DEBATE—continued

Is there a place for different isoforms of FSH in clinical medicine?

IV. The clinician’s point of view

David T.Baird

Centre for Reproductive Biology, University of Edinburgh, 37 Chalmers Street, Edinburgh, EH3 9ET, UK.
Email: dtbaird@ed.ac.uk

Follicle stimulating hormone (FSH) plays an important role in gametogenesis in both men and women. In men it is required for the establishment and probably maintenance of spermatogenesis. In women it stimulates the growth of ovarian follicles and fluctuations in its secretion are involved in the selection of the ovulatory follicle. It is now possible by recombinant DNA technology to synthesize a range of isoforms of FSH with differing biological action and half-life which would provide a greater degree of flexibility in the treatment of women with anovulatory infertility. Longer acting isoforms of FSH would find clinical application in the treatment of hypogonadotrophic men.

Key words: anovulatory infertility in women/clinical medicine/FSH isoforms/hypogonadotrophic men

Introduction

The first use of gonadotrophins extracted from human pituitary to induce ovulation in women in 1958 represented a major advance in reproductive medicine (Gemzell et al., 1958). Since then, gonadotrophins of urinary origin (HMG) or more recently recombinant FSH and LH have been used successfully to restore reproductive function in hypogonadotropic men and women (Baird, 1993). Although FSH obtained by the recombinant technique has slightly more basic forms than HMG, the pI of both preparations is much more acidic than pituitary FSH and, hence, has a longer half-life (~24 h) (Le Cotton et al., 1994; Diczfalusy and Harlin, 1998). As a consequence, significant concentrations of FSH persist in the blood for several days after a single i.m. injection. It is now possible with recombinant technology to design FSH preparations with shorter or longer half-lives than those which are currently available (Boime et al., 1990; Howles, 1996; Out, 1997).

For example, by site-directed mutagenesis the Asn N-linked oligosaccharides at position 52 on the α chain or 13 on the β chain could be deleted, resulting in a molecule which retained biological activity but had a much reduced half-life. In contrast, hybrids composed of FSHβ with C terminal HCG terminal extension result in a molecule with a much longer half-life. Would these preparations have any clinical application?

Before considering individual preparations and their potential application, it is worthwhile reviewing the physiological role of FSH and LH in men and women. In primates, including man, it is likely that spermatogenesis is initiated by both FSH and testosterone (Weinbauer and Nieschlag, 1998). Although there is some evidence that spermatogenesis, once initiated, can be maintained by LH-stimulated testosterone alone, it is likely that even in the adult man, FSH stimulates spermatogenesis by interacting with receptors on Sertoli cells. In women, antral follicles are totally dependent on FSH, the concentration of which fluctuates throughout the cycle (Baird, 1999). These variations in the concentration of FSH play a crucial role in the final stages of folliculogenesis and ensure that only a single follicle is selected for ovulation. This concentration of FSH is carefully controlled at each stage of the follicular phase by the feedback of oestradiol and inhibin from the dominant follicle (McGee and Hsueh, 2000). By limiting the time during which the concentration of FSH is elevated in the early follicular phase of the cycle, the number of follicles selected for ovulation is restricted. It is clear, therefore, that the feedback system must be sufficiently sensitive to signals from the dominant follicle that the concentrations of FSH fall promptly before additional follicles are recruited. The change in the secretion of isoforms of FSH from the pituitary prior to ovulation in response to increasing concentrations of oestradiol, may facilitate the more rapid clearance of FSH from the blood (Wide and Wide, 1984).

Clinical application

Men

In order to induce and maintain spermatogenesis in men with hypogonadotrophic hypogonadism, it is necessary to treat them for several months or years with a combination of FSH and LH (Schaison et al., 1993; Kliesch et al., 1995; Burgues et al., 1997). It is likely that the regimen which most closely simulated the physiological stimulus would be optimal i.e. a constant concentration of FSH without much fluctuation. The regimen most commonly used in clinical practice is a compromise between the ideal and practical, involving injections of HMG or r-FSH two or three times per week. In addition, 1500–3000 IU HCG are given as a surrogate for LH.

Although spermatogenesis can be stimulated and pregnancies achieved, the regime results in unphysiological fluctuations in the concentration of FSH and relatively high constant concentrations of HCG. A preparation of FSH with a longer half-life of several days would result in more constant concentrations of FSH and would be more convenient because it could be given less frequently e.g. once per week. Although small pulses of r-LH
Women

Gonadotrophins are used in women for (i) ovulation induction and (ii) stimulation of multiple follicular development in association with assisted reproduction techniques.

Ovulation induction

One of the major problems associated with the standard methods of ovulation induction with gonadotrophins is the high incidence of multiple ovulation and high order births (Baird, 1993). New regimens such as 'step down' or 'low dose' are designed to reproduce the changes in concentration of FSH which occur in the normal cycle when there is a single ovulatory follicle (Glasier et al., 1988; Fauser et al., 1993; Franks et al., 1994). Because of variations in responsiveness to FSH, it is necessary to tailor the dose to individual women by monitoring their response and adjusting the dose accordingly (Brown, 1978). Because of the long half-life of present preparations of FSH, there may be a considerable lag time between altering the dose of FSH and the concentration in blood falling. A shorter acting preparation of FSH would facilitate achieving the optimum concentration particularly after the threshold concentration of FSH has been reached. At least three preparations with differing half-lives e.g. 6, 12 and 24 h, would be necessary to provide the optimum flexibility (Figure 1) (Baird, 1999). A small constant amount of LH could be given throughout (~75 IU/day) to maintain adequate oestrogen secretion. At the initial stage of follicle recruitment a preparation of FSH with a longer half-life (~24 h) could be used until the threshold concentration required to activate one or two follicles had been reached. This preparation would then be replaced by FSH with shorter half-lives so that as soon as a dominant follicle had emerged (10–12 mm diameter) the dose could be lower to reduce the concentration of FSH below the threshold necessary to recruit or activate further follicles. By more closely reproducing the changes in FSH concentration which occur in the natural cycle with this 'step down' regimen, it should be possible to achieve ovulation of a single follicle more easily.
Stimulation of multiple follicular development

In contrast to ovulation induction, FSH is used prior to IVF or intruterine insemination (IUI) in order to stimulate the development of many follicles (Fauser et al., 1999). In this situation the normal physiological mechanism which selects a single ovulatory follicle is overridden by maintaining the concentration of FSH at supraphysiological concentrations until the desired number of follicles have been stimulated (Guzick et al., 1999). The relatively long half-life of FSH in HMG or recombinant preparations is an advantage ensuring that the injections do not need to be given more often than daily. Although there are minor differences in isoforms between follitrophin α and β, the two available commercial preparations, Puregon® and Gonal-F®, are equivalent for clinical purposes (Harlin et al., 2000). Both recombinant preparations are slightly more effective than those derived from urine (Baird and Howles, 1994; Out et al., 1996; Frydman et al., 2000). There may be some clinical convenience to using FSH with an even longer half-life, but there is individual variation in sensitivity between women which necessitates adjusting the dose to ensure the optimum response. Some women, e.g. those with polycystic ovarian syndrome (PCOS) are very sensitive to FSH and run an increased risk of hyperstimulation (Baird and Anderson, 1997). It may be that once the optimal dose has been determined in the first cycle, the same daily dose of longer acting preparation could be used. However, because the new preparation can be self-administered and the length of treatment between women which necessitates adjusting the dose to ensure the optimum response. Some women, e.g. those with polycystic ovarian syndrome (PCOS) are very sensitive to FSH and run an increased risk of hyperstimulation (Baird and Anderson, 1997). It may be that once the optimal dose has been determined in the first cycle, the same daily dose of longer acting preparation could be used. However, because the new preparation can be self-administered and the length of treatment is relatively short compared with that required to induce spermatogenesis, it is unlikely that FSH with a longer half-life than that of the current preparations would have much application in IVF. A shorter acting preparation given on the last day of FSH stimulation, might reduce the risk of hyperstimulation due to continued recruitment of additional follicles after oocyte retrieval.

In conclusion, it is unlikely that isoforms of FSH with half-lives longer than present preparations would have much clinical application except for stimulation of spermatogenesis. For induction of ovulation, a range of products with relatively short half-lives would permit more sensitive manipulation of the therapeutic dose and facilitate achieving mono-ovulation. The current preparations of FSH are likely to continue to dominate clinical use for ovarian stimulation prior to IVF.

References


