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Bio-equivalent doses of recombinant HCG and recombinant LH during ovarian stimulation result in similar oestradiol output: a randomized controlled study

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KEY MESSAGE

Functional and structural differences exist between LH and HCG. The results of the present randomized controlled study show that the late follicular phase oestradiol level is unaffected by whether stimulation is carried out with HCG or LH when used in bio-equal doses.

A B S T R A C T

In nature, HCG is secreted by the implanting embryo from peri-implantation and onwards. In contrast, LH is mandatory for steroidogenesis and follicular development during the follicular phase, working in synergy with FSH. Moreover, LH is mandatory for the function of the corpus luteum. Although LH and HCG bind to the same receptor, significant molecular, structural and functional differences exist, inducing differences in bioactivity. This randomized controlled study compared the effect of recombinant FSH stimulation combined with daily either micro-dose recombinant HCG or recombinant LH supplementation in a 1:1 bioactivity ratio from day 1 of stimulation in a long gonadotrophin releasing hormone agonist down regulation protocol. A total of 100 patients from a public clinic completed the study. The primary end-point was the oestradiol level on the day of ovulation trigger and the median oestradiol level in the HCG supplemented group was 8662 pmol/l versus 9203 pmol/l in the recombinant LH supplemented group; therefore, no significant difference was found. Moreover, no differences were observed in the number of oocytes retrieved or in the live birth rate. We conclude that recombinant HCG and recombinant LH are equally effective in boosting oestradiol synthesis during ovarian stimulation when used in a 1:1 bioactivity ratio.

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Introduction

During the past decade, numerous prospective randomized trials and meta-analyses have been published on the endocrine and reproductive outcomes in women subject to pituitary down-regulation with gonadotrophin releasing hormone (GnRH) analogues. The primary focus was usually on protocols and the superiority, or not, of one gonadotrophin preparation over the other.

One approach used during ovarian stimulation is the use of recombinant FSH (rFSH), containing no LH activity; another approach is the use of urinary human menopausal gonadotrophin (uHMG), which contains FSH and LH activity in a 1:1 ratio. Importantly, most (95%) of the LH activity present in uHMG derives from HCG (Wolfenson et al., 2005). Although, more oocytes are produced with rFSH owing to differences in isoforms, no difference was seen between uHMG and rFSH in live birth rates of the 'fresh transfer cycle' (Lehert et al., 2010; van Wely et al., 2011); therefore, it still remains to be explored whether differences in cumulative live birth rates exist between the two types of gonadotrophins, an issue of socioeconomic interest.

In previously published studies, uHMG has been shown to induce higher late follicular phase serum oestradiol levels compared with rFSH (Smitz et al., 2007; Van et al., 2003; Westergaard et al., 2004). Moreover, the pharmacodynamics and the number of so-called 'top quality' embryos were reported to differ significantly between the two compounds. This difference in number of top-quality embryos in favour of uHMG was suggested to be the result of the LH activity (HCG) present in uHMG (Andersen et al., 2006).

The function of HCG and LH is exerted through the LH–HCG receptor. On a structural level, significant similarities exist between LH and HCG, as they share the same alpha subunit and 85% of the amino acid residues of the beta subunit (Kessler et al., 1979; Lapthorn et al., 1994). Differences, however, exist in pharmacodynamics and gene-expression pattern; importantly, the half-life of HCG is over 24 h (Damewood et al., 1989), compared with the half-life of LH, which is around 60 min (Yen et al., 1968). Moreover, the gene-expression patterns induced by HCG and LH, respectively, differ significantly. Therefore, LH up-regulates the expression of its own receptor (LHR) as well as genes involved in steroidogenesis, cellular growth and follicular development, whereas HCG, because of its significantly longer half-life, down-regulates the same genes (Casarini et al., 2016).

According to the two-cell, two-gonadotrophin concept, both LH and FSH are required for normal follicular development and function, and FSH is the principal regulator of follicular recruitment. In contrast, the specific physiological and clinical requirement of LH in assisted reproduction techniques is less clear. The LHR, however, is constitutively expressed on the theca cell, and on granulosa cells from a follicle size of about 6 mm (Jeppesen et al., 2012). Activation of thecal LHR stimulates the synthesis of androgens in theca cells, which in turn act as the substrate for oestrogen synthesis by the granulosa cell under the action of FSH and aromatase. Therefore, at any time during the follicular phase of the menstrual cycle, circulating levels of oestrogen reflect the combined effects of FSH and LH. From basic steroidogenesis, it seems plausible that gonadotrophin preparations with different types of LH activity used for ovarian stimulation may result in differences in oestradiol biosynthesis, and possibly also oocyte maturation, embryo quality and reproductive outcome. Therefore, the aim of the present study was to evaluate the endocrine effect of stimulation with daily rFSH and HCG compared with daily rFSH and recombinant LH (rLH) when used in a 1:1 bioactivity ratio.

Materials and methods

Participants

Participants were enrolled between 2009 and 2011 in a public fertility centre in Denmark. All patients fulfilling the following inclusion criteria were considered eligible to participate in the trial: female age over 18 years and 35 years or younger; regular cycles (25–34 days); basal FSH and LH values on second to third day of the cycle not exceeding 12 IU/L; body mass index over 18 and less than 30 kg/m^2; first or second IVF and intracytoplasmic sperm injection cycle; and absence of uterine abnormalities. Patients were excluded if they had any medical diseases, polycystic ovary syndrome or if they previously had participated in the study. Most participants were white.

Stimulation, embryo transfer and luteal phase support

The protocol used was a long GnRH analogue down-regulation protocol commencing from day 21 of the cycle, using 0.5 mg buserelin subcutaneously daily (Suprefact®, Sanofi-Aventis, Denmark) for at least 12–14 days after which the dose was reduced to 0.2 mg daily. On the first day of stimulation (S1), randomization between groups took place, using computer-generated random numbers in sealed, unlabelled envelopes, each containing a unique study number.

The study was an open label study. In Group A, stimulation was initiated with 150 IU rFSH (Gonal-f®, Merck Serono, Denmark) and 25 IU rHCG (Ovitrelle®, Merck Serono, Denmark) daily, and in Group B stimulation was initiated with 150 IU rFSH and 150 IU rLH (Luveris®, Merck Serono, Denmark) daily. The dose of gonadotrophins was fixed for the first 6 days; subsequently the dose could be modified according to follicular development. If dose adjustment, however, was needed, the ratio between rFSH and rLH or rLH-activity should always be in a 1:1 ratio (**Table 1**).

As recombinant HCG (rHCG) is not readily available in these low doses, the patient prepared a new diluted rHCG suspension every day after instructions by a nurse. Therefore, 250 µg rHCG (Ovitrelle) was injected into a bottle of 100 ml saline solution and the patient injected the planned dose (**Table 1**). When at least three follicles reached 17 mm, oocyte maturation was induced by a bolus of rHCG (Ovitrelle, Merck Serono) 250 µg and oocyte retrieval was carried out 35 h later. Embryo transfer was carried out on days 2 or 3 after oocyte aspiration. Danish criteria for single embryo transfer were followed, allowing a maximum of two embryos for transfer.

Embryo transfer was cancelled if the endometrial thickness was less than 7 mm. Surplus good-quality cleavage embryos were frozen (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest

Table 1 – Equivalent doses of FSH, HCG, Ovitrelle suspension and LH.

Recombinant FSH dose (IU)	Recombinant HCG dose (IU)	Ovitrelle suspension (ml)	Recombinant LH (IU)
375	62.5	0.83	375
300	50	0.66	300
225	37.5	0.50	225
187.5	31.25	0.40	187.5
150	25	0.33	150
112.5	18.7	0.25	112.5
75	12.5	0.16	75

Group of Embryology, 2011). All patients received luteal phase support in the form of vaginal progesterone (Crinone®, Merck Serono, Denmark), 90 mg daily until the day of the pregnancy test, 12–14 days after embryo transfer. A pregnancy test was considered positive if HCG was over10 IU/l. Clinical pregnancy was documented by transvaginal ultrasound at 7th gestational week, and follow-up was carried out until live birth.

Written informed consent was obtained from all participants, and the study was carried out in accordance with International *Conference on Harmonization–Good Clinical Practice guideline* and *European Union Good Manufacturing Practice Annex 13*. The study was approved by The Ethics Committee of Mid-Jutland Project number: M-20080227. EUdraCT: 2009-009375-35; number: 2612–3960.

Hormone measurements

Blood samples were drawn in total five times, including the pregnancy test (**Table 3**). Serum aliquots were stored at −20°C and subsequently analysed for oestradiol, LH, progesterone, HCG, FSH and testosterone. Hormones were measured in one run, using the routine assays used by the clinical Biochemistry Department, University Hospital of Odense, Denmark.

Sample size

The sample size calculation was based on a previous trial comparing rFSH with highly purified HMG (Kilani et al., 2003). The primary end-point was the oestradiol level on the day of ovulation trigger. A total of 50 patients in each group were needed to detect a true difference of 1500 pmol/L (410 pg/ml) on the day of ovulation trigger, using a significance level of 5% and 80% power.

Secondary end-points were the number of FSH days and the total FSH consumption, number of follicles on trigger day, number of high-quality embryos, number of frozen embryos, serum levels of LH, FSH, progesterone and HCG during the follicular phase, and the reproductive outcome.

Statistics

In order to test for normal distribution, quantile quantile (qq) plots were computed. If data were asymmetrical, they were log transformed and new qq plots were computed. Variance homogeneity was assessed using the F-test. If the assumptions of normality and equal variance were fulfilled, a parametric test was used for differences in means between groups. For the primary outcome, the corresponding 95% CI of the ratio between medians in the two groups was computed using the exponential function of the log transformed data. In case of asymmetry, a non-parametric test was used for differences in medians. Fisher's exact test was used to test for differences in proportions. Some values were below the laboratory cut-off, unless described otherwise; these values were all treated as missing values in the statistical analyses. All *P*-values were two-sided, and the level of significance was 0.05. Stata software version 12.1 (Statacorp, 4905 Lakeway Drive, College Station, Texas, USA) was used for all statistical analyses.

Results

Flow chart and demographic data

A total of 156 patients were assessed for eligibility, resulting in a total of 51 patients enrolled in each group. The Consolidated Standards of Reporting Trials diagram shows the flow of participants through each stage of the study (**Figure 1**). Demographic data are presented in **Table 2**, and no significant differences were seen between groups.

Primary outcome parameter

The median oestradiol level on the day of ovulation trigger was 0.94 times lower in the HCG group compared with the LH group (95% CI 0.61 to 1.28) (**Table 3**). This was not statistically significant.

Secondary outcome parameters

No significant differences were observed between groups in the number of follicles at the time of ovulation induction, the number of oocytes, the number of good-quality embryos and frozen embryos (**Table 2**).

Follicular phase serum hormone levels

The levels of testosterone, progesterone and HCG during the follicular phase and on the day of oocyte retrieval were not significantly

Table 2 – Demographic data, follicles and reproductive outcomes.[a]

	Recombinant FSH + recombinant HCG	Recombinant FSH + recombinant LH
	n = 50	*n* = 50
Age	29.7 (±3.1)	30.1 (±3.2)
Body mass index, kg/m^2	24.2 (±3.7)	24.9 (±4.0)
Gravida, n	0 (1)	0 (1)
Parity, n	0 (0)	0 (0)
Baseline FSH, IU/l	6.1 (±1.8)	6.4 (±1.8)
Baseline LH, nmol/l	4.8 (3.4–6.7)	5.3 (4.1–6.8)
Total FSH, IU/l	1994 (±762)	2026 (±707)
Total LH activity, IU/l	1997[b] (±761)	2026 (±707)
Follicles 10–13 mm, n	4 (2–6)	4 (2–8)
Follicles 14–16 mm, n	5 (2–7)	5 (2–7)
Follicles >17 mm, n	6 (4–9)	6 (4–9)
Stimulation length, days	12.2 (±1.7)	12.2 (±1.3)
Oocytes aspirated, n	9 (7–11)	11 (7–13)
Metaphase II oocytes, n	8.2 (±4.1)	9.0 (±4.9)
Two-pronuclear zygote, n	4.5 (3–8)	4.5 (2–7)
Good-quality embryos, n[c]	3 (2–6)	4 (2–6)
Embryos transferred, n	1 (1–1)	1 (1–1)
Cancelled cycles, n	9	8
Ovarian hyperstimulation syndrome cases, n	0	2
Pregnancy rate (%)[d]	41.5	35.7
Clinical pregnancy rate 7th week % (n/n)[d]	31.7 (13/41)	26.2 (11/42)
Live birth rate % (n/n)[d]	26.8 (11/41)	19.0 (8/42)
Embryos frozen, n	2 (0–4)	2 (0–4)

There were no statistically significant differences between the groups.

[a] If not otherwise indicated, values in brackets state the standard deviation (±X) for means and interquartile range for medians.

[b] A total of 1997 IU LH like activity is approximately 333 IU recombinant HCG, which corresponds to the conversion factor 6.

[c] Good-quality embryos refers to transferable embryos, i.e. embryos transferred and frozen embryos.

[d] Reproductive outcome. A total of 41 patients in the HCG group and 42 patients in the LH group underwent embryo transfer.

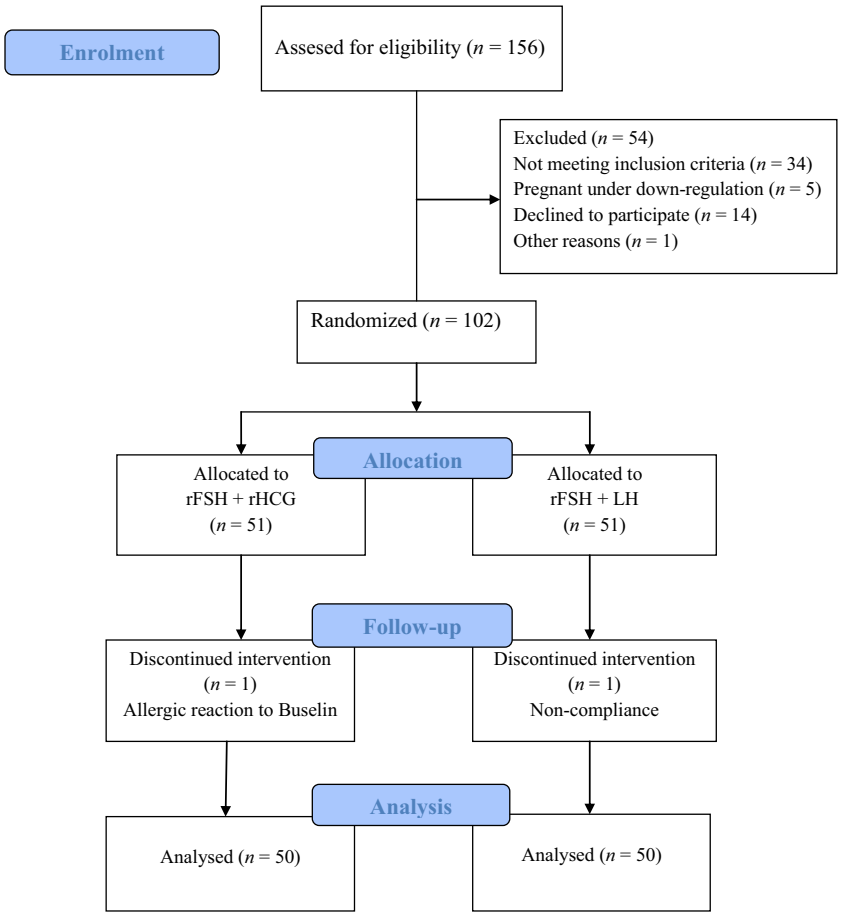

Figure 1 – The Consolidated Standards of Reporting Trials diagram. rFSH, recombinant FSH; rHCG, recombinant HCG.

different between groups. Because of the use of two different LH activity types, however, a significant difference in LH levels on stimulation day 7 was found ($P < 0.0001$). Further endocrine data from stimulation days 1, 7, HCG trigger day and the day of oocyte retrieval are shown in **Table 3**.

Reproductive outcome

For the reproductive outcome, including live birth rate, no significant difference was observed (**Table 2**).

Discussion

In this randomized controlled study, comparing daily low-dose rHCG with rLH supplementation in a 1:1 bioactivity ratio from day 1 of ovarian stimulation during IVF treatment, no significant difference was seen in the primary end-point parameter, the oestradiol level on the day of HCG trigger. Moreover, no differences were observed in any of the secondary outcome parameters, including the reproductive outcome.

In a previous study, Nyboe Andersen et al. (2006) reported that supplementation with LH-activity (HMG/HCG) to FSH in a long GnRH agonist down-regulation protocol was associated with improved embryo quality, higher late follicular phase oestradiol levels and lower late follicular progesterone levels, resulting in a more 'receptive endometrium (Andersen et al., 2006). As previously mentioned, the LH activity in HMG preparations derives almost entirely, and in the highly purified HMG (Menopur, Ferring), exclusively, from HCG (Wolfenson et al., 2005). Whether the suggested beneficial effect of HMG was caused by its content of HCG as a molecule, with its distinct pharmacodynamics characteristics or whether LH in the same bioactivity dose would have had the same positive effect until now has been an open question. The present study, however, clearly shows that when used in the same bioactivity ratio (1:1), no difference was seen in steroidogenesis and, in particular, the late follicular oestradiol level when comparing rHCG with rLH.

As the half-life of rLH is considerably shorter than that of rHCG, it can be envisioned that, in between injections, there will be a period during which the level of the supplemented rLH is low, resulting in a less active theca/granulosa cell compartment. It seems, however, that a daily bolus of rLH is still sufficient, despite its short half-life, to boost steroidogenesis and, in particular, oestradiol to levels similar to those induced by a daily bolus of rHCG. Over the years, studies have compared different low-dose HCG or rLH supplementation regimens with FSH stimulation (Drakakis et al., 2009; Kilani et al., 2003; Requena et al., 2014; Thuesen et al., 2012; Van Horne et al., 2007). Therefore, Van Horne et al. (2007) retrospectively analysed the outcomes of 190 cycles in which either rFSH alone or rFSH supplemented with uHCG (50–100 IU) daily were used for ovarian stimulation. The investigators reported no difference in reproductive outcomes; however, significantly less rFSH was used in the group of patients

Table 3 – Endocrine data from ovarian stimulation and oocyte retrieval.

		Recombinant FSH + recombinant HCG	Recombinant FSH + recombinant LH	P-value
		n = 50	*n* = 50	
Stimulation day 1	Oestradiol[a] (pmol/l)	65 (57–96)	78 (61–95)	NS
	LH (IU/l)	1.5 (1.1–1.9)	1.65 (1.1–2.1)	NS
	Progesterone[b] (nmol/l)	1.1 (2.7–4.9)	1.1 (0.9–1.4)	NS
Stimulation day 7	Oestradiol (pmol/l)	1357 (858–2724)	1578 (892–2451)	NS
	LH (IU/l)[c]	1.3 (0.7–1.6)	2.2 (1.9–2.9)	<0.0001
	HCG (IU/l)[d]	<2	<2	–
	Testosterone (nmol/l)[e]	1.5(1.0–2.0)	1.4 (1.0–1.8)	NS
HCG trigger day	Oestradiol (pmol/l)	8662 (5591–16470)	9203 (6523–17459)	NS
	LH (IU/l)	1.0 (0.7–1.7)	1.9 (1.3–2.8)	<0.0001
	Testosterone (nmol/l)	2.3 (1.9–3.4)	2.5 (1.9–3.3)	NS
	HCG (IU/l)[d]	<2	<2	–
	Progesterone (nmol/l)	3.4 (2.7–4.9)	3.2 (2.2–4.9)	NS
Oocyte retrieval	Oestradiol (pmol/l)	6494 (±2864)	6946 (±3389)	NS
	LH (IU/l)[f]	0.1 (0.1–0.1)	0.2 (0.1–0.3)	0.01
	FSH (IU/l)	4.5 (±2.3)	4.7 (±2.8)	NS
	HCG (IU/l)	108 (±45)	117 (±42)	NS
	Progesterone (nmol/l)	40 (27–57)	37 (26–48)	NS

NS, not statistically significant.
Value in brackets states the standard deviation (±X) for means and interquartile range for medians. Dashes mean that no comparison was made.
[a] A total of 35 patients were below the laboratory cut-off at 50 pmol/L (17 in the HCG group and 18 in the LH group).
[b] A total of 33 patients were below the laboratory cut-off at 0.8 nmol/L (nine in the HCG group and 24 in the LH group).
[c] A total of six and 32 patients were below laboratory cut off at 0.1 IU/L in HCG group and LH group, respectively.
[d] All HCG values were below the laboratory cut-off at 2 IU/L. Therefore, no statistical comparison was made.
[e] A total of 12 patients were below the laboratory cut-off at 0.4 nmol/L. Six in each group.
[f] A total of 44 and 32 patients were below laboratory cut-off at 0.1 IU/L in the HCG group and LH group, respectively.

supplemented with uHCG. Moreover, Drakakis et al. (2009), in a randomized controlled trial including a total of 114 IVF patients, explored possible differences between rLH (200 IU) and uHCG (200 IU) when used in a 1:6 bioactivity ratio for 5 days during ovarian stimulation. The investigators reported that the number of follicles, oocytes and transferable embryos as well as the clinical pregnancy rate were significantly higher in the HCG group. In a more recent study, Requena et al. (2014) compared the steroid profile after stimulation with rFSH and rLH versus HMG in 50 oocyte donors. Both groups had a FSH:LH activity ratio of 2:1 and the LH bioactivity ratio was 1:1. No significant differences in serum oestradiol, progesterone and androgens levels were observed on the trigger day. In the follicular fluid, a higher oestradiol level in the HMG group was observed. Finally, Moro et al. (2015) also compared rFSH with HMG using the same bioactivity ratio as Requena et al. (2014), albeit in an IUI setting, and reported a significantly higher serum oestradiol level and more follicles in the rFSH group.

Taken together, conclusions are conflicting, ranging from no difference to significantly increased numbers of mature oocytes retrieved (Drakakis et al., 2009), increased number of top-quality embryos (Andersen et al., 2006) and improved reproductive outcomes (Drakakis et al., 2009) by HCG supplementation. Interestingly, none of the above studies compared the endocrine effect of FSH stimulation with either HCG or LH when used in equivalent LH bioactivity doses, except for the studies by Requena et al. (2014) and Moro et al. (2015). These studies, however, compared different FSH isoforms, masking any true difference between LH and HCG.

In a more recent study, Thuesen et al. (2012) compared four different daily doses of rHCG either 0, 50, 100 or 150 IU added to the FSH stimulation regimen from day one of stimulation. The highest late follicular phase oestradiol level was seen in the groups treated with the highest rHCG doses. A ceiling effect, however, was seen at 100 IU rHCG, suggesting a saturation of the aromatase system. An important finding of that study was that late follicular phase progesterone rose proportionally with the HCG dose administered. Therefore, the study finally documented that HCG does not lower the late follicular phase progesterone level, but in fact increases it (Thuesen et al., 2012).

As outlined in *The British Pharmacopeia*, the converting factor used in the present study to calculate the daily rHCG dose comparable to the bio-potency of rLH was 6. This reflects that, *in vivo*, it is necessary to provide 6 IU of LH to obtain a stimulation similar to that of 1 IU of HCG (Giudice et al., 2001; Stokman et al., 1993). Therefore, HMG products normally contain around 12 IU of HCG (and only trace amounts of LH), which together with 75 IU of FSH provide a 1:1 ratio of FSH and LH-like activity. *The British Pharmacopeia* uses a 1:6 ratio between LH and HCG. This is the authority by which the pharmaceutical companies need to comply with and 1:6 ratio is used in this study. More recently others have suggested that HCG has a bio-potency five times higher than that of LH (Casarini et al., 2012).

In the present study, the HCG levels on day 7 of stimulation day and on the HCG-trigger day were less than 2 UI. These rather low HCG levels during supplementation corroborate the findings by others. Therefore, Thuesen et al. (2012) reported an HCG level of 3.1 IU in a group of women treated with 50 IU rHCG daily and, in the Merit Study (Andersen et al., 2006), HCG levels were 2.45– 2.94 after a dose of 225 IU highly purified HMG, which approximately equates to 30 IU HCG daily (Wolfenson et al., 2005). In the present study for the group of patients treated with rLH, the level of rHCG is expected to be zero; however, the assay used was not sensitive enough to detect values lower than 2 IU/L.

It might be considered a limitation of the present study that it did not include a control group of patients who were stimulated with rFSH, only. The primary end-point of the study, and for which it was powered,

was the possible difference in oestradiol biosynthesis between LH and HCG. Therefore, any conclusions about the reproductive outcome with the current sample size would be inappropriate.

Taken together, although functional and structural differences exist between LH and HCG, no differences were seen when these gonadotrophins were used in a 1:1 bioactivity ratio for daily supplementation during stimulation for IVF. Although it seems unlikely that differences in composition should have a clinical effect, the present study was not powered to explore any differences in reproductive outcomes between rHCG and rLH. With the present sample size, however, it is reassuring that no differences were observed between groups.

In conclusion, the results of the present study show that the late follicular phase oestradiol level is unaffected by whether stimulation is conducted with HCG or LH when used in bio-equal doses. Future larger studies are needed to explore possible differences in reproductive outcomes between LH and HCG.

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REFERENCES

Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum. Reprod. 26, 1270–1283.

Andersen, A.N., Devroey, P., Arce, J.C., 2006. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized assessor-blind controlled trial. Hum. Reprod. 21, 3217–3227.

Casarini, L., Lispi, M., Longobardi, S., Milosa, F., La Marca, A., Tagliasacchi, D., Pignatti, E., Simoni, M., 2012. LH and hCG action on the same receptor results in quantitatively and qualitatively different intracellular signalling. PLoS ONE 7, e46682.

Casarini, L., Brigante, G., Simoni, M., Santi, D., 2016. Clinical applications of gonadotropins in the female: assisted reproduction and beyond. Prog. Mol. Biol. Transl. Sci. 143, 85–119.

Damewood, M.D., Shen, W., Zacur, H.A., Schlaff, W.D., Rock, J.A., Wallach, E.E., 1989. Disappearance of exogenously administered human chorionic gonadotropin. Fertil. Steril. 52, 398–400.

Drakakis, P., Loutradis, D., Beloukas, A., Sypsa, V., Anastasiadou, V., Kalofolias, G., Arabatzi, H., Kiapekou, E., Stefanidis, K., Paraskevis, D., Makrigiannkis, A., Hatzakis, A., Antsakis, A., 2009. Early hCG addition to rFSH for ovarian stimulation in IVF provides better results and the cDNA copies of the hCG receptor may be an indicator of successful stimulation. Reprod. Biol. Endocrinol. 7, 110. 7827-7-110.

Giudice, E., Crisci, C., Altarocca, V., O'Brian, M., 2001. Characterisation of a partially purified human menopausal gonadotropin preparation. J. Clin. Res. 4, 27–34.

Jeppesen, J.V., Kristensen, S.G., Nielsen, M.E., Humaidan, P., Dal Canto, M., Fadini, R., Schmidt, K.T., Ernst, E., Yding Andersen, C., 2012. LH-receptor gene expression in human granulosa and cumulus cells from antral and preovulatory follicles. J. Clin. Endocrinol. Metab. 97, E1524–E1531.

Kessler, M.J., Reddy, M.S., Shah, R.H., Bahl, O.P., 1979. Structures of N-glycosidic carbohydrate units of human chorionic gonadotropin. J. Biol. Chem. 254, 7901–7908.

Kilani, Z., Dakkak, A., Ghunaim, S., Cognigni, G.E., Tabarelli, C., Parmegiani, L., Filicori, M., 2003. A prospective, randomized, controlled trial comparing highly purified hMG with recombinant FSH in women undergoing ICSI: ovarian response and clinical outcomes. Hum. Reprod. 18, 1194–1199.

Lapthorn, A.J., Harris, D.C., Littlejohn, A., Lustbader, J.W., Canfield, R.E., Machin, K.J., Morgan, F.J., Isaacs, N.W., 1994. Crystal structure of human chorionic gonadotropin. Nature 369, 455–461.

Lehert, P., Schertz, J.C., Ezcurra, D., 2010. Recombinant human follicle-stimulating hormone produces more oocytes with a lower total dose per cycle in assisted reproductive technologies compared with highly purified human menopausal gonadotrophin: a meta-analysis. Reprod. Biol. Endocrinol. 8, 112–7827-8-112.

Moro, F., Scarinci, E., Palla, C., Romani, F., Familiari, A., Tropea, A., Leoncini, E., Lanzone, A., Apa, R., 2015. Highly purified hMG versus recombinant FSH plus recombinant LH in intrauterine insemination cycles in women >/=35 years: a RCT. Hum. Reprod. 30, 179–185.

Requena, A., Cruz, M., Ruiz, F.J., Garcia-Velasco, J.A., 2014. Endocrine profile following stimulation with recombinant follicle stimulating hormone and luteinizing hormone versus highly purified human menopausal gonadotropin. Reprod. Biol. Endocrinol. 12, no pagination.

Smitz, J., Andersen, A.N., Devroey, P., Arce, J.C., 2007. Endocrine profile in serum and follicular fluid differs after ovarian stimulation with HP-hMG or recombinant FSH in IVF patients. Hum. Reprod. 22, 676–687.

Stokman, P.G., de Leeuw, R., van den Wijngaard, H.A., Kloosterboer, H.J., Vemer, H.M., Sanders, A.L., 1993. Human chorionic gonadotropin in commercial human menopausal gonadotropin preparations. Fertil. Steril. 60, 175–178.

Thuesen, L.L., Loft, A., Egeberg, A.N., Smitz, J., Petersen, J.H., Andersen, A.N., 2012. A randomized controlled dose-response pilot study of addition of hCG to recombinant FSH during controlled ovarian stimulation for in vitro fertilization. Hum. Reprod. 27, 3074–3084.

van Wely, M., Kwan, I., Burt, A.L., Thomas, J., Vail, A., Van der Veen, F., Al-Inany, H.G., 2011. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst. Rev. (2), CD005354. doi:CD005354.

Van Horne, A.K., Bates, G.W., Jr., Robinson, R.D., Arthur, N.J., Propst, A.M., 2007. Recombinant follicle-stimulating hormone (rFSH) supplemented with low-dose human chorionic gonadotropin compared with rFSH alone for ovarian stimulation for in vitro fertilization. Fertil. Steril. 88, 1010–1013.

Van, W.M., Westergaard, L.G., Bossuyt, P.M., Van der Veen, F., 2003. Human menopausal gonadotropin versus recombinant follicle stimulation hormone for ovarian stimulation in assisted reproductive cycles. Cochrane Database Syst. Rev. (1), CD003973.

Westergaard, L.G., Erb, K., Laursen, S.B., Rasmussen, P.E., Rex, S., Westergaard, C.G., Andersen, C.Y., 2004. Concentrations of gonadotrophins and steroids in pre-ovulatory follicular fluid and serum in relation to stimulation protocol and outcome of assisted reproduction treatment. Reprod. Biomed. Online 8, 516–523.

Wolfenson, C., Groisman, J., Couto, A.S., Hedenfalk, M., Cortvrindt, R.G., Smitz, J.E., Jespersen, S., 2005. Batch-to-batch consistency of human-derived gonadotrophin preparations compared with recombinant preparations. Reprod. Biomed. Online 10, 442–454.

Yen, S.S., Llerena, O., Little, B., Pearson, O.H., 1968. Disappearance rates of endogenous luteinizing hormone and chorionic gonadotropin in man. J. Clin. Endocrinol. Metab. 28, 1763–1767.