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Title:

Urinary hMG (Meropur) versus recombinant FSH plus recombinant LH (Pergoveris) in IVF: a multicenter, prospective, randomized controlled trial

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Urinary hMG (Meropur) versus recombinant FSH plus recombinant LH (Pergoveris) in IVF: a multicenter, prospective, randomized controlled trial

To compare IVF outcome in ovarian stimulation protocols with recombinant FSH plus recombinant LH versus hMG, 122 patients were randomized into two study groups: group A, patients treated with urinary hMG, and group B, patients treated with rFSH plus rLH. The two groups proved to be comparable to the main IVF outcome (pregnancy rate, implantation rate, oocytes, and embryos quality), with an increasing risk of ovarian hyperstimulation in the Pergoveris group. (Fertil Steril® 2010;94:2467–9. ©2010 by American Society for Reproductive Medicine.)

Key Words: Triptorelin, rLH, rFSH, uhMG

FSH and LH are well known for playing separate but complementary roles in the regulation of the follicle, leading to synergistic actions in stimulating follicular growth and ovulation (1, 2).

The relative importance of LH during the follicular phase and its role in the stimulation of the follicle is still subject to extensive debate, and questions surrounding the optimal amount of LH in the stimulation protocols and the drugs used for this purpose are still controversial (3, 4). Experience has shown that stimulation with FSH alone is sufficient to achieve optimal results in most patients (5–7).

Some investigators suggested that ovarian response is evoked when an FSH serum “threshold” is reached. The requirements for FSH vary during the follicular phase as follicles grow and are more sensitive to gonadotropin stimulation (8). Furthermore, Hillier (9) proposed that in addition to the threshold level of FSH, the follicle has a finite requirement for stimulation by LH, which enhances steroid genesis.

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The theory that both FSH and LH are required for the complete stimulation of follicular maturation dates back 50 to years ago: in 1959, Falck (10) proposed the two-cell, two-gonadotropin theory: the synergistic action of both gonadotropins is presumed to be necessary for follicular maturation and steroid genesis.

The administration of exogenous LH with FSH in controlled ovarian stimulation is obligatory for patients with hypogonadotropic hypogonadism (11).

Tesarik and Mendoza (12) showed that the inclusion of exogenous LH resulted in an increase in the number of mature oocytes and good-quality zygotes and embryos and higher implantation rates when compared with stimulation with FSH alone.

Some investigators have reported lower estradiol (E₂) biosynthesis, lower oocyte and embryo yield, and a higher frequency of early pregnancy wastage in normogonadotrophic women down-regulated with a GnRH agonist and stimulated with highly pure FSH preparations when compared with women stimulated with hMG or with a combination of hMG and FSH (13–15).

The aim of our study was to compare these two ovarian stimulation protocol in down-stimulated cycles and to confirm the paramount importance of LH in endometrial and follicular development, oocytes, and embryo quality, pregnancy and implantation rate, total number of oocytes retrieval, duration of stimulation, risk of ovarian hyperstimulation syndrome (OHSS).

From July 2008 to September 2009 122 patients were enrolled in this study with the following inclusion criteria: [1] main causes of infertility attributable to tubal, idiopathic, or male factors; [2] serum levels of FSH on day 3 of the ovarian cycle <12 IU/L; [3] regular menstrual cycle; [4] endogenous LH <1.2 IU/L; [5] normal uterine cavity. This study was a randomized controlled trial to establish which down-regulation protocol is most efficacious. The physicians were blinded to the randomization. All patients were counseled about the nature of the study and gave their written informed consent for their participation in the randomization procedure. Our local ethical committee approved the study. Only the patients undergoing their first cycle of IVF that satisfied the inclusion criteria were

TABLE 1**Embryologic characteristics and clinical outcome comparing groups A and B.**

	Group A (n = 58)	Group B (n = 53)	P value
Days of stimulation ± SD	14.1 ± 1.6*	10.9 ± 1.1*	.013*
Total IU of FSH per cycle ± SD	3,525 ± 232.5*	4,800 ± 345*	.0047*
Estradiol level at hCG day (pg/mL)	2,056 ± 560	1,987 ± 699	NS
Endometrial thickness at hCG day (mm) ± SD	10.8 ± 2.1	11.2 ± 3.1	NS
Total oocytes retrieval ± SD	4.1 ± 1.2*	7.8 ± 1.1*	.0021*
Mature oocytes (MII), %	48.2*	34.7*	.008*
Mature oocytes (MI), %	24.6	30.7	NS
Immature oocytes (GV), %	27.2	34.6	NS
Mean number of embryos transferred/patient	2.4 ± 0.7	2.6 ± 0.8	NS
Grade I embryos, %	46.2	47.4	NS
Grade II embryos, %	33.6	31.3	NS
Grade III embryos, %	16.0	19.2	NS
Grade IV embryos, %	4.2	2.1	NS
Pregnancy rate per cycle	29.3 (17)	28.3 (15)	NS
Implantation rate	12.8	12.1	NS
Canceled patients for high risk of OHSS, n (%)	1 (1.7)*	7 (11.1)*	0.042*

Note: NS = not significant; OHSS = ovarian hyperstimulation syndrome.

* Significant.

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enrolled in the study to reduce the heterogeneity of the patients and minimization of confounding variables that may have affected the results.

The patients were assigned to the two study groups after computerized randomization: group A (n = 60), patients treated with a down-regulation protocol consisting of Triptorelin 0.1 mg at day 21 of the cycle and an ovarian stimulation with hMG (Mero-pur, Ferring, Saint-Prex, Switzerland) starting with 225 IU from the second day of the cycle until hCG day; group B (n = 62), patients treated with a down-regulation protocol consisting of Triptorelin (Decapeptyl; Ipsen, Paris, France) 0.1 mg from day 21 and with rFSH plus rLH (Pergoveris, Serono, Darmstadt, Germany) starting with 225 IU daily from the second day of the cycle until hCG day. hCG 10,000 IU was given intramuscularly when 50% of the follicles reached >18 mm of diameter and E₂ level 2,540 pg/mL ± 467 pg/mL. Treatment monitoring was conducted throughout gonadotropin administration. Every other day (until hCG day) a blood sample was drawn between 8 and 9 a.m. in a regular manner to measure serum E₂. Transvaginal pelvic ultrasound (Sonoace 8000 SE) was performed during gonadotropin treatment. The participants were reviewed at the same time intervals and received the same amount of attention from researchers and staff. Transvaginal US-guided (Sonoace 8000 SE) oocyte retrieval was done 36 h after hCG injection. The oocytes were then inseminated in vitro by intracytoplasmic sperm injection, and the resultant embryos were scored according to established criteria: grade A had a number of six to eight or more equal and regular blastomeres without the presence of cytoplasm fragments; grade B had fewer than six to eight unequal blastomeres with or without cytoplasmic fragments; grade C were fragmented (>50%) embryos.

Of note, in Italy, only three oocytes are permitted to be inseminated; therefore, we performed intracytoplasmic sperm injection as an in vitro fertilization technique of choice to select good quality oocytes for insemination.

The luteal phase was supplemented with progesterone intramuscularly (Progeffik 200, Effik, Orion, MI). Ultrasound-guided embryo transfer was performed at day 2.

Statistical analysis was performed using the JMP software (version 4.0.4; SAS, Cary, NC). The parameters were compared using the two-tailed Student's *t* test for independent data and the chi-square test, setting the significance level at $P \leq .05$. The analysis of variance two-way test was also used to analyze continuous variables, including primary and secondary outcome parameters. Statistical power calculation was based on an α level of 0.05 (two-tailed test) with 80% power to detect a 20% difference with 50 evaluable patients per group. The difference between treatments was evaluated using a two-sided, 95% confidence interval. All analyses were adjusted for age stratum in line with the study design. Correction for multiple comparison analysis was performed using either Bonferroni's or Sidak's adjustment methods by lowering the alpha for each test to 0.0039 with a *t* value for double sided testing: ≥ 3.00 . The difference had greater significance of pregnancy and implantation rates when the linear mixed model, which controls for intrasubject variation was used to compare the data ($P \leq .001$).

Both groups were comparable to the main demographic characteristics (mean age, body mass index, duration of sterility, primary infertility), as well as sterility factors (tubal, male, and idiopathic) and main cycle parameters.

Eleven patients were lost during the study: 2 in group A: 1 low responder (with an estradiol level <100 pg/mL and less than two follicles enveloped) (1.7%), and 1 because of excessive ovarian response leading to a high risk of OHSS (1.7%); 8 in group B: 1 low responder and (1.6%) 7 for high risk of OHSS (11.1%). The difference in two group in term of in risk of OHSS was statistically significant ($P < .005$); Finally, 111 patients underwent oocyte retrieval: 58 in group A, 53 in group B.

As shown in Table 1, we find significant statistical differences comparing group A with group B in terms of mature oocytes (48.2% in group A and 34.7% in group B), days of stimulation (14.1 ± 1.6 and 10.9 ± 1.1 , respectively, in groups A and B), total units of FSH administered ($3,525 \pm 2,325.1$ in group A vs. $4,800 \pm 345$ in group B), total numbers of oocytes retrieval (4.1 ± 1.2 and 7.8 ± 1.1 in groups A and B, respectively), cancelled patient for high risk of OHSS (1(1.7%) in group A and 7(11.1%) in group B).

No statistical differences were found in the remaining outcomes.

Studies have carefully compared treatment characteristics and outcomes in patients treated with different medications (16–19). Urinary hMG contains 75 IU FSH and 75 IU LH, whereas recombinant FSH is completely free from any LH.

First meta-analyses have demonstrated that hMG was not inferior to rFSH with regard to pregnancy and live birth rates (15). The van Wely Cochrane review confirmed these data, finding a borderline significant difference of a 5% higher clinical pregnancy rate in women stimulated with menotrophins (27%) compared with FSH

(22%). Recent meta-analyses and reviews demonstrated that hMG is superior to rFSH with regard to clinical efficiency. Coomarasamy (20) concluded his review claiming that if the clinical superiority of hMG is because of the LH it contains, than it might be possible to add recombinant LH to achieve the same results.

Our finding confirm the hypothesis that treatment with hMG or with rFSH plus rLH could achieve the same results in term of pregnancy rate, implantation rate, and embryo quality, but we find a statistical difference in oocytes quality, with a better quality in the hMG group. This difference has leveled because of the total number of oocytes retrieval, which is higher in the rFSH + rLH group, so that total number of MII oocytes is approximately the same.

The reduction of the amount of FSH used in the hMG group also led to lower cost of the IVF cycle and of the babies born; also considering the differences in cost of the two preparations there is a significant money saving for the public health system, although this was not an issue in our study

Furthermore we have found little increase in the OHSS risk in the Pergoveris group, which explains the statistically significant difference in the cancelled patient rate.

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