

Growth hormone in the management of female infertility

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Abstract

Ovulation is a complex process which is controlled by multiple hormonal systems. While the role of gonadotrophins in the regulation of ovulation is well understood and characterized, growth hormone has been studied less vigorously as far as its effect on female reproduction is concerned. This review discusses the physiologic basis of growth hormone in the regulation of induction of ovulation in women. It also reviews clinical studies done using growth hormone as co-therapy in women with infertility

INTRODUCTION

A large number of intraovarian regulators modulate the ovarian response to gonadotropin stimulation. The principal regulatory systems in the human involve the growth hormone- IGF system (1), the epidermal growth factor (EGF) system (2), and the TGF- β and α system (3). In addition, inhibins and activins also exhibit local actions in the ovary (4).

Growth hormone (GH) is a pleiotropic, multifunctional hormone with effects ranging far beyond those on linear growth. GH is known to be involved in the regulation of male and female infertility. This review discusses the biochemical background and clinical studies of GH therapy in female infertility.

PHYSIOLOGY

Growth hormone, produced by the pituitary and locally by the ovary, binds to GH receptors on granulosa, thecal, and luteal cells and promotes steroidogenesis and gametogenesis (5). It acts at multiple levels in the ovulation cascade.

Growth hormone increases the sensitivity of ovaries to gonadotropin stimulation, and enhances follicular development (1). Similarly, addition of IGF-I to gonadotropins stimulates follicular development, estrogen production and oocyte maturation. Similar results are seen with GHRH. The actions of GH and IGF-I are partially independent of each other.

Growth hormone may induce steroidogenesis directly or

indirectly by potentiating gonadotropin action and may enhance aromatase and 3- β -hydrogenase activity, thus increasing the conversion of androgen into estrogens in females (5). This effect on the ovarian steroidogenic enzymes occurs through a direct and/or IGF-I-mediated mechanism (6). Although IGFs and their receptors are known to be present in developing human follicles, uncertainty remains regarding the individual role of the different IGFs their receptors, and binding proteins. Their effect is modulated by their degree of binding to IGF binding proteins. GH is the primary regulator of serum IGF level (1). However, GH does not affect IGF-I and IGF-II expression in granulosa cells in vitro.

Growth hormone increases the sensitivity to IGF-II acting through the IGF-I receptor, because IGF-II and IGF binding protein are abundantly present in human granulosa cells, whereas IGF-I is scarce (7). Therefore, GH acts indirectly by up regulating LH receptor and LH-induced luteinization, and directly through induction of production in the absence of gonadotropins (8).

Growth hormone affects the maturation of the follicle and gamete as well. IGF-I and IGF-II play a major role in folliculogenesis until the antrum formation stage. GH helps in the recruitment and early development of follicle without acting through FSH and IGF-I as well. (9)

GH may have a direct inhibitory action on follicle apoptosis in conjunction with gonadotropins, and may enhance follicular survival and cell proliferation by strengthening LH action. GH may help in follicle selection, as GH binding sites in granulosa cells are lost in atretic follicles (10). The

development of the dominant follicle is also known to be slow in GH receptor-deficient cattle (11).

Both GH and IGF-I play a role in the recruitment of the dominant follicle from its cohort, leading to monofollicular growth in women.(12) When GH is deficient, low serum levels of IGF-I prevent the dominant follicle from increasing IGF-I levels. This prevents of any difference in the sensitivity to FSH of the different cohort follicle, and allows equal multifollicular growth. With GH treatment, a differential in sensitivity to FSH between this follicle and its cohort are restored by higher IGF-I levels, leading to monofollicular growth.

As the follicle matures, nuclear and cytoplasmic events occur within the oocyte to allow oocyte fertilization. A direct correlation between follicular GH concentrations and human oocyte maturity has been reported,(13) and oocytes harvested from follicles with normal antral fluid GH concentration are more fertile than those from follicles with low GH concentrations. Growth hormone enhances oocyte quality by accelerating and coordinating cytoplasmic and nuclear maturation, as seen in bovine oocytes (14, 15)

Good patient selection has been shown to improve results of GH co-therapy for female infertility. Eugonadotrophic normoprolactinemic patients with long-standing infertility and documented growth hormone deficiency (23) or panhypopituitarism (24) respond well to this treatment. Growth hormone may also facilitate ovulation by increasing tissue plasminogen in adults with GHD (16).

OVARIAN STIMULATION

Ovarian stimulation, as an assisted reproductive technique (ART), is an important treatment technique for female infertility.

Ovarian stimulation aims to develop and mature multiple oocytes to improve the chances of conception with intrauterine or in vitro fertilization.

While ovarian stimulation is traditionally done with gonadotropins, clomiphene or letrozole, many adjuvant therapies have been used to improve the yield and results of the procedure.

Growth hormone is one such adjuvant therapy, which has been used in patients, with mixed results.

CLINICAL STUDIES

The use of GH for patients with GHD has been proven to be

successful in increasing ovarian sensitivity to endogenous gonadotropins. Cotreatment of GH combined with hMG and hCG for ovulation induction has been suggested as a way to improve follicle growth, and probably pregnancy rate, in patients with hypogonadotropic hypogonadism (17).

The addition of GH to gonadotropin therapy in hypogonadotropic patients reduced the gonadotropin dose required to achieve ovulation (18, 19). The duration of hMG treatment required for ovulation induction was reduced, while the success rate rose significantly. In a recent meta-analysis, a small but significant improvement in pregnancy rates appeared to be associated with GH supplementation (18).

Previous studies showed that women with isolated GHD, hypogonadotropic hypogonadism, or panhypopituitarism had smaller uterine dimensions compared with those found in healthy controls. Growth hormone might have an independent or an estrogen-mediated effect on uterine size (20) which may contribute to its therapeutic effect.

GH supplementation has been shown to improve pregnancy rates in poor responders.(21) In women with no history of poor response to IVF stimulation protocols, the use of growth hormone was not linked to better live birth rate or pregnancy rate (18).

In those with history of poor response in the past to IVF stimulation, odds ratio for live birth (OR 4.37 CI 95% 1.06 to 18.01) was in favour of GH. Similar results were noted for pregnancy rate (OR 3.2, 95% CI 1.05 to 9.72). The incidence of multiple pregnancy was higher while that of reported miscarriage, minor and major physical symptoms, as well as ecopic pregnancy was lower. (18) In another study in women aged > 40 years, undergoing IVF, more pregnancies (26% vs. 6%) and higher delivery rates (22% vs. 4%) were noted in GH-treated subjects (22) than those not given the hormone.

Good patient selection has been shown to improve results of GH co-therapy for female infertility. Eugonadotrophic normoprolactinemic patients with long-standing infertility and documented growth hormone deficiency (23) or panhypopituitarism respond well to this treatment (24). Workers have, however, used GH in non-GH deficient patients as well. (25)

DOSAGE OF GROWTH HORMONE

Doses used have ranged from 0.9 to 1.8 mg/week, and growth is discontinued once pregnancy is achieved (23) in

recent case reports. Previous studies have used much higher doses. Growth hormone has been given daily (25, 26) or on alternate days (6; 27-31), in doses ranging from 12 IU (27-29) to 18 IU (30) to 24 IU (6, 31). One of the authors has prescribed a daily weight-based dose (0.1 IU/kg/day) (25) while another has compared 4IU daily with 12IU daily. (26)

CONCLUSION

Growth hormone co-therapy has a definite role to play in ovarian stimulation, and is effective in appropriately selected cases. Further research needs to be done to identify effective and efficient growth hormone treatment regimes, as well as improve patient selection. Effort should also be made to study, in detail, the effect of GH therapy on oocyte fertilization and endometrial receptivity.

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