Efficacy of different gonadotropin combinations to support ovulation induction in WHO type I anovulation infertility: Clinical evidences of human recombinant FSH/human recombinant LH in a 2:1 ratio and highly purified human menopausal gonadotropin stimulation protocols

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ABSTRACT. Background: The World Health Organization (WHO) Group I anovulation, or hypogonadotropic hypogonadism (HH), is characterized by reduced hypothalamic/pituitary activity which results in abnormally low serum FSH and LH levels and negligible estrogen activity. Aim: To compare the efficacy of human recombinant FSH (r-hFSH) plus human recombinant LH (r-hLH) in a 2:1 ratio with highly purified human menopausal gonadotropin (hMG-HP) urinary extract, containing LH-like activity, in women with HH. Subjects and methods: This two-arm randomized open-label study included 35 HH women (aged 25-36 yr) attending our Center. Eighteen patients received 150 IU hMG-HP (150 IU FSH + 150 IU LH-like activity) and seventeen received 150 IU r-hFSH/75IU r-hLH daily for a maximum of 16 days. Ovulation was induced by a single administration of hCG on the day after the last hMG-HP or r-hFSH/r-hLH. Results: The primary efficacy endpoint was ovulation induction as measured by follicle ≥17 mm, pre-ovulatory estradiol (E2) ≥400 pmol/l and mid-luteal phase progesterone (P4) ≥25 nmol/l. Secondary efficacy endpoints included E2 levels/follicle at mid-cycle, number of follicles at mid-cycle and pregnancy rate (PR). Following a total of 70 cycles, 70% of r-hFSH/r-hLH treated patients met the primary endpoint vs 88% in hMG-HP group (p=0.11). However, PR in r-hFSH/r-hLH group was 55.6% compared to 23.3% in hMG-HP group (p=0.01). Conclusions: The primary endpoint achievement did not correlate with PR. This study has shown the superiority of LH compared to hCG in supporting FSH-induced follicular development in HH women. (J. Endocrinol. Invest. 35: 996-1002, 2012) ©2012, Editrice Kurtis

INTRODUCTION

The World Health Organization (WHO) type I hypogonadotropic anovulation [hypogonadotropic hypogonadism (HH)] is a rare alteration of the reproductive system with absent or decreased function of the gonads, caused by congenital, including genetic, or acquired reduced hypothalamic or pituitary activity (1, 2). This results in abnormally low serum levels of FSH and LH and negligible estrogen activity (3). The disorder may therefore be characterized by the failure to undergo the usual reproductive modifications during puberty or, if occurring after puberty, it might induce secondary amenorrhea. The diagnosis of HH is clinically confirmed by endocrine testing that demonstrates low gonadotropin serum levels and low estrogen levels (4).

The main consequence of absent ovarian function is anovulation and infertility during reproductive age. Absent ovarian function is caused by the lack of a combined effect of LH and FSH, both involved in the hypothalamic-pituitary axis. This leads to different treatment options in this group of patients, including administration of pulsatile GnRH therapy that is able to restore the periodic release of FSH and LH, resulting in ovulation and pregnancy (5). Alternatively, a more convenient treatment with daily injections of exogenous gonadotropins has also been proven to be effective. FSH has a role in the recruitment and growth of follicle cohorts during the follicular phase. Whereas LH activity promotes androgen production in theca cells and increases ovarian sensitivity to FSH in granulosa cells, it promotes estrogen secretion by the pre-ovulatory follicle, stimulates meiosis resumption and oocyte maturation. Physiologically, the synergic action of the two gonadotropins leads to good quality oocytes, normal endometrial growth, and normal luteal phase progesterone (P4) levels (6-9). In Controlled Ovarian Stimulation protocols, the majority of female infertile patients do not need LH supplementation as endogenous LH levels are sufficient to achieve success (10-13). Patients lacking effective hypothalamic-pituitary activity (WHO type I anovulation) do not produce sufficient threshold levels of endogenous LH, which is required to obtain optimal follicular development and steroidogenesis, when treated with FSH alone. Therefore, only combination therapy, with adequate doses of both FSH and LH in an optimal ratio, is effective in restoring fertility.

The first available source of human gonadotropins was a human menopausal gonadotropin (hMG) urinary extract containing both FSH and LH at a fixed combination of 1:1, 75 IU FSH and 75 IU LH-like activity, mainly generated by urinary hCG (u-hCG) present in the urinary prepa-
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Subsequently, follitropin α [recombinant human FSH (r-hFSH)] has been successfully used for ovarian stimulation for more than 20 years. Later, lutropin α was introduced into the market to be added to follitropin α for certain types of patients. Data from clinical trials of ovulation induction in the WHO type I population, have shown that the level of efficacy achieved when both r-hFSH and r-hLH are administered is clinically and statistically above that of r-hFSH alone (17-19). Recently, a new product containing a fixed combination of 150 IU of follitropin α and 75 IU of lutropin α has been developed to provide a combination therapy that ensures adequate doses of both FSH and LH at an optimal ratio for the purpose of stimulating follicular development (20, 21).

The aim of this study was to compare the efficacy of r-hFSH + r-hLH in a 2:1 ratio with highly purified hMG (hMG-HP) urinary extract, containing LH-like activity, in women with severe LH and FSH deficiency (WHO type I anovulation, HH). The clinical outcomes evaluated in this study included ovulation induction, estradiol (E2) serum parameters and pregnancy rate (PR).

MATERIALS AND METHODS

**Patients**

This 2-arm randomized, open-label study enrolled 35 HH women (aged 25-36 yr: 30.4±3.78) attending the Center of Reproduction and Andrology (CREA), Taranto, Italy between July 2008 and November 2011 and who fulfilled certain criteria. The treatment assigned to each subject was determined according to a computer-generated randomization list (1:1 blocks). Considering that WHO type I hypogonadotropic anovulation is a rare alteration of the reproductive system, it was decided to include in the study all patients affected by this condition who approached the center during the enrolment period. The sample size was not calculated according to power analysis. The study, a locally sponsored investigator trial, received institutional review board approval by the institute’s Scientific Committee (Approval Number: 022011; clinical trial.gov identifier: NCT01623570) and was carried out according to the Declaration of Helsinki on studies involving human subjects. All 35 enrolled patients signed an informed consent form for the use of their personal information in any type of data collection. Figure 1 shows a diagram with details on the different stages of the trial.

All patients were diagnosed with HH according to a negative P₄ challenge test, serum LH<1.2 IU/l and FSH<5 IU/l (Table 1), a transvaginal ultrasound showing a uterus with a midline echo, no ovarian tumor or cyst and ≤13 small follicles (mean diameter ≤10mm) on the largest section through each ovary, a bone mineral index between 18.4 and 31.4, and no systemic diseases. The majority of patients had primary amenorrhea (85.7%) while 5 patients (14.3%) had secondary amenorrhea. Age of menarche for the 5 patients with secondary amenorrhea ranged between 14 and 16 yr.

![Flow chart diagram illustrating the different stages of the study.](image-url)