

# Failure to increase the thickness of thin endometria with intrauterine infusion of granulocyte colony stimulating factor (G-CSF)

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## Summary

**Purpose:** To corroborate or refute a previous study suggesting that intrauterine infusion of granulocyte colony stimulating factor (G-CSF) could significantly improve endometrial thickness into more fertile levels when the endometrial thickness was  $\leq$  five mm. **Materials and Methods:** Three women whose endometrial thickness never exceeded five mm on the in vitro fertilization-embryo transfer (IVF-ET) cycle or subsequent attempted frozen ETs using graduated estradiol had intrauterine infusion of G-CSF to the estradiol regimen. **Results:** Not one of the three women improved the endometrial thickness beyond five mm and none conceived on the G-CSF cycle. One woman had a subsequent pregnancy following a frozen ET with only a four-mm thickness with no infusion of G-CSF. **Conclusions:** These data do not confirm the efficacy of intrauterine infusion of G-CSF for poor endometrial thickness. Perhaps only certain cases will respond. A larger series could take time to accumulate since other studies have shown that only 0.3% of women with  $\leq$  five mm endometrial thickness in the late proliferative phase during an IVF-ET cycle will not improve the endometrial thickness  $>$  five mm using graduated estradiol protocols.

**Key words:** Endometrial thickness; Granulocyte-colony stimulating factor (G-CSF); Graduated estradiol therapy.

## Introduction

Lower pregnancy rates (PRs) per embryo transfer have been demonstrated in women with thin endometria in the late proliferative phase at the time of human chorionic gonadotropin (hCG) injection [1,2]. One early review of the literature concluded that there were no successful pregnancies following in vitro fertilization-embryo transfer (IVF-ET) when the pre-ovulatory endometrium was  $<$  six mm [3]. However subsequent to this early study, a successful pregnancy following IVF was reported where the maximum endometrial thickness was only four mm [4]. A successful delivery was also reported without IVF-ET in a natural cycle with a maximum endometrial thickness in the late proliferative phase of four mm [5].

A study of 35 women having IVF-ET with a maximal thickness of  $\leq$  five mm found three clinical pregnancies (8.5% per transfer) and two live deliveries (5.7% per transfer) [6]. In that same study there was one live delivered pregnancy out of seven frozen embryo transfers (14.2%) with maximal endometrial thickness  $\leq$  five mm [6].

Most therapies to improve thin endometria have failed. Though at one time treatment during the follicular phase with vaginal sildenafil seemed promising, other studies failed to confirm any significant beneficial effect on pregnancy rates [7, 8]. Another promising treatment for unre-

sponsive thin endometrium has recently been published, i.e., the uterine perfusion of granulocyte colony-stimulating factor (G-CSF) [9]. Gleicher *et al.* reported four consecutive women with a history of multiple cycles of failing to attain an adequate endometrial thickness despite the use of higher dose graduated estradiol and vasodilators which resulted in cancellation of embryo transfer cycles. However, with intrauterine infusion of G-CSF, three improved the endometrial thickness to eight to ten mm and one increased to 7.3 mm [9]. Even more important all four conceived and three delivered live babies [9].

A recent study of 21 consecutive women whose endometria reached a maximum endometrial thickness of  $\leq$  six mm on the day of hCG injection in an IVF-ET cycle and were treated with G-CSF, the mean endometrial thickness increased from 6.4 mm to 9.3 mm from the day of hCG to ET [10]. However the endometrial thickness increased more in the 17 not conceiving than the four who did [10]. The authors published these cases ahead of two ongoing prospectively randomized studies of G-CSF "because of unexpectedly clear results in clinical circumstances without effective treatment options". They suggested that this small study could influence other centers to try this therapy and hopefully improve their success rates prior to the publications of the results of the large prospective study.

Revised manuscript accepted for publication August 3, 2015

The present study evaluated the authors' experience with the intrauterine infusion of G-CSF on improving endometrial thickness in women with thin endometria and subsequent PRs.

## Materials and Methods

Intrauterine infusion of G-CSF 30 MU was performed as previously described in a previous series of four published cases [9]. All women had their transfer on the IVF-ET cycle cancelled for inadequate endometrial thickness ( $\leq$  five mm) and in at least one subsequent attempt at frozen ET using a graduated oral and vaginal estradiol protocol.

## Results

Three women were identified who in previous attempts failed to attain an endometrial thickness of six mm despite multiple cycles of prolonged high dosage oral and vaginal estradiol to prepare for frozen ET and who were willing to try G-CSF experimentally. In the cycle of investigation with infusion of G-CSF, no woman improved the endometrial thickness to six mm and none conceived. In a subsequent cycle, one woman conceived with a frozen ET with a peak endometrial thickness of four mm with graduated estradiol only without G-CSF.

## Discussion

In this case series of three women, none improved their thin endometrium to a more fertile level with G-CSF and all failed to conceive in the cycle where G-CSF was given. Interestingly, one woman successfully conceived on a succeeding cycle without G-CSF and with only a four-mm endometrial thickness.

In a previous study the authors found that graduated oral and vaginal estradiol in frozen ETs failed to attain a six-mm endometrium in only ten of 2,598 ET cycles (0.3%) [11]. Thus a large study by one IVF center evaluating G-CSF for poor endometrial thickness is unlikely. Therefore more small case control studies are needed to determine how frequently does intrauterine infusion of G-CSF work to im-

prove endometrial thickness to  $\geq$  seven mm when previous cycles achieved an endometrial thickness of  $\leq$  five mm.

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