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Short Communication

Adjusting the PIVET rFSH Dosing Algorithm for the Biosimilar Bemfola Product

John L Yovich[1-4]*, Peter M Hinchliffe[1], Sunthra Lingam[1,3], Shanthi Srinivasan[1,4] and Kevin N Keane[1,2]

[1]*PIVET Medical Centre, Perth, Western Australia*
[2]*School of Pharmacy and Biomedical Sciences, Faculty of Health Sciences, Curtin University, Perth, Western Australia*
[3]*Cairns Fertility Centre, Cairns, Queensland, Australia*
[4]*PIVET Fertility Darwin, Stuart Park, Darwin, Northern Territory, Australia*

Abstract

This short-communication introduces the biosimilar product Bemfola into the fold of gonadotrophin hormonal preparations for safe and efficient application in IVF programmes. It enables recombinant follicle stimulating hormone dosage selection on the basis of personal characteristics of the woman undergoing treatment and allows for appropriate variations according to her plans for preimplantation diagnosis or screening, the idea of segmental treatment whereby embryos are vitrified for future FET procedures and the considerations of oocyte banking or oocyte donation. It does not cover considerations of clinical effectiveness although the cited studies indicate Bemfola has similar clinical outcomes to its reference product Gonal-F.

Keywords: *In vitro* fertilization; rFSH dosage; Ovarian hyperstimulation syndrome; Antral follicle count; Anti-mullerian hormone level; Body mass index; Age

Introduction

Controlled ovarian hyperstimulation: Historical

Although the first infants born from *In Vitro* Fertilization (IVF) and Embryo Transfer (ET) arose from tracking the natural menstrual cycle, that was a default position born of a decade of frustration using urinary gonadotrophins (Pergonal: Serono, Geneva, Switzerland). Estimating the current number of IVF infants world-wide as being in excess of 7 million, the vast majority have arisen from so called controlled ovarian hyper stimulation (COH) which saw a return to using urinary gonadotrophins, followed by an evolution to recombinant (r) hormones namely rFSH (Recombinant follicle stimulating hormone) and rLH (Recombinant luteinizing hormone) [1]. It would also appear that the increased success in using gonadotrophins related to resolving the deficiencies of the ensuing luteal phase which was originally demonstrated as a problem by IVF pioneer Edwards [2]. Furthermore the hazards of gonadotrophin stimulation; namely the life threatening condition to the woman of ovarian hyperstimulation syndrome (OHSS); and the life-threatening condition to the infants of multiple gestations have been progressively "tamed" in modern day. This has been achieved by better "controlled" COH combined with a Single Embryo Transfer (SET) strategy and careful luteal support strategies adjusted for follicle and oocyte numbers arising. The further evolution of applying gonadotrophin releasing hormone (GnRH) analogues - both agonists (a) and antagonists (ant) has enabled more sophisticated COH strategies including triggering with GnRHa as well as the idea of segmentation of IVF treatment avoiding fresh ET and deferring to frozen ET (FET) procedures after vitrifying blastocysts [3,4].

Personalised ovarian hyperstimulation

Against this historical setting and evolving background, the modern approach increasingly examines the characteristics of the individual women entering into IVF programmes with a view to personalized adjustments of the various stages and modes of treatment. In this article the focus is on rFSH dosage where the aim is to collect 10 (8-12) mature (metaphase II) oocytes and avoid cases of overstimulation (especially >20 oocytes) where the risks for OHSS rise dramatically. With this in mind our IVF facility PIVET (an acronym for programmed IVF & ET) developed its first personalized algorithm based on 8 criteria - Age, AFC; Antral follicle count, AMH; Anti-mullerian hormone level, BMI; Body mass index, day 2 FSH, smoking history, autologous vs. donor cycle and plan for transfer (e.g. deferred for oocyte banking or pre-implantation genetic diagnosis). The algorithm was facilitated by the introduction of metered rFSH pens enabling small dosage increments. The first was Puregon (MSD, New Jersey, USA) in 2007 with ~8.3 IU per click followed by Gonal-f (Merck Serono, Darmstadt, Germany) in 2011 with 12.5 IU per click. The first study showed that oocyte numbers could be adequately controlled (COH) in all age groups without compromising pregnancy rates [5]. This was also associated with a significant reduction in OHSS risk as measured by the proportion of women under 40 years requiring entry to the increased monitoring protocol (IMP) during the luteal phase. The data reported pre-algorithm (149/572 cases; 26.1% reducing to 30/371 cases; 8.1% during the algorithm: $p<0.0001$). The actual number of cases hospitalized for OHSS was 1/540 cases; <0.2% and that case was deemed totally avoidable if the protocol was followed. These improvements were achieved by significant reductions in the number of oocytes recovered, particularly the proportion with >15 oocytes falling from 25% to 9% and with no reduction in pregnancy rates in younger women (<40 years) during the period even though there was a rising SET rate.

Better controlled ovarian hyperstimulation

A second study on the PIVET algorithm reported on a modification whereby the maximum rFSH dosage was reduced from the previous 600 IU to 450 IU per dose [6]. Again, the mean number of oocytes recovered was 10.0 for women <40 years and showed that this was

***Corresponding author:** John L Yovich, PIVET Medical Centre, 166-168 Cambridge Street, Perth 6007, Australia, Tel: +61 8 9422 5400; Fax: +61 8 9382 4576; E-mail: jlyovich@pivet.com.au

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achieved with <150 IU in 24% of women. Furthermore the selected rFSH dosage required no change in almost 80% of women and even 30.1% of those with high AFC ratings receiving ≤ 75IU required no change in dosage. There was no reduction in pregnancy or live birth rates and the two rFSH dosing Algorithms (Puregon and Gonal-F) showed comparable live birth rates per initiated cycle. Only 3.9% of women had >20 oocytes collected and OHSS rates remained under 0.3% with each case shown to be avoidable if the protocols were more strictly followed. A further rFSH dosage study for the long-acting corifollitropin alfa (Elonva; MSD) shows a safe range across rFSH dosages between 200-400 IU [7]. However Elonva should be avoided in women with AFC >20 antral follicles because of a greater risk of OHSS. Furthermore individualized rFSH dosages are preferable for women with <5 antral follicles requiring ≥400 IU to optimize oocyte retrievals.

Bemfola: A biosimilar gonadotrophin

Bemfola (Finox AG, Burgdorf, Switzerland) is categorized as a biosimilar rFSH meaning it has the same make-up as follitropin alfa, with the established reference product being Gonal-F. It was released in Europe in 2014 following expiry of the patent for the originator, Gonal-F and shown to be comparable for cost-efficiency for generating live births [8]. It was actually the second biosimilar rFSH (Follitropin Alfa) released in the European Union, the first, Ovaleap (Teva Pharma B.V. Utrecht, The Netherlands) was released the year prior, in 2013. There are differences in the glycan profile and sialylation pattern between Gonal-F and Bemfola and these differences do have relevance with respect to binding on the FSH receptor (FSHR) and translational bioactivity. This needs to be considered in relationship to the fact that pituitary derived human FSH (hFSH) contains a heterogeneous population of glycovariants with varying degrees of sialylation, sulfation, antennarity (branching index) and core fucosylation in both the alpha and beta subunits. There are 4 naturally occurring glycoforms of hFSH and their ratios vary according to the stage of the follicular phase, the more acidic glycoforms prevailing in the early phase with a shift to less acidic forms in the periovulatory phase. Furthermore there are age related differences with di-glycosylated hFSH being more abundant in younger and tetra-glycosylated forms more prevalent in older women. These differences in the natural state enable acceptable variations in biosimilar products such as Bemfola but could lead to differences in clinical outcomes [9]. However the phase 3 clinical trial enabling Bemfola approval did not reveal any significant clinical differences although the trial has not been without its critics [10,11]. The manufacturing process for Bemfola is similar to that of Gonal-F involving cultivation of Chinese hamster ovary cells which have been genetically modified by viral transfection in a serum free cell culture medium within a bioreactor. Bemfola 75 international units (IU) contain 5.5 µg of follitropin alfa per 0.125 ml injection solution. It has now been presented to the fertility market word-wide in 5 separate pre-filled pens (Figure 1). It is indicated for the treatment of anovulatory infertility where clomiphene citrate is contra-indicated or the woman has been unresponsive. It is particularly useful for women with hypogonadotrophic hypogonadism where it is used in conjunction with rLH in such cases. It can be similarly indicated for males with hypogonadotrophic hypogonadism for the stimulation of spermatogenesis. Its widest use however is in assisted reproduction for COH.

Prescribing bemfola: In Australia Bemfola is categorized as an S4 drug, only available on prescription and provided at a low prescription charge (A$38.80) under the Medicare System when prescribed according to the Schedule of Pharmaceutical Benefits (PBS). It is a clear colourless solution designed for subcutaneous injection. Other ingredients included in the cartridge are sucrose, di-Sodium hydrogen phosphate dihydrate, Sodium dihydrogen phosphate dihydrate, phosphoric acid, polaxamer and methionine all dissolved in water. Unlike Gonal-F there is no m-Cresol preservative as Bemfola is designed for single-use only. There are currently 5 strengths available for the Bemfola Pen Injector enabling selected usage; namely 75IU, 150 IU, 225 IU, 300 IU and 450 IU (Figure 1). There are 3 pack sizes for each strength being 1 (single), 5 and 10 pre-filled pens. Each pen enables the selection of dosages of rFSH with 12.5 IU increments within set ranges e.g. the 75 IU pen covers 37.5 IU to 75 IU in 3 steps whilst the 300 IU pen covers 225 IU to 300 IU in 6 steps. The devices are single use pre-filled syringes and patients are instructed to discard the pen following their selected single dosage injection (Figure 2).

With respect to choosing the appropriate pen for the rFSH dosing algorithm, it needs to be borne in mind that although 80% of women will not require any change, some cases may require a higher dosage than shown. This has been considered in the colour coding which ensures feasibility for raising the dosage by up to 3 increments for the 75 IU pen and up to 8 increments for the 450 IU pen (Figure 2). For

Figure 1: The 5 Bemfola pens containing biosimilar follitropin alfa to the innovative reference product Gonal-f. The specific dosage pens are colour coded being yellow for 75 IU, orange for 150 IU, red for 225 IU, purple for 300 IU and blue for 450 IU.

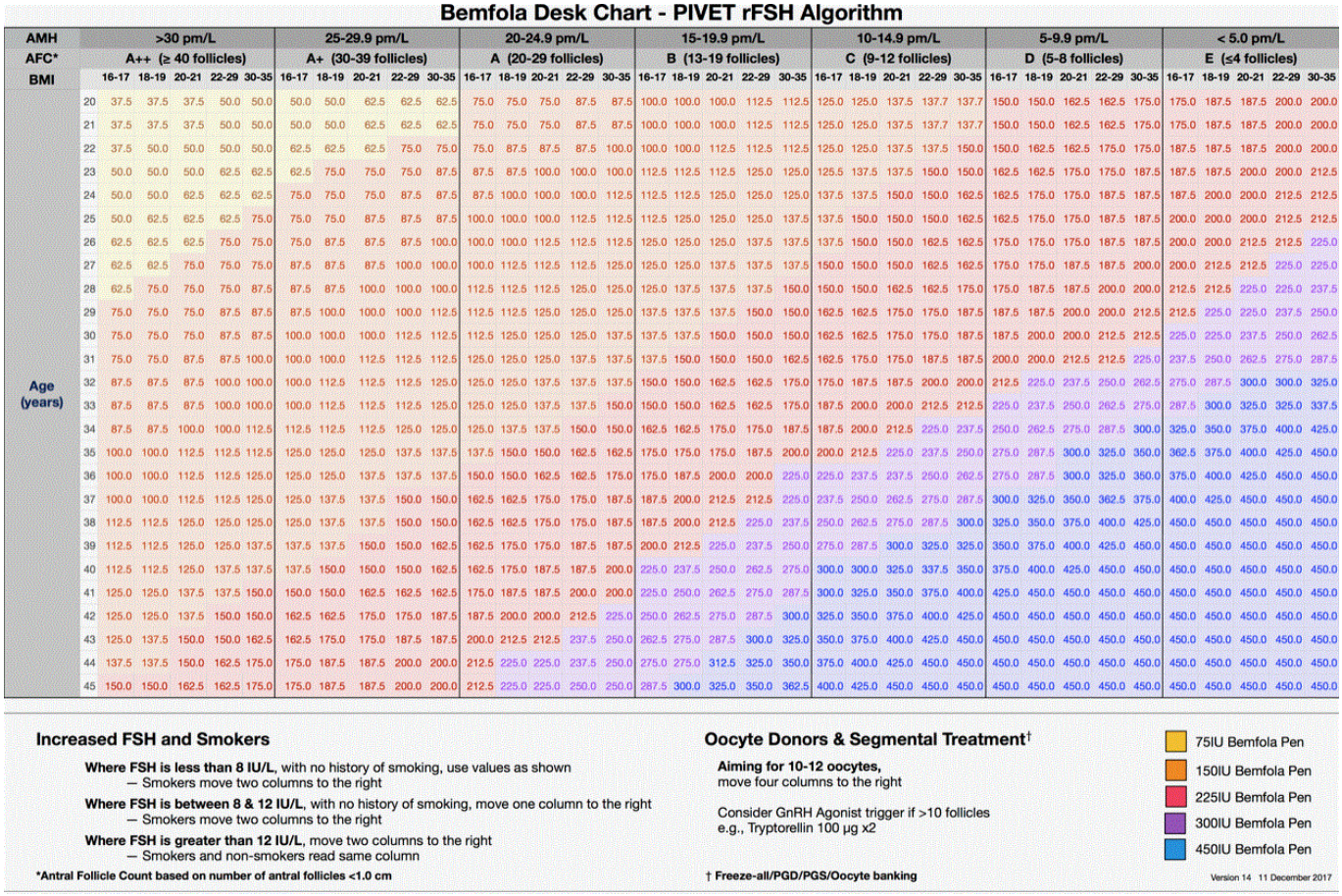

Figure 2: The PIVET rFSH dosing algorithm for Bemfola adapted from that used for the innovative reference product Gonal-F. It contains unique colour coding to enable easy selection of the appropriate Bemfola pen to suit the precise rFSH dosage and enable some flexibility to increase the increments when necessary. Selecting the rFSH dosage by the algorithm.

most a single or 2-step increment will suffice for the 20% of women who may require this. In the poorer-responding 450 IU patient group a larger incremental step is safely feasible. Each of the 5 pens enables coverage across the various dosages defined in the PIVET algorithm which was designed for Gonal-F with 12.5 IU increments but modified with colour specifications for Bemfola. For standard autologous usage, aiming for 8-12 oocytes, with a maximum of 15 oocytes, the rFSH dosage is decided stepwise, beginning with the woman's age then selecting according to the AFC category, choosing that dosage covered within the BMI column. In 87% of cases the AMH category will accord but if there is a higher rating, the rFSH dosage should be adjusted downwards accordingly (i.e., AMH category over-riding the AFC category) [12]. If the AMH indicates a lower rating, it should be ignored (i.e., do not increase the rFSH dosage above that indicated by the AFC). Minor considerations relate to the baseline (Day 2) serum FSH level and history of smoking, adjusting the rFSH dosage upwards according to the notations in the algorithm. Where the woman is acting as an ovum donor, banking oocytes for her own usage or segmenting treatment for reasons including preimplantation genetic diagnosis or screening, deferment of ET or elective freeze-all, the trigger is usually by GnRHa following on GnRHant down-regulation. Such cases do not have fresh ET and the luteal phase hormones estrogen and progesterone can be suppressed by various strategies. In this scenario, it is reasonable to aim for 12-15 oocytes to maximize the utility of the cycle hence rFSH dosage can be increased by adjusting 4 columns or steps, to the right.

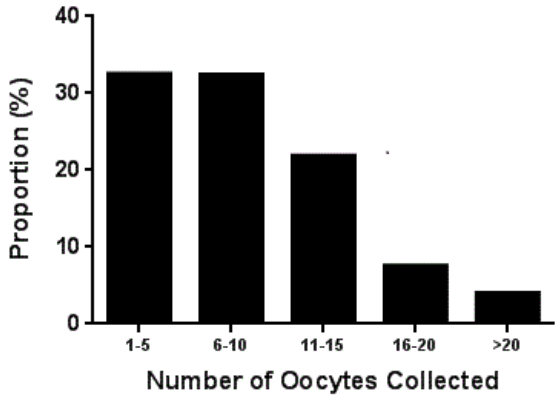

Figure 3: Shows the distribution of oocytes recovered applying rFSH using the PIVET algorithm. Almost 90% of women had ≤15 oocytes collected, the lower numbers (1-5) being from women with low antral follicle counts (categories D and E). Figure derived from Dovepress article; Yovich et al. [6].

The reported oocyte recovery rates using this Algorithm is shown in Figure 3 where 90% of women will have ≤15 oocytes collected and hospitalization for OHSS is rare, potentially avoidable completely (Figure 3).

Conclusion

This short-communication introduces the biosimilar product Bemfola into the fold of Gonadotrophin hormonal preparations for safe and efficient application in IVF programmes. It enables rFSH dosage selection on the basis of personal characteristics of the woman undergoing treatment and allows for appropriate variations according to her plans for preimplantation diagnosis or screening, the idea of segmental treatment whereby embryos are vitrified for future FET procedures and the considerations of oocyte banking or oocyte donation. It does not cover considerations of clinical effectiveness although the cited studies indicate Bemfola has similar clinical outcomes to its reference product Gonal-F.

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