Growth hormone: in search of the Holy Grail for poor responders (or a felony)

Growth hormone has been used as an adjunctive treatment in reproductive medicine for more than 25 years. Through its stimulation of hepatic production of insulin-like growth factor 1, growth hormone is thought to potentiate the action of follicle-stimulating hormone via folliculogenesis and granulosa cell differentiation (1). There have been several retrospective and prospective studies over the years which have sought to identify a role for growth hormone in patients with polycystic ovaries, advanced maternal age, poor oocyte or embryo quality, and even thin endometria. Presently, growth hormone is most commonly used in the treatment of women classified as "poor responders." A 2010 Cochrane Database review by Duffy et al. (2) suggested that adjuvant use of growth hormone in poor responders was associated with an increase in live birth and pregnancy rates (odds ratio [OR] = 5.39, 95% confidence interval [CI] = 1.89−15.35, and OR = 3.28, 95% CI = 1.74−6.20).

Cozzolino and colleagues share the results of their updated systematic review and meta-analysis on the use of growth hormone co-treatment for poor responders undergoing in vitro fertilization (IVF) (3). In the 10 years since the review by Duffy et al. (2), seven new trials were added, whereas four studies from the Cochrane review did not meet inclusion criteria for this current review. A total of 12 randomized controlled trials (RCTs) including 1,139 patients classified as poor responders were included. The investigators concluded that the use of growth hormone during IVF led to a higher clinical pregnancy rate (OR = 1.34, 95% CI = 1.02−1.77) but did not result in an increased live birth rate (OR = 1.34, 95% CI = 0.88−2.55). Notably, when the Bologna Criteria were applied to identify poor responders, no difference in clinical pregnancy rates were noted. The authors do, however, point out that significant differences were observed in the total number of mature oocytes retrieved (mean difference = 2.06, 95% CI = 1.56−2.56, $P<.01$) as well the number of embryos available for transfer (mean difference = 0.76, 95% CI = 0.43−1.10, $P<.01$).

When considering these findings, it is important to highlight the significant heterogeneity of the trials included. All but one study (n = 5) published after 2012 used the Bologna Criteria to characterize their patient population as "poor responders." The remaining studies used a markedly different criteria to identify patients with poor response, ranging from number of ampules of human menopausal gonadotropin consumed in a cycle to estradiol level on the day of trigger. In addition, stimulation protocols included both GnRH agonist (~60%) as well as GnRH antagonist protocols, with 25% failing to report the type of luteal phase support that patients received. The dose and timing of growth hormone administration also varied significantly, from 1 IU every other day pre-IVF to 12 IU daily during stimulation. This all to say that comparing one study to the other is challenging; analyzing all of them in bulk, particularly with these studies, is fraught with peril.

Despite the inconsistent results compared to the Cochrane Review from 2010, this meta-analysis highlights a more pervasive problem in the field of reproductive medicine: a lack of attention to scientific rigor. Of the 20 eligible randomized trials reviewed, four were excluded because of the lack of a control group, and another four were excluded for reporting insufficient data. Methodologic deficiencies are further magnified when we review the quality of the data that qualified for analysis. In all, 50% of the studies failed to report a randomization method, a similar number failed to report whether the investigators were blinded to treatment allocation, and nearly 60% reported no power analysis in their methods section. As evidenced by these shortcomings, how can we, in good conscience, counsel patients toward or against growth hormone?

The addition of growth hormone to an IVF cycle is one of several clinical decisions that patients have to make that have significant financial implications. One study reported an added cost of approximately $2,400 dollars per cycle for the addition of growth hormone treatment—a treatment that may not improve live birth rates for poor responders (4). Unfortunately, there is no shortage of patients who would spend money on non−evidence-based therapies with the hope of improving their cycle outcomes. To this end, the most recent randomized trial examining growth hormone in poor responders, by Norman et al. (5), failed to reach its enrollment quota after 4 years, as private clinics in Australia were already widely offering growth hormone therapy to patients. The authors surmised that patients were unwilling to be randomized to placebo when they could easily pay for the therapy out of pocket at a private clinic, rather than miss out on the potential clinical benefit.

Beyond the efficacy and cost, the matter still remains that human growth hormone is a substance regulated by the U.S. Food and Drug Administration and requires a provider to give justification for use. Permissible indications for prescribing include short bowel syndrome, growth hormone deficiency due to pituitary tumors or their treatments, and muscle-wasting disease associated with HIV/AIDS. There are currently no reproductive indications for the prescribing of growth hormones in the United States, and those who prescribe these agents may be subject to felony charges.

Like many adjunctive treatments in reproductive medicine, adoption of a line of therapy has far outpaced a robust evidence base that demonstrates efficacy. With growth hormone, Cozzolino et al. (3) remind us that even 10 years after the initial signal of potential efficacy, far too few high-quality data have been published to reassure us that growth hormone has a role in the treatment of poor responders. We can only hope that, in the next 10 years, we as a profession will strive to conduct high-quality trials that answer our most pressing clinical questions and improve the prognosis of our most challenging patients.

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