Evidence Against the Utility of Growth Hormone in the Enhancement of Ovulation

MARCO FILICORI

Ovulation induction is a commonly used procedure for the treatment of infertility. Traditionally, anovulatory women receive stimulatory drugs that result in follicular maturation, ovulation, and, hopefully, conception. Drugs used for ovulation induction include such antiestrogens as clomiphene citrate (1), gonadotropin releasing hormone (GnRH) (2), and exogenous gonadotropins. More recently, the introduction of assisted reproduction techniques prompted the use of human menopausal gonadotropin (hMG) in normal ovulatory women for the recruitment of multiple follicles; the availability of an elevated number of oocytes is essential for the optimal outcome of in vitro fertilization (IVF).

Recent evidence suggests that growth hormone (GH) directly or indirectly through the action of insulin-like growth factors (IGFs) can stimulate granulosa cell function (3) synergistically with follicle stimulating hormone (FSH). This finding has prompted the combined use of hMG and GH for clinical ovulation induction. The basic goals of GH supplementation in gonadotropin ovulation induction are listed in Table 24.1. Several recent studies have tested the feasibility of this approach; this chapter briefly reviews such studies and their impact on the pharmacology of ovulation induction.

hMG Supplementation with GH in Normal Ovulatory Women

Most women treated with hMG in assisted reproduction protocols have regular ovulatory menstrual cycles; exogenous gonadotropins are used to achieve multiple folliculogenesis and increase oocyte yield. The
Table 24.1. Goals of GH supplementation in hMG ovulation induction.

- Improve treatment in suboptimal responders.
- Shorten follicular stimulation.
- Lower hMG requirements.
- Increase follicle number.
- Improve oocyte yield.

Table 24.2. GH supplementation in hMG ovulation induction: studies in normal women.

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>GH dose (IU/cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaker et al., 1992 (6)</td>
<td>GH vs. control cycles</td>
<td>10</td>
<td>144</td>
</tr>
<tr>
<td>Tapanainen et al., 1992 (7)</td>
<td>Randomized, placebo-controlled</td>
<td>54</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Younis et al., 1992 (8)</td>
<td>Randomized, placebo-controlled, double-blind</td>
<td>42</td>
<td>48</td>
</tr>
</tbody>
</table>

development of pharmacologic regimens that result in the maturation of a greater follicle number in a shorter time period and with the use of lesser amounts of hMG is considered highly desirable. Early results with GH supplementation (4, 5) suggested that at least some of these goals could be achieved. However, these early studies were mostly carried out in resistant or amenorrheic women. Only more recent extensive studies have addressed the issue of the efficacy of GH supplementation for the enhancement of ovulation induction procedures in normal women; a list of these studies is shown in Table 24.2.

Shaker et al. (6) studied 20 women undergoing IVF; 10 of them were normal women with regular menstrual cycles. Cycles in which GH supplementation was provided were compared to cycles with hMG only carried out in the same patients. The duration of stimulation, hMG dose, day of first response, preovulatory estradiol (E<sub>2</sub>) levels, and number of follicles >14 mm in diameter were all unaffected by GH supplementation (Table 24.3). Furthermore, the number and quality of oocytes and embryos did not vary between the control and the GH-treated cycles. Similar clinical results were reported in the randomized, placebo-controlled study of Tapanainen et al. (7). However, serum E<sub>2</sub> and progesterone levels were lower, while follicular fluid (FF) testosterone concentrations were higher in the GH-treated subjects, suggesting that GH may somewhat affect ovarian steroidogenetic activity. Furthermore, IGF-I levels of the GH-treated cycles were increased in serum but not in FF, suggesting that FF IGF-I does not derive from local ovarian