

URINARY GONADOTROPINS VERSUS RECOMBINANT PRODUCTS: STILL NO EVIDENCE OF RECOMBINANT SUPERIORITY

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The randomised clinical trials performed to date to compare urinary versus recombinant gonadotropins have not shown any significant difference for any product in assisted reproduction techniques (ART). Although meta-analyses have claimed superiority of recombinant follicle-stimulation hormone (rFSH), they have doubtful value as they have compared studies with different kinds of urinary and recombinant products and different desensitisation protocols. More recently, a Cochrane Review found urinary human menopausal gonadotropin (uhMG) to be at

least as effective as rFSH in terms of ongoing pregnancy or live birth rate. Urinary gonadotropins have been used for more than 40 years and have an impeccable safety profile with few adverse events.

The costs of infertility treatments to society should also be taken into account, when choosing the right gonadotropin, especially when expensive recombinant products have not made any significant difference in terms of clinical efficacy or safety.

INTRODUCTION

To date, there have been numerous randomised controlled trials comparing urinary and recombinant gonadotropins and several meta-analyses have been conducted to determine which type of product is most effective.

rFSH VERSUS uFSH

In 1999, Daya and Gunby analysed randomised controlled trials between rFSH versus non-purified or highly purified (HP) uFSH, suggesting a benefit for the recombinant product. Although they never claimed so as such, many clinicians drew the inferred conclusion that alpha rFSH (Gonal-F) was superior to beta rFSH (Puregon). However in this analysis, in 97% of all cycles, alpha rFSH was compared with highly purified urinary FSH (Metrodin HP), whereas this was only true for 13% of all cycles with beta rFSH. This product was mainly compared to non-purified urinary FSH (Metrodin) and therefore a real comparison between the two can only be made when both products are shown to be equivalent (Figures 1 and 2). There are, however, no prospective randomised controlled comparisons between non-purified uFSH and HP uFSH, neither will there ever be.

In addition, different uFSHs may have different acidic or basic isoform profiles. Metrodin HP has been shown to have a more acidic isoform profile when compared to Metrodin (Lambert 1995) and as a result may be less potent. Different FSH preparations with varying isoform profiles have different in-vivo effects (Barrios de Tomasi 2002). Therefore, the purported superiority of alpha rFSH is mainly due to a self-fulfilling prophecy as a result of the inferiority of Metrodin HP, and cannot be applied to other uFSHs.

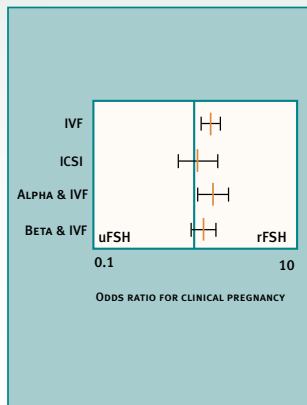


Figure 1. ART trials of clinical pregnancy per cycle start: rFSH versus uFSH (Daya and Gunby 1999)

uhMG VERSUS uFSH

Meta-analyses of randomised controlled trials between uhMG and uFSH have also resulted in conflicting results (Daya et al 1995, Agrawal et al 2000; Figure 2).

The meta-analysis by Daya et al (1995) has been criticised for not taking into account the various pituitary down-regulation protocols that are commonly used in IVF treatment. Hormone levels during these protocols vary so that conclusions made on all types of treatment are of uncertain value.

Agrawal et al (2000) conducted a meta-analysis of uFSH and uhMG taking into account the different down-regulation protocols. Even after this differentiation, there were no significant differences between uhMG and uFSH.

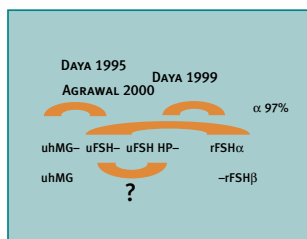


Figure 2. Meta-analyses of gonadotropins

uhMG VERSUS rFSH

A recent Cochrane Review (Van Wely et al 2003) also confirms this evidence. In four individual randomised controlled trials (n=1213), uhMG was shown to be at least as effective as rFSH in terms of ongoing pregnancy or live birth and when the four trials were pooled together (OR 1.27 in favour of HMG (NS); 95% CI 0.98 to 1.64). The safety and amount of gonadotropin used also appeared to be comparable.

In the largest study, the efficacy and safety of highly purified uhMG (Menopur) was compared with rFSH (Gonal-F) in 727 females (Diedrich et al 2002). The primary endpoint of ongoing pregnancy rate demonstrated that HP-hMG was at least as effective as rFSH. Furthermore, the highly purified gonadotropin preparation shared a similar safety and tolerability profile to the recombinant preparation.

COST-EFFECTIVENESS

The costs of infertility treatments to society should also be taken into account, when choosing the right gonadotropin, especially when expensive products have not made any significant difference in terms of clinical efficacy or safety. The Cochrane Review stated that as "uhMG is cheaper than rFSH, a cost-effectiveness analysis is expected to be in favour of uhMG in down-regulated women".

SUMMARY

Overall, the results of the trials and meta-analyses of recombinant and urinary gonadotropins have shown:

- a meta-analysis claiming superiority of rFSH with uFSH is of questionable value
- in the recent Cochrane Review, uhMG was at least as effective as rFSH
- as uhMG and rFSH are comparable in terms of efficacy and safety, costs should dictate the preferred treatment, ie uhMG.

FUTURE ANALYSIS

A secondary analysis of the data available from such trials would be necessary to explore other variables that have an important role in the outcome of ART including:

- type of fertilisation used (in-vitro fertilization [IVF] or intracytoplasmic sperm injection [ICSI])
- type of desensitisation protocol used
- reproductive quality of the oocytes, rather than focusing on the origin of the gonadotropins.

Most importantly, a suitable stimulation protocol that reproduces reproductively competent oocytes without risk of ovarian hyperstimulation syndrome or multiple pregnancies should be found.

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