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ORIGINAL ARTICLE

A prospective, randomised, investigator-blind, controlled, clinical study on the clinical efficacy and tolerability of two highly purified hMG preparations administered subcutaneously in women undergoing IVF

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Abstract

The aim of this multicentre, prospective, randomised, investigator blind, controlled clinical trial was to evaluate the clinical efficacy and tolerability of a highly purified human menopausal gonadotrophin (hMG) preparation (Merional-HG) when administered to patients undergoing controlled ovarian stimulation (COS) for in-vitro fertilisation (IVF) procedure enrolled in hospital departments.

One hundred fifty-seven patients were randomised in two parallel groups: 78 started COS with Merional-HG and 79 with Menopur. Results of the study showed that both highly purified hMG preparations were equivalent in terms of number of oocytes retrieved (primary endpoint: 8.8 ± 3.9 versus 8.4 ± 3.8, $p = 0.54$). In the patients treated with Merional-HG, we observed a higher occurrence of mature oocytes (78.3% versus 71.4%, $p = 0.005$) and a reduced quantity of gonadotrophins administered per cycle (2.556 ± 636 IU versus 2.969 ± 855 IU, $p < 0.001$). Fertilisation, cleavage, implantation rates and the number of positive β-human chorionic gonadotrophin (hCG; pregnancy) tests and the clinical pregnancy rate were comparable in the two groups. Both treatments were well tolerated. In conclusion, the results of this study support the efficacy and safety of Merional-HG administered subcutaneously for assisted reproduction techniques. Efficiency of Merional-HG appears to be higher due to reduced quantity of drug used and the higher yield of mature oocytes retrieved.

Keywords

Controlled ovarian stimulation, human menopausal gonadotrophin, IVF, Merional-HG, Menopur

History

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Background

Controlled ovarian stimulation (COS) is an integral part of assisted reproductive technologies (ARTs), including standard in-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) programs. In such cases, COS is usually performed by the use of gonadotrophins in association with different gonadotropin-releasing hormone (GnRH) analogues regimens. Up to the 1990s, only human-derived gonadotrophins (urine extracted) were available, including follicle stimulating hormone (FSH) and human menopausal gonadotrophin (hMG), the latter being characterised by the presence of both FSH and LH activities in a 1:1 ratio. In the last decades, the number of gonadotrophins available for COS has rapidly expanded. In addition to the introduction of various types of recombinant (r) preparations, such as rFSH (follitropin α and β), r-luteinising hormone and r-human chorionic gonadotrophin (rhCG), highly purified (HP) human-derived gonadotrophins have been introduced on the market. Merional-HG, a new preparation of HP hMG (HP-hMG) is the latest addition to this family of infertility drugs.

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Merional-HG (IBSA Institut Biochimique SA, Pambio-Noranco, Switzerland) contains 75 IU of FSH activity and 75 IU of LH activity, mostly provided through the addition of HP hCG (spiking). It is produced using a patented purification method and is characterised by a high degree of purification. This purity level allows subcutaneous (s.c.) self-administration with clinical effectiveness comparable to the intramuscular (i.m.) route [1] and a local tolerability equivalent to the recombinant products [2].

This trial was aimed to compare, for the first time, the clinical efficacy and the overall safety and tolerability of two different HP hMG preparations in patients undergoing IVF, with or without ICSI.

Methods

Patients' selection

Three fertility clinics in Italy participated in this randomised trial between March 2006 and May 2008. Eligible women with an indication for IVF/ICSI treatment were recruited. The main inclusion criteria were age between 18 and 37 years, body mass index (BMI) between 18 and 28 kg/m^2, less than three previous completed IVF cycles, basal FSH level less than 10 IU/L and normal uterine cavity.

The main exclusion criteria were primary ovarian failure or poor responder; polycystic ovarian syndrome, according to the Rotterdam Criteria [3]; one or more ovarian cysts >10 mm; hydrosalpinx; stage III or IV endometriosis; abnormal bleeding of undetermined origin and hyperprolactinaemia.

Study design

The study was carried out according to a prospective, controlled, randomised, parallel group, investigator blind, multicentre design. The study protocol was reviewed and approved by the independent ethics committee of the centres where the trial was carried out. Furthermore, the study was performed in accordance with the International Conference on Harmonisation guidelines, the Directive 2001/20/EC, the Declaration of Helsinki and the Italian Law on Assisted Reproduction (Legge 40/2004). The trial was registered with clinicaltrials.gov with the identifier: NCT00335894. Reporting of this study follows the recommendations of the CONSORT 2010 Statement.

Stimulation regimen and ART procedures

Following written informed consent, admitted patients underwent a standard, long down-regulation protocol using GnRH agonist, 0.1 mg s.c. triptorelin (Decapeptyl, IPSEN SpA, Milan, Italy). Patients were randomised to receive the study drug or the reference product in a 1:1 ratio, according to a computer generated list. In both groups, a starting hMG dose of 225 IU was maintained for the first 4–5 days. Thereafter, hMG dose adjustments were allowed depending on the ovarian response monitored by means of serum E_2 levels and ultrasonographic measurement. One hundred fifty-seven patients were randomised, with 78 patients randomised to the test group and receiving Merional-HG, and 79 patients randomised in the reference group and receiving Menopur (Ferring Pharmaceuticals, St-Prex, Switzerland).

Daily gonadotrophin administration was continued until at least two follicles >16 mm in diameter were observed on transvaginal ultrasound and serum E_2 levels were appropriate for the total number of developing follicles, but in any case for not more than 18 days. Patients fulfilling these criteria were to be given a 10 000 IU dose of s.c. hCG (Gonasi-HP, IBSA Italia, Lodi, Italia).

Oocytes and partner's sperm were collected 34–36 h following hCG administration, after which the oocytes were artificially fertilised with or without ICSI. Embryo transfer was performed two to three days after oocyte collection.

Luteal phase support was performed using progesterone (Prontogest, IBSA Italia, Lodi, Italy) administered i.m. at a dose of 100 mg/day for 3 days following oocyte retrieval and then at a dose of 50 mg/day for at least an additional 11 days or until menses.

Fifteen days after oocyte collection, patient performed a pregnancy test (serum hCG measurement). Pregnant patients were also evaluated 35 ± 7 days after embryo transfer.

Outcome measures

All randomised patients who received the study medication and for whom there was at least one post-baseline efficacy assessment were included in the efficacy and safety analysis.

The total number of oocytes retrieved was considered the primary efficacy endpoint.

The secondary efficacy endpoints were the daily and the total dose of hMG (IU and vials), the stimulation duration (from stimulation onset until hCG injection), serum E_2 concentrations on the day of hCG injection, the number of follicles >16 mm on the day of hCG injection, the number of mature oocytes (grade III – metaphase II (MII)) and of inseminated oocytes, the fertilisation rate, the embryo score according to the Veeck criteria [4], the number of transferred embryos, the implantation rate and the clinical pregnancy rate (per stimulated cycle, per oocyte retrieval and per embryo transfer).

Occurrence of (serious) adverse events (AEs), including the incidence of ovarian hyperstimulation syndrome (OHSS) according to the Golan classification [5].

Sample size calculation and statistical methods

According to a non-inferiority design, the sample size was determined having the number of oocytes retrieved as primary endpoint. The Sasabuchi test was used, assuming an α and β level of 0.05 and 0.20, respectively, a non-inferiority margin of 20% and a coefficient of variation of 0.40 (based on previously observed mean value of 10 oocytes retrieved with a standard deviation of about 4). This led to consider that 144 patients (72/group) would be sufficient to grant a power of 80% needed for the analysis of the primary endpoint using the one-way analysis of the variance (i.e. Schuirmann test) showing non-inferiority.

Statistical calculations were performed with SAS 8.2 (SAS Institute Inc., Cary, NC) for Windows. Data management was performed using Microsoft SQL Server version 2000 (Microsoft Corporation, Redmond, WA).

Baseline characteristics of the treatment groups were assessed by Student t test and χ^2, as appropriate. The primary outcome variable, number of oocytes retrieved, was used to test non-inferiority between the two treatment groups. The one-way analysis of variance (ANOVA) was performed to calculate the 95% confidence interval (CI) of the difference between the two treatments. The 20% of the mean number of retrieved oocytes observed in the reference group was used to set the non-inferiority limits. A multivariate ANOVA was used to calculate the 95% CI for the difference between treatment groups using women's age, BMI, infertility diagnosis and investigational centre as covariate. The secondary outcome variables were compared for the efficacy analysis according to unpaired Student t test or according to χ^2 test. Laboratory data, the consumption of concomitant medication in the two groups, the number of AEs recorded in the two groups were compared using unpaired Student t test or χ^2 test.

Differences between the two treatment groups were declared to be significant if the p value for the test was less than 0.05 (two-tailed).

Results

One hundred fifty-seven women, aged between 19 and 37 years, undergoing controlled ovarian hyperstimulation for the purposes of oocyte retrieval for IVF, were included in the study.

Demographic and infertility history data are summarised, together with analysis results and vital signs, in Table 1. After randomisation, the mean age and the BMI of the women enrolled in the study were similar in the two groups. The two groups were also comparable with regard to basal FSH and E_2. There was no statistically significant difference between the two groups in terms of primary cause of infertility and infertility duration.

Patients' disposition is reported in Figure 1. Among the 78 patients in the test group and 79 patients in the reference group, who were randomised, 12 patients (six per group) did not start or interrupted gonadotrophin treatment due to cyst development (one in the test group), risk of OHSS (five in the test group and two in the reference group), poor ovarian response (three in the reference group) and for voluntary choice (one in the reference group). Therefore, 72 patients in the test group and 73 in the reference group underwent oocyte retrieval.

The mean number of collected oocytes in all patients having had oocytes retrieval was equivalent in the test and in the reference group: 8.8 ± 3.9 and 8.4 ± 3.8, respectively (Table 2). Results of the non-inferiority analysis according to Schuirmann indicate a mean difference of +0.4 (95% CI −0.87 to +1.65) in the number of oocytes collected between the test and the reference, i.e. a 95% CI lower limit greater than the predefined clinically significant difference (−1.68, i.e. 20% of the reference). Therefore, the analysis of the primary study endpoint showed non-inferiority of the test drug compared to the reference product. Age and centre correlation was highlighted by the ANOVA model as expected the number of oocytes retrieved negatively correlated with patient's age. Neither the infertility diagnosis nor the BMI resulted to affect the primary endpoint outcome.

Table 1. Patients' characteristics[a].

	Test ($N=78$)	Reference ($N=79$)	p value[b]
Age (years)	31.8 (3.7)	32.6 (2.9)	0.16
BMI (kg/m^2)	23.0 (2.5)	22.5 (2.2)	0.20
Infertility duration (years)	4.7 (2.6)	4.6 (3.1)	0.87
Primary cause of infertility	–	–	
Male factor, *n* (%)	41 (52.6)	39 (49.4)	
Male factor + tubal factor, *n* (%)	25 (32.1)	21 (26.6)	
Male factor + other[c], *n* (%)	7 (9.0)	10 (12.7)	0.47
Tubal factor, *n* (%)	4 (5.1)	4 (5.1)	
Unexplained, *n* (%)	1 (1.3)	5 (6.3)	
Basal FSH (IU/l)	7.0 (1.6)	6.5 (1.9)	0.12
Basal 17β-estradiol (pg/ml)	49.2 (30.1)	46.6 (36.6)	0.63

[a]Where not specified, data are expressed as mean (SD)
[b]Student *t* test for continuous variables, χ^2 test for categorical variables.
[c]Other: including endometriosis, uterine malformation and oligovulation.

As shown in Table 2, the total hMG dose administered was significantly lower in the test group. Furthermore, we found a statistically significant difference relative to the mean daily hMG dose, and the duration of treatment was significantly shorter in the test group. Nevertheless, the number of follicles with a diameter >16 mm and serum E_2 level on the day of hCG triggering were comparable in the two groups.

The mean number of MII oocytes and the total number of immature oocytes did not significantly differ between the two groups (Table 2). However, a higher ratio between number of mature MII oocytes retrieved and total number of oocytes retrieved was found in the test product group. The opposite trend was observed in the ratio between immature oocytes retrieved and total number of oocytes retrieved, with a lower ratio in the test product group. In compliance with the assisted reproduction legislation in force in Italy at the time of the study (Legge 40/2004), no more than 3 oocytes per patient were inseminated;

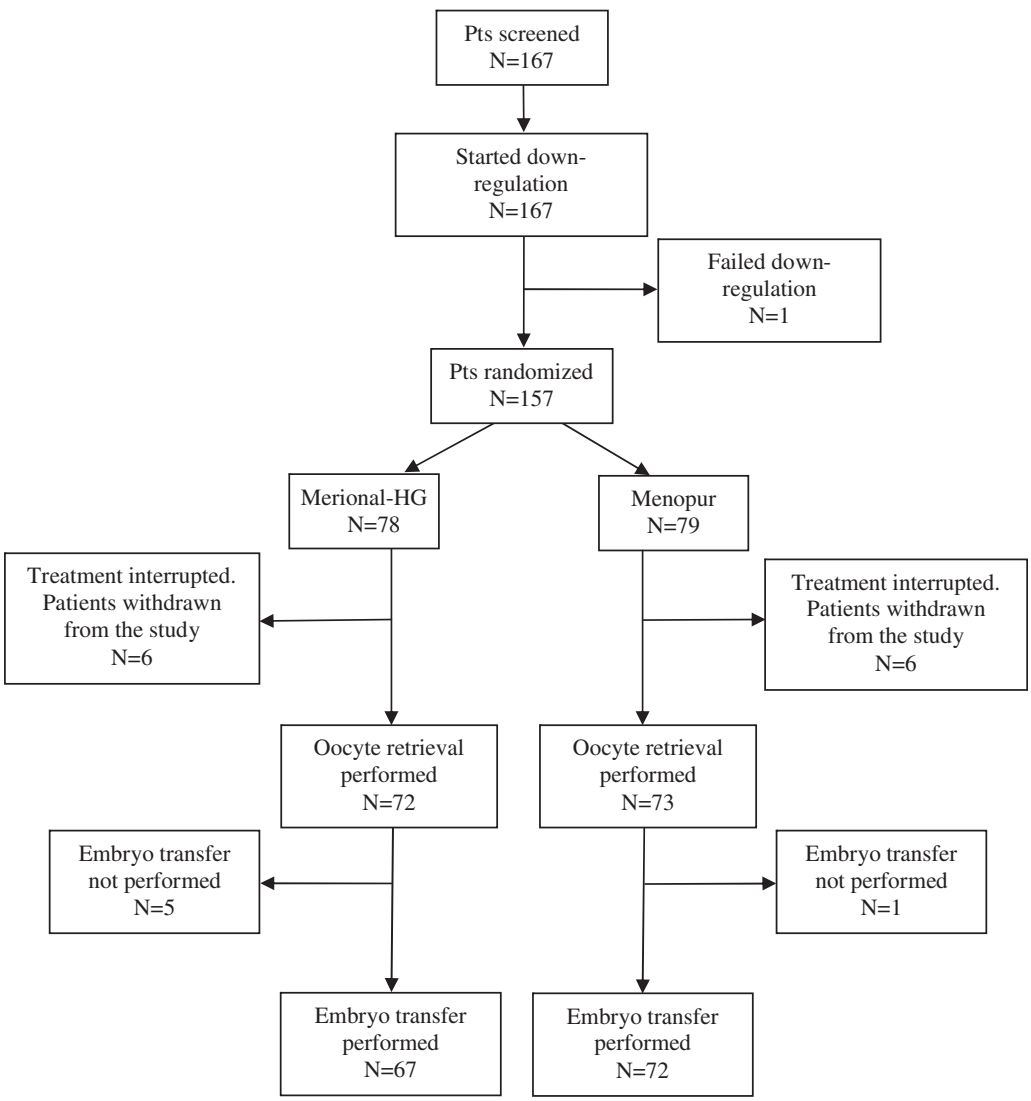

Figure 1. Patients disposition.

Table 2. Cycle characteristics and clinical outcomes[a].

	N	Merional-HG	*N*	Menopur	*p* value[b]
COS duration (days)	78	11.3 (1.5)	79	12.3 (2.1)	<0.001
hMG units, total	78	2555.8 (635.9)	79	2968.7 (854.8)	<0.001
hMG units, daily	78	224.2 (37.0)	79	238.6 (48.7)	0.04
E_2 at hCG day (pg/ml)	78	2136.8 (1224.6)	79	2143.0 (1384.3)	0.98
Follicles >16 mm at hCG day	72	8.8 (4.1)	73	8.6 (4.0)	0.73
Nr of collected oocytes	72	8.8 (3.9)	73	8.4 (3.8)	0.54
Nr of mature (MII) oocytes	72	6.9 (3.6)	73	6.0 (3.0)	0.11
Nr of immature oocytes	72	1.8 (1.3)	73	2.2 (1.8)	0.12
Ratio MII/total oocytes retrieved (%)	72	78.3	73	71.4	0.005
Ratio immature/total oocytes retrieved (%)	72	20.4	73	26.3	0.01
Number of inseminated oocytes	72	2.7 (0.7)	73	2.7 (0.7)	0.42
Fertilisation rate[c]	70	88.5	72	92.5	0.18
Cleavage rate[c]	70	86.9	72	91.0	0.20
Mean number of embryos transferred	67	2.5 (0.6)	72	2.5 (0.7)	0.66
1 embryo transfer, *n* (%)	67	5 (7.5)	72	8 (11.1)	
2 embryos transfer, *n* (%)	67	25 (37.3)	72	18 (25.0)	0.66
3 embryos transfer, *n* (%)	67	37 (55.2)	72	46 (63.9)	
Embryo quality[d]					
Grade I (%)	67	45 (27.1)	72	46 (25.3)	0.92
Grade II (%)		40 (24.1)		36 (19.8)	0.65
Grade III (%)		44 (26.5)		57 (31.3)	0.20
Grade IV (%)		24 (14.5)		29 (15.9)	0.49
Grade V (%)		13 (7.8)		14 (7.7)	0.85
Positive β-hCG test, *n*		25		27	–
/OPU, %	72	34.7	73	37.0	0.78
/Transfer, %	67	37.3	72	37.5	0.98
Implantation rate[e], %	67	15.7	72	15.4	0.94
Clinical pregnancies, *n*		20		20	–
/OPU, %	72	27.8	73	27.4	0.96
/Transfer, %	67	29.9	72	27.8	0.79
Abortion rate, *n* (%)		1 (5.0)		2 (10.0)	–

[a]Where not specified, data are expressed as mean (SD). COS: controlled ovarian stimulation.
[b]Student t test or continuous variables, χ^2 test for categorical variables.
[c]Fertilisation rate and cleavage rate calculated per inseminated oocyte.
[d]Embryo quality (according to Veeck criteria): grade I: embryos with blastomeres of equal size and no cytoplasmic fragmentation; grade II: embryos with blastomeres of equal size and minor cytoplasmic fragmentation covering <10% of the embryo surface; grade III: embryos with blastomeres of distinctly unequal size and variable fragmentation; grade IV: embryos with blastomeres of equal or unequal size and moderate-to-significant cytoplasmic fragmentation covering >10% of the embryo surface; grade V: embryos with few blastomeres of any size and severe fragmentation covering >50% of the embryo surface.
[e]Implantation rate defined as the total number of gestational sacs divided by the total number of embryos transferred.

no between-group difference in the number of inseminated oocytes was found (2.7 ± 0.7 versus 2.7 ± 0.7, $p = 0.42$ in the test and in the reference group, respectively).

Among the 72 patients in the test group and 73 in the reference group who had hCG injection and oocytes pickup (OPU), zero oocytes retrieved in 2 patients (1 patient in each group) and 4 additional patients (all in the test group) had no embryos transferred because of failed oocyte fertilisation. Thus, 139 embryos transfers were done, 67 and 72 in the test and reference group, respectively.

As reported in Table 2, the fertilisation rate (88.5% versus 92.5%, p = not significant of inseminated oocytes) and the cleavage rate (86.9% versus 91.0%, p = not significant of inseminated oocytes) were equivalent in the two groups.

Each embryo was evaluated before transfer and scored according to the Veeck criteria [4]. No statistically significant difference between treatment groups was found (Table 2).

Embryo transfer was achieved in most patients in both groups; no embryo transfer was performed in four patients of the reference group due to embryo development failure.

The occurrence of a positive serum hCG pregnancy test, the implantation rate and the clinical pregnancy rate were not significantly different in the two groups. Three patients had a miscarriage, one in the test group and two in the reference group.

Few AEs were reported during the study. AEs reported in the test product treated patients included two mild OHSS cases and one ovarian cyst. The ovarian cyst development leads to hMG treatment interruption.

Discussion

Menotrophin, a combination of FSH, LH and hCG, was the first gonadotrophin formulation used in ovulation induction and, later, in COS for ART procedures. For many decades, this class of medications proved to be effective, reliable and safe in this therapeutic area. Later developments included the introduction of purified FSH, HP FSH, rFSH and more recently HP hMG. In spite of several large prospective trials published in the last decade [2,6–9], a substantial clinical equivalence was shown between HP hMG and FSH-only gonadotrophin preparation.

The great majority of clinical studies with HP hMG were performed with Menopur, an HP hMG preparation manufactured by Ferring Pharmaceuticals. More recently, IBSA Institut Biochimique SA has made available a novel HP hMG preparation commercially known as Merional-HG.

The current study is the first truly randomised controlled trial comparing the safety and the clinical efficacy of two highly purified (HP) hMG preparations.

The randomisation procedures achieved well-balanced treatment groups for demographic and baseline couple characteristics. No difference in term of mean patient age, BMI, basal vital signs and laboratory parameters at screening as well as in infertility

duration, number of patients with previous pregnancies (both spontaneous and induced) and the total number of previous IUI or IVF cycles were reported. There was no difference in term of infertility diagnosis.

With reference to the primary outcome variable (i.e. number of oocytes retrieved), the results of the Schuirmann interval hypothesis test suggested that the test product was not inferior to the reference. All secondary parameters taken into consideration in this study were standard parameters routinely evaluated in fertility centres. The analysis of ovarian stimulation parameters (duration of the treatment, daily dosage and total units of hMG used, the number of follicles >16 mm and the E_2 level at hCG day) showed an higher efficiency for the test drug compared to the reference. Actually, to obtain the same number of follicles >16 mm and the same E_2 level at triggering day, patients allocated to the Merional-HG group needed significantly less medication. Moreover, even if the total number of oocytes retrieved was equivalent between treatment groups, the yield of mature oocytes was higher in the test group.

One limitation of this study was that the oocyte fertilisation procedure and embryo transfer had to be performed in compliance with the Italian legislation on assisted reproduction in force at the time of the study (Legge 40/2004); according to this law (later modified by the Italian Supreme Court), no more than three oocytes per patient were inseminated and all the available embryos were transferred. No oocytes, two pronuclear zygotes or embryos were frozen and no embryo was discarded. There was no significant difference in the number of mature oocytes microinjected, and the fertilisation and cleavage rates were comparable between the treatment groups. Before transfer, embryos were scored according to the criteria established by Veeck [4], showing no differences between treatment groups.

The implantation rate per embryo transfer, the positive β-hCG (pregnancy) test and the clinical pregnancy rate were equivalent between treatment groups.

The effectiveness of IVF treatment mainly depends on the characteristics of the couple seeking treatment. According to classical approach, the age of the woman, the duration of infertility [10], basal serum levels of FSH and outcome of previous stimulation cycles are crucial for individualising COS, including the choice of both GnRH analogues and gonadotrophin regimens. Thus, the administration of gonadotrophins is tailored to the patient's characteristics and previous known response in each treatment cycle.

In this study, different outcomes between treatment groups were not expected due to the similar composition of the drugs, the standardisation of the therapy and the equivalent basal characteristics of the patients included in the study. In fact, clinical outcome in the two treatment groups was comparable, with no significant differences in total and mature oocyte number, fertilisation, embryo cleavage, implantation and clinical pregnancy rates. The occurrence of relevant complications such as OHSS and miscarriage was similar in patients treated with Merional-HG or Menopur.

Conversely, significantly lower duration of treatment and gonadotrophin consumption were associated with Merional-HG use. Foutouh et al. [11] also reported lower drug consumption associated with Merional in a study comparing an HP hMG (Merional) to a traditional, not HP hMG preparation (Menogon – Ferring). The reason for this difference is not clear and additional studies should be performed to confirm or refute the result.

In summary, Merional-HG and Menopur were proven to be equally effective to achieve proper outcome of ART. Merional-HG appears to be more efficient than Menopur in this setting as it allows reducing drug consumption and treatment duration and may provide additional practical advantages in the management of ART procedures.

Declaration of interest

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