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Growth Hormone Co treatment for Poor Responders in IVF: To All? To None? or Only to those who Really Need it?

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Commentary

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Commentary

In the last decades, there has been an increasing interest in adding exogenous recombinant GH to ovulation induction, following publications that addition of GH may up-regulate the intra-ovarian IGF-I, and thus augment the stimulatory effect of FSH on the ovary [1-7].

Indeed, a few publications by others, and by us, reported that GH co-treatment along FSH or human menopausal gonadotropin/human chorionic gonadotropin (HMG/HCG) might decrease the gonadotropin requirements, duration of ovulation induction, and the daily effective dose of FSH or HMG [8-10]. However, it is not only the economic impact of reduction in HMG requirement that is important [3-6,11]. The gain from the GH/HMG co-treatment should be more than just a reduction in the gonadotrophin requirements [1,3-6]. The final common aim of ovulation induction and assisted reproduction is to augment the induced conception rate.

Recently, Kulvinder, et al. [12] claim that the addition of GH to the stimulation protocol in poor responders is an attractive option for increasing pregnancy rates in failed IVF cycles. They may be right, that in some patients this expensive addition to controlled ovarian hyperstimulation (COH) may be helpful and possibly increase pregnancy and delivery rates. However, not in all poor responders. Dakhly, et al. [13] have conducted a prospective study in 240 poor responders according to the Bologna criteria for poor responders, in a parallel open label randomized trial. The patients were randomized into two groups: one group has undergone COH with the long GnRHa protocol, whereas the second was stimulated with the same protocol and GH [13]. The authors' primary outcome was the live birth rate (fresh, frozen and cumulative) [13]. Despite an improvement in the number of retrieved oocytes, metaphase II (MII), fertilized oocytes, and transferred embryos; no significant difference in the live birth rate between the two groups was observed [13]. In another prospective randomized placebo-controlled double-blind study in IVF poor responders, addition of adjuvant GH did improve neither follicular recruitment, nor estradiol secretion by mature follicles or the number of retrieved oocytes [11].

The confusion and equivocal results regarding GH cotreatment in IVF and COH is even greater; Several studies have reported on greater number of overall and MII oocytes, higher fertilization rates, increased number of overall generated embryos, top-quality and cryopreserved embryos, in GH cotreatment cycles [14-18]. On the other hand, others found no difference in the number of overall and metaphase II (MII) oocytes, no improvement in embryo quality, no difference in clinical pregnancy rates and no difference in live birth outcomes [11-15,19-22].

Albu and Albu [23] have reported a case of a 29 years old, GH deficient, infertile patient, who successfully

conceived and delivered a healthy boy, on the second IVF cycle after GH cotreatment for 3 months, despite no difference in the number of retrieved ova, compared to the previous, unsuccessful control IVF cycles, without GH. The GH co-treatment improved the eggs' and generated embryos quality [23]. Similarly, 30 years ago, we reported on a panhypopituitary patient who did not conceive on several previous cycles of hMG/hCG COH, and after addition of a small amount of daily GH, along hMG/hCG, she successfully conceived and gave birth [24]. The hMG consumption, in the previous four unsuccessful cycles was 76 to 96 ampules/cycle [24]. Addition of only four daily units of GH (16 to 24 units/cycle) to hMG COH was associated with a significant diminution in hMG consumption (35 to 36 ampules/cycle) [24]. The patient conceived on the second cycle of combined GH/ hMG/hCG treatment and delivered, at term, a healthy boy [24]. Indeed, the synergistic effect of GH and gonadotropins in achieving conception has been proven in infertile patients with GH deficiency, but not in those who are not GH deficient [3-6,23,24]. The addition of GH cotreatment to COH for IVF patients is very expensive, ranging from 11,400-15,000$/cycle, and 102,000$ overall for achieving a successful delivery, according to Kulvinder, et al. calculations [12]. It is, therefore, of utmost importance to deliver it only to those patients who may clinically benefit from it, by improving the pregnancy rate and "take home baby" rate [3-6,24,25].

The clonidine test is a simple test, capable of identifying GH deficient patients or those with very low GH reserve [3-6,24-27]. Based on this simple test, it is possible to prospectively identify those "poor responders" who may benefit from GH co-treatment along COH for either IVF or in vivo fertilization [3-6]. Whereas, 14 pregnancies were successfully generated in 24 clonidine negative patients, (58.3%), either in the GH/hMG/hCG co-treatment cycle or in the succeeding one, GH co-treatment did not generate any pregnancy in eight clonidine positive patients [3,4].

Different from studies who did not find a correlation between the response to tests for GH release and the ovarian response to combined treatment, we conclude that the clonidine test can play a discriminatory role in identifying patients who may benefit from the GH addition to COH [3-6,24,25].

We conclude, therefore, that GH may increase the pregnancy rate when combined with hMG/hCG in clonidine negative but not in clonidine positive infertile patients [3-6,24,25].

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