Gonadotrophins in ovulation induction

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Abstract

For anovulatory women who fail to ovulate or conceive with clomiphene citrate, gonadotrophin ovulation induction has been the conventional second-line therapy. The aim of treatment is to achieve monofollicular development and ovulation. This differs fundamentally from the aim of ovarian stimulation for IVF, in which multiple follicular development is the goal. The small therapeutic window of ovulation induction requires a rigorous approach to monitoring, and willingness to cancel the cycle when multiple follicle development occurs. The two most widely used approaches are the low-dose step-up and the step-down protocols. While the latter more closely mimics the normo-ovulatory cycle, outcomes are similar. For safety reasons, the step-down protocol has not been widely adopted. The principle risks of ovulation induction are ovarian hyperstimulation syndrome and multiple pregnancy. There is a need to individualize treatment if outcomes are to be optimized. The role of adjuvant therapies remains unclear. However, prediction models based on initial screening parameters enable the optimal dose of FSH to be determined, and the identification of patients with a poor prognosis for successful treatment.

Keywords: *anovulation, FSH, gonadotrophins, monofollicular, step-down, step-up*

Introduction

Ovulation induction aims to restore normal fertility to anovulatory women by generating normo-ovulatory cycles (i.e. to mimic physiology and induce single dominant follicle selection and ovulation). Representing one of the most common interventions for the treatment of infertility (Collins and Hughes, 1995), ovulation induction can achieve excellent cumulative pregnancy rates if normal menstrual cyclicity is restored. Women with WHO II anovulation who fail to ovulate or conceive following ovulation induction with anti-oestrogens can be successfully treated with exogenous gonadotrophins. However, the challenge presented by the small therapeutic window for achieving monofollicular development is further complicated by variability in response to gonadotrophin treatment (Fauser and Macklon, 2004). In this article, contemporary approaches to ovulation induction will be addressed, and the direction of future developments considered.

Principles

Current approaches for gonadotrophin ovulation induction are based on the concept of intervening late on in the development of follicles, at the stage where they become FSH responsive. In the normo-ovulatory cycle, demise of the corpus luteum during the late luteal phase of the menstrual cycle leads to a fall in concentrations of oestradiol, inhibin A and progesterone. This results in an increased frequency of pulsatile gonadotrophin-releasing hormone (GnRH) secretion inducing rising FSH concentrations at the end of the luteal phase (Hall *et al*., 1992; Le Nestour *et al*., 1993). Only those follicles that happen to be at a more advanced stage of maturation during this inter-cycle rise in FSH (concentrations surpassing the so called *threshold* for ovarian stimulation) gain gonadotrophin dependence and continue to grow (Fauser and van Heusden, 1997). Decremental follicular phase FSH concentrations (effectively restricting the time where FSH concentrations remain above the threshold, referred to as the FSH *window*) appear to be crucial for selection of a single dominant follicle from the recruited cohort (van Santbrink *et al*., 1995). Only one follicle escapes from atresia by increased sensitivity for stimulation by FSH (Fauser *et al*., 1997). Recent evidence also points to a central role for LH in mono-follicular selection and dominance in the normal ovulatory cycle (Sullivan *et al*., 1999; Filicori *et al*., 2002; Hugues *et al*., 2005). While granulosa cells from early antral follicles respond only to FSH, those from mature follicles (the exhibiting receptors to both

gonadotrophins) are responsive to both FSH and LH. The maturing dominant follicle may become less dependent on FSH because of the ability to respond to LH.

Preparations

Gonadotrophin preparations containing only FSH (u-FSH) first became available in 1983 (Lunenfeld, 2004). The development and application of production techniques based on immunoaffinity chromatography with monoclonal antibodies enabled the production of highly purified u-FSH. Recombinant DNA technology led to the development, and later, the clinical introduction of human recombinant FSH (r-FSH) (Fauser, 1998). This advance promised not only unlimited availability, but improved purity and batch-to-batch consistency compared with urinary-derived products. Recombinant FSH has been clinically available since 1996 in the form of follitropin alfa and follitropin beta. More recently, a long-acting r-FSH (Devroey *et al*., 2004), a recombinant LH (European Recombinant Human LH Study Group, 2001) and a recombinant human chorionic gonadotrophin (HCG; European Recombinant Human Chorionic Gonadotrophin Study Group, 2000) have been added to the clinical arsenal for ovarian stimulation.

The degree to which the type of FSH compound employed may influence outcomes in ovulation induction remains the subject of controversy. Two recent meta-analyses comparing the effectiveness of daily urinary FSH to daily human menopausal gonadotrophin (HMG) for inducing ovulation in women with polycystic ovary syndrome (PCOS) who had not responded to clomiphene citrate demonstrated no difference in pregnancy rate per treatment cycle. However, the women given FSH were less likely to have moderately severe or severe ovarian hyperstimulation syndrome (OHSS) (Hughes *et al*., 2000; Nugent *et al*., 2000). With respect to r-FSH, a multi-centre prospective trial found that the cumulative ovulation rates were comparable with those achieved with purified urinary FSH (95% after three cycles) (Coelingh Bennink *et al*., 1998). The total dose of r-FSH needed and duration of treatment was less, and the complication rates were similar. A retrospective study comparing urinary and recombinant FSH showed that the mean daily FSH dose required to achieve the threshold of follicular selection was significantly lower in women receiving r-FSH (Hugues *et al*., 2001). In a recent meta-analysis of randomized controlled trials comparing r-FSH with u-FSH for ovulation induction in women with clomiphene citrate resistant PCOS, no significant differences were demonstrated for the ovulation rate [OR 1.19 (95% CI 0.78–1.80)]. Furthermore, the odds ratios for pregnancy rate [0.95 (95% CI 0.64–1.41)], miscarriage rate [1.26 (95% CI 0.59–2.70)], multiple pregnancy rate [0.44 (95% CI 0.16–1.21)] and for OHSS [1.55 (95% CI 0.50–4.84)] showed no significant difference between r-FSH and u-FSH (Bayram *et al*., 2001). The success in clinical studies with pure FSH preparations, increasingly devoid of LH, has served to enhance the impression that excess LH is detrimental to oocyte development and chances of pregnancy following therapeutic intervention. However, a number of recent clinical studies, together with an increasing understanding of the function played by LH in oocyte maturation, have begun to redefine the role of LH as a therapeutic agent in anovulatory fertility.

In normogonadotrophic anovulation, endogenous LH does not normally require supplementation. Indeed, the focus on LH in this group of patients has been primarily directed at reducing the potential detrimental effects associated with excessive LH (Shoham *et al*., 1993). The improved outcomes referred to above following ovulation induction with r-FSH devoid of LH activity have further supported this view. More recently, however, the demonstration of the importance of late follicular LH in optimizing dominant follicle development oocyte quality has reopened the debate as to the role of LH in ovulation induction (Filicori *et al*., 2002). Supplementation of LH activity may offer advantages in some patients by hastening large follicle development and therefore shortening the duration of treatment. Moreover, the work of Zeleznik and co-workers referred to a potential therapeutic role for LH in effecting monofollicular stimulation as part of a sequential ovarian stimulation protocol following initiation with r-FSH (Sullivan *et al*., 1999). This concept of an LH therapeutic window (Yong *et al*., 1992; Hillier, 1994; Shoham, 2002) has been subject to a number of recent clinical studies. Anovulatory women with a hyper-response to r-FSH were randomized to continue treatment with the addition of either placebo or r-LH (Loumaye *et al*., 2003). In those in whom LH was administered, a trend towards fewer preovulatory follicles was observed. In contrast, treatment with recLH alone in the late follicular phase was found to be detrimental to preovulatory follicle development. Further evidence supporting the 'LH ceiling' concept whereby addition of recLH is able to control development of the follicular cohort was provided by a recent study in which anovulatory women undergoing ovulation induction who over-responded to FSH treatment were randomized to receive in addition to rFSH, either placebo or recLH for up to 7 days (Hugues, 2005). Doses of up to 30 μg recLH/day were associated with an increased rate of single dominant follicle selection in this group of previous high responders. As the availability of recombinant gonadotrophins leads to increasing knowledge of the processes of follicular development and selection, further refinements in the efficacy and safety of ovulation induction are likely.

Regimens

In order to achieve development of a single dominant follicle with exogenous gonadotrophins, specific treatment and monitoring protocols are needed. The two most frequently encountered in the literature and in clinical practice are the low-dose step-up and step-down protocols. The initially described 'standard' step-up protocol had a starting dose of FSH 150 IU/day. However, this regimen was associated with a high complication rate. Multiple pregnancy rates of up to 36% were reported, while ovarian hyperstimulation occurred in up to 14% of treatment cycles (Fauser and van Heusden, 1997). This approach has been largely abandoned.

The concept of the FSH 'threshold' proposed by Brown (1978) postulated that FSH concentrations must exceed a certain level before follicular development will proceed. Once this level is reached, normal follicular growth requires only a minor further increase above this threshold. Exposure to excessive FSH serum concentrations may lead to excessive follicular development. This experimentally substantiated concept (van Weissenbruch *et al*., 1993) formed the theoretical basis for