Biotechnological Drugs for Reproductive Disorders
A Review of Developments

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Summary

Recombinant gonadotrophins, in particular recombinant follitropin (follicle-stimulating hormone; FSH), are now available for ovarian hyperstimulation for assisted reproduction. In contrast with urinary FSH (urofollitropin), follitropin is available in virtually unlimited quantities. Follitropin is as potent as urofollitropin in all protocols of ovarian stimulation. Furthermore, it shows an improved purity without contamination by urinary proteins not related to FSH, and can be injected subcutaneously by the patients themselves. In patients with complete luteinising hormone (LH) deficiency, follitropin stimulates follicular development, although serum levels of estradiol remain low. For this group of patients the addition of LH is necessary. Ongoing phase III studies on the use of recombinant LH in this indication will provide an answer to how much LH is needed in order to guarantee sufficient follicular growth and hormonal response.

Gonadorelin (gonadotrophin releasing hormone; GnRH) analogues are used to avoid the surge of endogenous LH in ovarian stimulation protocols. Gonadorelin antagonists are now in clinical testing for the same indication. Gonadorelin antagonists allow sufficient suppression of endogenous LH levels. In contrast with gonadorelin analogues, they avoid any flare-up effect, i.e. an initial release of gonadotrophins from pituitary reservoirs.
Recombinant gonadotrophins and gonadorelin antagonists are new tools towards a more individual approach to ovarian stimulation.

This review focuses on new developments in biotechnologically produced drugs that assist female reproduction. Two groups of drugs will be discussed in detail: firstly, the development of recombinant gonadotrophins and their application in assisted reproduction and follicular maturation and, secondly, the use of antagonists of gonadorelin (gonadotrophin releasing hormone; GnRH) as tools for ovarian downregulation when added to ovarian hyperstimulation protocols.

Gonadotrophins have been widely used for ovarian stimulation since the early 1960s.[1,2] They are the treatment of choice in cases of ovulatory disorders that do not respond to clomiphene citrate after other causes of anovulation have been excluded.[3] Furthermore, gonadotrophins are commonly used for ovarian superovulation prior to assisted reproductive techniques, introduced worldwide after the birth of the first in vitro fertilisation (IVF) baby in 1978.[4] Initially, ovarian hyperstimulation was based on human menopausal gonadotrophins (menotropins; HMG) which contain the gonadotrophic hormones luteinising hormone (LH) and follicle-stimulating hormone (FSH) in almost equal amounts. First pregnancies using gonadotrophins extracted from postmenopausal urine have been reported by Lunenfeld et al.[1] However, it has been clearly shown that it is the FSH component that is responsible for sufficient follicular development, and that additional LH administration is not necessary in almost all groups of patients.[5]

In order to eliminate LH from HMG, purification of HMG from postmenopausal urine was performed, leading to a pharmaceutical preparation of urinary FSH (urofollitropin) that contained only minimal amounts of LH. This preparation came into routine clinical use in the 1980s. Urofollitropin was successfully used in ovarian stimulation in patients with polycystic ovarian syndrome (PCOS)[6] and in ovarian hyperstimulation for IVF.[7] In order to obtain a still higher purification grade, monoclonal antibodies to capture the FSH protein and a number of high performance liquid chromatography steps to remove non-FSH proteins were applied. This highly purified preparation was also successfully used in ovulation induction.[8,9] Finally, different preparations of gonadotrophins with varying degrees of purity, based on urinary sources, became available in the early 1990s.

The worldwide demand for gonadotrophins is steadily increasing: more than 100 000 IVF cycles are performed per year.[10] Since the availability from urinary sources is limited, alternative methods to obtain FSH as a monotherapeutic preparation with almost unlimited access, a high degree of batch-to-batch consistency, safety and a user-friendly application are needed.

1. Recombinant Follitropin

1.1 Physiology

The FSH molecule is a heterodimeric glycoprotein with 2 subunits, α and β.[11] According to the two-cell/two-gonadotrophin hypothesis,[12] FSH stimulates the aromatase activity of granulosa cells. In contrast, LH is responsible for the synthesis of androgens in the thecal cell layer (fig. 1).