Original Article

Growth Hormone: A Potential Treatment of Patients with Refractory Thin Endometrium: A Clinical Trial Study

Soghra Hosseini Aghdam, M.D.[1, 2], Alyeh Ghasemzadeh, M.D.[1, 2*], Laya Farzadi, M.D.[1, 2], Kobra Hamdi, M.D.[1, 2], Nazli Navali, M.D.[1, 2], Parvin Hakimi, M.D.[1, 2], Marayam Baradaran-Binazir, Ph.D.[3], Mohammad Nouri, Ph.D.[4], Amir Fattahi, Ph.D.[1, 4*], Ralf Dittrich, Ph.D.[5]

1. Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
2. Department of Gynecology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
3. Community Medicine Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
4. Department of Reproductive Biology, School of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
5. Department of Obstetrics and Gynecology, Erlangen University Hospital, Friedrich-Alexander University of Erlangen–Nürnberg, Erlangen, Germany

Abstract

Background: Growth hormone (GH) is a potential treatment in the assisted reproductive technology (ART) to improve endometrial receptivity and thickness. In the current study, we investigated the effect of the intrauterine administration of GH on the endometrial thickness (EMT) and ART outcomes in the patients with refractory thin endometrium.

Materials and Methods: In this clinical trial study, women with a refractory thin endometrium and a history of one or more frozen embryo transfer (FET) cancellation who were referred to the infertility center of the Tabriz Al-Zahra hospital (Tabriz, Iran) and Milad Infertility Clinic (Tabriz, Iran) received intrauterine injections of GH every other day from day 14 of the menstrual cycle until the EMT reached ≥7 mm in addition to the routine endometrium preparation protocol. EMT was evaluated during the treatment and in the cases with EMT ≥7 mm, biochemical/clinical pregnancy was evaluated after embryo transfer.

Results: Thirty-one women aged 35.29 ± 6.21 years were included in this study. The mean amount of EMT was significantly increased following the GH treatment (7.03 ± 1.23 mm) vs. before treatment (5.14 ± 1.1 mm, P<0.001). The EMT reached ≥7 mm in the 65% patients (20/31). Also, the embryo transfer resulted in pregnancy in the patients, biochemical pregnancy: 9/20 (45%) and clinical pregnancy: 7/20 (35%). There was a positive correlation between EMT on the day 13 of cycle (before the treatment) and the maximum EMT (r=0.577 and P=0.001). The EMT was statistically different on the embryo transfer day between clinically pregnant and non-pregnant women (7.18 ± 0.56 vs. 6.21 ± 0.72 mm, P=0.007).

Conclusion: The intrauterine administration of GH could be an appropriate therapeutic strategy for patients with refractory thin endometrium. This treatment could significantly increase the EMT as well as implantation and pregnancy rates in these patients (registration number: IRCT20210220050429N1).

Keywords: Assisted Reproductive Technology, Growth Hormone, Implantation, Pregnancy

Citation: Hosseini Aghdam S, Ghasemzadeh A, Farzadi L, Hamdi K, Navali N, Hakimi P, Baradaran-Binazir M, Nouri M, Fattahi A, Dittrich R. Growth hormone: a potential treatment of patients with refractory thin endometrium: a clinical trial study. Int J Fertil Steril. 2022; 16(4): 251-255. doi: 10.22074/IJFS.2022.541389.1210.

Introduction

Although assisted reproductive technology (ART) has greatly advanced in recent years (1), clinical studies show that even with the application of comprehensive chromosome screening of embryos, the ongoing pregnancy rate with euploid embryo transfer (ET) is about 45% (2, 3). This means that factors other than chromosomal abnormalities are responsible for more than 50% of ART failures. More recently, attention has been directed to the endometrium in an attempt to optimize the chance of embryo implantation. The embryo implantation can be occurred in the window of implantation from day 22 to 24 of a 28-day cycle (4).

The thin endometrium, the thickness <7 mm, with the incidence of about 1% to 2.5% is one of the common issues that can cause cycle cancelation or implantation failure (5). It has been shown that the recovery of endometrium thickness in patients with thin endometrium could improve endometrial receptivity, implantation, and live birth rates (6, 7). Currently, several therapeutic strategies have been applied to restore endometrial thickness (EMT) and receptivity in patients with refractory thin endometrium, including administration of Tamoxifen, Pentoxifylline, a high dose of estradiol, vitamin E, low dose of human chorionic gonadotropin, low dose Aspirin, L-Arginine, acupuncture and neuromuscular electrical stimulation, Nitroglycerin patches, intrauterine infusion of granulocyte

Received: 22/October/2021, Accepted: 06/February/2022
*Corresponding Address: P.O.Box: 5138665793, Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
Emails: alghasemzadeh@yahoo.Co.uk, amirfattahi@gmail.com

Royan Institute
International Journal of Fertility and Sterility
Vol 16, No 4, October-December 2022, Pages: 251-255

colony-stimulating factor (GCSF), and stem cells (8, 9). However, the above-mentioned therapeutic methods have not been able to produce very good results, especially in patients with refractory thin endometrium; therefore, novel treatments are required to improve the endometrial thickness as well as the pregnancy rate in these patients.

Growth hormone (GH) is used as an adjuvant treatment in the ART. Studies have demonstrated that this hormone and its receptors are expressed in the endometrium and might involve in the EMT and endometrial receptivity (10-12). There are contradictory results regarding the effectiveness of intravenous GH administration on the EMT in the ART cycles (13, 14). The mechanism through which GH improves the EMT and *in vitro* fertilization (IVF) outcomes are almost unknown; however, different molecules have been suggested to be involved in this process, including insulin-like growth factor (IGF), leukemia inhibitory factor (LIF), integrin, and home box containing transcription factors (15). Since the local administration of GH may be more effective on the EMT and endometrial receptivity, for the first time, Yu et al. (11) evaluated the intrauterine perfusion of GH for the treatment of human thin endometrium. This study demonstrated that intrauterine administration of GH could positively affect EMT and endometrial receptivity.

Given the potential of GH to improve endometrial status as well as pregnancy outcome and also, lack of sufficient data on the effect of the intrauterine administration of GH, the present study aimed to evaluate the effect of intrauterine administration of GH on the EMT and ART outcomes in the patients with refractory thin endometrium.

Materials and Methods

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and all procedures were approved by the Ethical Committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.REC.1399.1039). Moreover, signed informed consent was obtained from each participant before entering the study. The study has been registered in the Iranian Registry of Clinical Trials (IRCT20210220050429N1).

Study population

In this clinical trial study, the participants were recruited from patients who were referred to the infertility center of the Tabriz Al-Zahra hospital (Tabriz, Iran) and Milad Infertility Clinic (Tabriz, Iran), for frozen ET (FET) in the hormonal replacement cycle due to reduced ovarian reserve the recruitment procedure is detailed in the Figure 1. All participants had a history of one or more ET cancellations due to EMT <7 mm after standard hormone replacement therapy (HRT). The previous HRT treatment included estradiol valerate tablets with a constant dose of 6 mg per day for 7 days and increasing the dose of estradiol valerate, up to 8mg/day for four more days in patients with EMT<7 mm.

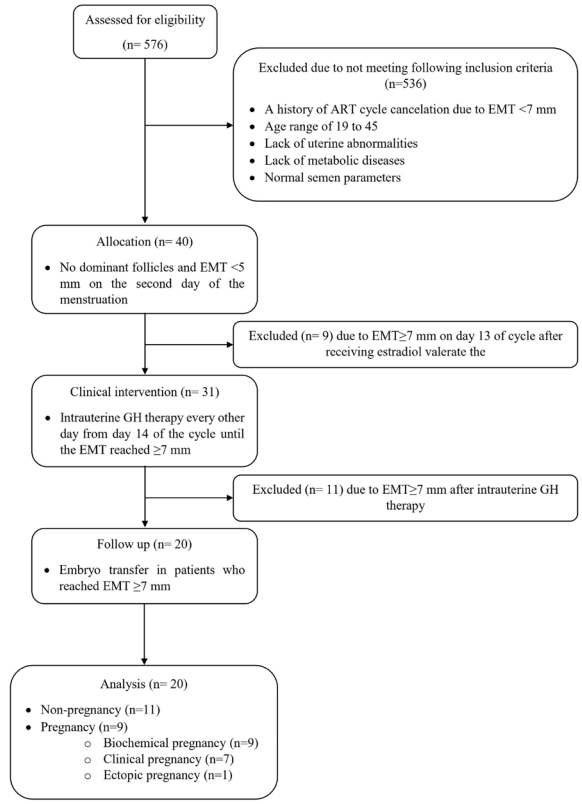

Fig.1: Consolidated standards of reporting trials (CONSORT) flow diagram. EMT; Endometrial thickness.

Inclusion criteria were as follows: i. Age range of 19 to 45 years, ii. EMT <7 mm at the end of estrogen priming day in the frozen embryo cycle in the previous cycle(s), and iii. No obvious abnormality during hysteroscopy examination within the past 6 months. Patients with a history of cancer, cardiovascular disease, uterine abnormalities (e.g. Asherman's syndrome, fibroid, polyp, and adenomyosis), any medical contraindication for GH treatment such as having diabetes, hyperlipidemia, metabolic diseases, and thyroid disorders were excluded from the study. Moreover, we excluded couples with abnormal semen analysis (possibility of male infertility).

Treatments and ultrasound assessment

After collecting some demographic data (weight, height, and age) of patients, the HRT in the FET cycle was started after confirmation of no dominant follicles in the ovaries and EMT <5 mm on the second day of the menstruation period by using ultrasound. The EMT was measured by ultrasonography (Micromaxx, Sonosite.inc, USA) in the median sagittal plane at the thickest three-line pattern part. In the HRT, the endometrium was prepared by estrogen. In this regard, on the second day of the cycle, all patients received estradiol valerate tablets (2 mg, Aburaihan CO., Tehran, Iran) with a constant dose of 6 mg per day for 7 days (days 2 to 8 of the cycle) to prevent follicular recruitment. After the one-week treatment (day 9 of the cycle), the second ultrasound evaluation was performed. If the EMT was <7 mm at the thickest part of the uterine longitudinal axis, the dose of estradiol valerate

was increased up to 8 mg/day for four more days. Then, the ultra-sonography evaluation was repeatedly done two times and the refractory thin endometrium was approved in patients (n=31) when the EMT was still less than 7 mm. These patients received intrauterine injections of GH (CinnaTropin®, CinnaGen, Tehran, Iran) every other day from day 14 of the cycle until the EMT reached ≥7 mm (maximum of five times injection). The GH solution was prepared by dilution of 1.5 ml recombinant GH (5 mg/1.5 ml, CinnaTropin®, CinnaGen, Tehran, Iran) with 0.3 ml of 0.9% saline (Iranian Parenteral and Pharmaceutical Company (IPPC), Tehran, Iran). For intrauterine GH therapy, cervical mucus was wiped out using a cotton swab (Deltalab, Barcelona, Spain) and then 0.6 ml diluted GH solution (contained 5 mg GH) was slowly injected into the endometrial cavity at the bottom of the 0.5 cm-1. 0 cm at the distance, by a soft catheter (Labotec, Gottingen, Germany) and then let the patient rest at 15-30 degrees of hip elevation position for 15 minutes. In cases whose EMT did not reach 7 mm, the FET cycle was canceled.

In the cases with EMT ≥7 mm, serum estrogen levels were measured after 48 hours using competitive chemiluminescent immunoassay and the patients received 100 mg intramuscular progesterone (50 mg/ml Amp, Aburaihan, Tehran, Iran) 3-5 days before ET depending on the stage of the embryo. After transfer of 2-3 high-quality embryos, progestin supplementation was done until two weeks. If the pregnancy was achieved it was continued till 12 weeks of pregnancy. The biochemical pregnancy was confirmed when serum beta human chorionic gonadotropin (β-hCG) levels reached >20 IU/L two weeks after the ET. The clinical pregnancy was defined when the gestational sac was observed four weeks after the ET by ultrasonography examination. Ongoing pregnancy was defined as a ≥12 weeks of gestation.

Statistical analysis

Data were statistically analyzed by SPSS (version 20, Chicago, USA). We demonstrated mean ± standard deviation (SD) of numerical data and the categorical data was shown as a number and percentage. The independent t test was used to compare the body mass index (BMI), EMT, and blood estrogen levels between the pregnant and non-pregnant groups. The EMT before and after the treatment was compared using the paired-samples t test. To compare the frequency of GH injection between pregnant and non-pregnant groups, the Chi-Square test was used. Moreover, the association between quantitative factors was evaluated by the Pearson coefficient correlation test. The statistical significance was considered as $P<0.05$.

Results

Thirty-one patients with a mean age of 35.29 ± 6.21 years and BMI of 28.4 ± 3.65 kg/m^2 were included in this study. Before and after the GH treatment, the mean amount of EMT was 5.14 ± 1.1 mm and 7.03 ± 1.23 mm, respectively, that shows a statistically significant increase in the EMT following the treatment ($P<0.001$). Despite the significant increase in the EMT following GH administration, the ET was canceled in the 11 (35.5%) patients since the EMT did not reach 7 mm. There was a significant positive correlation between the EMT on the menstrual cycle day 13 (before starting the treatment) and the maximum amount of the EMT ($r=0.577$ and $P=0.001$). However, we found no significant correlation among the EMT of pre- or post-treatment with age, BMI, and estradiol levels ($P>0.05$).

Following the ET in the 20 patients with EMT ≥ 7 mm, we observed 17 pregnancies occurrence: 9 (45%) biochemical pregnancy and 7 (35%) clinical pregnancy, and also, one (5%) ectopic pregnancy. The EMT was not statistically different on the day of ET between biochemically pregnant and non-pregnant women ($P=0.266$, Fig.2A). However, we found a significant difference in the EMT on the day of ET between clinically pregnant and non-pregnant women (7.18 ± 0.56 vs. 6.21 ± 0.72 mm, $P=0.007$, Fig.2B). The maximum EMT amount between pregnant (biochemically or clinically) women with non-pregnant ones was not significantly different (7.89 ± 0.57 vs. 7.68 ± 0.57 mm, $P=0.432$ and 8.07 ± 0.49 vs. 7.66 ± 0.55 mm; $P=0.126$, respectively). Moreover, we found no significant difference in the EMT on the menstrual cycle day 13 (before the GH treatment), BMI, age, and estrogen levels among pregnant (biochemically or clinically) with non-pregnant women ($P>0.05$).

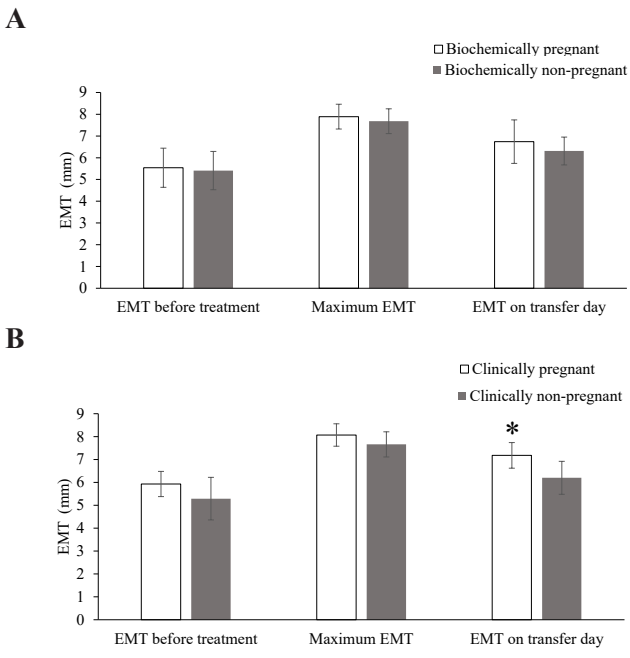

Fig.2: The endometrial thickness (EMT) of pregnant and non-pregnant women. **A.** Biochemically pregnant women (serum beta human chorionic gonadotropin >20 IU/L) vs. non-pregnant women and **B.** Clinically pregnant women (existing of gestational sac) vs. non-pregnant women. *; Significant differences ($P<0.007$) by using independent t test.

Discussion

The refractory thin endometrium is currently an unresolved clinical problem which its underlying

mechanism is not very clear (5). However, it has been suggested that the endometrial stem cell damage and subsequent impairment of endometrial tissue repair can be the possible reason for the non-response thin endometrium (11). Since thin endometrium is one of the reasons for ART cycle cancellation, in the current study, we investigated the potential of intrauterine GH administration in the improvement of EMT and preparation of these patients for the FET cycle.

Our results demonstrated that intrauterine administration of GH could significantly increase EMT. In this regard, the EMT of 64.5% of our patients who had the refractory thin endometrium reached ≥ 7 mm. Previous studies consistently reported a positive effect of subcutaneous (SQ) injection of the GH on the EMT in the infertile women with repeated implantation failure (RIF) and thin endometrium (16-18). In a meta-analysis study, it has been also documented that GH could enhance the EMT in the women with thin endometrium [odds ratio (OR)=10.62, 95% confidence interval (CI) (2.97, 38.00)] (19); however, this effect of GH was not confirmed by others (13, 14). Such controversial findings regarding the effect of the GH on the EMT could be due to the differences in the doses of GH, starting time and duration of GH treatment, EMT evaluation method as well as the patient selection. In this respect, it has been observed that starting GH treatment earlier in the menstrual cycle could improve better the EMT (13). Moreover, in contrast to this study, GH was systematically administrated by the subcutaneous (SQ) or intravenous (IV) or intraperitoneal (IP) injection, and as far as we know there is only one report on the intrauterine administration of GH in the only five patients with thin endometrium (11). In this regard, they indicated that intrauterine administration of GH at 8-12 days after menstruation every other day could significantly increase the EMT in the patients with refractory thin endometrium. The current study also confirmed the effectiveness of the intrauterine perfusion of GH in the increasing EMT of 31 patients. It seems local administration (intrauterine) of the GH could be more beneficial in comparison with the systematic treatment (SQ, IV, and IP) due to i. Higher effect on the endometrial cells because of the direct delivery of the GH to the cells, ii. Application of a lower dose in comparison with the systemic administration, and iii. Lack or negligible side effect of the GH on the body. Regarding the latter reason, it has been mentioned that the GH may induce malignancy and metabolic disorder in the individuals without GH deficiency (20). Moreover, it has been documented that the GH can negatively affect insulin resistance and glucose tolerance (21).

The mechanism(s) by which the GH can increase the EMT has not been completely described. However, it has been shown that this hormone can induce vascularization, glandularization, and stromal loosen in the endometrium via interacting with its receptor and IGFs. Moreover, the GH stimulates the expression of inflammatory cytokines such as integrin and LIF, and consequently mitosis of endothelial cells and the endometrial blood flow (22). Since the vascular endothelial growth factor expression, vascularization, and glandular epithelium growth are decreased and the uterine artery blood flow is decreased in the thin endometrium (23, 24), GH can promote EMT amount by the above mentioned mechanisms.

We found that the transfer of embryos in the patients with an EMT score ≥7 mm after GH administration, resulted in 45% biochemical pregnancies and 35% clinical pregnancies which are almost satisfying rates among patients with refractory thin endometrium. Moreover, it has been seen that the EMT score was significantly higher among patients who got clinically pregnant in compared to those who did not. These findings can confirm the positive effect of the GH on the endometrial preparation and receptivity and consequently the chance of pregnancy in addition to increasing its thickness. Several studies have also demonstrated a beneficial effect of the GH on the embryo implantation and clinical pregnancy in the infertile women , RIF affected as well as refractory thin endometrium patients (12-14, 16-18). For example, Cui et al. (16) reported that administration of the 4.5 IU GH since the day of progesterone administration of the ET day, every alternate day, could significantly increase the EMT amount and subsequent implantation rate and clinical pregnancy rate in patients with thin endometrium. However, some studies observed a lack of beneficial effects of the GH on the pregnancy rate (10, 25). Previous studies have revealed positive associations between the EMT with implantation and pregnancy rates (26, 27). It has been also found that women with thicker endometrium on the day of hCG injection had a higher pregnancy rate than those who had thinner ones (28, 29). Therefore, it can be postulated that one of the mechanisms of the GH that increases the chance of pregnancy may be promoted the EMT amount. Moreover, the GH induces production of different factors by the endometrium such as LIF, vascular endothelial growth factor (VEGF), IGFs, matrix metalloproteinase-9 (MMP-9), and tissue inhibitors of matrix metalloproteinase-1 (TIMP-1) which can positively affect endometrial receptivity and subsequent pregnancy outcome (16, 30); nevertheless, we did not evaluate the molecular mechanisms underlying the positive effect of the GH on the implantation and pregnancy and further studies are required to shed more light on this issue. Moreover, some confounding factors might be able to affect our results, particularly the implantation and pregnancy rates, such as genetic abnormalities of the embryos, the difference in the stage of transferred embryos (cleave or blastocyst) also the relatively small sample size.

Conclusion

This study showed that intrauterine administration of the GH every other day from day 14 of the menstrual cycle could be an appropriate therapeutic strategy for the patients with refractory thin endometrium. This treatment could significantly increase the EMT as well as implantation and pregnancy rates in the patients with refractory thin endometrium. Intrauterine perfusion of

the GH in comparison with the systemic administration of GH can have negligible side-effects, while we did not observe any adverse effects in our patients.

Acknowledgements

We appreciate the patients that contributed to this research project. We thank the staff of Tabriz Al-Zahra Hospital (Tabriz, Iran) and Milad Infertility Clinic (Tabriz, Iran) for providing the patients. This study was financially supported by the Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. The authors declare that they have no competing interests.

Authors' Contributions

A.Gh., S.H.A.; Involved in the conception and design of the study. S.H.A, L.F., K.H., M.B.-B.; Participated in the acquisition, planning of the analysis, and data interpretation. S.H.A., A.F., R.D., M.N.; Conducted statistical analysis, critical revisions, and drafted the manuscript. R.D., A.F., A.G., M.N.; Revised the manuscript critically. N.N., P.H.; Provided samples, follow upped patients, and gave clinical advises. All authors read and approved the final version of the manuscript.

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