium in assisted reproductive technology: An ongoing challenge

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ABSTRACT

Thin endometrium is identified to adversely affect reproductive success rates after assisted reproductive technology (ART). Several treatment modalities have been presented to patients with thin endometrium, to improve endometrial thickness and the subsequent endometrial receptivity. These approaches comprising hormonal management by estradiol, tamoxifen, human chorionic gonadotropin (hCG) and gonadotropin-releasing hormone (GnRH) agonist, vasoactive agents such as aspirin, vitamin E, pentoxifylline, nitroglycerin and sildenafil, intra-uterine infusion of growth factor such as Granulocyte Colony Stimulating Factor (*G-CSF*) and the latest application of platelet-rich plasma, electrical stimulation, regenerative medicine and presentation of endometrial receptivity array. In spite of the large variety of treatment, most of the choices achieve only minor modification in the endometrium thickness and have not been validated so far. Treatment of thin endometrium remains a challenge and future enormous investigations are required to further clarification and ideal management of patients with thin endometrium.

Contents

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1. Introduction

Despite recent developments in assisted reproductive techniques (ART), the implantation rates still remain relatively low. Successful implantation requires high quality embryo, receptive endometrium, and perfect embryo transfer technique [1]. The receptive endometrium define as a healthy uterine milieu containing the transformation of endometrial cells into decidua cells appropriate for implantation of blastocysts, and rapid growth of placenta [2]. Therefore, endometrial assessment is routinely performed during in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). In addition endometrial thickness (EMT) have been considered as a marker of endometrium receptivity [3] and a prognostic factors for embryo transfers during IVF/ICSI treatment [4,5]. It is known that appropriate endometrial thickness is essential for a successful pregnancy [6,7] and several studies have stated low pregnancy rates in the presence of thin endometrium [8–11]. The optimal endometrial thickness for conception remains controversial among clinicians. EMT less than 7 mm on ultrasound is generally considered sub-optimal for embryo transfer and is correlated to a decreased probability of pregnancy. Thin endometrium remains a challenge in gynecology and reproductive science with only slight enhancements attained with the currently available treatment. In this review, we focus on developing and promising treatment options for refractory thin endometrium.

2. Pathophysiology of thin endometrium

It has been supposed that a thin endometrium is caused by a diminished normal endometrial growth. However, little evidence is presented with regards to reasons for impaired endometrial growth in patients with thin endometrium. Acute or chronic infection like genital tuberculosis may result in destruction of endometrium basal layer due to replacing healthy endometrium by fibroid tissue after healing [12]. Iatrogenic thin endometrium can be occurred by surgical procedures such as repeated curettage, polypectomy, laparoscopic or hysteroscopic myomectomy as well as immethodical drug usage such as clomiphene citrate [12]. It is also indicated that thin endometrium may be a result of individual uterine structural pattern [13].

Angiogenesis plays a key role in different female reproductive developments, including growth of dominant follicles, formation of a corpus luteum, and endometrial pattern [14–18]. Endometrial angiogenesis is vital for regeneration endometrium after menstruation and to provide a vascularized receptive endometrium for implantation [14,17]. The majority of studies has focused on vascular endothelial growth factor (VEGF) as a regulator for endometrial angiogenesis, and a number of works stated that VEGF is expressed differentially in the uterine with thin endometrium [17,19–21]. Uterine blood flow is an essential marker regulating endometrial growth and is narrowly related to vascular development of the endometrium [22–25]. Recent improvements in ultrasonography have provided new opportunities for noninvasive evaluation of endometrial perfusion. A significant reduced pregnancy rate in IVF-ET patients with low uterine blood flow, displayed a close relationship between uterine blood flow and uterine receptivity [26,27]. Asherman's syndrome is one of the causes of thin endometrium. Transvaginal ultrasonography usually reveals minimal endometrial thickness in this patients [28]. Impaired uterine perfusion is the reason for atrophy of the remaining endometrium due to restricted exposure to circulating hormones. This syndrome may occur followed myometrial fibrosis that is remarkably increased among women with intrauterine adhesions (IUAs) compared to healthy controls [29].

3. Treatment of thin endometrium

Since a thin endometrium is a multifactorial condition, its management should be cause-related, with the aim of increasing endometrial receptivity and simplifying implantation [30,31]. However, improving endometrial growth in patients with thin endometrium is very challenging; several regimens have been tried in the literatures [21,29,30].

3.1. Estradiol

Infertile patients, who display inadequate endometrium thickness, will be initially treated with oral estradiol. As the endometrium is a hormone dependent tissue estrogen supports endometrial proliferation by causing spiral artery contraction and decreasing oxygen tension in the functional layer, that simplifies embryo implantation [32,33]. The best method for prescription of estradiol is oral administration, and there are no significant differences between micronized estradiol or estradiol valerate [34]. The extended administration of estradiol valerate during controlled ovarian hyperstimulation (COH) cycles for 14–82 days, improve the mean endometrial thickness from 6.7 to 8.6 mm as well as significant increase of pregnancy rate (38.5 vs. 4.3%) [35]. Similarly a case of repeated implantation failure due to unreceptive thin endometrium received extended estrogen supplementation for an extended period, using 16 mg/day of estradiol valerate from the third day of her menstrual cycle for 9 days before COH. IVF in this patient led to a twin pregnancy and delivery at term [36]. In contrast Demir et al. reported that estradiol supplementation with estradiol hemihydrate 4 mg/day started on the day of hCG among women with thin endometrium undergoing ICSI, did not improve clinical pregnancy rate, implantation rate (16% vs. 10.4%), and endometrial thickness [37]. According to a meta-analysis results, administration of pure ethinyl estradiol (EE) for treatment of thin endometrium, increase the endometrial thickness in comparison to patients whom used placebo. Moreover, the best result were achieved while EE administration is starting on 7th–10th day of menstrual cycle with the dose of 0.02–0.05 mg/day for 5 days [38]. As the highest serum and endometrial level of estrogen occur after vaginal administration, it is considered as the desirable route in cases that do not response to the other ways. Therefore, Cetinkaya and colleagues administered estrogen vaginally 25 mg daily from 4th day of the cycle for 15 days in Clomiphene citrate induced cycle. They reported significant increase in endometrial thickness on the day of ovulation in estrogen + clomiphene citrate group compare to the group where only Clomiphene citrate was used, but there was no difference in pregnancy rate [39]. In the same way another study compared oral and vaginal administration of estradiol among donor oocytes recipients. The results showed an increase in endometrial thickness as well as ongoing pregnancy rate when vaginal estradiol administration extended to 4–6 weeks in women who failed to achieve acceptable endometrial thickness after oral estradiol administration [40]. Oral estrogens were also used for endometrium preparation in FET, where prior IVF failure was believed to be due to thin endometrium. Jimenez and colleagues administered oral estradiol 2 mg three times a day from day 1st for 12 days. They stated satisfactory development of endometrium in 67% patients [41].

3.2. Human chorionic gonadotropin (hCG)

hCG play a local paracrine role in the endometrium differentiation and endometrial receptivity by regulating different cytokines and growth factors [42,43]. Papanikolaou and colleagues recruited seventeen infertile patients with the history of implantation fail-

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