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A new concept of cotreatment with human growth hormone and menotropins in ovulation induction protocols

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Abstract — Follicular development in the primordial and preantral stages is almost completely independent of gonadotrophins or steroids and is mainly dependent on growth factors and local regulators. Since human growth hormone (hGH) was found to facilitate ovarian response to gonadotrophin stimulation, we hypothesized that the administration of hGH in an hypogonadotrophic state and *prior* to ovarian stimulation with menotropins, may initiate or facilitate the propagation of the primordial and preantral follicles to the gonadotrophin-dependent stages. We suggest that treatment with hGH prior to menotropin administration may be useful to improve results for poor responders to gonadotrophins.

Introduction

Follicular development in the primordial and preantral stages is almost completely independent of gonadotrophins or steroids and is mainly dependent on growth factors and local regulators (1). Furthermore, Gougeon (2) showed that it takes as long as 70 days for a primordial follicle to become a Graafian follicle. Since the early stages of follicular growth are dependent on growth factors, and human growth hormone (hGH) was found to facilitate ovarian response to gonadotrophin stimulation (3), we hypothesized that the administration of hGH in an hypogonadotrophic state and *prior* to ovarian stimulation with menotropins may initiate or facilitate the propagation of the primordial and preantral follicles to the gonadotrophin-dependent stages.

Poor-responder patients in ovulation induction

Women treated in infertility clinics represent a heterogeneous group with wide divergences in their responses to exogenous gonadotrophin stimulation. This extreme variability in the ovarian response to ovulation induction may result in some patients who will produce a very small number of follicles, if any at all (4). Resistance or nonresponsiveness to gonadotrophin might be due to various factors, including abnormal intraovarian modulatory mechanisms, of which the role of several growth factors has been the subject of intense investigation (5,6). Another possible explanation for ovarian hyporesponsiveness is a scarcity or absence of gonadotrophin-dependent (early small antral or antral) follicles during gonadotrophin administration in a routine ovulation induction protocol.

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Follicular development

More than a decade ago, Gougeon (2) studied the duration of human follicular growth from the primordial follicle up to ovulation. It was estimated that follicular growth and maturation continued for as long as 70 days. Furthermore, the development of the primordial and preantral follicles is almost completely independent of gonadotrophins or steroids (1).

Growth factors and follicular development

Adashi et al (7) recognized the role of insulin-like growth factor-1 (IGF)-1 in follicular development. It has been shown that IGF-1 has a synergistic effect with follicle-stimulating hormone (FSH) on granulosa cell differentiation through stimulation of aromatase activity, induction of luteinizing hormone receptors, and synthesis of progestins and proteoglycans (7). The production of IGF-1 is known to be growth-hormone (GH) dependent. This has been the rationale for the use by Homburg et al (3) of hGH in vivo to facilitate ovulation induction by human menopausal gonadotropin (hMG) in women with hypopituitarism. In a subsequent study, Homburg et al (8) found that women treated with GH/hMG, as compared with hMG, had a significant reduction in the required dose of hMG, duration of treatment, and the daily effective dose of gonadotrophins. Furthermore, Burger et al (9) have described that GH treatment effect is prolonged and observable in subsequent treatment cycles without further GH administration.

While many studies have shown an improved response in young, poor-responder patients cotreated with GH and hMG (10,11), Shaker et al (12) in a well-conducted study showed no influence of GH treatment on follicular recruitment, E_2 secretion by mature follicles, or oocyte yield and quality, and Owen et al (13) showed no overall improvement in the ovarian response to the GH-augmented regimen of stimulation of 20 poor-responder patients.

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As a consequence of the aforementioned observations, we suggest a new mode of hGH coadministration starting 2 weeks prior to ovulation induction with hMG. This protocol includes the administration of hGH, starting on the day of gonadotropin-releasing hormone analog (GnRH-a) administration, every alternate day for 2 weeks, in routine controlled ovarian stimulation using the long GnRH-a suppression protocol. This method was chosen in an attempt to cause a propagation of preantral follicular (gonadotrophic-independent) stages to the early small antral (gonadotrophic-dependent) stage in the presence of an hypogonadotrophic milieu.

The importance of this hypogonadotrophic milieu is to prevent the propagation of all follicles which arrive at the small antral gonadotrophic-dependent stage to more advanced stages by the influence of the endogenous gonadotrophin. With this mode of administration, the hMG is given while more follicles arrive at the gonadotrophin-dependent stage and await gonadotrophin stimulation. Bergh et al (14) have studied the influence of GH in poor responders during in-vitro fertilization (IVF) cycles. In their study, GH pretreatment was started after the establishment of ovarian down-regulation and just prior to standard hMG stimulation, so that not enough time had elapsed to allow propagation of the preantral follicles to the early small antral (gonadotrophic-dependent) stage. Despite this dissimilarity from our protocol, some advantage was achieved, in that the time to initial response (50% increase in serum estradiol) was significantly shorter in those patients who had received GH as pretreatment compared with placebo. Probably, if more time would have been elapsed between GH pretreatment and hMG stimulation, more preantral follicles could have reached the early small antral (gonadotrophic-dependent) stage, and more oocytes could have been recruited during this stimulation protocol.

Conclusions

If our assumptions regarding the role of hGH in initiating or facilitating the development and the conversion of the primordial and preantral to the antral ovarian follicles are true, this protocol may be applicable in ovulation induction protocols in poor-responder patients during IVF-ET. However, prior to its introduction to routine clinical use, it should be further tested in larger studies of low-responders.

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