European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 300–305

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Recombinant LH supplementation in patients with a relative reduction in LH levels during IVF/ICSI cycles: A prospective randomized controlled trial

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ARTICLE INFO

Article history:
Received 11 September 2016
Received in revised form 31 December 2016
Accepted 6 January 2017
Available online xxx

Keywords:
Recombinant LH
Low LH
Controlled ovarian hyperstimulation
IVF
RCT

ABSTRACT

Purpose: The aim of this study was to assess the use of recombinant luteinizing hormone (rLH) supplementation in patients who experience a reduction in LH concentration during controlled ovarian hyperstimulation (COH) for IVF/ICSI.
Methods: A multi-center prospective randomized controlled trial (RCT) was performed over three years. Two hundred and forty patients aged between 24 and 42 years undergoing IVF/ICSI treatment with a long down regulation (LDR) protocol were recruited. LH was measured on the day FSH was started and again 6 days later. 100 patients had a 50% or greater reduction in LH levels and these were randomized to receive either recombinant LH (rLH) supplementation (group 1, n = 43) or no additional rLH supplementation (group 2, n = 57). Group 1 received rLH 75IU daily from day 7 of FSH stimulation to the day of HCG trigger.
Results: There were no differences in either live birth or clinical pregnancy rates per embryo transfer between the two groups (27.8% vs. 37.0%, p = 0.39, RR = 0.75, 95%CI 0.39–1.44 and 36.1% vs. 43.5% p = 0.51, RR = 0.84, 95%CI 0.5–1.48, respectively).
Conclusion: In conclusion the addition of rLH in patients with a relative reduction in serum LH concentration during COH for IVF/ICSI did not improve live birth or clinical pregnancy rates. However the results were not conclusive and further large well-designed RCTs are required to confirm these findings.

Introduction

The need for Luteinizing Hormone (LH) during follicular development has been well established. Luteinizing Hormone is essential for estrogen production according to the 2-cell theory [1]. In women with hypogonadotrophic hypogonadism ovarian stimulation for both ovulation induction and IVF using FSH without LH activity has been found to be inferior [2,3].

During controlled ovarian hyperstimulation (COH) for IVF/ICSI, serum LH is profoundly suppressed due to the use of GnRH agonists and antagonists. Despite earlier evidence to the contrary [4], doubt exists whether this suppression of LH has a detrimental effect on IVF outcomes [5,6] and whether LH supplementation is beneficial [7,8].

A Cochrane review on recombinant LH (rLH) supplementation in COH for IVF concluded that there is not enough evidence to recommend LH supplementation in general [7]. In contrast Pezzutto in 2009 published the results of a randomized controlled trial (RCT) of rLH supplementation during COH for IVF [9] showing a significant improvement in pregnancy rates in the rLH supplementation group when serum LH levels were low (LH < 0.5 pmol/L).

In 2007 the current authors published a retrospective cohort study assessing the impact of a reduction in LH levels during COH on live birth rates during GnRH long-down regulation IVF treatment. This study revealed a negative effect on live birth rates in cases of a greater than 50% reduction in LH levels from day 0 to day 6 of COH in long down regulation agonist cycles [10].

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http://dx.doi.org/10.1016/j.ejogrb.2017.01.011
0301-2115/

The aim of the current study was to assess the effect on treatment outcomes of supplementing rLH (Luveris) in patients with a greater than 50% reduction of serum LH concentrations during COH during GnRH long-down regulation IVF treatment.

Patients and methods

A prospective RCT was performed from 2007 to 2009 at IVFAustralia, a multi-center IVF organization based in Sydney, Australia. The IVFAustralia ethics committee approved the study. The trial was registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12610000064000.

Inclusion criteria included the following: Infertility, IVF/ICSI using long pituitary down regulation, no more than 3 previous stimulated IVF/ICSI treatment cycles, age 18 to 42, not an oocyte donor, not already taken part in the study, no current endocrine disorder including pituitary disease, thyroid disease, or adrenal disease.

Study protocol

All patients underwent COH for IVF/ICSI with a mid-luteal long down-regulation protocol. This involved starting treatment with a daily GnRH agonist on Day 21 of the preceding cycle. The GnRH agonist used was either leuprolide (Lucrin®, Abbott Australasia, Botany) 10–20 IU daily by SC injection or nafarelin (Synarel®, Pfizer Australia, West Ryde) two nasal sprays twice daily, depending on the direction of the managing doctor.

After 12 days of GnRH agonist a measurement of oestradiol, LH and progesterone was performed. If the concentration of oestradiol was less than 300 pmol/L down-regulation was considered to have been achieved. If down-regulation was not achieved, the GnRH agonist was continued until down regulation was achieved. Once down-regulation was achieved, the patient was started on rFSH (either Gonal F®, Merck Serono Australia, Frenchs Forrest or Puregon®, Merck Sharp & Dohme Australia, South Granville) at a dosage determined by the managing doctor according to IVFAustralia guidelines.

Serum LH measurements were taken on day 0 and day 6 of FSH administration. A LH ratio was calculated by dividing the LH concentration on the day 6 of FSH injections by the LH concentration on LH day 0.

$$\text{LH ratio} = \frac{\text{LH day 6}}{\text{LH day 0}}$$

Where the ratio was less than or equal to 0.5 (LH ratio $<=0.5$), the patient was randomised to one of two study groups as described below (see flow diagram, Appendix A):

Group 1: In addition to the routine protocol of GnRH agonist and rFSH each patient also received rLH supplementation 75IU (Luveris®, Merck Serono Australia, Frenchs Forrest) subcutaneously daily starting on days 7 or 8 of FSH injections and continuing daily until the day of rhCG trigger (Ovidrel®, Merck Serono Australia, Frenchs Forrest).

Group 2: As per group 1 but no rLH supplementation.

Where the LH ratio was greater than 0.5 (LH ratio > 0.5), the participant was not randomized but acted as a third study group. No placebo was used in this trial. Hence this trial was not blinded.

Group 3: As per group 1 but no rLH supplementation.

Randomisation was performed using concealed allocation and online computer-generated randomization, compliant with CONSORT (Piaggio [11]).

Each patient underwent regular monitoring with bloods (oestradiol, LH and progesterone) and transvaginal ultrasound every 2–3 days. Once more than three follicles greater than 17 mm were noted on ultrasound, an injection of 250 mcg rhCG (Ovidrel, Serono) was administered 36 h before oocyte recovery, which was performed as a transvaginal ultrasound guided ovum pick-up.

The oocytes were either inseminated (IVF) or subjected to ICSI with prepared sperm 2–4 h after collection, and fertilization was confirmed 16–18 h later. Embryos were mostly cultured for day 5 embryo transfer. Embryo freezing was performed on day 5 or 6 of culture.

Following recovery of the oocytes, the patients received luteal support in the form of 8% progesterone gel (Crinone®, Merck Serono Australia, Frenchs Forrest) daily starting the day after the oocyte retrieval and continuing until the serum pregnancy test 16 days after the egg collection.

The primary outcomes were live birth rate per embryo transfer and clinical pregnancy rate per embryo transfer. Secondary outcomes included miscarriage rate, total amount of FSH used, days of FSH stimulation, peak estradiol level, progesterone concentration on day of HCG trigger, number of oocytes retrieved, number of top grade embryos and the number embryos for cryopreservation. A clinical pregnancy was defined as a pregnancy exhibiting an intra-uterine gestational sac on ultrasound or an ectopic pregnancy. A miscarriage was defined a clinical pregnancy that was lost before 20 weeks of gestation. A top grade embryo was defined under the modified Gardner's scoring system as a full or expanded Blastocyst scoring at least a B grade for both trophectoderm and inner cell mass [12].

Statistics

Power calculations were performed to calculate the sample size required with a power of 80% and a type 1 error of $\alpha = 0.05$. The trial by Lisi et al. [13] reported a IVF/ICSI clinical pregnancy rate of 36% in a low basal LH group supplemented with 75IU rLH compared to 17% without rLH supplementation. Based on these figures, a total of 210 patients were required to be randomized.

A prior retrospective study found that 30% of women undergoing IVF/ICSI at IVFAustralia have a 50% or greater reduction in serum LH concentrations from starting ovarian stimulation to the day 7/8 of FSH injections [10]. Based on these findings a total number of approximately 650 women will require to be enrolled into the study in order to have a total of 210 women with a 50% reduction in LH concentration between day 0 and day 6 (I.e. LH ratio $<=0.5$).

Statistical analysis

Categorical variables were analysed using the Chi-square test, or Fisher's Exact test where appropriate. Continuous variables were analysed using either unpaired Student's *t*-test or Mann-Wittney *U* test depending on whether the data was normally distributed or not. Analyses were performed on an intention to treat basis. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using Smith's Statistical Package version 2.80 (Claremont, California) and SPSS version 17.0 (Chicago, Illinois).

Results

Two hundred and ninety four patients were approached to take part in the study and 240 patients were enrolled. Two protocol violations occurred prior to randomization and these patients were excluded leaving 238 patients who completed the study (flow diagram, Appendix A).

A total of 238 patients undergoing a single stimulated cycle of IVF/ICSI were included in the data analysis. For 99% of patients