Recombinant follitropin alfa/lutropin alfa in fertility treatment

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Abstract: Recombinant human follicle stimulating hormone (rFSH) and luteinizing hormone (LH), also known as follitropin alpha and lutropin alpha, are manufactured by genetic engineering techniques which ensure high quality and batch to batch consistency. Follitropin alpha can be used for controlled ovarian hyperstimulation in assisted reproduction, ovulation induction for WHO group I and II anovulatory infertility and in men with hypogonadotrophic hypogonadism (HH) or idiopathic oligo-asthenospermia. Current evidence suggests superiority of urinary human menopausal gonadotropin (HMG) over follitropin alpha in controlled ovarian hyperstimulation for IVF in terms of live birth rate per couple. Addition of lutropin to follitropin alpha in an unselected IVF population does not appear to confer any benefit; however, it may have a role in ovulation induction in women with hypothalamic hypogonadism. Urinary HMG preparations (especially currently available highly purified preparations) are more cost effective than rFSH in terms of cost per ongoing pregnancy. However, women using rFSH injection pen devices have higher levels of satisfaction as compared to those using urinary HMG by means of conventional syringes.

Keywords: infertility, follicle stimulating hormone, luteinizing hormone, follitropin alpha, lutropin alpha, in-vitro fertilization, urinary gonadotrophins

Introduction

The pivotal role of the pituitary gland in reproductive function was established in the 20th century, when it became clear that it secreted two key hormones – follicle stimulating hormone (FSH) and luteinizing hormone (LH).1,2 This discovery allowed clinicians to treat infertile couples by means of pituitary extracts.2,3 Animal pituitary extracts of follicle stimulating hormone (FSH) were the first commercially available gonadotropins in the 1930s while the first use of cadaveric human gonadotropins for induction of ovulation was reported in 1958.4,5 Human pituitary gonadotropins (HPG) continued to be used in clinical practice for a number of decades before being withdrawn following reports of an association between its use and cases of Creutzfeld-Jakob disease (CJD).5–7 Meanwhile, increasing demands for gonadotropins, which could not be met from cadaver specimens, led to the extraction of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from urine in 1950.3 Human menopausal preparations contain both FSH and LH activity in a ratio of 1:1, though some of the LH activity was achieved by addition of human chorionic gonadotropin (HCG).8,9 Subsequently the development of advanced immunopurification and fractionation techniques using specific monoclonal antibodies led to the introduction of highly purified urinary preparations.3,5,10,11 More recently, use of genetic engineering technology led to the
development of the recombinant human gonadotropins preparations.12,13 Follitropin alpha was the world’s first recombinant human FSH preparation and lutropin alpha the first recombinant human luteinizing hormone (LH).14,15 A mixture of follitropin alpha and lutropin alpha (follitropin alpha/lutropin alpha 150 IU/75 IU) has been recently commercially available in a single product called Pergoveris™ (Merck Serono).16 Biapatity studies have confirmed that the new drug is treated in the body similarly as if each product were administered separately.14,16 This combination could be of value for the stimulation of follicular development in infertile women with severe endogenous FSH and LH deficiency, using a single daily injection.17

Pharmacology

Structure
Follitropin alpha and lutropin alpha are glycoproteins which are structurally similar to endogenous FSH and LH. They possess similar alpha but different specific beta subunits.18,19 The nomenclature “alpha” differentiates it from another recombinant human FSH product which was marketed later as follitropin beta.20

Isoforms
Endogenous gonadotropins exist in a number of different isoforms which have similar amino acid sequences but differ in their terminal sialic acid content.21-24 Different isoforms can vary in their biophysical characters; but their clinical roles have yet to be determined.19,25,26 An isoform isolated at any particular time in the human body can be affected by gender, age, source of the sample, endocrine state and phase of menstrual cycle.27-29 Follitropin alpha is similar to the natural FSH isoform detected at mid cycle while Follitropin alpha resembles that detected in the early follicular phase.30 Recombinant FSH preparations differ from urinary HMG preparations of this cell line are then extracted and purified by a genetically engineered Chinese hamster cell line.20,46 The products of this cell line are then extracted and purified by means of a series of immunochromatographic techniques,46,47 which help to maintain quality assurance and batch to batch consistency.48,49 The current manufacturing process permits the follitropin alpha active ingredient to be quantified by its protein content (mass in µg); a technique called filled by mass (FbM) rather than the conventional method which relied on a product’s biological activity (bioassay).50,51 It has been suggested that the use of follitropin alpha filled by mass (FbM) may lead to more consistent ovarian stimulation,

most cases.34,35 However, the role of LH for optimal follicular development has been recently described — especially in profoundly LH deficient women with hypogonadotrophic hypogonadism.36,37 Although a minimum level of serum LH is required for optimum growth, excess LH can cause follicular growth arrest and prevent growing follicles from reaching the late antral stage.38,39 Follitropin alpha administration has been associated with a significant increase in serum levels of estradiol level, inhibin A and inhibin B.40,41 Significant increases in follicular levels of insulin and growth hormone have been detected in follitropin stimulated women.20

Pharmacokinetics
The pharmacokinetic properties of follitropin alpha and lutropin alpha are similar to those of urinary derived FSH and LH, respectively.20,42 Both are eliminated by means of the liver and kidney.32,43 Although subcutaneous (SC) administration is recommended, both products can also be administrated by the intramuscular route (IM).7,44 Subcutaneous administration had been found to produce shorter absorption half life and time to maximum plasma concentration. Following a single subcutaneous 150 IU dose, follitropin alpha has a terminal half-life of about 37 hours, bioavailability of 74%, mean peak serum drug concentration (Cmax) 3 IU/L and the time to maximum plasma concentration (tmax) was 16 hours.45 Lutropin alpha has a one compartment first-order process.42 Following subcutaneous administration of 150 IU lutropin alpha, a mean Cmax of 1.1 IU/L is reached after 6 hours (tmax).42 Lutropin alpha has a terminal half-life of about 18 hours and a bioavailability of 56% (following a single subcutaneous 10,000 IU dose).44

Manufacturing
Both follitropin alpha and lutropin alpha are manufactured by recombinant DNA technology.12,32 The gene encoded for the bio formation of each hormone is incorporated into a genetically engineered Chinese hamster cell line.20,46 The products of this cell line are then extracted and purified by means of a series of immunochromatographic techniques,46,47 which help to maintain quality assurance and batch to batch consistency.34,35 The current manufacturing process permits the follitropin alpha active ingredient to be quantified by its protein content (mass in µg); a technique called filled by mass (FbM) rather than the conventional method which relied on a product’s biological activity (bioassay).50,51 It has been suggested that the use of follitropin alpha filled by mass (FbM) may lead to more consistent ovarian stimulation,
less need to dose adjustment and fewer cycle cancellations.\textsuperscript{31,52} The biological activity of lutropin alpha is determined by bioassay.\textsuperscript{43}

**Safety**

**General**

Clinical trials have shown that follitropin alpha and lutropin alpha are very well-tolerated by patients. Ovarian hyperstimulation syndrome and multiple pregnancy are the most serious side-effects linked to gonadotropin use.\textsuperscript{54} Recombinant FSH is not believed to increase the risk of miscarriage.\textsuperscript{55} No fetal effects had been reported after accidental first trimester exposure to follitropin alpha.\textsuperscript{36} Headache, nausea, abdominal pain, breast pain, ovarian cyst formation are the most common side-effects of both follitropin alpha and lutropin alpha, while ovarian hyperstimulation is a serious, albeit rare side-effect.\textsuperscript{57}

Side effects have been reported in 46.5% of patients who used follitropin alpha alone and 42.4% women receiving follitropin alpha/lutropin alpha. These include headache, nausea, mastalgia, fatigue, abdominal pain and development of functional ovarian cysts.\textsuperscript{6,20,33,57–59}

A case report has described subclavian deep vein thrombosis and mild ovarian hyperstimulation associated with treatment with recombinant FSH.\textsuperscript{40} Bar et al have suggested diminished platelet aggregation in women using urinary FSH compared to rFSH.\textsuperscript{61} Local skin reaction including mild irritation, pain, erythema and pruritus has been reported in 1.8% of a total of 1093 follitropin alpha injections.\textsuperscript{38} Subcutaneous injection of lutropin alpha was not associated with any adverse local skin reactions in almost 90% of the injected cases,\textsuperscript{38} only 3.4% women reported anything more than a mild skin reaction after SC injections with recombinant LH.\textsuperscript{37} No antibodies to follitropin alpha have been discovered in women receiving any of these preparations.\textsuperscript{33,37,57} There were two case reports describing two separate IVF cycles where follitropin alpha was used successfully in inducing follicular growth in the absence of any allergic reactions in two women with severe allergic reactions to urinary FSH.\textsuperscript{53,64} Data from randomized trials and case series suggest that follitropin alpha is associated with better local tolerance and fewer injection site side effects than follitropin beta.\textsuperscript{65–67}

**OHSS**

Severe ovarian hyperstimulation syndrome (OHSS) is a serious and a life-threatening complication with an incidence of about 0.5% to 2%.\textsuperscript{68,69} Polycystic ovarian syndrome (PCOS), previous episodes of OHSS and high doses of exogenous gonadotropins are known to increase the risk of developing OHSS.\textsuperscript{70–72} There is some evidence that individual sensitivity to FSH stimulation may be more important than the total amount of gonadotropins used.\textsuperscript{73} The incidence of OHSS in women in women using recombinant FSH in IVF treatment has been reported in two recent systematic reviews to range between 0% to 4.6% when rFSH was used for controlled ovarian hyperstimulation (COH) in IVF.\textsuperscript{74–76} The overall incidence was 2.6% after pooling results from 9 studies including a total of 1454 women in the rFSH group.\textsuperscript{68} There was no difference in the rate of OHSS between women on rFSH versus urinary FSH.\textsuperscript{77,78}

After pooling results from 4 randomized trials including 381 participants undergoing IVF in GnRH agonist down regulated cycles, the reported incidence of OHSS was 2.8% when lutropin alpha was co-administrated with rFSH.\textsuperscript{79}

### Table 1

<table>
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<th>Group</th>
<th>Description</th>
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<td>Low FSH</td>
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<tr>
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<td>Hypo-estrogenic</td>
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<td>Low estradiol</td>
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<tr>
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<td>Normoprolactinemic</td>
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<td>Normal prolactin</td>
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<td>Hypogonadotrophic</td>
<td>Hypothalamic-pituitary ovarian axis</td>
<td>Normal FSH</td>
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<tr>
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<td>Normal estradiol</td>
</tr>
<tr>
<td></td>
<td>Normoprolactinemic</td>
<td></td>
<td>Normal prolactin</td>
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<tr>
<td>WHO type III</td>
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<td>Ovarian failure</td>
<td>High FSH</td>
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<td>High prolactin</td>
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**Abbreviation:** FSH, follicle stimulating hormone.
There was no difference in the incidence of OHSS between women who received rLH plus rFSH and those who received rFSH alone.79

Multiple pregnancy

Gonadotropin stimulation of the ovaries in assisted reproduction leads to multifollicular growth.80,81 Unlike IVF, where the number of embryos replaced determines the incidence of multiple gestations,81 the release of more than one oocyte in ovulation induction or superovulation with IUI could potentially increase chances of multiple pregnancy.82 Phase III trials of follitropin alpha show a multiple birth rate of 20% when the drug is used for ovulation induction and 35% when it is used in IVF.53

A number of different strategies have been proposed to decrease the chance of multiple births after ovulation induction but their impact has been limited.84 The two systematic reviews of trials comparing rFSH to urinary HMG in IVF showed no difference in multiple pregnancy rates between the two treatment groups.77,78

Clinical efficacy

FSH and LH have significant roles in ovarian follicle differentiation, selection and survival.85 Exogenous gonadotropin administration has been suggested as an effective means of treatment in WHO group I and II anovulation, and in males with hypogonadotropic hypogonadism.59,84,85 In normogonadotropic women, COH is an essential prerequisite for successful in vitro fertilization (IVF) treatment.86 The aim in IVF is to stimulate multiple follicular growth in order to enhance the increase of oocytes.87 Superovulation is also used in conjunction with intrauterine insemination even in absence of evidence of anovulation, though the rationale for this intervention has been challenged recently.88,89

Different protocols for COH had been described. In IVF, these protocols usually involve pituitary suppression by GnRH agonists or antagonists.90-92 Variable long, short or ultrashort protocols for GnRH agonists have been suggested.90,93 The commonest is the long luteal phase protocol where GnRH agonists are started in the luteal phase of the cycle preceding the IVF cycle.94,95

Efficacy in IVF/ICSI

Follitropin alpha

Recently, two systematic reviews of randomized trials comparing recombinant FSH (rFSH) and urinary HMG (uHMG) in unselected subfertile women undergoing IVF/ICSI (intracytoplasmic sperm injection of eggs), have been published.77,78

In the first, results from a meta-analysis of 12 randomized controlled trials (RCTs), with a total of 2937 participants have shown an overall live birth rate of 21.8% in the rFSH group compared to 24.9% in the uHMG group.77 The second systematic review included only 7 RCTs which compared rFSH and HMG in IVF cycles where a long pituitary down-regulation protocol was used.78 The pooled results based on a total of 1259 women showed that the live birth rate per woman treated with rFSH was 21.6% compared to 25.4% in the HMG group (Figure 1).78

Al-Inany et al77 found live birth rate per woman in the HMG group to be significantly higher than in the rFSH group (odds ratio [OR] 1.20, 95% confidence interval [CI] 1.01 to 1.42).77 Coomarasamy et al38 showed live birth rate per woman in the uHMG group to be significantly higher than the rFSH group (OR 1.18, 95% CI 1.02 to 1.38).78 These results are based on a general population of women undergoing IVF. It has been suggested that specific groups of patients such as older women or poor responders might benefit from rFSH.96,97 However, there is a need for relevant evaluative studies in order to elucidate the role of rFSH in those women. Neither systematic review has shown any differences in rates of multiple pregnancy rates, ovarian hyperstimulation or miscarriage.77,78 Unlike Coomarasamy and his colleagues, Al-Inany et al reported a significant reduction in dose and duration of stimulation and available embryos in the rFSH group.77

Traditional uHMG preparations contained FSH and LH in a ratio of 1:1, while more recent highly purified FSH (HP FSH) products using monoclonal antibody techniques for extraction and purification of FSH contain negligible amounts of LH ($P < 0.001\%)$.9 In their systematic review,77 Al-Inany et al examined the effect of the type of HMG (purified versus conventional) compared with rFSH on IVF outcome. They performed a subgroup analysis to compare HP HMG with rFSH and showed a similar outcomes in the HP-HMG group in terms of live birth rate (OR 1.21, 95% CI 1.02 to 1.44) and clinical pregnancy rate (OR 1.26, 95% CI 1.04 to 1.53).77 Two recent RCTs, one using a long downregulation protocol along with a GnRH agonist and the other a GnRH antagonist, failed to demonstrate any significant difference in pregnancy rates between HPFSH and rFSH.98,99

Follitropin alpha and follitropin beta represent two isoforms of the same molecule.20 Although some authors have suggested a difference in clinical efficacy between the two
molecules. Live birth rates and clinical pregnancy rates have been shown to be comparable in four randomized controlled trials.  

**Lutropin alpha in IVF**

It has been reported that high LH levels in the follicular phase of the IVF cycle could have a detrimental effect on the outcome of IVF but a minimum threshold serum concentration of LH is required for optimum folliculogenesis. According to Loumaye and colleagues, the effect of LH on the growing cohort of follicles demonstrates a ceiling effect and exceeding a certain threshold can compromise follicular development.

Results of a recent Cochrane review do not confirm an increase in live birth rates associated with the addition of rLH to rFSH in GnRH agonist downregulated IVF cycles compared to rFSH only stimulated cycles (two trials: OR 1.51, 95% CI 0.79 to 2.87).

Meta-analyses of RCTs where GnRH antagonists (rather than GnRH agonist) were used for pituitary suppression also failed to find any significant differences in terms of clinical pregnancy rates, as none of the studies included reported live birth.

There was no difference in the risk of early miscarriage between women on rFSH who were co-treated with rLH (eight trials: OR 0.59, 95% CI 0.35 to 1.02) compared to women who were treated with rFSH alone. However, after exclusion of a single trial that used a flare up GnRH protocol, a trend towards reduced miscarriage rates (of borderline significance) was found in women co-treated rLH (seven trials: OR 0.57, 95% CI 0.33 to 1.00). There was a significant difference in live birth rate in favor of rLH supplementation in poor responders (three trials: OR 1.85, 95% CI 1.10 to 3.11). There were no differences in other IVF outcomes such as OHSS, number of oocytes retrieved, amount of rFSH used, serum estradiol level on the day of HCG administration and miscarriage rate.

These findings are in accordance with results from a previous meta-analysis of results from 4 RCTs examining the effect of adding rLH to rFSH in GnRH agonist downregulated IVF cycles.

An RCT which included 84 participants found no significant difference in pregnancy rate between poor responders treated with either rFSH alone or rLH and FSH in an GnRH agonist flare up protocol.

In a systematic review where trials using GnRH agonists and antagonist cycles were pooled, live birth rates and clinical pregnancy rates were similar regardless of whether rLH was co-administered with rFSH or not. Although some clinicians have reported that rLH administration prior to rFSH in IVF cycles increased the number of antral follicles, this did not translate into improved rates of live birth pregnancy. Thus, there is no evidence at the present time that co-administration of rLH to rFSH, in controlled ovarian hyperstimulation for IVF, has a beneficial effect in IVF.

In the European Union, a combination of follitropin alpha and lutropin alpha (Pergoveris™) is currently available for single subcutaneous injection. The ratio of follitropin alpha to lutropin alpha in that preparation is 2:1, respectively. A randomized crossover trial had demonstrated bioequivalence between follitropin alpha and lutropin alpha administered alone or in this fixed 2:1 combination.

**Use of follitropin alpha in ovulation induction**

**Hypogonadotrophic hypogonadism**

WHO group I anovulation is a rare condition that can be caused by a hypothalamic or pituitary defect due to congenital or acquired causes (Table 1). Management options include exogenous replacement of gonadotropins and pulsatile GnRH therapy can be used. The advantages of pulsatile GnRH compared with gonadotropins are that there is a lower risk of hyperstimulation and multiple pregnancies and the need for monitoring is minimal. Exogenous gonadotropins administration is the alternative therapeutic option in hypothalamic dysfunction and the first line treatment if the defect is primary pituitary failure.

Currently available evidence indicates that rFSH alone may not be sufficient to promote optimum follicular growth in severely gonadotropin deficient women. It has been suggested that a minimum threshold of serum LH is required to re-establish meiosis and final stages of growth of antral follicles. Meanwhile, follicular growth arrest might occur, should LH exceed that threshold, in what is called an LH ceiling. Antral follicle growth arrest (at 10 mm diameter) has been observed in LH deficient cycles.

A dose finding trial included 38 WHO type I anovulatory patients, who were randomly assigned to receive either 0, 25, 75, or 225 IU rLH once daily in addition to 150 IU follitropin alpha once daily for up to 20 days. None of the 8 patients who received follitropin alpha alone ovulated in the absence of rLH. Fourteen percent of patients who received follitropin alpha and 25 IU/L rLH ovulated compared to
However, a small RCT powered by TCPDF (www.tcpdf.org) reported a live birth rate of 17% to 20%.

WHO group II anovulation

It had been estimated that 90% of women in women in WHO type II anovulation would be expected to have polycystic ovarian syndrome (PCOS). According to the Rotterdam consensus criteria, PCOS should be considered when two of three features are diagnosed: ovarian dysfunction, features of hyperandrogenism (clinical or biochemical) and PCO morphology. Although serum LH is not included as a diagnostic feature, the large majority of women with PCOS would have excess elevated LH concentrations when measured at the appropriate time. This may justify the potential advantages in preparations devoid of LH activity as follitropin alpha. Currently, there is no role of lutropin alpha in the management of women with PCOS.

The first baby born after ovulation induction by follitropin in a clomiphene resistant PCOS patient was reported in 1992. Randomized trials comparing follitropin alpha to other gonadotropins preparation or other ovulatory medications, in infertile women with WHO type II anovulation, have reported a live birth rate of 17% to 20%. The rate of successful ovulation has been reported to be between 57% and 85%. The pooled ovulation rate per cycle after rFSH in clomiphene citrate resistant PCOS women has been calculated to be 71% in a Cochrane review (Figure 2). Recent randomized trials have reported higher ovulation rates from 85% and up to 97% in this group of women with comparable clinical pregnancy rates per woman ranging from 17% to 20% after one cycle, and a cumulative clinical pregnancy rate per woman of 42%. A similar cumulative live birth rate of 43% was reported by a subsequent RCT.

There were no significant differences in ovulation rates, pregnancy rates or live birth rates between follitropin alpha and highly purified FSH. However, a small RCT showed more favorable pregnancy rates with rFSH compared to urinary FSH. Two protocols have been suggested for ovulation induction with gonadotropins in this group of patients. In the step-up protocol the FSH dose is increased by 75 IU every 5 to 7 days, while in the low-dose regimen, it is administrated at a low dose for 14 days followed by small incremental dose increases (when necessary), at intervals not shorter than 7 days, until follicular development is initiated. The type of the protocol, has not been shown to affect ovulation or pregnancy rates in studies using follitropin alpha. However, the low dose protocol significantly reduces the incidence of OHSS and multiple pregnancy.

Male subfertility

FSH and LH are gonadotropins and have an important role in the process of spermatogenesis, though the actual mechanism of action is poorly understood. LH may stimulate testosterone secretion from the Leydig cells of the testicle, while FSH stimulates Sertoli cells to facilitate germ cell differentiation. Follitropin alpha alone or with human chorionic gonadotropin (HCG) had been used to improve sperm parameters in male factor infertility. A Cochrane review included RCTs that compared pregnancy rates (spontaneous and after ART) following treatment of couples with idiopathic male factor infertility with urinary or recombinant gonadotropins (compared to placebo or no treatment), showed a significantly higher spontaneous pregnancy rate per couple randomized within three months of completing gonadotropin therapy (OR 4.17, 95% CI 1.30 to 7.09). However, there were only three trials with a total of 234 participants and the authors concluded that more studies were needed to confirm this finding. The two RCTs included in this meta-analysis, where follitropin alpha was administered, showed no significant difference
in pregnancy rates between groups which received rFSH injections compared to those which received placebo or no treatment.\textsuperscript{136,137} Treatment of azospermic men with rFSH for 10 months prior to ICSI may lead to detection of sperms in the ejaculate and spare these men surgical sperm retrieval procedures.\textsuperscript{138} As age of the female partner is considered the single most important factor in predicting success of other interventions such as ICSI, the benefit of this relatively long period of treatment may need to be weighed up against the expected advancement in maternal age, especially in women above 35.

There are few data on the use of lutropin alpha in male factor infertility. Due to its structural similarity, purified HCG may be an effective substitute for LH as the two hormones act through the same Leydig cell receptor.\textsuperscript{139} In normal men, a single IV injection of 150 IU lutropin induces a 25% rise in plasma testosterone levels by comparison with placebo.\textsuperscript{140} We are not aware of any published randomized trials investigating the effect of lutropin alpha for male factor infertility.

In males with hypogonadotrophic hypogonadism presented by azospermia or severe oligoasthenoteratospermia, rFSH may be effective in achieving spermatogenesis in 84% of men with hypogonadotrophic hypogonadism.\textsuperscript{145} A number of baseline factors, including mean testicular volume, body mass index, age of disease onset and response to previous therapy, has been shown to influence the response.\textsuperscript{145,146}

### Patient satisfaction
Recombinant FSH can be used either as subcutaneous or intramuscular injection. Both follitropin alpha and beta are currently available in prefilled pen like devices for self injection. This delivery system has been shown to improve patient compliance and satisfaction.\textsuperscript{82,147,148} A randomized trial comparing follitropin alpha in a pen device to the conventional syringe has shown that the former is associated with significantly higher rates of self-administration and satisfaction, with significantly less pain and local reactions at the injection site.\textsuperscript{149} A questionnaire based study on ease-of-use, safety and efficacy of two follitropin injection pens found the follitropin alpha pen to be effective, well tolerated with higher patient and nurse acceptance than the follitropin beta pen.\textsuperscript{150}

### Economic evaluation
A number of economic analyses comparing rFSH versus uHMG have been published.\textsuperscript{151–154} Two studies compared

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<th>hMG n/N</th>
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<td>1083</td>
<td>100.00 1.18 (1.02–1.38)</td>
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Test for heterogeneity (Chi-square test): $P = 0.97$.
Test for overall effect: $P = 0.03$.

Figure 1 Meta-analysis of randomized trials of hMG versus rFSH following a long down-regulation protocol for the outcome of live births. Adapted with permission from Coomarasamy A, Afnan M, Cheema D, van der Veen F, Bossuyt PM, van Wely M. Urinary hMG versus recombinant FSH for controlled ovarian hyperstimulation following an agonist long down-regulation protocol in IVF or ICSI treatment: a systematic review and meta-analysis. Hum Reprod. 2008;23(2):310–315.\textsuperscript{78} Copyright © 2008 Oxford University Press.

**Abbreviations:** HMG, human menopausal gonadotropin; rFSH, recombinant follicle stimulating hormone.
highly purified FSH with rFSH.\textsuperscript{155,156} Results from these studies, which were supported directly or indirectly by pharmaceutical companies, were conflicting. One of these analyses\textsuperscript{156} was based on data from a large randomized trial comparing the use of HP HMG to rFSH in IVF treatment.\textsuperscript{73} The results have shown urine-derived highly purified HMG to be a cost-effective alternative to follitropin alpha. The median cost per live birth was significantly lower in the HP HMG group than in the rFSH group (£8893 and £11741, respectively, \( P < 0.001 \)).\textsuperscript{156}

An economic analysis based on data from a meta-analysis of 8 RCTs, comparing rFSH to uHMG, has estimated an average cost of an ongoing pregnancy at 13,946 Egyptian pounds (EGP) for a HMG cycle versus 18,721 (EGP) for a rFSH cycle.\textsuperscript{157,158} This economic analysis was based on the prices of rFSH and uHMG in the Egyptian market (150 Egyptian pounds for 75 IU rFSH, and 50 Egyptian pounds for 75 IU uHMG). The cost was calculated on the base of the fees charged by the authors’ IVF center. Al-Inany et al showed that a 60% reduction in the cost of rFSH would be needed in order to provide a cost per ongoing IVF pregnancy similar to that achieved with uHMG.\textsuperscript{158} HMG use would result in 4565 more pregnancies in a hypothetical model based on 100,000 IVF cycles. Wechowski et al\textsuperscript{156} estimated that the savings associated with HP-HMG (as opposed to rFSH) would fund one additional IVF cycle in every 10 cycles while Lloyd et al\textsuperscript{155} projected a 13% increase in the number of cycles possible with the same budget.\textsuperscript{135,156}

The use of uHMG for ovulation induction in anovulatory women can lead to 9.4% reduction in the cost per live birth.\textsuperscript{124}

Two separate economic analyses have demonstrated that uHMG is more cost-effective than rFSH in superovulation with IUI.\textsuperscript{159,160}

### Conclusion

Follitropin alpha and lutropin alpha are human rFSH and rLH, respectively. They are manufactured by genetic engineering techniques which ensure high quality and batch to batch consistency. Current evidence suggested superiority of uHMG over follitropin alpha in controlled ovarian hyperstimulation for IVF in terms of live birth rate per couple. Currently, there is no evidence to recommend the routine use of lutropin to follitropin alpha in an unselected IVF population. The use of follitropin alpha is comparable to HP FSH for ovulation induction in WHO group II anovulation. There is evidence that uHMG preparations (especially currently available highly purified preparations) are more cost effective than rFSH in terms of cost per ongoing pregnancy. However, patient satisfaction and quality of life in women using rFSH injection pen devices are higher than those using the conventional syringes for uHMG.

### Disclosures

The authors declare no conflicts of interest.

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Recombinant follitropin alfa/lutropin alfa in fertility treatment


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