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EDITORIAL

Recombinant or Urinary Human Chorionic Gonadotropin in Ovulation Induction?

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The onset of the spontaneous LH surge in women is relatively abrupt with concentrations doubling within 2 h to between 100 and 200 IU/l being sustained for 12–14 h over a mean duration of 50 h [1]. This mid-cycle surge, in addition to follicular rupture [2], promotes several peri-ovulatory events including disruption of the oocyte–cumulus oophorus cell contact and induction of the resumption of the oocyte's meiotic maturation [3], cumulus oophorus mucification, luteinization of the follicular granulosa cells [4] and secretion of progesterone.

These events are also induced by an injection of human chorionic gonadotropin (hCG) through exactly the same sequence, the only difference being in the pharmacokinetic profile where the mean duration of the 'surge' after an IM injection of 5,000 IU u-hCG is longer than for LH ($\sim$96 h) and maximum concentrations may be less [5]. Current practice is that $\geq$5,000 IU u-hCG is an acceptable ovulatory dose and that lesser concentrations can lead to reduced oocyte recovery and a lower fertilization rate in assisted reproductive treatments [6].

The first preparations of hCG were investigated in the late 1930 s [7]. Subsequent studies and improved preparation of hCG from the urine of pregnant women (u-hCG), where its abundance allowed ease of extraction, meant that for almost 40 years it has been the sole hormonal preparation commercially marketed for induction of ovulation in anovulatory women. For the last three decades patients undergoing assisted reproductive treatments have also used u-hCG to induce the final maturation of follicles and oocytes before their collection and additionally to support the luteal phase of the cycle.

The history of gonadotropin use when derived from either animal or human tissues has, however, not always been without clinical danger (e.g. antibody formation from pregnant mare serum gonadotropin; Creutzfeld–Jacob disease from human pituitary gonadotropin) so, as recombinant technology evolved, the logic of increasing both a compound's purity and safety could not be ignored. Such a uniform, specific product would mean that drug production would no longer be dependent on the vagaries of urine collection and hormone extraction, allowing commercial production to be adjusted according to market requirements. In addition all urinary contaminants would also be removed. Furthermore this would allow the safe subcutaneous administration of a compound with less batch-to-batch variation than has been demonstrated for urinary menopausal gonadotropins preparations [8].

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Recombinant hCG (r-HCG) had been initially manufactured by transfecting non-human cell lines (Chinese hamster ovary cells) with genetic material capable of replicating identical amino acid sequences to the human compound and developed as a pharmaceutical product named Ovitrelle (Merck Serono, Switzerland). Today you have bio-similar molecules available in India (Triggerix, Lupin Ltd, India). However, prescribing a biosimilar to a patient calls for certain basic understanding by physicians of the scientific factors associated with the safety and efficacy of these products. Substituting an innovator brand by a biosimilar brand calls for caution in terms of quality, safety and efficacy aspects due to clear differences between biosimilars and their reference products [9].

A randomized, controlled, double-blind, double-dummy, phase III clinical trial was conducted in 84 women to compare the efficacy of a s.c. injection of 250 μg r-hCG to an i.m. injection of 5,000 IU u-hCG in inducing folliculogenesis, resumption of oocyte meiosis and luteinization after ovulation induction with r-FSH. Since the confidence intervals for the difference of the number of oocytes retrieved between the two treatment groups were within the bounds defined by the multi-trial protocol, equivalence between r-hCG and u-hCG could be declared [10].

The International r-hCG Study Group conducted a Phase III, double-blind, double-dummy, randomized, parallel-group, multicenter study to compare the safety and efficacy of 250 μg r-hCG and 5,000 IU u-hCG, both administered s.c., for ovulation induction in anovulatory/oligo-ovulatory patients after follicular stimulation with r-FSH [11]. Subcutaneous r-hCG and u-hCG show equivalent efficacy in ovulation induction; however, r-hCG is better tolerated [11].

The European Recombinant Human Chorionic Gonadotropin Study Group conducted a multicenter, double-blind, double-dummy, randomized, parallel-group study comparing the efficacy and safety of r-hCG and u-hCG for inducing final follicular maturation and early luteinization in women undergoing ovulation induction for ART [12]. Following long down-regulation and stimulation with r-FSH, a total of 190 women received a single, SC injection of either 250 μg r-hCG or 5,000 IU u-hCG. The mean number of mature oocytes was statistically higher ($P = 0.027$) for the r-hCG group than the u-hCG (9.4 vs. 7.1). Serum progesterone concentrations on day 1 and days 6–7 post-hCG, and serum hCG concentrations at all post-hCG time points were statistically significantly in favor of r-hCG. The clinical pregnancy rate was somewhat higher (not significant) in the r-hCG group (33 vs. 25%) as was the live birth rate (27 vs. 23%, not significant). Both treatments were well tolerated, though the incidence of adverse events was significantly higher in the u-hCG group (45.1 vs. 22.7%, $P = 0.0004$). The incidence of injection-site reactions was significantly lower in the r-hCG group ($P = 0.0001$). In conclusion, for triggering ovulation, r-hCG seems to have significant advantages compared with u-hCG in terms of number of mature oocytes retrieved, luteal progesterone and local tolerance [12].

Farrag et al. conducted a prospective randomized study in order to investigate the effect of r-hCG on oocyte nuclear and cytoplasm maturity compared to u-hCG, for inducing ovulation in women treated with ICSI for male factor infertility [13]. Their results showed that r-hCG increases the rate of metaphase II oocytes, the number and the rate of MII oocytes with mature cytoplasm compared to u-hCG [13].

An age-matched retrospective analysis compared the clinical outcomes of r-hCG and u-hCG in patients undergoing fresh, non-donor IVF cycles and concluded that r-hCG was as effective as u-hCG for final follicular maturation in IVF cycles [14].

A prospective, randomized and blinded comparison between 10,000 IU urinary and 250 μg r-hCG for oocyte maturation in IVF cycles summarized that r-hCG is at least as effective for inducing final stages of oocyte maturation as 10,000 IU u-hCG and is also associated with significantly better patient tolerance and thus higher patient acceptability [15].

Kovacs et al. conducted a prospective randomized study between 250 μg of r-hCG and 7,500 IU of u-hCG as the final trigger of ovulation during IVF [16]. They concluded that recombinant and urinary hCG provided similar serum and follicular hormonal environments during the final stages of oocyte maturation. The IVF outcome parameters were also comparable. The two medications appear to be equally effective [16].

Chan et al. set up a study to compare the effectiveness of 250 and 500 μg r-hCG, which represented the lower and upper limits of the dose range, in inducing final oocyte maturation during IVF and ICSI cycles. The two doses of r-hCG were equally effective in inducing final oocyte maturation [17]. It remains unclear whether the higher midluteal estradiol and progesterone levels in the 500 μg r-hCG group confer any benefit.

Littman and Milki described three cases in which the addition of r-hCG to u-hCG to trigger ovulation in IVF improved oocyte recovery in patients with a history of scant oocyte yield in previous cycles [18].

Conclusions

The published data consistently show that single doses of 250 μg r-hCG and 5,000 IU u-hCG produce similar clinical outcomes when used in infertility treatment cycles for timed intercourse, IUI, and IVF in terms of the number of

oocytes retrieved, number of mature oocytes harvested, and fertilization and pregnancy rates attained [8, 10, 12, 13, 17, 19]. Single doses of 10,000 IU u-hCG also gave results comparable to single doses of 250 μg r-hCG [15]. *P* levels in the midluteal phase were significantly higher with the use of r-hCG compared with u-hCG, and local injection site adverse effects were significantly less frequent, demonstrating the higher purity of the recombinant product [11, 12]. A single dose of 250 μg r-hCG was at least as effective as single doses of 5,000 or 10,000 IU u-hCG but offered the advantages associated with use of a recombinant product; local injection site adverse effects were significantly less frequent with r-hCG than with u-hCG [11–13, 17].

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