

# Successful pregnancy in recurrent thin endometrium: a case report

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## Abstract

Human endometrium plays an important role in the implantation process. Endometrial thickness is considered to be one of the valuable parameters contributing to the successful outcome of the assisted reproductive technique. Young patients less than 35 years have a better chance of conceiving even if they have thin endometrium. It is suggested that a frozen cycle instead of fresh transfer allows for a better and more detailed study of the endometrium. Many modalities have been applied to improve endometrial thickness but their effectiveness remains controversial. Here we present a 30-year-old female trying for conception for 8 years and has a history of four times recurrent IVF failure. On ultrasonography, the endometrium lining was always in the range of 5 to 6.5 mm. Frozen embryo transfer (FET) was done with mild-ovarian stimulation (OS) protocol, the dominant follicle was tracked, and trigger given and was followed by three blastocyst transfers. The patient came positive with a twin pregnancy. Endometrium potential cannot be judged only based on thickness, other parameters like endometrial blood flow and its pattern equally should be considered. Although hormone replacement therapy and NC (natural cycle)/modified NC are the most commonly used protocols, the present case suggests that mild OS may be an emerging and viable option for FET.

**Keywords:** Assisted reproductive transfer, frozen Embryo transfer, IVF failure, mild-ovarian stimulation frozen embryo transfer, pregnancy outcome, recurrent thin endometrium, thin endometrium

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## INTRODUCTION

Successful pregnancy depends on synchronized and coordinated cross talk between an embryo and an endometrium over a suitable internal environment. It has been reported that there is a steady and gradual increase in pregnancy rates as endometrial thickness increases.<sup>[1]</sup> There is an increasing trend in pregnancy rate as endometrial thickness increases from 8 to 14 mm.<sup>[2]</sup> An endometrial thickness of <7 mm on ultrasound is mostly considered a thin endometrium.<sup>[3]</sup>

But how thin is not completely known, as pregnancies have also been reported when the endometrial thickness is 4 to 5 mm, suggesting that endometrial thickness may not be the only sole factor for receptivity.<sup>[4]</sup> That's why not only endometrial thickness but also its pattern and vascularity remain the most researched parameters.

Trials to improve the overall endometrial growth and pattern have not been validated so far. Several treatment modalities including operative hysteroscopy, improving blood supply to the endometrium such as aspirin, vitamin

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E, pentoxifylline, l-arginine or sildenafil, intrauterine infusion of G-CSF, and regenerative medicine have been tried. In spite of the vast diversity of treatment, most of the options accomplish only minor changes in the endometrium thickness and the subsequent pregnancy rate finally resulting in dismay. So the overall effectiveness of these modalities remains controversial.

Frozen embryo transfer (FET) cycles improve the endometrial receptivity, which gives better results. Letrozole mild-ovarian stimulation (OS) for endometrial preparation in FET has a higher pregnancy rate and a lower abortion rate than HRT (hormone replacement therapy)-FET. Letrozole mild-OS exhibits clinical progression and outcomes similar to those of patients undergoing a natural cycle (NC) or modified NC. The evidence for the best protocol for FET is poor as the number of high quality randomized controlled trials (RCTs) is less, so there is a need for future research to compare both the pregnancy and neonatal outcomes between HRT, NC FET, and other protocols.<sup>[5]</sup>

## CASE REPORT

A 30-year-old female trying for conception from 8 years, nulligravida, has a history of four times recurrent IVF failure. She has regular menstruation with no menstrual abnormalities. The sexual history is normal. Her Anti Mullerian Hormone (AMH) is 4.37 ng/mL. The endocrine profile was within normal limits. The male factor seems to be normal. The previous cycle details are not completely available but the patient gave a history that she was told that she had some endometrium problem. On ultrasonography, the endometrium lining was always in the range of 5 to 6.5 mm. Endometrium was studied for three cycles consecutively, on the first month maximum 6 mm, second month 6.6 mm, third month 6.5 mm, but all the time it was triple lined with good blood flow up to Zone-3. Hysteroscopy was normal with TB PCR of endometrium negative. The patient was planned for stimulation long agonist cycle with recombinant FSH 225IU and six blastocysts were formed. She was further planned for FET and was prepared with downregulated programmed cycle. Tab Tamoxifen 40 mg for 5 days with estradiol 12 mg, sildenafil, enoxaparin 40 mg with GCSF three doses alternate day was given with endometrium 7 mm on day 17 of estradiol, and progesterone was started but pregnancy test was negative. Endometrium was again studied after 1 month endometrium maximum up to 6.5 mm. HRT was given for two consecutive cycles. It was also seen that during the stimulation cycle, endometrium was 7.4 mm. So this time FET was

planned without downregulation and directly endometrium was prepared without leupride and HRT. Stimulated FET was planned with letrozole 2.5 mg (Sun Pharma, India) for 5 days, and in addition vitamins E and C were added, with low dose aspirin with Low molecular weight Heparin (LMWH) (Intas Pharma, India), amino acids with three doses of GCSF (Emcure Pharma, India) was given and just when the endometrium was increased by 1.5 mm from previous 4 to 5 days reading and endometrium was 7.2 mm with good vascularity, dominant follicle was tracked and trigger given was followed by then three blastocyst transfer. The patient came positive with a twin pregnancy.

## DISCUSSION

The management of thin endometrium is a common challenge for patients undergoing assisted reproduction. The measurement of endometrial thickness is most commonly used in clinical practice. Even though the results of the studies are conflicting with no consensus on the correlation between endometrial thickness and IVF outcome, an endometrial thickness of less than 7 mm is not a good sign. A young patient with a greater number of embryos still has a better chance of conceiving even with thin endometrium as suggested by Kumbak *et al.*<sup>[3]</sup> Clinical pregnancy, implantation, and live birth rates per embryo transfer in their patient group were examined according to age, the number of oocytes retrieved, and the number of embryos transferred. Significantly better results were obtained when the patient's age was <35 years or the number of retrieved oocytes was over five or the number of embryos transferred was three or more. These findings also support the view that endometrial thickness alone is not a determinant of treatment outcome as is shown in the present case. So, the young couple should try the further method of endometrium preparation before giving up.

In the present case, it is suggested that a frozen cycle instead of fresh transfer allows a better and more detailed study of endometrium. It also gives us the advantage of postponing transfer if lining has not grown to a satisfactory level. Biochemical pregnancy rates, clinical pregnancy rates, and live birth rates were significantly higher in the FET than in the fresh ET over 35 years of age.<sup>[6]</sup> FET seems to be better compared to fresh embryo transfer in patients over 35 years. But if we see in terms of cumulative live birth rates, moderate-quality evidence suggests that one method is not superior to the other. Low-quality evidence indicates that frozen transfer lowers the Ovarian Hyper Stimulation Syndrome (OHSS) risk.<sup>[7]</sup>

Mild-OS preparation of FET cycle can also be considered as compared to HRT or NC preparation. In the latest Cochrane meta-analysis, when stimulation with gonadotropins, letrozole, or CC was pooled, the clinical pregnancy rate was significantly higher with mild-OS when compared to HRT cycles.<sup>[8]</sup> The letrozole was comparable with HRT in terms of LBR in the only available RCT.<sup>[9]</sup>

A recent meta-analysis of 26 RCTs comparing different FET protocols showed that when compared with HRT, significantly higher LBRs were achieved with mild-OS using gonadotropin or mild-OS using letrozole.<sup>[10]</sup> However, an insignificant difference in LBR was noted between t-NC, modified-NC, and mild-OS protocols. In a recent retrospective study of 2664 patients with PCOS undergoing FET, in terms of endometrial thickness, on the day of starting exogenous progesterone as well as on the day of FET, significantly higher ET was shown in the letrozole group when compared to HRT.<sup>[11]</sup> In conclusion, although HRT and NC (t-NC/modified-NC) are the most commonly used protocols, recent upcoming evidence suggests that mild-OS can be a viable option for FET. Since managing a thin endometrium case is always a challenge, the present case shows its importance and lays down certain methods that can be resorted to if a thin endometrium case comes across.

## CONCLUSION

Endometrium potential cannot be judged only on the basis of thickness, other parameters like endometrial blood flow and its pattern equally holds a place. A young patient has a good chance of implantation even with thin endometrium. A frozen cycle instead of fresh transfer allows a better and detailed study of endometrium. Endometrial study should be done before index cycle in cases of thin endometrium, need to prepare your armamentarium for the index cycle, and also each transfer has its own psychological implications. In cases of thin endometrium if you are planning for FET preparation, always consider endometrium status during the stimulation cycle. Use repeated HRT cycles before FET to stimulate regeneration of the endometrium. Always evaluate a thin endometrium. If it is subsequent to endometrial destruction by an inflammatory process, then it may be less receptive than one that is due to the individual architecture of the uterus.

Downregulated FET is not a good method for subsets of patients. We need to resort to other methods of endometrial preparation. Mild-OS may be an emerging and viable option for FET. Tamoxifen with other

adjuvants such as GCSF, sildenafil, ecosprin, LMWH, and vitamin E can be tried for thin endometrium cases. We need to even put more embryos if we are not doing PGT before transfer in recurrent implantation failure cases as blastocyst euploidy rate is 60% to 70%. When a thin endometrium case is being managed, explore your armamentarium before actually denying a case.

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## Conflicts of interest

There are no conflicts of interest.

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