Effectiveness of highly purified HMG plus r-FSH vs r-FSH alone vs r-FSH plus r-LH in IVF-ET/ ICSI patients：a retrospective cohort study

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Abstract

Objective: To evaluate the effectiveness of highly purified human menopausal gonadotropins (hp-HMG) plus recombinant follicle stimulating hormone (r-FSH) vs r-FSH vs r-FSH plus recombinant luteinizing hormone （r-LH） in vitro fertilization (IVF) / intracytoplasmic sperm injection (ICSI) patients

Design : Retrospective cohort study

Methods: This was a retrospective study. Among a total number of 3568 patients who had undergone IVF/ICSI applications, 409 eligible patients were included.Total units of follitropin alpha preparations used in ovulation induction, total number of meiois-2 phase oocytes, total number of used oocytes in ICSI cycle, fertilization rate and clinical pregnancy rates of both groups were analyzed. In this retrospective cohort study, women undergoing IVF/ICSI Gonadotropin releasing hormone (GnRH) antagonist cycles downregulation. 409 patients were included in the study. Among them One group followed the current standard protocol of no LH or hp-HMG supplementation given(n=64). The other had LH supplementation in the form of r -LH (Luveris; Merck Serono, Switzerland) (n=221), Another group had hp-HMG supplementation in the form of hp-HMG (Menopur , Ferring,Germany)(n=121).In the Subgroup analysis were decided by AFC ,7 < AFC（20 or AFC>20 of the three group.

Result: Mean duration of stimulation and was longer in the group of patients treated with hp-HMG plus rFSH compared to the group of patients treated with r-FSH and the group of r-LH plus r-FSH (13.24 days and 12.72days and12.21days, respectively; P<0.05). The amount of GN does for patients treated withhp-HMG plus rFSH compared to the group of patients treated with r-FSH plus r-LH and the group of r-FSH alone respectively (P<0.05). Clinical pregnancy rates were 76.6% and 60.9% and 62.9% （P<0.05）in the groups of patients treated with hp-hMG plus rFSH, r-FSH plus r-LH,r-FSHalonerespectively. What's morea greater live birth rate was noted in the hp-hMG plus r-FSH group, there was statistically significant difference between the three groups (P>0.05).in the subgroup analysis when AFC>20 hp-HMG plus rFSH group have more lower ovarian hyperstimulation syndrome （OHSS） than r-FSH plus r-LH and rFSH alone,respectively.

Clonclusion: The higher oocyte yield with r-FSH does not result in higher quality embryos.hp-HMG or r-LH supplementation is an option for improving IVF outcome in patients ovulation induction with r-FSH during GnRH agonist down-regulation. Particularly, hp-HMG is recommended as it may have a beneficial action on implantation in selected group especially AFC more than 20patients.

Introduction

Nowdays, different gonadotropin preparations such as human menopausal gonadotropins (hMG), including both LH and FSH activity, and recombinant FSH (rFSH) preparations are used in controlled ovarian stimulation (COS) in pituitary-suppressed patients undergoing in vitro fertilization/intra cytoplasmic sperm injection (IVF/ICSI) procedures.Some evidence suggests that administering medications with LH activity to patients undergoing IVF could improve IVF outcome with respect to using

FSH alone. In some studies, ovarian stimulation performed with hMG after pituitary suppression with a GnRH-agonist resulted in a slightly increased (3–4%) clinical pregnancy rate [1, 2]and in a higher embryo ploidy rate [3] compared to FSH alone. In a recent multicenter, prospective, randomized trial, hMG and rLH were shown to have similar effects on IVF outcome [4]. Experience has shown that stimulation with FSH alone is sufficient to achieve optimal results in most patients[1–3]. Mounting evidence indicates that LH or human chorionic gonadotropin (hCG) activity during ovarian stimulation treatment is capable of modulating folliculogenesis by reducing the number of smaller or intermediate sized [5]follicles.

We aimed to evaluate the clinical efficacy of hp-HMG or r-LH supplementation to r-FSH vs r-FSH alone in patients undergoing assisted reproduction with early follicular gonadotropin releasing hormone antagonist (GnRH-a) down-regulation and stimulation with r-FSH.

Material And Methods

This retrospective cohort study was conducted in the third Affiliated Hospital of Zhengzhou University reproductive center. Records of all agonist cycles from 1 January 2016 to 1 February 2018 were reviewed. The Institutional Research and Ethics Board approved the study. Among a total number of 3568patients who had undergone IVF/ICSI applications, 409 eligible patients were included, and their data were evaluated retrospectively. Among them One group followed the current standard protocol of no LH or hp-HMG supplementation given(n = 64). The other had LH supplementation in the form of r -LH (Luveris; Merck Serono, Switzerland) (n = 221), Another group had hp-HMG supplementation in the form of hp-HMG (Menopur ,Ferring,Germany)(n = 121).Total units of follitropin alpha preparations used in ovulation induction All patients underwent an ovarian hyperstimulation in a early follicular stage GnRH agonist protocol

Inclusion criteria were: (i) patients aged 23–39; (ii) body mass index between 18 and 30 kg/m2; (ii) AFC ≥ 7 (iii) baseline FSH 12 IU/l; baseline E2 80 pg/ml; (iv) the presence of both ovaries and uterine cavity capable of sustaining a pregnancy; (v) who were having their first IVF trial. Patients were excluded if they met any of the following criteria: (i) grade III-IV endometriosis; (ii) who had a single ovary; (iii) previously diagnosed with a space occupying lesion in the uterine cavity. Patients who did not meet any one of the exclusion criteria were enrolled in the study .

Stimulation protocol was previously described by our group Briefly, on day28-30of the down regulation treatment cycle, ovarian stimulation was started by daily injection of FSH (r-FSH; Gonal-F, Merck Serono, Switzerland) at a dose of 150–225 IU/day. The starting dose of r-FSH was individually based on age, body mass index (BMI), hormone levels, number of antral follicles, and previous response to stimulation. either r-FSH was continued (FSH only group) or 75 IU of hp-hMG (Menopur, Ferring, Kiel, Germany) was added to stimulation protocol (FSH plus hp-hMG group),75 IU of LH (Luveris; Merck Serono, Switzerland) was added to stimulation protocol (FSH plus r-LH group). When the leading follicle reached to a mean diameter of 18 mm, and at least two follicles developed to a mean of 16 mm in diameter, urinary or recombinant hCG injection (Ovitrelle250 ug, Merck Serono)was administered to trigger final maturation.

Transvaginal oocyte retrieval was performed 36 h following hCG trigger. ICSI was performed and embryos were cultured until the day of transfer. Embryo quality was determined according to the characteristics of blastomeres including count, uniformity, and fragmentation rate .

Subgroup analysis by AFC

Subgroup analysis for AFC was performed for the entire cohort Subgroup analysis for$7 \leq AFC \leq 20$ or $AFC > 20$ was also performed. Cycle characteristics and outcomes were compared among the three groups for each AFC category.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (SPSS Inc, Chicago, IL). Patient characteristics and clinical outcomes were tabulated by grade. We used the Kolmogorov–Smirnov test to evaluate the distribution of the quantitative parameters. Comparisons the three groups were analyzed using the ANOVA,or when appropriate. Differences between categorical parameters were compared with the Chi- Square test or the Fisher exact test. parity, p value < 0.05 was considered statistically significant.

Results

The two treatment protocols were compared regarding the patients' demographic data (age, parity, BMI, and basal FSH), the cycle characteristics (amount of gonadotropins used, endometrial thickness, and estradiol levels on day of hCG administration) and the cycle outcomes (number of oocytes retrieved, fertilization rates, top quality embryos, clinical pregnancy and live birth rates, miscarriage rates, and implantation rates).

In this study, 124patients were administered r-FSH plus hp-HMG (Group 1), 221 patients received r-FSH supplemental r-LH (Group 2) and 64 patients received only r-FSH who were in the control group (Group 3) .Patients in each group did not significantly differ for age, variables related to ovarian reserve (antral follicle count and day 3 FSH level).

Patients' demographics, treatment characteristics, and cycle outcomes are summarized in Table 1. Age, basal FSH, The duration of stimulation and the endometrial thickness on the day of hCG administration were comparable among the three groups. Patients in the hp-hMG group consumed significantly higher doses of gonadotropins, but had lower estradiol levels on the day of hCG administration. The average number of oocytes retrieved, were significantly higher in the rFSH group. Fertilization rates andtop quality embryos rates the number of embryos transferred were comparable among the three groups, There were no significant difference

Table 1

	r-FSH + hp-HMG N = 124	r-FSH + r-LH N = 221	r-FSH N = 64	P
Age(y)	29.18±3.72	28.73±3.80	28.50±4.12	0.438
Body mass Index(kg/m2)	22.91±2.81	22.30±2.93	21.45±2.54	P123 = 0.002 P12 = 0.061 p13 = 0.000 P23 = 0.019
bFSH (IU/l)	6.42±1.97	5.94±1.58	6.12±1.85	P123 = 0.043 P12 = 0.011 P13 = 0.320 P23 = 0.402
bLH	5.34±3.46	5.18±3.21	5.31±2.45	0.892
bE2	49.77±55.37	44.73±50.52	40.38±15.74	0.422
AFC	18.80±5.64	19.26±5.55	19.45±5.34	0.666

	r-FSH + hp-HMG N = 124	r-FSH + r-LH N = 221	r-FSH N = 64	P
Total injected dosage (IU)	2415.93±685.14	1741.29±452.07	1697.07±512.27	P123 = 0.000 P12 = 0.000 P13 = 0.000 P23 = 0.505
No.of stimulation days	13.42±2.14	12.72±1.67	12.21±1.98	P123 = 0.000 P12 = 0.001 P13 = 0.000 P23 = 0.041
Endometrium thickness,day of hCG injection (mm)	11.46 ± 2.15	11.10±2.35	10.73±2.07	0.097
Serum LH levels, day of HCG injection (IU/l)	0.98±0.82	1.03±0.90	1.52±1.83	P123 = 0.002 P12 = 0.597 P13 = 0.007 P23 = 0.004

	r-FSH + hp-HMG N = 124	r-FSH + r-LH N = 221	r-FSH N = 64	P
Serum E levels, day of hCG injection (ng/L)	3414.42±1719.23	3680.00±1614.00	4372.70±2050.46	P123 = 0.02 P12 = 0.539 P13 = 0.001 P23 = 0.006
Serum Plevels, day of hCG injection (ug/L)	0.91±0.39	1.10±0.47	1.21±0.43	P = 0.000 P12 = 0.173 P13 = 0.000 P23 = 0.075

Table 2

	r-FSH + hp-HMG N = 124	r-FSH + r-LH N = 221	r-FSH N = 64	P
No.of oocytes retrieved	12.27±4.60	14.78±4.97	14.83±4.68	P123 = 0.000 P12 = 0.000 P13 = 0.000 P23 = 0.953
No.of oocytes fertilized(%)	62.0(943/1521)	65.5(2139/3268)	66.6(632/949)	0.840
Rate of excellent embryos (%)	42.7(403/943)	44.3(947/2139)	43.03(272/632)	P = 0.686
Implantation rate in fresh cycle (%)	62.0(137/221)	49.2(184/374)	45.5(50/110)	P123 = 0.003 P12 = 0.002 P13 = 0.004 P23 = 0.490
No.of embryos transferred	1.78±0.41	1.70±0.46	1.72±0.45	0.255
Prengnancy rates(%)	76.6(95/124)	62.9(139/221)	60.9(39/64)	P123 = 0.019 P12 = 0.009 P13 = 0.024 P23 = 0.776
Abortionrate(%)	11.6(11/95)	9.4(13/139)	10.3(3/39)	0.860
Live birth rate(%)	64.5(80/124)	54.3(120/221)	56.3(36/64)	0.177
OHSS(%)	3.2(4/124)	7.24(16/221)	7.8(5/64)	0.233

	r-FSH + hp-HMG N = 124	r-FSH + r-LH N = 221	r-FSH N = 64	P
ICSI(%)	29.8(37/124)	28.1(62/221)	26.6(17/64)	0.885
Primary infertility(%)	59.7(74/124)	61.5(138/221)	64.1(41/64)	0.840
Ovulatory dysfunction (%)	9.7(12/124)	7.2(16/221)	9.4(6/64)	0.694

Table 3
7≤AFC ≤ 20

	r-FSH + hp-HMG N = 71	r-FSH + r-LH N = 124	r-FSH N = 38	P
No.of oocytes fertilized(%)	61(520/852)	64.9(1095/1687)	66.5(376 /565)	0.066
Rate of excellent embryos (%)	39.2(204/520)	46.9(514/1095)	40.4(152/376)	P123 = 0.005 P12 = 0.004 P13 = 0.718 P23 = 0.029
Implantation rate in fresh cycle(%)	60(75/125)	44.8(96/214)	42.8(27/63)	P123 = 0.015 P12 = 0.10 P13 = 0.026 P23 = 0.712
Prengnancy rates(%)	74.6(53/71)	62.9(78/124)	55.2(21/38)	P = 0.094
Live birth rate(%)	54.9(39/71)	50.8(63/124)	61.5(16/26)	0.829
OHSS(%)	4.2(3/71)	4.8(6/124)	0(0/38)	0.191

Table 4
AFC≥20

	r-FSH + hp-HMG N = 53	r-FSH + r-LH N = 97	r-FSH N = 26	P
No.of oocytes fertilized(%)	63.2(423/669)	66(1044/1581)	66.7(256/384)	0.378
Rate of excellent embryos (%)	47(199/423)	41.4(433/1044)	46.8(120/256)	P = 0.079
Implantation rate in fresh cycle(%)	64.5(62/96)	55(88/160)	48.9(23/47)	P = 0.320
Prengnancy rates(%)	79.2(42/53)	62.8(61/97)	69.2(18/26)	P = 0.001 P12 = 0.039 P13 = 0.328 P23 = 0.712
Live birth rate(%)	77.3(41/53)	58.7(57/97)	61.5(16/26)	P = 0≥001 P12 = 0.022 P13 = 0.14 P23 = 0.789
OHSS(%)	1.8(1/53)	10.3(10/97)	19.2(5/26)	0.045

Distributions of transferred embryo counts and ratios related to the transfer days are similar among the groups and no statistically significant difference was found ($p > 0.05$). Implantation ratios were found to be 62% (137/221)in Group 1, 49.2%(184/374) in Group 2, 45.5% (50/110)in Group3. Ratios were significantly higher in Groups 1 and 2 compared to Group 3.

Clinical pregnancy ratios were 76.6% (95/124) in Group 1, 62.9% (139/221) in Group 2 and 60.9% (39/64) in Group 3. Group 1 was observed to have higher clinical pregnancy ratios compared to other groups, more over there was statistically significant difference between Groups 2 and 1 ($p = 0.009$). On the other hand, a difference of high-degree significance was established between Groups 1 and 3 (p50.01). Implantation rate were found to be 62% (137/221) in Group 1, 49.2% (184/374) in Group 2, and 45.5% (50/110) in Group 3. But in Group 1, Implantation rate were significant increased compare to Group 3. Abortion ratios in Groups 1, 2 and 3 were respectively 11.6%(11/95), 9.4%(13/139), 10.3%(3/39) and

there were no significant difference between groups. Live birth rate in Groups 1, 2 and 3 were respectively 64.5%(80/124), 54.3% (120/221), 56.3%(36/64). In Group 1, live birth rate was increased compared to Groups 2 and 3, but there were no statistically significant difference among the three groups (p = 0.177).

Subgroup analysis

Subgroup analysis for AFC was performed for the entire cohort. Table II shows the results of the subgroup analysis for patients' 7 < AFC < 20, orpatients'AFC > 20.

Patients which in the7 < AFC < 20 group, in the rFSH group and r-FSH + r-LH group had better cycle outcomes compared with those in the r-FSHhp-hMG group in terms of oocytes retrieved(12.0 ± 4.72vs 13.6 ± 4.95 vs14.8 ± 4.73 p = 0.009), lower gonadotropin administration(1791.8 ± 515.65 vs1842.44 ± 489.10 vs2407.4 ± 699.21,p = 0.000). but Cycle outcomes for7 < AFC < 20 patients were comparable. Live birth rate (54.9 (39/71) vs 50.8 (63/124) vs 61.5 (16/26), p = 0.829) and clinical pregnancy (74.6% (53/71)vs62.9%(78/124)vs55.2%(21/38), p = 0.094)were all better in r-FSH + hp-HMG group in comparison to r-FSH + r- LH group and r-FSH group but there were no significant difference .

Patients in AFC > 20 groups,in the rFSH group and r-FSH + r-LH group had better cycle outcomes compared with those in the r-FSH hp-hMG group in terms of oocytes retrieved (12.6 ± 4.43 vs 16.3 ± 4.60 vs14.8 ± 0.93, p = 0.000), lower gonadotropin administration (3299.0 ± 1456.03 vs 4040.1 ± 1601.07 vs 4433.2 ± 1778.82, p = 0.006). The Implantation rate in fresh cycle and No.of embryos transferred, No.of oocytes fertilized rate have no significant differences among the groups; The clinical pregnancy and live birth rate was significantly higher in patients who received rFSH + hp-HMG. The hp-HMG group have lower OHSS than rFSH alone group and rFSH plus rLH group(1.8% vs 10.3vs19.2%) respectively (p = 0.045)

Discussion

As we all known both FSH and rLH are essential from the modifollicular phase for optimal physiologic function. High levels of serum LH in follicular phase is thought to negatively affect fertility by causing early atresia of oocytes. Over-suppressed LH levels by GnRH agonist cycles were also demonstrated to negatively affect IVF outcomes .So efforts are being made to answer the questions like, "How should the clinical administration of ovulation hp-HMG or rLH be?", "In what conditions should hp-HMG or LH be added. Hp-HMG or rLH which one is the best.The hMG shows two types of LH activity, one is derived from LH and the other one, which is also known to be stronger, comes from human chorionic gonadotropin (hCG) content[6] .It was shown that LH and hCG bind to the same receptor, the luteinizing hormone-chorionic gonadotropin receptor because they are the same in more than 80% of amino acids sequence [7]. On the other hand, LHCGR responds differently to LH and hCG which causes different effects of each molecule in human physiology during both follicle development and first trimester of pregnancy [8].

In our study Comparing the effect of rFSH-only vs hp-hMG plus rFSH vs LH plus rFSH preparations in IVF/ICSI by using a long GnRH-a protocol. In the hp-HMG plusrFSH group has lower number of oocytes retrieved than FSH-only group and rLH plus rFSH group, But highly purified hMG treatment resulted in a

higher Implantation rate and PR in fresh cycle per started cycle ($p < 0.05$), as compared with rFSH. In our subgroup analysis Cycle outcomes for $7 < AFC < 20$ patients were comparable. Live birth rate and clinical pregnancy were all better in r-FSH plus hp-HMG group in comparison to r-FSH plus r- LH group and r-FSH group. but there were no significant difference .These results suggest thata higher PR with highly purified hMG supplementation, compared with rFSH alone, was found, despite a lower number of oocytes retrieved. hp-HMG activity plays a role in improving the oocyte and embryo quality and/or the endometrial receptivity. It has been suggested that the cumulus cells exposed to LH activity could play a role in oocyte and embryo development [9, 10]. Recent identification of gene expression in cumulus cells during oocyte maturation [11]supports this hypothesis. However, because we did not use stratification for the fertilization method, this result only has an exploratory character. These results of the present trial are very similar to the results of the Cochrane meta-analysis [12]and to those of a recent trial comparing highly purified hMG with rFSH in IVF [9].

In two large studies performed elsewhere that compared highly purified hMG and rFSH in a long down-regulation protocol for IVF and/or ICSI, the OHSS incidences were similar in both treatment groups (13,9). The results of oursubgroup analysis Research demonstrate that the $AFC > 20$ patient highly purified hMG and rFSH group induce a low OHSS ($p < 0.05$). At an equal dose, highly purified hMG displays a milder stimulation pattern, reflected in a lower cancellation rate, a lower mean number of oocytes, lower E2 serum levels, a lower incidence of ovarian hyperresponse, and a trend toward a smaller incidence of OHSS. The lower E2 levels could be attributed to the lower mean number of follicles on the day of hCG in the highly purified hMG plus group.

The most important LH activity in highly purified hMG appeared to be provided by the longer-acting hCG[14.15.16] It is not worthy that increased concentrations of hCG stimulation in the highly purified hMG group were associated with a better endometrial receptivity and higher PRs in IVF cycles[7, 10]. It also became evident that in the rFSH group, a higher proportion of patients had increased P levels (> 4 nmol/L) at the end of stimulation, associated with an advanced hyperechogenic transformation of the endometrium and lower implantation and PRs ($P < .05$)[17, 18] .

In addition, another recent study [14]that compared highly purified hMG and rFSH for ovulation induction demonstrated that the LH activity in highly purified hMG induces a more modulated folliculogenesis that is associated with a lower risk of excessive ovarian response, comparable to our findings, and an ovulation rate similar to that obtained with rFSH.

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[19], although this was not an issue in our study

In conclusion, hp-HMG addition could be used as an option for the correction of results in those whose response is unexpectedly suboptimal to ovulation induction with r-FSH during GnRH agonist protocol. Particularly, hp-HMG is recommended as it may have a beneficial action on implantation in the selected group. But, to prove the efficacy, wide prospective randomized control trials should be conducted.

Abbreviations

iIVF: In vitro fertilization; ICSI:Intracytoplasmic sperm injection; hp-HMG:Highly purified human menopausal gonadotropins; r-FSH:Recombinant follicle stimulating hormone; r-LH:Recombinant luteinizing hormone; GnRH:Gonadotropin releasing hormone; LH:Luteinizing hormone;FSH:Follicle stimulating hormone; AFC:Antral follicle count; OHSS:Ovarian hyperstimulation syndrome; COS:Controlled ovarian stimulation; GnRH-a:Gonadotropin releasing hormone antagonist; BMI:Body mass index.

Declarations

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Authors' contributions

Zhong-Kai Wang and She-Ling Wu contributed to the conception and design. Zhong-Kai Wang and She-Ling Wu conntributed to statistical analyzing andg article writing. She-Ling Wu contributed to data collection. Xiao-Na Yu, Hong-Wu Qiao, Lou-Hua, Xing-Ling Wang, Wen-Zhang, Yi-Chun Guan contributed to revising the article critically for important intellectual content. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was performed in accordance with guidelines outlined in the Declaration of Helsinki. All the methods and information collection protocols were approved by the institutional review board of Zhengzhou University Third Hospital and Henan Province Women and Children's Hospital, China. Our

research has obtained the waiver from institutional review board for the medical review for selective variable analysis in the center.

Competing interests

The authors declare no competing interests.

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References

1. Filicori M, Cognigni GE, Pocognoli P, Tabarelli C, Ferlini F, Perri T, et al. Comparison of controlled ovarian stimulation with human menopausal gonadotropin or recombinant follicle-stimulating hormone. FertilSteril2003;80:390–7.
2. Filicori M. The role of luteinizing hormone in folliculogenesis and ovulation induction. FertilSteril1999;71:405–14.
3. Mannaerts BM, Rombout F, Out HJ, CoelinghBennink H. Clinical profiling of recombinant follicle stimulating hormone (rFSH; Puregon): relationship between serum FSH and efficacy. Hum Reprod Update. 1996;8:543–57.
4. Pacchiarotti A, Sbracia M, Frega A, Selman H, Rinaldi L, Pacchiarotti A. Urinary hMG (Meropur) versus recombinant FSH plus recombinant LH (Pergoveris) in IVF: a multicenter, prospective, randomized controlled trial. FertilSteril. 2010;94:2467–9.
5. Platteau P, Andersen AN, Balen A, Devroey P, Sorensen P, Helmgaard L, et al. Similar ovulation rates, but different follicular development with highly purified menotrophin compared with recombinant FSH in WHO Group II anovulatory infertility: a randomized controlled study. Hum Reprod. 2006;21:1798–804.
6. Requena A, Cruz M, Ruiz FJ, García-Velasco JA. Endocrine profile following stimulation with recombinant follicle stimulating hormone and luteinizing hormone versus highly purified human menopausal gonadotropin. ReprodBiol Endocrinol. 2014;12:10.
7. Wolfenso-derived gonadotrophin. preparations compared with recombinant preparations. Reprod Biomed Online. 2005;10:442–54.
8. Gadkari RA, Roy S, Rekha N, Srinivasan N, Dighe RR. Identification of a heterodimer-specific epitope present in human chorionic gonadotrophin (hCG) using a monoclonal antibody that can distinguish between hCG and human LH. J Mol Endocrinol. 2005;34:879–87.

9. Andersen AN, Devroey P, Arce JC. Clinical outcome following stimula- tion with highly purified hMG or recombinant FSH in patients undergo- ing IVF: a randomized assessor-blind controlled trial. Hum Reprod. 2006;21:3217–27.
10. Platteau P, Smitz J, Albano C, Sorensen P, Arce JC, Devroey P. Exoge- nous luteinizing hormone activity may influence the treatment outcome in in vitro fertilization but not in intracytoplasmic sperm injection cycles. FertilSteril2004;81:1401–4.
11. Assou S, Anahory T, Pantesco V, Carrour TL, Pellestor F, Klein B, et al. The human cumulus-oocyte complex gene-expression profile. Hum Reprod. 2006;21:1705–19.
12. Van Wely M, Westergaard LG, Bossuyt PM, Van der Veen F. Human menopausal gonadotropin versus recombinant follicle stimulation hor- mone for ovarian stimulation in assisted reproductive cycles. Cochrane Database Syst Rev 2003;(1):CD003973.
13. European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating Hormone. Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hor- mone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial. FertilSteril2002;78:520–8.
14. Platteau P, Andersen AN, Balen A, Devroey P, Sorensen P, Helmgaard L, et al. Similar ovulation rates, but different follicular development with highly purified menotrophin compared with recombinant FSH in WHO Group II anovulatory infertility: a randomized controlled study. Hum Reprod. 2006;21:1798–804.
15. Filicori M, Cognigni GE, Gamberini E, Parmegiani L, Troilo E, Roset B. Efficacy of low-dose human chorionic gonadotropin alone to complete controlled ovarian stimulation. FertilSteril2005;84:394–401.
16. Filicori M, Cognigni GE, Pocognoli P, Tabarelli C, Spettoli D, Taraborrelli S, et al. Modulation of folliculogenesis and steroidogenesis in women by graded menotrophin administration. Hum Reprod. 2002;17:2009–15.
17. Andersen AN, Devroey P, Arce JC. Clinical outcome following stimula- tion with highly purified hMG or recombinant FSH in patients undergo- ing IVF: a randomized assessor-blind controlled trial. Hum Reprod. 2006;21:3217–27.
18. Smitz J, Andersen AN, Devroey P, Arce JC, Merit Group. Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinat FSH in IVF patients. Hum Reprod. 2007;22:676–87.
19. Barriere P, et alCost-Effectiveness Analysis of the Gonadotropin Treatments HP-hMG and rFSH for Assisted Reproductive Technology in France: A Markov Model Analysis Appl Health Econ Health Policy 2018.