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Case Study

New Criteria for the Use of Growth Hormone in the Treatment of Female Infertility: Minireview and a Case Series

Jan Tesarik* and Raquel Mendoza-Tesarik

MARGen Clinic, Granada, Spain

***Corresponding Author**: Jan Tesarik, MARGen Clinic, Granada, Spain.

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Abstract

Most studies published so far suggest that the administration of growth hormone (GH) during ovarian stimulation improves in vitro fertilization (IVF) outcomes, especially in older women, but also in some younger ones who suffered repeated IVF failures during their previous IVF attempts. However, clearly defined criteria with which to distinguish between those women who are likely to benefit from GH treatment and those who are not are still lacking. This minireview resumes the latest advances as to the indication of GH for female infertility treatment. A small case series, showing one way how to address this question, is also included.

Keywords: *Growth Hormone Treatment; Insulin-Like Growth Factor-1; Female Infertility; Diagnostic Criteria; Treatment Strategies*

Introduction

A number of studies suggest that the administration of growth hormone (GH) during ovarian stimulation can improve live birth rate in women of > 40 years [1-5], but also in some younger ones with previous repeated in vitro fertilization (IVF) failures and/or poor oocyte morphology [2,4,6,7]. This improvement was originally attributed to an effect of GH on oocyte quality rather than quantity [1,8]. However, other findings have suggested that the beneficial effect of GH can also be due to an improvement of uterine receptivity for embryo implantation [9]. In spite of considerable effort, strict criteria with which to identify those women who would benefit from GH administration are still lacking. It appears that some women with previous IVF failures may not necessarily benefit from GH treatment, as evidenced by two studies in which no improvement of IVF outcomes was demonstrated with the use of GH co-stimulation [10,11]. In order to cope with these issues, a research topic project dedicated to different aspects of GH action in the female reproductive tissues, coordinated by three guest editors, Drs. Jan Tesarik, Yves Menezo and John Lui Yovich, was launched recently, resulting in a series of articles published in Frontiers in Endocrinology. These new results have made it possible to understand better the mechanism of GH action in the human ovary and uterus and thus distinguish between those women who are likely to benefit from GH treatment and those who are not.

Mechanism of GH action

GH is a 191 amino acid protein which can exert its effects both directly, via the GH receptor (GHR), and indirectly, by activating the expression of insulin-like growth factor-1 (IGF-1). GH is mainly secreted by somatotropic cells of the anterior pituitary gland, and most of the GHRs are located in liver cells that are responsible for the production of more than 50% of circulating IGF-1 [12,13]. However, both GH and IGF-1, as well as their respective receptors, are also expressed in a wide variety of other tissues and organs, including the reproductive ones [14].

It was shown previously that both GH and IGF-1 concentrations in follicular fluid samples aspirated at the time of oocyte recovery are positively correlated with clinical pregnancy [15] and that the GH concentrations in follicular fluid tend to decrease with female age,

although this is not necessarily the case for any individual woman [1]. Unlike follicular fluid, GH concentrations in serum show considerable fluctuations, so that the decision of whether GH should be used, based on a direct serum GH determination, is difficult before the beginning of ovarian stimulation [5,16,17]. In contrast, fluctuations of IGF-1 concentrations in serum are much less pronounced, leading to the preferential use of IGF-1 as an indirect marker of GH deficiency in the treatment of infertility. Here we present a case series showing our preliminary results concerning the relationship between serum IGF-1 concentrations and effectiveness of GH treatment in relatively young women with a previous IVF failure.

Case Study

This case series includes preliminary data concerning the diagnostic value of serum IGF-1 determination as a guide to be used for the selection of women who are likely to benefit from GH administration during ovarian stimulation for IVF. The series involves 17 women, between 29 and 36 years of age, in whom a previous IVF attempt failed. Women whose partners suffered from severe sperm disorders, including high levels of sperm DNA fragmentation, were excluded. Ovarian stimulation and GH administration were carried our as described [1]. Serum IGF-1 concentration was determined and interpreted according to a recent publication, with the use of reference ranges to attribute "GH/IGF age" to each of the women [18].

The GH/IGF age of most of the women who became pregnant with the use of GH treatment was higher as compared with their chronological age (Table 1). By contrast, the GH/IGF age of most of the women who did not become pregnant with the use of GH treatment was equal or even lower as compared with their chronological age (Table 2). This suggests that the IVF failure might be related to other, GH-independent issues in this latter group of women. It is evident that the numbers of women in both groups are far too low to perform a valid statistical analysis. However, a trend is here. It appears that low levels of IGF-1 with regard to chronological age should encourage the therapeutic use of GH to improve IVF outcome in relatively young women, as also supported by a number of other recent studies [3-5,9,14,17,20]. Additional studies, involving larger numbers of participants, are needed to refine further the current decision criteria as to the therapeutic use of GH in the treatment of female infertility.

Patient	Chronological Age (yr)	Serum IGF-1 (ng/mL)	GI-I/IGF age (yr)[1]
1	31	144.8	50 - 54
2	33	129.0	60 - 64
4	35	158.6	45 - 49
5	30	189.7	30 - 34
6	33	147.1	45 - 49
7	34	170.6	35 - 39
8	29	159.9	40 - 44

Table 1: *Women in whom GH treatment enabled pregnancy after previous IVF failure.*

[1]: Calculated with the use of serum IGF-1 reference ranges according to Zhu., et al [18].

Patient	Chronological Age (yr)	Serum IGF-1 (ng/mL)	GH/IGF Age (yr)[1]
1	33	195.4	30 - 34
2	35	151.2	45 - 49
4	36	172.3	35 - 39
5	31	191.0	30 - 34
6	32	189.8	30 - 34
7	35	174.8	35 - 39
8	30	185.2	30 - 34
9	32	220.1	25 - 29

Table 2: *Women in whom GH treatment failed to enable pregnancy after previous IVF failure.*

[1]: Calculated with the use of serum IGF-1 reference ranges according to Zhu., et al [18].

Discussion and Conclusion

Until now, GH administration has been used as adjuvant for ovarian stimulation treatment mainly in three clinical scenarios: women close to, or over, 40 years of age, younger women with repeated implantation failures, and oocyte recipients after one or more previous failures of IVF with donated oocytes. This treatment was successful in many, but not all, of these cases, suggesting an urgent need for development of more accurate criteria to define the subpopulation of those women who are likely to benefit from GH treatment. Based on recent studies, and on our own small case series, this paper suggests that the determination of serum concentration of IGF-1, reflecting the patient's GH/IGF age, may be of help. Women whose GH/IGF age is higher than their chronological age are suitable candidates for GH treatment. Further larger-scale studies are needed to confirm this hypothesis and to point out other players of the GH-IGF system to be used for diagnosis of GH deficiency involvement in female infertility in each individual case, in order to choose appropriate treatment.

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