AMERICAN JOURNAL OF PHYSIOLOGY, BIOCHEMISTRY AND PHARMACOLOGY, 2018
VOL 8, NO. 1, PAGE 19–27
10.5455/ajpbp.20180522062326

eJManager

ORIGINAL RESEARCH

Open Access

Comparison of serum progesterone levels and incidence of pregnancy with urinary and recombinant HCG in women undergoing ICSI

Mohamed Mosaad[1], Hesham M. Shaban[1], Gamil M. Abd-Allah[1], Gaber A. Rezk[2]

[1]Biochemistry Department, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo, Egypt

[2]Obstetrics and Gynecology Departments, Al-Hussein University Hospital, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

ABSTRACT

Objective: Luteinizing hormone (LH) surge is important in the final maturation of the oocyte and in oocyte retrieval. The structural similarity of human chorionic gonadotropin (HCG) and LH allows its binding to HCG/LH receptor. So, we aimed to compare the efficacy of urinary HCG (uHCG) and recombinant HCG (rHCG) for induction of oocyte maturation, triggering ovulation, and incidence of pregnancy through assessing the serum levels of estradiol (E2), progesterone (P), and β-subunit HCG (βHCG) in infertile women undergoing intracytoplasmic sperm injection (ICSI) cycles.

Subjects and Methods: Eighty-one Egyptian females were recruited in this study including 71 infertile females undergoing ICSI and 10 apparently healthy females as a control group. The infertile female patients were classified based on the treatment used for triggering of mature follicles into two groups: 35 infertile females who had received 10000 International Units (IU) uHCG and 36 infertile females who had received 500 μg rHCG. Serum levels of basal follicle stimulating hormone (FSH) and LH, estradiol (E2), P, and βHCG were measured at different times of menstrual cycle by enzyme-linked immunosorbent assay methods.

Results: Serum FSH and LH were similar in all the studied groups. Serum P level at day 5 embryo transfer (ET) and the number of retrieved and mature oocytes were comparable in the rHCG and uHCG groups while serum P level at the day of oocyte pick up was significantly higher in the rHCG group than in the uHCG group. The successful pregnancy was higher in the uHCG group than in the rHCG group.

Conclusion: The uHCG showed more effective biochemical pregnancy rate than the rHCG. However, rHCG showed equivalent efficacy to uHCG in terms of serum P level at day 5 of ET, the number of retrieved oocytes and mature oocytes in female patients undergoing ICSI. On the other hand, rHCG increases the serum P level at the day of oocyte pick up to abnormally high level, which may reduce the incidence of pregnancy in females received rHCG.

ARTICLE HISTORY

Received May 22, 2018
Accepted July 19, 2018
Published August 02, 2018

KEYWORDS

HCG; ICSI; pregnancy; progesterone; recombinant; urinary

Introduction

Luteinizing hormone (LH) surge is important for follicular maturation, follicle rupture, and expelling the oocyte from the follicle. Moreover, it promotes luteinization and forming an active corpus luteum. These effects of LH are essential for conception to occur [1].

The human chorionic gonadotropin (HCG) is a member of glycoprotein family. It consists of α and β subunits. The α subunit is identical within a species and β subunit is a unique and hormone specific. In assisted conception, HCG has been used for several years to mimic the endogenous LH surge due to the structural similarities between HCG and LH. Therefore, they stimulate the same receptor [2].

The HCG has been used as a therapeutic analog for LH to induce ovulation in women. In patients undergoing in vitro fertilization (IVF) and

Contact Mohamed Mosaad ✉ drm_mosaad82@yahoo.com Biochemistry Department, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo, Egypt.

intracytoplasmic sperm injection (ICSI) cycles, follicular stimulation with gonadotrophins was followed by administration of HCG to induce final follicular maturation and formation of the corpus luteum [1].

The urinary HCG (uHCG) collected from the urine of the pregnant women has been used instead of LH for triggering of ovulation and luteinization in ovulatory women undergoing IVF and ICSI. However, some disadvantages associated with uHCG include batch-to-batch inconsistency, large quantities of urine required for production, and possible contamination by other urinary proteins [3].

Recently, recombinant HCG (rHCG) with high specificity and a high degree of purity has become available. The rHCG is produced in a Chinese hamster ovary cell line and the protein is purified from fetal bovine serum protein, nucleic acid, or other contaminants using stepwise chromatography [4].

The pharmacokinetic profile of rHCG is comparable to that of uHCG with linearity over a dose range of 500–10,000 IU and a terminal elimination half-life of approximately 30 hours [1].

Several trials have been performed to compare the safety and efficacy of uHCG and rHCG preparations from different points of views. Some studies have reported an equal efficiency between uHCG and rHCG preparations while others have found better result associated with rHCG, but a systemic review stated that uHCG is the best option for ovulation induction [5].

Therefore, this study was aimed to compare the efficacy of uHCG and rHCG for induction of oocyte maturation, triggering ovulation, and incidence of pregnancy by assessing the serum levels of estradiol (E2), progesterone (P), and HCG in infertile women undergoing ICSI cycles.

Subjects and Methods

Subjects

Eighty-one Egyptian females were recruited in this study including 71 infertile females aged between 20 and 35 years undergoing ICSI with no assisted reproductive treatment attempts for at least two full menstrual cycles and no ovarian stimulation treatment in the preceding 2 months and 10 apparently healthy females with regular menstrual cycle age-matched representing a healthy control group. Female patients were recruited from assisted reproductive clinics for treatment of infertility at the Department of Obstetrics and Gynecology, Al-Hussein University Hospital, Faculty of Medicine, Al-Azhar University, Cairo, Egypt during the period between January 2016 and December 2016. They were classified into two groups according to the triggering drugs. All subjects were informed about the purpose, nature, and potential risks of the study and a written informed consent was obtained from all the study subjects. The study was approved by the Ethics Committee of Al-Azhar University Hospitals. Inclusion criteria for infertile female patients were:

1. Indication for ICSI procedures and long protocol.
2. Age 20–35 years old.
3. Normal ovarian reserve based on antral follicle count >5 and on basal follicle stimulating hormone (FSH) < 12 IU\l.
4. The presence of two functional ovaries.
5. The presence of a normal uterine cavity.

While the exclusion criteria for infertile female patients were:

1. Contraindications to any type of gonadotropin agent.
2. Polycystic ovarian syndrome.
3. Poor ovarian response to controlled ovarian hyperstimulation in the recent cycle [3].

The infertile female patients in this study were classified based on the treatment used for triggering of mature follicles into two groups: 35 infertile females who received 10000 IU HCG (Choriomon 5000 IU ®, IBSA, Switzerland) representing females received uHCG group and 36 infertile females who received 500 μg HCG (Ovitrelle 250 μg®, MERCK, Italy) representing females received rHCG group.

The females of the control group did not receive any medication for ovarian induction and were subjected to menstrual history taking and laboratory investigations including serum levels of basal FSH and LH (at day 3 post menstrual cycle), serum E2 level (at day 12 post menstrual cycle), and serum P level at the day of ovulation and day 21 post menstrual cycle which were measured in Biochemistry Department, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo, Egypt.

All infertile females were subjected to full history taking including personal and menstrual history, transvaginal ultrasound examination for sonographic measurement of follicle size and laboratory investigations including serum levels of basal FSH and LH (at day 3 post menstrual cycle), serum E2 level at the day of HCG administration, serum P level at the day of oocyte pick up (day of oocyte retrieval), serum P level at the day 5 after oocytes pick up [the day 5 embryo transfer (ET), and serum β-subunit

HCG (βHCG) level (10 days after ET). All laboratory investigations were measured in Biochemistry Department, Faculty of Pharmacy (Boys), Al-Azhar University, Cairo, Egypt.

All female patients underwent a standard long protocol using gonadotropin-releasing hormone analog (GnRH-a) (Decapeptyl 0.1®, Ferring, Switzerland) at a subcutaneous daily dose of 0.05–0.1 mg commencing on the day 20 of the natural menstrual cycle as a pretreatment. Once pituitary desensitization was confirmed (endometrial thickness <5 mm and serum estradiol level <50 pg/ml), the GnRH-a dose was reduced to half, and the ovarian stimulation was initiated. Ovarian stimulation started with a dose of highly purified human menopausal gonadotrophin (Merional®, IBSA, Switzerland) with regard to the patients' age, basal FSH levels, and antral follicle count and it was continued until the day of ovulatory HCG administration according to the ovarian response. The first ultrasound was performed on day 6 of stimulation. The dose of the gonadotropin could be increased or decreased at this point based on response. Ultrasound was used to monitor follicle growth. Once two follicles at least became greater than 18 mm, the uHCG and rHCG were administrated to induce follicle maturation.

Transvaginal oocyte retrieval was scheduled 35–36 hours after final injection. After the retrieval, the oocytes were evaluated for maturity and ICSI was performed after 2 hours of incubation. One or two of the best embryos (blastocyst) were transferred on day 5 after oocyte retrieval.

Methods

Blood sampling and storage

Two milliliters of venous blood samples were withdrawn from each subject at five different times of menstrual cycle in gel separating tubes. Serum was obtained by allowing the blood in a gel separating tube to clot at a room temperature for 10 minutes, followed by centrifugation at 4,000 rpm for 15 minutes, and the serum was separated. It was divided into aliquots, then stored at −80°C till the time of analysis.

Measurement of serum follicle stimulating hormone and luteinizing hormone

Serum levels of FSH and LH were measured at day 3 post menstrual cycle by enzyme-linked immunosorbent assay (ELISA) method using commercially available human FSH and LH ELISA kits in accordance with manufacturer's instructions (Catalog No. EIA-1288, DRG International, Inc., USA and Catalog No. EIA-1289, DRG International, Inc., USA).

Assessment of serum level of estradiol hormone

Serum level of E2 was measured at the day of HCG administration by ELISA method using commercially available human E2 ELISA Kit according to manufacturer's instructions (Catalog No.: BC-1111, BioCheck Inc., Foster City, CA).

Evaluation of serum levels of progesterone hormone

Serum level of P was measured at the day of oocyte pick up and at the day 5 ET by ELISA method using commercially available human P ELISA Kit according to manufacturer's instructions (Catalog no. BC -1113, BioCheck Inc., CA).

Determination of serum level of human chorionic gonadotropin

Serum level of βHCG was measured 10 days after ET by ELISA method using commercially available human βHCG ELISA Kit according to manufacturer's instructions (Catalog no. 10002, Chemux BioScience Inc., San Francisco).

Statistical analysis

GraphPad Prism 6.0 (GraphPad software 2010, San Diego, CA) was used to analyze the data in this study. All quantitative data were expressed as mean ± standard deviation while qualitative data were expressed as frequency and percent at 95% confidence interval (CI). D' Agostino-Pearson omnibus test was used to identify whether the variables were normally distributed or not. One-way analysis of variance was followed by Tukey's multiple comparison tests for parametric data, Kruskal-Wallis test, and then followed by Dunn's multiple comparisons test for non-parametric data and Chi-squared test for qualitative data. Differences were considered statistically significant when a P value <0.05.

Results

The baseline characteristics of total female patients and control subjects enrolled in the study were reported in Table 1. Females who received uHCG and rHCG showed no statistically significant differences in terms of age, serum levels of basal FSH,

Table 1. Baseline characteristics of all the studied groups.

Variables		uHCG	rHCG	Controls	*P* value
Age (years)	Range	20–34	20–35	22–30	0.448
	M ± SD	27.4 ± 4.27	26.4 ± 3.77	26 ± 3.13	
FSH (mIU/ml)	Range	3.91–10.5	2.81–10.8	4.84–8.84	0.572
	M ± SD	6.65 ± 1.88	7.08 ± 1.84	6.66 ± 1.34	
LH (mIU/ml)	Range	2.24–6.55	2.19–6	1.68–4.85	0.109
	M ± SD	3.97 ± 0.90	4.19 ± 0.92	3.49 ± 1.07	

M ± SD: mean ± standard deviation and significance *p* value < 0.05.

basal LH, and ethnicity as compared to healthy control females.

Estradiol level of the studied groups

In the present study, the results showed no statistically significant differences between the mean values of serum E2 level in females who received uHCG and in females who received rHCG while the mean values of serum E2 level in both groups of females such as females received uHCG and females received rHCG groups were significantly elevated when compared to healthy control females as shown in Table 2.

Progesterone levels of the studied groups

Interestingly, the serum P level was measured at the day of oocyte pick up (day of oocyte retrieval) and then, it was measured at the day 5 after oocytes pick up (the day 5 ET) in this study. Regarding the P levels at the day of oocyte pick up, the results showed a statistically significant elevation in serum P level at the day of oocyte pick up in both groups of females such as females who received uHCG and females who received rHCG when compared to females of healthy control group. Moreover, the serum P level at the day of oocyte pick up was significantly higher in females received rHCG group when compared to uHCG group as illustrated in Table 2.

On the other hand, the serum P level at the day 5 ET were significantly higher in both groups of females such as females who received uHCG and females who received rHCG when compared to healthy females while it was observed that there was no statistically significant difference between the serum P level at the day 5 ET in females received uHCG when compared to females received rHCG groups as demonstrated in Table 2.

Follicle maturation in females received uHCG and females received rHCG groups

In the present study, the results showed that there were no statistically significant differences between females received uHCG when compared to females received rHCG groups in terms of expected follicles, retrieval oocytes, and mature oocytes as shown in Table 3.

Incidence of pregnancy in females received uHCG and females received rHCG groups

In this study, the incidence of pregnancy in females received uHCG and females received rHCG groups was assessed. The successful pregnancy was defined as serum HCG ≥ 5 mIU/ml measured 10 days after embryo (positive HCG level) while unsuccessful pregnancy was defined as serum HCG < 5 mIU/ml measured 10 days after embryo (negative HCG level). The successful biochemical pregnancy was highly distributed in females received uHCG group when compared to females received rHCG group while the unsuccessful pregnancy was highly distributed in females received rHCG when compared to females received uHCG as illustrated in Table 4.

Moreover, the successful clinical pregnancy, that was defined as the presence of a gestational sac with fetal heart rate on ultrasound, was highly distributed in females received uHCG group when compared to females received rHCG group as shown in Table 4.

Table 2. The serum E2 and P levels in all the studied groups.

Variables		uHCG	rHCG	Controls	*P* value
E2 (pg/ml)	Range	112–3,990	334–4,000	110–406	<0.0001
	M ± SD	1,789[a] ± 1,006	2,131[a] ± 980	184.9 ± 88	
P at the day of oocyte pick up	Range	0.85–35.5	1.73–22.3	0.87–4.01	<0.0001
	M ± SD	8.56[a,b] ± 7.4	10.8[a] ± 5.5	2.37 ± 1.3	
P at the day 5 transfer	Range	11.6–42	26.5–41.5	10–19.2	<0.0001
	M ± SD	36.7[a] ± 5.60	37.6[a] ± 3.1	13.2 ± 2.7	
P difference	Range	6.2–37.9	13.7–35.6	7.93–15.2	<0.0001
	M ± SD	28.2[a] ± 7.39	26.8[a] ± 5.2	10.9 ± 2.1	

E2 = estradiol, P difference: the difference between P at the day 5 transfer and P at the day of oocyte retrieval, M ± SD: mean ± standard deviation, a: significance *p* value from control group, b: significance *p* value from uHCG group.

Table 3. The follicles maturation in all the studied groups.

Variables		uHCG	rHCG	Controls	*P* value
Expected follicles	Range	1–24	3–33	-	0.116
	M ± SD	12.2 ± 6.4	14.8 ± 6.9	-	
Retrieval oocytes	Range	1–24	2–26	-	0.116
	M ± SD	10.2 ± 6.1	11.5 ± 6.2	-	
Mature oocytes	Range	1–21	1–23	-	0.764
	M ± SD	9.2 ± 5.5	9.5 ± 5.6	-	

M ± SD: mean ± standard deviation and significance *p* value < 0.05.

Table 4. Incidence of successful pregnancy in females received uHCG and females received rHCG groups.

Variables	uHCG (%)	rHCG (%)	OR (95% CI)	*P* value
Biochemical pregnancy %	68.6 (24/35)	41.7 (15/36)	0.33 (0.12–0.87)	0.023
Clinical pregnancy %	65.7 (23/35)	36.1 (13/36)	3.39 (1.28–8.99)	0.018

OR = odds ratio, significant *P* value < 0.05.

The serum P level at day 5 embryo transfer in total positive HCG females and total negative HCG females

In this study, total female patients (received uHCG and rHCG) can be classified according to the incidence of pregnancy into positive HCG females who have a successful pregnancy and negative HCG females who have an unsuccessful pregnancy, whereas the serum P level at day 5 ET was evaluated in positive HCG females and negative HCG females. The results showed that a statistically significant elevation in serum P level at day 5 ET was observed in positive HCG group when compared to negative HCG group as demonstrated in Table 5.

Correlation between follicles maturation and other variables in total female patients

In the present study, the correlation between the follicles maturation and the hormonal levels in total female patients was illustrated in Table 6. There were statistically significant positive correlations between expected follicles, retrieval oocytes, and mature oocytes with E2, P at the day of oocyte pick up, and P at the day 5 ET in total female patients.

Discussion

Infertility affects millions of couples worldwide resulting in distress and depression. Although there are various causes leading to infertility, IVF and ICSI followed by ET have been widely recommended to treat most cases of infertility. ICSI techniques allow the evaluation of oocyte morphology and the injection of a single sperm into a single egg for fertilization [6].

Over the last several decades, IVF and ICSI have been rapidly developed with high efficiency and success rate. Controlled ovarian stimulation (COS) has been employed as an essential component for assistance of reproductive technology. It triggers the development of multiple ovarian follicles following exogenous gonadotropin administration. Luteal phase support as one COS method is commonly used in IVF involving GnRH analogs, HCG, P, E2, and GnRH agonists to obtain a higher number of oocytes and an increased chance of achieving pregnancy and birth [7].

The importance of LH surge in the final maturation of the oocyte and in oocyte retrieval has been well characterized. The structure of HCG is similar to the LH secreted by the pituitary. So, HCG and LH can bind and function through a common HCG/LH receptor [3].

In infertile women undergoing ovulation induction, the use of HCGs to achieve final follicular maturation and triggering follicular rupture is well established [8]. For the last few decades, uHCG has been used to trigger final oocyte maturation in IVF and ICSI cycles. rHCG is manufactured with a high purity that can be used for the same purpose, to mimic the natural surge of LH [5].

In clinical practice, several trials have found the same efficacy between uHCG and rHCG whereas

Table 5. The P levels at the day 5 ET in total positive HCG females and total negative HCG females.

Variables		Positive HCG females (*N* = 39)	Negative HCG females (*N* = 32)	*P* value
P at the day 5 ET	Range	33.3–42	11.6–40.7	0.002
	M ± SD	38.7 ± 2.2	35.3 ± 5.77	

Significant *P* value < 0.05.

Table 6. Correlation between the follicles maturation and hormonal levels in total infertile females.

Variables	Expected follicles		Retrieval oocytes		Mature oocytes	
	r	*P* value	*r*	*P* value	*r*	*P* value
E2	0.85	<0.0001	0.83	<0.0001	0.83	<0.0001
P at the day of oocyte pick up	0.68	<0.0001	0.64	<0.0001	0.64	<0.0001
P at the day 5 Embryo Transfer	0.57	<0.0001	0.53	<0.0001	0.54	<0.0001

E2: estradiol, *r*: correlation coefficient, significant *P* value <0.05.

some others have observed better efficiency in females received rHCG while others studies reported a higher efficacy of uHCG in ovulation induction [3].

So, this study was aimed to compare the efficacy of uHCG and rHCG for triggering ovulation and incidence of pregnancy through determination of E2, P, and βHCG serum concentrations in infertile women undergoing ICSI cycles.

In this study, 10 apparently healthy control females, with regular menstrual cycle and who did not receive any medication, were selected to assess the response of infertile females to the induction protocol and to monitor the levels of E2 and P after ovulation induction.

In the present study, the baseline characteristics including age, serum levels of basal LH and FSH showed no statistically significant differences in females received uHCG group when compared to females received rHCG group. These results were in agreement with the findings of Yang et al. [9] who reported that there were no significant differences between uHCG and rHCG groups regarding age and basal levels of FSH and LH on the day before exogenous gonadotropin administration which support our results.

Moreover, Farrag et al. [10] reported that there were no statistically significant differences found between women received uHCG and women received rHCG groups in terms of basal LH and FSH which confirm the results of the present study.

The absence of significant difference in the baseline characteristics including age, the basal FSH and LH between the studied groups was considered during the selection of all subjects to avoid their effect on the results of the study.

Failure of treatment procedure in assisted reproductive clinics suggests a lack of implantation due to the failure of coordination between maternal and fetal interfaces. One of the factors which are responsible for inadequate preparation of endometrial bed for encroaching blastocyst is a scarcity of optimal concentration of E2 and P [11].

It was found that there is a significant correlation between expected follicles and serum E2 at the day of triggering and it was correlated to the pregnancy rate [12]. Furthermore, it has been found that peak E2 levels measured on the day of HCG administration helps in the assessment of response to COS while higher peak E2 levels are associated with better pregnancy rates achieved [13].

In the present study, the serum E2 level was measured at the day of HCG administration (day of triggering) and the results showed that there was a statistically significant elevation in serum E2 level observed in female patients who received either uHCG or rHCG when compared healthy females as a response to COS.

On the other hand, no statistically significant difference was observed between serum levels of E2 in females received uHCG group when compared to females received rHCG group. These results were supported by an important study [9] which reported that the serum level of E2 on the day of HCG administration showed no statistically significant difference between uHCG group when compared to rHCG group.

P is required for successful embryonic implantation into the endometrium and maintenance of the pregnancy in natural cycles and IVF cycles [14]. It has been debated for many years whether P increases has a detrimental effect on the outcome of IVF or not and reduced implantation and pregnancy rates were reported by few, but not all investigators [15].

Therefore in the present study, serum P level was measured in infertile females at two different times (at the day of retrieval and at the day 5 ET) to assess its correlation with success of ICSI and incidence of pregnancy.

Several trials have assessed the impact of elevated P at the time of HCG trigger in agonist protocol cycles and conflicting results were observed. Several studies have supported the concept that elevated P level has a negative impact on the pregnancy rate while other researchers have been unable to verify this finding. Fewer studies have assessed the impact of elevated P at a time more proximal to ET. So, the determination of P at the day of oocyte retrieval is a provocative time point.

In this study, the serum P level was assessed at the day of oocyte pick up (day of oocyte retrieval). It was observed that the serum P level at the day of oocyte retrieval was significantly elevated in the rHCG group as compared to the uHCG group. These results were confirmed by Kovacs et al. [16] who recorded that the serum P level on the day of retrieval was higher in women received rHCG group than in women received uHCG group which supports the findings of the present study.

In contrast to the present study results, Youssef et al. [5] reported that no statistically significant difference was found in serum P level on the day of retrieval between women received rHCG group and women received uHCG group.

The elevation of P level at the day of oocyte retrieval may negatively affect the incidence of pregnancy in females received rHCG group because Nayak et al. [17] reported that the elevated P on the day of oocyte retrieval is associated with significantly lower implantation and ongoing pregnancy rates.

In this study, it was observed that the serum P at the day 5 ET showed no statistically significant difference in females received uHCG group as compared to females received rHCG group which was in agreement with Youssef et al. [5] who reported the results.Also in contrast to the present study results, European rHCG study [18] reported that a significant elevation in the P level at the day of ET in rHCG group as compared to uHCG group.

In the present study, it was observed that the number of expected follicles showed no statistically significant difference in females received uHCG as compared to females received rHCG. These results came in line with that of Madani et al. [3] who concluded that rHCG showed equivalent efficacy to urinary HCG in terms of the number of aspirated follicles in selected patients undergoing ICSI.

Successful oocyte retrieval in ICSI cycles is closely associated with HCG efficacy due to stimulation of a series of intrafollicular events essential for ovum release from the follicle. The absence of LH/HCG effect is associated with failed oocyte retrieved or empty follicle syndrome [4].

In the present study, there was no statistically significant difference observed in the number of retrieved oocytes between females received uHCG group when compared to females received rHCG group. These findings were in agreement with Madani et al. [3] who reported that same efficacy of both rHCG and uHCG regarding the number of retrieved oocytes in selected patients undergoing ICSI, however, 500 μg rHCG seems to be more advantageous than the lower dose in this indication.

Moreover, Eftekhar et al. [2] found that the numbers of retrieved oocyte were similar in both rHCG and uHCG groups. Also, Sidhmalswamy et al. [4] reported that there was no statistical difference between rHCG and uHCG groups regarding oocytes retrieved which support our results.

Furthermore, Youssef et al. [5] reported opposite results. It was found that rHCG was associated with an increase in the number of retrieved oocytes when compared to uHCG. Also, on the contrary, in a retrospective analysis of 744 patients, a significantly higher percentage of oocytes was retrieved in women received uHCG when compared to women received rHCG group [19].

In this study, no statistically significant difference was found between the numbers of mature oocytes in patients received uHCG for ovulation induction and those that received rHCG. These results were in agreement with the recent review performed by Youssef et al. [5] who reported the same results.

In addition, Madani et al. [3] reported that there was no statistically significant difference found between both groups of females such as females received uHCG and females received rHCG in the number of mature oocytes.

Moreover, the present study results were consistent with the results of Yang et al. [9] that concluded that there was no evidence of a difference between rHCG and uHCG in achieving final follicular maturation in IVF. Also, there were two important studies [2,4] that reported the absence of significant difference in the number of mature oocytes between females received uHCG group and females received rHCG group which supports our results.

However, Al-Inany et al. [8] systematic review concluded that no significant difference was found between females received either uHCG or rHCG in oocyte maturation after revision of seven randomized controlled trials. So, all of these findings confirm our study results.

In contrast to our finding, some previous randomized trials as Farrag et al. [10] recorded that the oocytes maturation was improved by the administration of rHCG rather than the administration of uHCG. Also, an age-matched retrospective analysis Uhler et al. [20] showed an increase in the number of mature oocytes in patients treated with rHCG compared with patients who received uHCG, although this data did not reach statistical significance.

Apparently in our study, we didn't find any superiority in the administration of rHCG to uHCG regarding oocyte maturation while the observation of lower oocyte maturity in the uHCG group is not definitely understood [10].

In the present study, the incidence of biochemical and clinical pregnancy between females received uHCG group and females received rHCG group was assessed and important results were observed. The results showed that the incidence of successful biochemical and clinical pregnancy was significantly higher in females received uHCG group when compared to females received rHCG group. This finding was in agreement with Krotz et al. [19] who reported that higher implantation rate and clinical

pregnancy were observed with the uHCG received women as compared to the rHCG received women.

The higher pregnancy rate associated with uHCG received females may be due to the higher sialic acid content of the oligosaccharides part of uHCG than that of rHCG. So, the higher sialic acid content of uHCG leading to formation acidic uHCG. The acidic uHCG has longer half-life and stronger biological action than less acidic rHCG that reflects on LH surge, final oocytes maturation, oocytes retrieval and stimulating progesterone secretion by corpus luteum which improve implantation and incidence of biochemical and clinical pregnancy.

In contrast to the present study results, Youssef et al. [5] reported that there was no evidence of a difference between women received rHCG and women received uHCG regarding the ongoing pregnancy/live birth rate, clinical pregnancy rate, and miscarriage, whereas rHCG is as effective as uHCG in the incidence of pregnancy.

Contrary to our findings, Madani et al. [3] reported that no significant differences have been shown between both rHCG and uHCG groups in terms of implantation rate and chemical and clinical pregnancy rates. Also, a study performed by Yang et al. [9] reported that there were no significant differences in implantation rate, biochemical pregnancy rate, clinical pregnancy rate, and multiple pregnancy rates between uHCG and rHCG groups.

Furthermore, some studies reported that no significant difference was found between both uHCG and rHCG regarding clinical and biochemical pregnancy [2,4,21].

Moreover, although Farrag et al. [10] recorded that the oocytes maturation was improved by administration of rHCG rather than uHCG, there was no significant difference between the incidence of biochemical or clinical pregnancy between both uHCG and rHCG groups.

The higher biochemical pregnancy rate associated with females received uHCG group in the present study may be explained with Liu et al. [22] who observed that the elevated P on the day of HCG administration (more than 1.5 ng/ml) and day after HCG administration (more than 9.5 ng/ml) are considered as abnormally high, resulting in a significant reduction in implantation rate and clinical pregnancy rate, the matter that may justify the reduction in pregnancy rate observed in females received rHCG group in the present study.

Interestingly, it was observed that the serum P level at the day 5 ET was significantly elevated in positive HCG group (total women with successful pregnancy) as compared to negative HCG group (total women with unsuccessful pregnancy). These finding may suggest a possible correlation between the elevated serum P level at the day 5 ET and success of pregnancy. Thus, more studies should be performed to clarify the correlation between the serum P level at the day 5 ET and the incidence of pregnancy to justify these results.

In the present study, significant positive correlations were observed between expected follicles, retrieval oocytes, and mature oocytes and E2, P at the day of oocyte pick up, and P at the day 5 ET in total female patients reflecting the important role of E2 and P levels in follicles maturation.

In conclusion, this study indicates that the uHCG is associated with higher biochemical and clinical pregnancy rate than rHCG. However, rHCG showed equivalent efficacy to uHCG in terms of serum E2, serum P level at the day 5 ET, the number of retrieved oocytes and mature oocytes in female patients undergoing ICSI while rHCG increases the serum P level at the day of oocyte pick up to abnormal high level which may reduce the incidence of pregnancy in females received rHCG. Furthermore, serum P level at the day 5 ET was elevated in positive HCG females than in negative HCG females, which may have a role in successful pregnancy.

References

[1] Khrait Z. Comparison of recombinant and urinary HCG on oocyte/follicle ratio and oocytes maturation in advanced maternal age. J Reprod Endocrinol Infertil 2017; 2:1–4.

[2] Eftekhar M, Khalili MA, Rahmani E. The efficacy of recombinant versus urinary HCG in ART outcome. Iran J Reprod Med 2012; 10:543–8.

[3] Madani T, Mohammadi Yeganeh L, Ezabadi Z, Hasani F, Chehrazi M. Comparing the efficacy of urinary and recombinant hCG on oocyte/follicle ratio to trigger ovulation in women undergoing intracytoplasmic sperm injection cycles: a randomized controlled trial. J Assist Reprod Genet 2013; 30:239–45.

[4] Sidhmalswamy GA, Srinivas M, Dipika K, Anu K, Rao KA, Mekhala D. Comparing the efficacy of urinary hCG vs recombinant hCG for final maturation of oocyte in GnRH antagonist IVF/ICSI cycle. IJIFM 2012; 3:92–6.

[5] Youssef MA, Abou-Setta AM, Lam WS. Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles. Cochrane Database Syst Rev 2016; 4:CD003719.

[6] Cui N, Zhang J, Xu Y, Jiang L, Yang A, Hao G. Premature progesterone rise positively correlates

with clinical pregnancy rate in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) patients with good ovarian response. Horm Metab Res 2017; 49:372–9.

[7] Check JH. Luteal phase support for in vitro fertilization-embryo transfer--present and future methods to improve successful implantation. Clin Exp Obstet Gynecol 2012; 39:422–8.

[8] Al-Inany H, Aboulghar MA, Mansour RT, Proctor M. Recombinant versus urinary gonadotrophins for triggering ovulation in assisted conception. Hum Reprod 2005; 20:2061–73.

[9] Yang J, Zhang JY, Song NH. The role of miRNAs in androgen-independent progression of prostate cancer. Zhonghua Nan Ke Xue 2013; 19:831–4.

[10] Farrag A, Costantini A, Manna C, Grimaldi G. Recombinant HCG for triggering ovulation increases the rate of mature oocytes in women treated for ICSI. J Assist Reprod Genet 2008; 25:461–6.

[11] Rehman R, Hussain Z, Siddiq AA. Role of progesterone in human embryo implantation. Rawal Med J 2012; 37:194–8.

[12] Gonca S, Gün I, Ovayolu A, Şilfeler D, Sofuoğlu K, Özdamar Ö, et al. Effect of lower than expected number of oocyte on the IVF results after oocyte-pickup. Int J Clin Exp Med 2014; 7:1853–9.

[13] Kondapalli L, Molinaro T, Sammel M, Dokras A. A decrease in serum estradiol levels after human chorionic gonadotrophin administration predicts significantly lower clinical pregnancy and live birth rates in in vitro fertilization cycles. Human Reprod 2012; 27:2690–7.

[14] Kofinas JD, Blakemore J, McCulloh DH, Grifo J. Serum progesterone levels greater than 20 ng/dl on day of embryo transfer are associated with lower live birth and higher pregnancy loss rates. J Assist Reprod Genet 2015; 32:1395–9.

[15] Jensen F, Woudwyk M, Teles A, Woidacki K, Taran F, Costa S, et al. Estradiol and progesterone regulate the migration of mast cells from the periphery to the uterus and induce their maturation and degranulation. PLoS One 2010; 5:e14409.

[16] Kovacs P, Kovats T, Bernard A, Zadori J, Szmatona G, Kaali SG. Comparison of serum and follicular fluid hormone levels with recombinant and urinary human chorionic gonadotropin during in vitro fertilization. Fertil Steril 2008; 90:2133–7.

[17] Nayak S, Ochalski ME, Fu B, Wakim K-M, Chu TJ, Dong X, et al. Progesterone level at oocyte retrieval predicts in vitro fertilization success in a short-antagonist protocol: a prospective cohort study. Fertil Steril 2014; 101:676–82; e671.

[18] European Recombinant Human Chorionic Gonadotrophin Study G. Induction of final follicular maturation and early luteinization in women undergoing ovulation induction for assisted reproduction treatment—recombinant HCG versus urinary HCG. Human Reprod 2000; 15:1446–51.

[19] Krotz S, Bhagavath B, Hackett R, Pagidas K, Carson S, Robins J. Comparison of IVF retrieval and clinical outcomes in 744 patients using recombinant versus urinary human chorionic gonadotropins to trigger ovulation. Fertil Steril 2008; 90:S224–5.

[20] Uhler ML, Beltsos AN, Grotjan HE, Lederer KJ, Lifchez AS. Age-matched comparison of recombinant and urinary HCG for final follicular maturation. Reprod Biomed Online 2006; 13:315–20.

[21] Sakhel K, Khedr M, Schwark S, Ashraf M, Fakih MH, Abuzeid M. Comparison of urinary and recombinant human chorionic gonadotropin during ovulation induction in intrauterine insemination cycles: a prospective randomized clinical trial. Fertil Steril 2007; 87:1357–62.

[22] Liu L, Zhao L, Li TC, Zhu H, Lin X, Jin X, et al. Comparison of progesterone measurement on day of, and day after, HCG administration in IVF-embryo transfer cycles. Reprod Biomed Online 2015; 30:157–65.