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Comparison of Recombinant and Urinary HCG on Oocyte/Follicle Ratio and Oocytes Maturation in Advanced Maternal Age

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Abstract

Objectives: To study the efficacy of recombinant HCG (rHCG) compared to urinary HCG (uHCG) for triggering of ovulation and stimulation of final Oocyte maturation in advanced age woman with the poor ovarian response that underwent ovarian stimulation and ICSI.

Design: This study was an observational study performed in Medcare Fertility Centre, Dubai, UAE between April 2016 to July 2017. This study was reviewed and approved by the institutional review board and Ethics Committee of Medcare Fertility Centre.

Patients: Subfertile couples undergoing triggering of ovulation as part of an assisted reproductive cycle using either recombinant HCG versus urinary HCG.

Interventions: rHCG preparations versus uHCG for triggering of ovulation. Dose, route and schedule of rHCG and uHCG injected were considered.

Primary outcomes: Measure the numbers of oocytes retrieved per number of aspirated follicles and determines the Oocytes/follicles ratio. Secondary outcomes measures were the total number of oocytes retrieved, the number of mature oocytes.

Results: The primary outcome indicated that uHCG was more effective than rHCG in regards to the number of follicles retrieved. The ratios of oocytes retrieved per follicle and total matured oocyte per oocyte retrieved is also greater for Pregnyl (uHCG).

Conclusion: The two types of HCG (uHCG and rHCG), both medicines have effect on triggering ovulation and stimulation of maturation of oocytes. But with advanced maternal age there is a clear significant effect on the ratio of total matured oocyte per oocyte retrieved which is greater for Pregnyl (uHCG).

Pregnyl therefore has more effect on triggering ovulation and oocyte maturation in comparison with rHCG. For antagonist protocol was the preferred medicine is Ovitrelle® (rHCG) while, for Long Agonist, the preferred triggering medicine is Pregnyl® (uHCG).

Keywords: Human chorionic gonadotropin (HCG); *In-vitro* fertilization (IVF); Oocyte/Follicle ratio; Advanced maternal age; Poor Ovarian response

Introduction

Luteinizing hormones (LH) surge is essential in the final stages of follicular maturation for triggering follicle rupture, expelling the oocyte from the follicle. In addition, the LH surge promotes luteinization, forming an active corpus luteum. These effects of LH are essential for conception to occur. In assisted conception, human follicle (HCG) has been used for several years to mimic the endogenous LH surge due to considerable structural similarities between HCG and human LH, and hence both hormones stimulate the same receptor [1]. Human Chorionic Gonadotrophin (HCG) has been used for over 25 years as a therapeutic analogue for LH to induce ovulation in women [2]. Specifically, in patients undergoing *In-vitro* fertilization (IVF) cycles, follicular stimulation with Gonadotrophins (urinary or recombinant FSH and LH) [3,4] is followed by administration of HCG, which is used for inducing final follicular maturation and formation of the corpus luteum [5].

For at least 3 recent decades, uHCG is collected from urine of pregnant women, which has been clinically used for triggering of ovulation and luteinization in anovulatory women [6]; however, there are potential disadvantages associated with uHCG, including interbatch inconsistencies; large quantities of starting material required for purification; possible contamination by other urinary proteins that may result in local, post-injection side-effects experienced by some patients; and a movement to avoid human source materials [7].

More recently, recombinant HCG (rHCG) with high specific activity has become available. Recombinant HCG is produced in a Chinese hamster ovary cell line expressing the genes for the alpha and beta subunits of HCG, and the protein is purified using stepwise chromatography [6]. The pharmacokinetic profile of rHCG is comparable to that of uHCG with linearity over a dose

range of 500–20,000 IU and a terminal elimination half-life of approximately 30 h [8,9].

The objective of this study was to evaluate the clinical outcomes of patients undergoing IVF using rHCG, compared with patients using uHCG for final follicular maturation in IVF programme. Patients recruited for this study are those with a poor responder indications needing assisted reproduction. The effect of findings in the poor ovarian response patients was evaluated in addition to the type of HCG [10].

Material and Methods

Study design

This observational study was conducted using data accumulated in a group practice that utilizes a single IVF laboratory (Medcare Fertility Clinic- Dubai). This study was reviewed and approved by the institutional review board and Ethics Committee of Medcare Fertility Centre and all volunteers for participation in this study were informed regarding the purpose and method of the study.

All Poor responder patients undergoing IVF from April 2016 to July 2017 "16 months", (were available for review), and Institutional review board approval was not collected because this was an observational study which was not routinely done.

The patients for the study were considered according to the Bologna criteria definition of poor ovarian response (POR) in a simple and reproducible manner, at least two of the following three features must be present: (i) advanced maternal age or any other risk factor for POR; (ii) a previous POR; and (iii) an abnormal ovarian reserve test. The aim was to study randomized controlled trials (RCTs) comparing rHCG preparation with uHCG for inducing final follicular maturation in patients undergoing assisted conception and methods of randomization and allocation concealment were considered.

Patient selection

Patients were advanced age women undergoing triggering of ovulation as part of an assisted reproductive cycle using either rHCG preparation versus uHCG in the protocol of ovulation induction. A total of 85 patients were eligible using the inclusion criteria for ovarian stimulation cycles by the ICSI program for Oocytes freezing (Pooling) and were recruited into this study. These Inclusion criteria are:

- Age ≥ 38 years.
- Basal Follicular Stimulation Hormone (FSH)<16 IU/L.
- Low ovarian reserve based on antral follicle count ≤ 5.
- Low Antimullerian Hormone (AMH) ≤ 0.8 ng/mL.

The patients were stimulated and treated in the same clinic and by same physicians and Embryology team.

Drug administration

The rHCG preparation versus uHCG for triggering of ovulation, drug dose, route and schedule of rHCG and uHCG injected were considered. Patients underwent ovarian stimulation by either GnRH Agonist Long Protocol (Gonapeptyl0.1, Ferring Pharmaceuticals, Germany) or GnRH antagonist protocol (Cetrorelix Acetate Injection®; Cetrotide®, Serono, Italy). Ovarian stimulation was administered as recombinant FSH (rFSH; Gonal-F®, Serono) alone or in combination with human menopausal Gonadotrophins (Menopure®, Ferring Pharmaceuticals, Kiel, Germany).

Group A: Patients who received an intramuscular injection urinary HCG (PREGNYL®, Organon, Oss, The Netherlands) 10,000 IU.

Group B: Patients who received a subcutaneous injection of 250 µg recombinant hCG (Ovitrelle®, Merck Serono, Modugno-Italy).

Monitoring of cycle was done by serial vaginal ultrasonography and measurement of serum Estradiol level, stimulation sheets were well completed with the number of follicles with different sizes. When at least two dominant follicles reached to 18 mm in mean diameter or two follicles with a mean diameter larger than 16 mm diameter and one by mean diameter>18 mm was observed in vaginal sonography, the patients were randomly divided according to the Triggering Medicine into two groups:

Oocyte retrieval

In both groups, Transvaginal ultrasound-guided oocyte retrieval by using a 17 gauge needle was performed 35 h after menopausal injection. The numbers of retrieved oocytes were recorded. Standard laboratory protocols were followed and approximately two hours after retrieval the cumulus cells were removed and an assessment of Oocyte maturity under an inverted microscope (germinal vesicle, metaphase I, metaphase II, atretic or degenerative) was made. Metaphase II oocytes (mature oocytes) were characterized by the presence of the first polar body, metaphase I oocytes was characterized by the absence of both germinal vesicle and first polar body and prophase I oocytes was characterized by its distinct germinal vesicle.

Outcome assessment

Primary Outcomes: The primary outcome was (i) the numbers of oocytes retrieved per number of aspirated follicles; and (ii) find out Oocytes/follicles ratio.

Secondary Outcomes: Secondary outcome was (i) the number of mature oocytes obtained; maturation rates of oocyte were defined as the numbers of mature oocytes per numbers of total retrieved oocytes.

Statistical analysis

Statistical analysis was carried out using the statistical package for the social science (IBM SPSS version 20.0 for Windows).

Results

For the study, A total of 94 patients participated, and were divided into two groups, group A (received uHCG) 51 patients, and group B (received rHCG) 43 patients respectively.. Basic characteristics of patients observed include age, number of total number of follicles; oocyte and matured oocyte retrieved were expressed in mean, standard deviation, minimum and maximum values are shown in **Table 1.**

Table 1: Baseline characteristics of all patients treated with uHCG or rHCG (n=94).

	Age	No. of follicles<14 mm	No. of oocytes retrieved	No. of matured oocytes retrieved
Mean	41.51	6.77	5.81	4.5
Standard deviation	± 2.53	± 4.19	± 3.96	± 3.22
Minimum	38	1	0	0
Maximum	46	18	17	14

Group A and B were also assessed individually in the similar fashion and shown in **Table 2 and Table 3**.

Table 2: Baseline characteristics of patients treated with uHCG (n=51).

	Age	No. of follicles<14 mm	No. of oocytes retrieved	No. of matured oocytes retrieved
Mean	41.29	7.27	6.69	5.33
Standard deviation	± 2.41	± 4.26	± 4.14	± 3.47
Minimum	38	1	1	1
Maximum	46	18	17	14

Table 3: Baseline characteristics of patients treated with rHCG (n=43).

	Age	No. of follicles<14 mm	No. of oocytes retrieved	No. of matured oocytes retrieved
Mean	41.77	6.16	4.77	3.51
Standard deviation	± 2.67	± 4.07	± 3.51	± 2.60
Minimum	38	1	0	0
Maximum	46	17	16	14

Retrieved oocyte to follicle ratio was shown in **Table 4** and **Figure 1**. Mature oocyte to retrieved oocyte ratio was shown in **Table 5** and **Figure 2**. Finally, an independent sample t-test was done which showed significant differences in the number of oocytes retrieved and the number of matured oocyte between group A and B (p-value 0.019 and 0.006 respectively).

Table 4: Number of oocytes per number of follicles.

All patients (n=94)	0.86
Group A (received uHCG, n=51)	0.91
Group B (received rHCG, n=43)	0.77

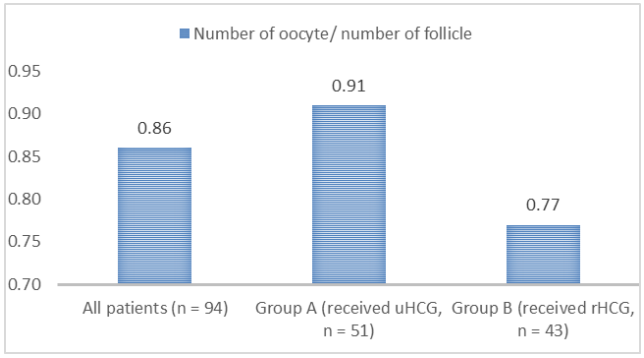

Figure 1: Showing oocytes to follicle ratio.

Table 5: Number of matured oocyte per number of oocyte retrieved.

All patients (n=94)	0.77
Group A (received uHCG, n=51)	0.8
Group B (received rHCG, n=43)	0.74

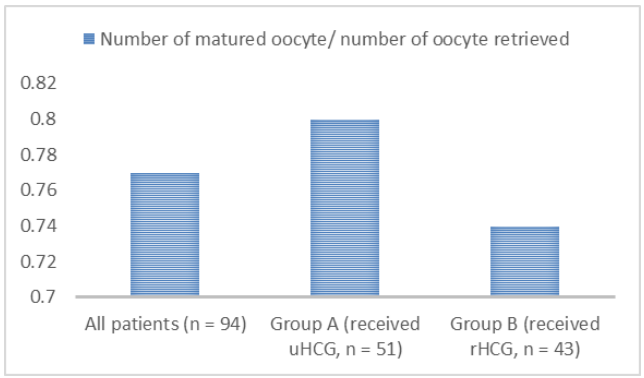

Figure 2: Showing number of mature oocytes per number of oocytes retrieved.

An independent samples t-test was conducted to compare the number of oocytes retrieved and the number of mature oocytes in uHCG and rHCG groups.

There was a significant difference in the scores for the number of oocytes retrieved in two groups (p-value=0.019, mean difference 1.92 when uHCG>rHCG, df: 92, SE: 0.80).

There was also a significant difference in the scores for the number of matured oocyte in two groups (p-value=0.006, mean difference 1.82 when uHCG>rHCG, df: 92, SE: 0.64).

Discussion

This study was observe and compare two HCG types (uHCG and rHCG) and their effect on follicular Triggering, number of oocytes retrieved and total number of matured oocyte in relation to advanced maternal age in women with poor ovarian response and the primary outcome indicated that indeed uHCG was more effective than rHCG in regards to the number of follicles retrieved, The ratios of oocytes retrieved per follicle and total matured oocyte per oocyte retrieved is also greater for Pregnyl (uHCG).

Pregnyl therefore has more effect on triggering ovulation increasing retrieval and oocyte maturation, This is contrary to the result of the study by The European Recombinant Human Chorionic Gonadotrophin Study Group 2000, which found that recombinant HCG is associated with more improvement in stimulation of ovulation and with more matured oocyte and improved tolerance and is thus likely to have higher patient acceptability which is a clear, clinical advantage.

In this study, we observed that uHCG performed well at every stage. So, to sum up, urinary HCG shows higher efficacy than recombinant HCG in terms of the number of oocytes per aspirated follicles and oocyte maturation in selected patients undergoing ICSI. However, larger randomized trials are needed to generalize the use of uHCG over HCG.

Conclusion

The two types of HCG (uHCG and rHCG), both medicines have effect on triggering ovulation and stimulation of maturation of oocytes. But with advanced maternal age there is a clear significant effect on the ratio of total matured oocyte per oocyte retrieved which is greater for Pregnyl (uHCG).

Pregnyl therefore has more effect on triggering ovulation and oocyte maturation in comparison with rHCG.

For antagonist protocol was the preferred medicine is Ovitrelle® (rHCG) .while for Long Agonist, the preferred triggering medicine is Pregnyl® (uHCG).

Implications for Research

Wide analysis is needed between urinary and recombinant HCG to assess the role of rHCG and uHCG in bringing about follicular development and matured oocytes retrieval.

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