The Potential Role of Growth Hormone on the Endometrium in Assisted Reproductive Technology

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INTRODUCTION

Growth hormone (GH), also called as somatotropin, is a protein of 191 amino acids with a three-dimensional structure that interacts with its receptor (1). The synthesis and secretion of GH is dynamically regulated by growth-hormone releasing hormone and somatostatin, which are both produced by the hypothalamus (2). In recent decades, GH has been considered to regulate many physiological functions including growth, metabolism, and reproduction (3, 4). Its therapeutic use in reproduction has been growing but remains controversial for its efficacy (4, 5). It has been used in assisted reproductive technologies (ART) in humans with an emphasis on potentially improved oocyte quality and pregnancy rates (6, 7). Little attention has been paid to the endometrium, despite the documented presence of GH receptors in this tissue (8). Our review of the literature indicates that study and application of GH for modulating the endometrium has been overlooked in understanding normal endometrial function in ART and reproduction generally.

The endometrium undergoes changes via integrated interactions between the different uterine cell types and various growth factors and hormones (9). Several methods can be used to evaluate receptivity of the endometrium, including ultrasound, histology and molecular biomarkers (9, 10). Recent evidence has indicated that GH supplements may modulate endometrial receptivity and improve pregnancy outcomes in ART (10–13). Among women undergoing in vitro fertilization (IVF) treated with GH, changes of endometrial thickness (EMT) and endometrial perfusion have been described by ultrasound evaluation (11–14). The alteration of several biological markers of endometrial receptivity has also been detected with adjuvant administration of GH in animal models and cell-line studies (15–18). While short-term use of GH would not be expected to have...
proliferation with the use of GH replacement therapy compared to control subjects. The higher the EMT, the better the endometrial receptivity, as evidenced by the increased implantation rate (IR) and clinical pregnancy rate (CPR) (36, 37). However, some studies have reported a lack of significant increases in EMT between control and GH treated groups (38, 39). Nonetheless, the EMT appears to be a site of expression of both GH and GHR (40, 41).


growth hormone receptors (GHRs) are found in various tissues throughout the body, including the liver, kidneys, brain, and reproductive tissues (42, 43). The localization of GHR mRNA in human endometrial glands, vessels, and placenta from bovine species (44) indicates potential functions of GH in endometrial physiology. In human myometrial and leiomyoma cells, GHR mRNA has been detected in the cytoplasm of proliferating uterine epithelial cells during the mid and late luteal phases and in decidual tissue cells throughout pregnancy (45). Additionally, GHR mRNA was also detected in the uterine epithelium, glands, vessels, and placenta from bovine species (46) with biomolecular expressions including GHR and insulin-like growth factor-I (IGF-I) demonstrated in the uterus of dairy cows (47). In the pig, mRNA analyses demonstrated a high level of expression for endometrial somatotropin receptors (STR) (48).

In women, GHR mRNA has been detected in the nuclei and cytoplasm of both human myometrial and leiomyoma cells (49). All these findings indicate a potential role for GH on the endometrium.

CLINICAL EVIDENCE OF GH ON ENDOMETRIAL RECEPTIVITY

Endometrial thickness (EMT) and uterine perfusion are important clinical indicators of endometrial receptivity in ultrasound studies (10). It has been suggested that ultrasonographic parameters including EMT and uterine perfusion can predict implantation potential in infertile patients undergoing embryo transfer (27). Although this is controversial (28), recent studies suggest a positive relationship between EMT and pregnancy outcome (29–32). Patients with positive pregnancy outcomes following IVF treatment had thicker endometrium readings on the day of hCG administration compared with those where a pregnancy did not result (29). The thicker the endometrium evaluated on the day of human chorionic gonadotropin administration, the higher the pregnancy rates reported following IVF (30, 31). EMT can also be measured on the day of oocyte retrieval and has been alleged to predict the endometrial receptivity during fresh IVF cycles (32). In general, EMT should exceed 8 mm as the threshold of endometrial receptivity in fresh embryo transfer cycles (33), although other studies suggest 10 mm of EMT may be better for a more stable implantation of embryos and minimization of pregnancy losses (34). Hence, increasing endometrial thickness and uterine perfusion might be beneficial goals for improving endometrial receptivity.

Two reports of women with panhypopituitarism causing either primary or secondary infertility who were treated with GH and gonadotropins are illustrative of the potential role for GH in fertility promotion (35, 36). After GH treatment, an improvement in their response to gonadotrophin stimulation was demonstrated with an acceptable endometrial growth and successful pregnancies ensued (35, 36). Standard infertile patients also show different endometrial changes and different pregnancy outcomes after adjuvant GH treatment (Table 1). For infertile women classified as poor responders, GH treatment has been promoted for improving the chances of pregnancy and live birth outcomes. Although no significant increases in implantation or clinical pregnancy rates are consistently demonstrated, there appears to be an increase of retrieved oocyte numbers and EMT (39, 42). A large scale retrospective clinical trial of infertile women classified as normal responders also had an increase in endometrial thickness in the older group (age ≥ 35 years) utilizing GH treatment and an improvement of implantation rate (IR) and clinical pregnancy rate (CPR) was claimed in the GH treatment group across all ages (45). An effect on weight-related infertility has also been seen with a significant improvement of EMT, IR, and CPR in a group of infertile women who were overweight and obese (BMI ≥ 24 kg/m²) (43, 45).

In patients with repeated implantation failure (RIF), a thicker endometrium on the day of hCG and an increase of IR, CPR, and live birth rate (LBR) was found in a GH-treated group, consistent with the previous results reported by others (11, 38). In another recent randomized clinical trial (RCT), the patients with RIF in an oocyte donation program also showed an increase of EMT, CPR, and LBR with GH supplements. Since the oocytes were donated by fertile women, further effects of GH on endometrium could be claimed (12).

In infertile women with poor endometrial development (EMT < 7 mm), additional GH treatment is alleged to improve the EMT through uterine perfusion as well as the classical endometrial trilaminar pattern, although there was no significant alteration of pregnancy outcomes in this study (40). A meta-analysis including
| Years | Study design            | Objectives                                      | Samples | Programme | Intervention                                                                 | Outcomes | Effects | References |
|-------|-------------------------|-------------------------------------------------|---------|-----------|-------------------------------------------------------------------------------|----------|---------|------------|
| 2007  | Retrospective study     | Infertile women with GH deficiency              | 20      | IVF/ICSI  | 12 IU GH every third day, starting on the day of gonadotropin stimulation, till the administration of hCG | EMT      | (-)     | (37)       |
| 2011  | Prospective study       | Infertile women with RIF                        | 55      | IVF-ET    | 4 IU GH daily until the day of hCG administration                              | EMT      | ↑       | (38)       |
| 2012  | Randomized prospective study | Infertile women with poor responder          | 40      | IVF-ET    | 4 IU GH from day 21 of previous cycle until the day of hCG injection           | EMT      | (-)     | (39)       |
| 2013  | Prospective study       | Infertile women with endometrial dysplasia     | 32      | FET       | 4 IU GH daily until the day of hCG administration                              | EMT      | ↑       | (40)       |
| 2015  | Retrospective study     | Infertile women with thin endometrium (EMT <7 mm) | 35      | FET       | 4 IU GH daily, starting from the 3–6th day of menstrual cycle, until the day of progesterone administration | EMT      | ↑       | (41)       |
| 2016  | Parallel randomized, open-label study | Infertile women with poor responder          | 68      | IVF/ICSI  | 2.5 mg(7.5IU) GH daily, starting on day 6 of hMG stimulation until the day of hCG triggering | EMT      | ↑       | (42)       |
| 2016  | Prospective study       | Infertile women with overweight/obesity        | 33      | IVF-ET    | 4.5 IU GH daily, starting from the day of hMG administration until the day of hCG | EMT      | ↑       | (43)       |
| 2016  | Prospective study       | Infertile women with thin endometrium (EMT <8 mm) | 34      | IVF-ET    | 4.5 IU GH every alternate day, starting from the day of hMG administration till the day of hCG | EMT      | ↑       | (43)       |
| 2016  | Prospective study       | Infertile women                                | 5       | FET       | 4–5 times of GH intratruterine perfusion (6IU/0.5 ml 0.9% saline) on the ninth to twelfth day of hormone replacement cycle | EMT      | ↑       | (44)       |
| 2016  | Prospective study       | Infertile women                                | 77      | FET       | 4 IU of rhGH daily from day 3 of the menstrual cycle until the day of progesterone injection | Serum E2 | ↑       | (13)       |
|       |                         |                                                 | 76      | FET       | 4 IU of rhGH daily from day 8 of HRT until the day of progesterone injection    | IGF-I    | ↑       | (13)       |
|       |                         |                                                 |         |           |                                                                                | VEGF     | ↑       |            |
|       |                         |                                                 |         |           |                                                                                | EMT      | ↑       |            |
|       |                         |                                                 |         |           |                                                                                | Perfusion of the uterine endometrial arcuate artery | IF/CPR/LBR | ↑ | (13) |
| 2016  | Retrospective clinical trial | Infertile women with a normal ovarian response to controlled ovarian hyperstimulation (COH) | 556     | IVF-ET    | 4.5 IU of GH daily, starting from the initial day of gonadotropin treatment and lasting for 5 days | EMT in older group (≥35 years old) | ↑ | (45)       |
| 2018  | Randomized controlled trial | Infertile women with RIF                      | 35      | IVF/ICSI  | NM                                             | EMT      | ↑       | (12)       |
| 2018  | Prospective study       | Infertile women with RIF                       | 22      | IVF-ET    | 4 IU GH daily until the day of hCG administration                              | EMT      | ↑       | (11)       |
| 2018  | Randomized controlled trial | Infertile women with thin endometrium (EMT <8 mm) | 63      | NM        | 4 IU GH daily for 10 days                                                      | EMT      | ↑       | (46)       |

(Continued)
| Years | Study design | Objectives | Samples | Programme | Intervention | Outcomes | Effects | References |
|-------|--------------|------------|---------|-----------|--------------|----------|---------|------------|
| 2018  | Prospective study | Infertile women with thin endometrium (EMT < 7 mm) | 40 IVF/ICSI | 5 IU GH daily, starting at the first 4 days till the 18th day of the cycle | EMTIR/CPR | ↑↑ (14) | | |
| 2019  | Retrospective study | Infertile women with thin endometrium (EMT < 8 mm) | 184 FET | 4.5 IU GH every alternate day, starting from the day of progesterone administration till the day of ET | EMTIR/CPR | (–) | ↑ (47) | |

↑ = increase; (–) = No significant change. Ref, Reference; NM, Not mentioned. RIF, Repeated implantation failure; IVF, In vitro fertilization; ICSI, Intracytoplasmic sperm injection; ET, embryo transfer; rhGH, recombinant human GH; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; EMT, endometrial thickness; FR, Fertilization rate; IR, Implantation rate; CPR, Clinical pregnancy rate; LBR, Live birth rate.

four RCTs demonstrated an enhancement effect of GH on EMT in infertile women with poor endometrial development (EMT < 6 mm or non-trilaminar type endometrium) [OR = 10.62, 95% CI (2.97, 38.00)] (48). Other studies also demonstrated that EMT with GH treatment was significantly increased on day 3 (the 18th day of cycle) with subsequent increased IR and CPR (14) and an increased EMT was also detected in five patients with thin endometrium (EMT < 8 mm) after intrauterine perfusion of GH or parenteral injection of GH (41, 44, 46). These observations are not confirmed by others however (13, 37, 39, 47). Different patient selection, doses, starting time as well as the different measurements and interpretations may be the reasons resulting in the varied outcomes of GH treatment (Table 1). This is illustrated in a recent prospective study where the same dose of recombinant human GH (rhGH) was applied to infertile women but with different starting times resulting in quite different clinical outcomes (13). Those women who started with rhGH treatment earlier in the cycle had a significant increase of EMT, perfusion of the uterine artery index, IR, CPR, and LBR as well as estradiol, IGF-I and vascular endothelial growth factor (VEGF) on the day of embryo transfer (13).

### POTENTIAL MECHANISMS OF GH ON ENDOMETRIAL RECEPTIVITY

The mechanisms of GH effects on the endometrium to improve the EMT and uterine perfusion and IVF outcomes are still unclear. Currently, several molecules, including IGF, leukemia inhibitory factors (LIF), integrins (Itg), homeobox-containing transcription factors-HOX family genes, etc. contribute to the molecular basis of regulating endometrial receptivity while some molecules closely related to the implantation process have been demonstrated to be involved in the potential mechanisms of GH effects on endometrium (9, 49) (Table 2).

### Animal Models

Increased concentrations of cytosolic estrogen receptor but not the concentration of progesterone receptor was found in the rabbit uterus after GH treatment, indicating a potential estrogen mediated function (50). Consistent with this, an increase in the concentration of estrogen receptor in the guinea-pig uterus after treating with GH has also been demonstrated (51). Research in the ovine uterus indicates that GH could regulate endometrial gland proliferation via interferon tau (52) and could alter the endometrial gene expression related to maintenance of pregnancy. GH may increase the expression of oxytocin receptor, progesterone receptor mRNA, and the mRNA of estrogen receptor α in non-lactating cows (53) with an increased pregnancy rate in lactating cows after injection of GH at the initiation of timed artificial insemination following a synchronized ovulation protocol (54). Knockout of the GHR in mice leads to a negative impact on reproduction with fewer uterine implantation sites during early pregnancy (55).
GH-mediated increase in uterine IGF-I levels may be the mechanism underlying the increase in endometrial thickness (56). Exogenous porcine GH elevates the expression of endometrial STR, IGF-I mRNA, IGF-II mRNA, and IGFBP2 mRNA in the uterus, supporting the role of the so-called GH/IGF axis in the uterus (25, 56). Both IGF-I and IGF-II can be detected in endometrial stroma, but have different roles (2, 57). IGF-II is more closely related to endometrial differentiation (57), while IGF-I is a potential mediator of the mitogenic effects of estrogen on the uterus, so-called oestromedin (56). Other studies in the mouse also indicate an alteration of other molecular biomarkers of endometrial receptivity after treating GH (16, 17). GH-treated mice show a significant increase of leukemia inhibitory factors (LIF), integrin alpha v beta 3 (Itgαβ3) and matrix metalloproteinase (MMP)-9 in the endometrium, molecules which have been implicated in implantation (16, 17). Exogenous GH supplementation in Sprague Dawley (SD) rats may also increase osteopontin (OPN) and Itgαβ3 expression with an associated improvement in endometrial receptivity (18).

**In vitro Studies**

Addition of hGH to the cultured endometrial and decidual cells increases the proliferation of endometrial and decidual cells, when these cells were harvested and separated from the human endometrial pieces and decidual tissue, respectively (15). When transfected to the human endometrial cell line RL95-2, there is an enhancement of cell proliferation, survival and invasion (58) and increased cell proliferation and expression of VEGF, Itgα3, and IGF-I (14). Janus kinase (JAK) 2 inhibitor AG490 addition with GH suppresses VEGF, Itgα3, and IGF-I expression in RL95-2 cells, indicating that GH might regulate the expression of these factors via the JAK2 pathway. However, no change in expression of LIF, Itgαv, Hox family gene (HOXA10) and SPP1 could be found in RL95-2 cells after treatment with GH (14). Therefore, the effects of GH on endometrial receptivity-related molecules in vitro remains to be elucidated.

**THE POTENTIAL RISKS OF GH TREATMENT IN ART**

GH may play a pathological role in body systems in view of the fact that it may have a potential of being an oncogene (59). Transplantation of GH transfected RL95-2 cells suspension to BALBc nu/nu mice led to a larger tumor size and a more aggressive progression of endometrial carcinoma (58). When RL95-2 cells cultured with the GH receptor antagonist (pegvisomant) were inoculated into immunodeficient NIH-III mice and continuously treated the mice with antagonist for 16 weeks, a delayed tumor growth rate and decreased IGF serum level could also be found (60). A systematic review concluded that long-term GH treatment actually had a positive effect on reducing cardiovascular disease, stroke, and fractures, without a simultaneous increase in malignancy risk (61). While there are few indications of problems, the long-term safety of GH for the cancer risk, metabolic disorder and other unforeseen adverse events should be under constant surveillance (62).

Although metabolic sequelae improve with GH in GH deficient patients (63), some advocate that addition of GH in patients with diabetes mellitus should be cautioned due to its potential negative effects on insulin resistance and glucose tolerance (19, 64). GH can also result in significant metabolic changes by elevating cholesterol and disturbing the renin-angiotensin mechanism (65). Therefore, in consideration of the potential risks, personalized comprehensive assessment, and professional guidance in usage and dosage is required before deciding to use GH in ART.

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**TABLE 2 | The effects of GH on endometrial receptivity via molecular biomarkers.**

| Years   | Species  | Samples | Intervention                          | Outcomes                                      | Effects | References |
|---------|----------|---------|---------------------------------------|-----------------------------------------------|---------|------------|
| 2005    | Porcine  | 33      | 6 mg of porcine somatotropin          | Endometrial STR, IGF-I, IGF-II, IGFBP2        | ↑       | (25)       |
| 2006    | Mouse    | 25      | 0.15 IU GH/100 g estrous cycle        | LIF, Itgαβ3, MMP-9                           | ↑       | (17)       |
| 2007    | Mouse    | 25      | 1.5 IU GH/g proestrus stage           | VEGF, LIF, MMP-9, TIMP-1                      | ↑       | (16)       |
| 2012    | SD rats  | 25      | 0.15 IU GH/100 g proestrus stage      | Itgαβ3, OPN                                   | ↑       | (18)       |

**In vitro cell studies**

| Years   | Cell types  | Intervention                           | Outcomes                                      | Effects | References |
|---------|--------------|----------------------------------------|-----------------------------------------------|---------|------------|
| 2019    | RL95-2 cells | Cultured for 48 h in the presence of GH (10 nM) | Cell proliferation; Activates cell cycle; VEGF, Itgαβ3 and IGF-I | ↑       | (13)       |
| 2010    | Endometrial stromal cells | 4 ng/ml GH; 5 ng/ml IGF-I | Cell proliferation | ↑       | (15)       |
|         | Decidual cells | 5 ng/ml IGF-I | Cell proliferation | ↑       | (15)       |

↑ = increase; ↓ = no significant change.

STR, Somatotropin receptor; IGF(BP), Insulin-like growth factor (binding protein); LIF, Leukemia inhibitory factors; Itg, Integrin; MMP, Matrix metalloproteinase; VEGF, Vascular endothelial growth factor; TIMP, Tissue inhibitor of metalloproteinase; OPN, Osteopontin; SD rats, Sprague Dawley rats; EGF, Epidermal growth factor; HOXA, HOX family; SPP1, Secreted phosphoprotein.
CONCLUSION

Clinical evidence for efficacy of GH in improving reproductive function remains controversial. Generally, the majority of studies show positive effects of GH on endometrial receptivity, but there is no general agreement about the dosage and usage of GH in ART and there are few useful RCTs (Table 1). Hence, more evidence is still required to determine the purported value of GH treatment in ART and provide more specific guidance in the clinical setting.

Even if clinical evidence currently encourages the view that GH might be helpful for endometrial receptivity, the mechanisms are still not known. The studies of molecular biomarkers included in this review are few (Table 2), but also may provide some foundations for future exploration of the mechanisms of GH in the endometrium. As GH is administered systemically during ART, it is difficult to separate the effect on GHR in the ovary from that in the endometrium and if GH alters receptor action in the ovary, it could potentially have an effect on the endometrium receptors too.

The risk of GH used in ART should be noticed but not overstated. There is a relationship between autocrine GH and endometrial cancer, but further studies of the mechanisms under this phenomenon and the confirmation of increased diseases risk of exogenous GH are still needed. In general, further explorations of the mechanisms underlying the effects of GH on endometrium should spread some light on our basic knowledge and clinical actions.

AUTHOR CONTRIBUTIONS

F-TL and RL were responsible for writing the first draft. RL, ZW, JY, and RN performed the critical revisions. All authors listed did contributed to the writing and review of the manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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