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Review Article / Derleme

The use of growth hormone in *in vitro* fertilization

İn vitro fertilizasyonda growth hormon kullanımı

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Abstract

Growth hormone (GH) is a 191 amino acid, single chain polypeptide hormone, produced, stored and secreted by somatotroph cells in the anterior pituitary gland. Normal fertility does not seem to require a normal GH axis. Aim of this review is to evaluate GH medication for controlled ovarian hyperstimulation (COH) protocols in IVF. All of the randomized controlled trials (RCTs) in the literature about this topic are small numbered. There is currently enough evidence to be moderately confident that adjuvant GH treatment undergoing IVF/ICSI treatment results in higher delivery rates but caution is required. Fertility specialists must design larger RCTs that may detect the effect of GH in IVF/ICSI treatment clearly.

Keywords: Growth hormone, controlled ovarian hyperstimulation

Özet

Büyüme hormonu (BH), ön hipofiz bezindeki somatotrof hücrelerce üretilen, depolanan ve salgılanan, 191 amino asitlik tek zincirli polipeptit bir hormondur. Normal fertilite için normal bir BH aksı şart değildir. Bu derlemede kontrollü ovaryan hiperstimülasyon sikluslarında BH kullanımının yeri irdelenmiştir. Literatürde bu konu işe ilgili randomize kontrollü çalışmalar küçük örneklem sayısı içerirler. Ancak, IVF sikluslarında adjuvan BH kullanımının daha yüksek doğum oranları ile ilişkili olduğunu söylemek için yeterli kanıt mevcuttur. İnfertilite uzmanları BH'nın IVF tedavisi üzerindeki etkisini daha net açıklayabilmek amacıyla daha büyük çapta randomize kontrollü çalışmalar dizayn etmelilerdir.

Anahtar sözcükler: Büyüme hormonu, kontrollü ovaryan hiperstimülasyon

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Introduction

Growth hormone (GH) is a 191 amino acid, single chain polypeptide hormone, produced, stored and secreted by somatotroph cells in the anterior pituitary gland. The secretion of GH is controlled by growth hormone releasing hormone (GHRH) and somatostatin. Pituitary GH release stimulates the secretion of insulin like growth factor 1 (IGF-1) by liver. GH also stimulates production of IGF-1 within the target organs. The ovary is a target organ for IGF-1. IGFs are important regulators of ovarian steroidogenesis in humans [1]. There is strong evidence suggesting that GH also affects the ovarian function folliculogenesis and oocyte maturation and also A significant amount of literature supports a role for GH in the production of viable gametes, since GH modulates gonadotropin-independent early folliculogenesis and gonadotropin-dependent late folliculogenesis by increasing cell proliferation and inhibiting atresia. GH also increases oocyte fertility by enhancing nuclear and cytoplasmic maturation and facilitating ovulation [2-4].

Normal fertility does not seem to require a normal GH axis. Many GH-deficient women require assisted reproductive technologies to conceive, principally for the induction of ovulation but it is known that a proportion of GH-deficient and GH-resistant women have normal menstrual cycles and conceive normally [5].

Animal studies have suggested that growth hormone treatment may increase the intra-ovarian production of the IGF-1 [6]. The addition of IGF-1 to gonadotropins in granulosa cell cultures increased gonadotropin action on the ovary by augmentation of aromatase activity, 17-beta estradiol and progesterone production and luteinizing hormone receptor formation [7].

Previous reports showed that he ability of human oocytes to form morphologically normal and implantation-competent embryos are related to the concentration of different hormones in follicular fluid. Among these hormones GH had the most consistent relation [8]. GH can be synthetically produced using recombinant DNA technology and is licensed to be used in the human population. GH as an adjuvant for controlled ovarian stimulation has been postulated to improve pregnancy outcome. Clinical trials have shown that GH may be useful for some subgroup of infertile women. It must be kept in mind that medical treatment with GH may result side effects such as joint swelling, joint pain, carpal tunnel syndrome and sleep loss. Aim of this review is to evaluate GH medication for controlled ovarian hyperstimulation (COH) protocols in IVF.

Routine use of growth hormone as an adjuvant in IVF protocols

There is paucity of data that supports routine use of GH as an adjuvant in IVF protocols. There is one randomized controlled trial (RCT) performed in normo-ovulatory women who were 38 years of age or less undergoing ovulation induction for IVF. Gonadotropin-releasing hormone agonist (GnRHa) was initiated in the midluteal phase for down regulation of hypophyseal-ovarian axis. Human menopausal gonadotropin (hMG) was used for ovulation induction and GH (12 IU/d) or placebo was administered on days 1, 3, 5, and 7 of hMG treatment. Stimulation parameters were similar in both groups. Clinical pregnancy rate (PR) per embryo transfer and implantation rate were not different between two groups [9].

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GH as an adjuvant in poor responders in IVF protocols

There are numerous strategies that have been suggested to improve the outcome in the poor responder women despite their limited successes. It is still controversial whether GH as an adjuvant in poor responders is associated with a better COH parameters and pregnancy outcome in IVF.

Owen et al. [10] explored the effect of co-treatment with growth hormone (GH) for ovarian stimulation after pituitary suppression by an RCT in polycystic ovary syndrome with a history of insufficient ovarian response. Co-treatment with GH was associated with a significant reduction in gonadotropins requirement [10].

Berg et al. [11] performed an RCT to investigate the effect of GH in COH protocols in poor responders. The number of oocytes retrieved did not differ significantly between the groups. The fertilization rate increased in patients who had received GH but this result did not support GH as a clinically useful adjuvant treatment [11].

GH or a placebo were administered in a prospective randomized double-blind manner in poor responders by Dor et al. [12]. Follicular recruitment, estradiol secretion by mature follicles and the number of oocytes retrieved in poor responders were not improved by GH supplementation [12].

Tesarik et al. [13] randomized women of >40 years old undergoing IVF/ICSI between GH and placebo. In patients of the GH treatment group, a similar number of oocytes, embryos and pregnancies was achieved as compared with the placebo group. However, the patients treated with GH suffered fewer pregnancy losses, resulting in higher delivery and live birth rates [13].

Kucuk et al [14], evaluated the efficacy of growth hormone co-stimulation to long luteal GnRHa regimen in poor responders in a RCT. This study stated that poor responder women undergoing repeated assisted reproduction treatment and co-stimulated with GH achieve more oocytes, higher fertilization rate if growth hormone started in the luteal phase of previous cycle, as compared with women of the same status treated with GnRHa long protocol [14].

GH use as an adjuvant treatment in poor responders was evaluated in a sequential crossover study and this study concluded GH co-treatment significantly improved the clinical pregnancy rate per fresh transfer well as per frozen-thawed embryo derived from GH cycles. The effect was significant across all age groups, especially in younger patients [15].

Two systematic reviews have critically analyzed GH use as an adjuvant in IVF protocols. In 2009, Kyrou et al. [16] performed a review of the literature to evaluate best treatment modality in poor responders. Many different strategies were analyzed. Based on limited evidence, the only interventions that appear to increase the probability of pregnancy were the addition of GH to ovarian stimulation [16].

The most recent meta-analysis is an update by Duffy et al. [17] of a previously published Cochrane review. A total of 440 infertile couple was included from 10 studies. Their results showed no difference in outcome measures and adverse events for the use of adjuvant GH in IVF protocols in unselected patients. However, meta-analysis

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demonstrated a statistically significant difference in both live birth rates and pregnancy rates favoring the use of adjuvant growth hormone in in-vitro fertilization protocols in women who are considered poor responders without increasing adverse events. It must be kept in mind that the confidence intervals around the odds ratios derived from the latest meta-analysis indicate that there is still large amount of uncertainty [17].

Conclusion

All of the RCTs in the literature about this topic are conducted with a small number of patients. The number of patients participated in each study range from 14 to 61. There is only one study included the patients over age 40. Significant heterogeneity between studies had been detected and this was due to the different definitions of poor responders. There is also debate about the dosage of GH. The dosage of GH ranged from 8 IU to 24 IU per day. There is currently enough evidence to be moderately confident that adjuvant GH treatment undergoing IVF/ICSI treatment results in higher delivery rates but caution is required. Fertility specialists must design larger RCTs that may detect the effect of GH in IVF/ICSI treatment clearly.

Conflict of Interest

Authors declare that there is no conflict of interest.

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