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Comparison of urinary hCG and recombinant hCG during ovulation induction in intrauterine insemination cycles; a clinical trial

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Abstract

Objective: to compare urinary human chorionic gonadotropin (uhCG) and recombinant human chorionic gonadotropin (rhCG) during ovulation induction in intrauterine insemination (IUI) cycles in infertile women.

Materials and Methods: In this randomized clinical trial, we evaluated 385 healthy women (428 cycles) aged between 20 and 44 years undergoing controlled ovarian hyper stimulation-intrauterine insemination (COH-IUI) cycles in Zanan Hospital, Tehran, Iran, from 2010 to 2011. The patients were randomized into two groups before starting the cycle. Group 1 (n =224) received uhCG, while group 2 (n =204) received rhCG. Then two groups were compared regarding the rate of ovulation and pregnancy

Results: We evaluated 385 women (428 COH-IUI cycles), and showed that the pregnancy rate in uhCG group was higher than rhCG group(28.6% vs.27.5%),butthedifference between two groups was not significant(p=0.965).Sixdays after hCG injection, progesterone level (P4≥3 ng/ml) (ovulation rate) in uhCG group was higher than rhCG group (93% vs. 88.6%), but the differences between two groups were not significant (p = 0.19).The differences between two groups regarding the type of infertility, duration of infertility, the cause of infertility and age were not significant (p>0.05).

Conclusion: Our finding confirmed that rhCG and uhCG did not show significant difference regarding ovulation and pregnancy rates in intrauterine insemination cycles in infertile women. Furthermore, our results indicated that age, duration of infertility and cause of infertility did not impact the outcome of treatment.

Keywords: Urinary Human Chorionic Gonadotropin (UhCG), Recombinant Human Chorionic Gonadotropin (RhCG), Ovulation, Intrauterine Insemination (IUI), Pregnancy, Infertility

1. Introduction

Human chorionic gonadotropin (HCG) is a common drug for inducing maturation of follicles and ovulation after ovarian stimulation [1]. Previously, urinary HCG (uhCG) has been used widely, whereas recombinant HCG (rhCG) has recently shown some beneficial effects, such as decreasing the risk of disease transmission, protein impurities and batch-to-batch inconsistencies [2, 4]. Moreover, the studies using highly purified urine-derived preparations reported variations in response both between patients and between cycles in the same patient. On the other hand, recent studies have been indicated that the use of rhCG in *in vitro* fertilization (IVF) cycles is as effective as urinary HCG (5-7).A European report signified that treatment with rhCG resulted in higher numbers of mature oocytes, higher serum progesterone levels, and remarkably higher hCG levels compared with uhCG [8]. Additionally, clinical pregnancy rates were similar among those who had treated with the recombinant and urinary-derived products, while the incidence of adverse events, like injection- site reactions, was significantly lower among those receiving rhCG compared with those who had treated with uhCG [2, 8]. However, previous studies have reported conflicting results and demonstrated that the clinical use of rhCG is associated with certain adverse effects due to its biological power, longer half-life and affinity to the common receptors [9, 11]. Moreover, another study by Guinera *et al*. (2009) indicated that ovarian hyperstimulation syndrome (OHSS) has occurred in patients who treated with HCG [12]. Hence, to address these concerns, the purpose of the present randomized clinical trial was to compare the use of rhCG with uhCG *in vivo* during controlled ovarian hyper stimulation-intrauterine insemination (COH-IUI) cycles in Iranian infertile women.

2. Materials and Methods

In this randomized study, we evaluated 385 healthy women (428 cycles) aged between 20 and 44 years with unexplained infertility (Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation, or after six months in women 35 or older) [13] undergoing COH-IUI from 2010 to 2011 in Zanan Hospital (Mirza Koochek Khan), Tehran, Iran. We included the patients referred for non-tubal infertility treatment, such as ovulatory disorders, early-stage endometriosis, mild male factor (The 2010 WHO sperm reference values for these parameters include a semen volume of 1.5 mL, sperm concentration of 15 million/mL, sperm total motility of 40%, and sperm with a normal morphology of 4%) [14], and idiopathic infertility. The criteria for PCO was hyper androgenism (hirsutism), oligomenorrhea, more than 10-12 follicles in each ovary [15]. The ethic approval was not obtained because the use of uhCG and rhCG is routine in our unit for final maturation and triggering of ovulation during COH-IUI. The study procedure was explained to all participants and informed written consent was taken. The exclusion criteria

were a history of ovarian hyper stimulation syndrome (OHSS), positive human immunodeficiency virus (HIV) serology, positive hepatitis B surface antigen (HBsAg) serology, acute uterine bleeding (AUB), ovarian cyst, and history of active drug use. Included women were randomized into two groups before starting the cycle: To randomization we used sequential numbers, in this case the first number was given to the first patient and received intramuscular injection of uhCG (10,000 IU Profasi; Serono Inc., Rockland, MA, USA), group 1 (n =224) sequentially the next number was given to next patient and received subcutaneous injection of rhCG (250 micg Ovidrel; Serono Inc., Rockland, MA, USA) group 2 (n =204). Both participants and study staff (site investigators and trial coordinating center staff) were masked to treatment allocation. Demographic information, gynecology medical histories, as well as results of physical examination and routine laboratory screening [including baseline luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin level (PRL)], were assessed for all women. On day 3 of the cycle, clomiphene 100 mg was started and continued for five days; furthermore, on day 7 of the cycle, daily intramuscular injection of one ampoule of human menopausal gonadotropins (hMG; (menoghan, a kind of menotropins) was administered and continued for three days. On day 12 of the cycle, the ovarian response was monitored by vaginal ultrasound when at least a follicle with mean diameter ≥ 18 was observed, while uhCG (pregnyl 10000 unit /IM) or rhCG (ovidrel 250 microgram/SC) as a trigger of ovulation was administrated. After 36 hours, a single IUI was performed with 0.5ml fresh sperm wash medium. It is noted that all semen specimens were obtained by masturbation, collected in a clean container, centrifuged based on standard criteria, and drawn into an insemination catheter. Ovulation was documented by the serum progesterone measurement, six days after HCG injection (≥ 3 ng). Moreover, pregnancy was documented by the serum HCG level two weeks after the insemination. When the pregnancy was confirmed, a vaginal ultrasound was performed two weeks later. Statistical analysis of the obtained data was performed by the SPSS, version 18.0. Student t-test, chi-squared test, and exact Fischer test were used to analyze and to compare the findings between two groups. The significance level for all analyses was $p<0.05$.

3. Results

We evaluated 385 women (428 COH-IUI cycles) and showed that the pregnancy rate/cycle in uhCG group was higher than rhCG group (28.6% vs. 27.5%), but the difference between two groups was not significant (p = 0.965) (Table 1). Six days after HCG injection, progesterone level (P4≥3 ng/ml) (ovulation rate) in uhCG group was higher than rhCG group (93% vs. 88.6%), but the difference between two groups was not significant (p = 0.19) (Table 1). The differences between two groups regarding the type of infertility, duration of infertility, age (Table 2) and cause of infertility were not significant (p>0.05). (Table 3, 4). We did not detect any side effects related to treatment courses in two groups.

Table 1: Pregnancy rate and progesterone level six days after hCG injection between uhCG and rhCG groups

groups	rhCG N (%)	uhCG N (%)	p-value
P4<3 ng/ml	12(11.4)	13(0.7)	0.21
P4≥3 ng/ml	93(88.6)	169(93%)	
Total	105(100)	182(100)	
βhCG+	56(27.5)	64(28.6)	0.79
βhCG-	148(72.5)	160(71.4)	

Table 2: The demographic data and clinical characteristic in uhCG and rhCG groups

Groups Variables		uhCG	rhCG	p-value
age		28.16±5.46	28.83±5.36	0.19
Duration of infertility		4.71±3.62	4.32±3.41	0.31
Infertility type	primary	173(77.2%)	152(74.5%)	0.51
	secondary	51(22.8%)	52(25.5%)	

Table 3: Comparing the different causes of infertility between uhCG and rhCG groups

Groups Couse of infertility		uhCG	rhCG	p-value
PCO	βhCG+	18(27.3%)	17(23%)	0.55
	βhCG-	48(77.7%)	57(77%)	
Male factor	βhCG+	5(17%)	13(31.7%)	0.17
	βhCG-	24(82.8%)	28(68.3%)	
Tubal factor (unilateral)	βhCG+	7(46.7%)	5(20%)	0.07
	βhCG-	8(53.3%)	20(80%)	
endometriosis	βhCG+	2(36.4%)	7(63.6%)	0.17
	βhCG-	6(63.6%)	4(36.4%)	
unexplained	βhCG+	32(30.6%)	14(26.4%)	0.62
	βhCG-	74(69.4%)	39(73.6%)	

Table 4: the pregnancy rate in follicle dominant ≥3 and <3

	Pregnancy	Dominant ≥3	Dominant <3	P
PCO	positive	18(30%)	25(23.4%)	0.34
	negative	42(70%)	82(76.65)	
Male factor	positive	8(30.8%)	13(21%)	0.32
	negative	18(69.2%)	49(79%)	
Tubal	positive	7(31.8%)	7(18.4%)	0.23
	negative	15(68.2%)	31(81.6%)	
Endometriosis	positive	3(50%)	8(50%)	-
	Negative	3(50%)	8(50%)	
unexplained	positive	28(32.6%)	31(27.2%)	0.41
	Negative	58(67.4%)	83(72.8%)	

4. Discussion

The administration of hCGs to achieve final follicular maturation and triggering follicular rupture is well recognized in infertile women undergoing ovulation induction [6, 9]. In the final stages of follicular maturation, LH surge is essential for triggering follicle rupture, expelling the oocyte from the follicle and leading to its capture by the fallopian tube. Additionally, it promotes luteinization and forms an active corpus luteum [9, 10]. Human chorionic gonadotropin (hCG), produced by the trophoblasts around six days after conception, induces ovulation in a similar manner to LH; stimulates the corpus luteum; and causes early fetoplacental endocrine function [9, 10]. Hence, human chorionic gonadotropin has been

usually used in IUI cycles to stimulate the final maturation and follicles ovulation [7, 10]. The impact of rhCG has been extensively studied in IVF cycles and has been also shown to be comparable in efficacy with uhCG [2, 5]. Our experience was in line with these studies while there were no significant differences between two groups (rhCG and uhCG) regarding pregnancy and ovulation rates six days after hCG injection. In harmony with our finding, Lorusso *et al*. (2008) compared the efficacy and safety of rhCG and uhCG for the induction of follicle maturation in women undergoing intrauterine insemination (IUI), then they signified that rhCG and uhCG showed equivalent efficacy and safety in ovulation induction [16]. Another study in agreement with our experience was a report by Sakhel *et al*. (2007) in which evaluated the efficacy of rhCG and uhCG in IUI cycles. They specified rhCG was as effective as uhCG in achieving pregnancy during COH-IUI cycles [17]. Additionally, Al-Inany *et al*. (2005) in a review declared that there is no difference in clinical outcomes between rhCG and uhCG used for induction of final follicular maturation. They suggested that additional factors including safety, cost and drug availability should be considered when choosing the gonadotropin procedure [18]. Consistently, Madani *et al* (2013) did not indicate any difference between recombinant hCG and urinary hCG regarding the number of oocytes per aspirated follicles in selected patients undergoing ICSI [19]. In another similar study Abdelmassih *et al* (2005) signified the effectiveness of r-hCG is as equal as 10,000 IU u-hCG for inducing final stages of oocyte maturation, however, they emphasized better patient tolerance and higher patient acceptability for r-hCG [20]. To increase the efficacy of rhCG, some authors have used the higher dose of rhCG in various IVF treatment protocols and showed the different doses of rhCG were equally effective in inducing final oocyte maturation [16, 17]. In spite of the non-significant difference between rhCG and uhCG in our experience, the pregnancy and ovulation rates in uhCG group were higher than rhCG group (28.6% vs. 27.5% and %93% vs. 88.6%, respectively).In the similar study, Alsina *et al*. (2003) evaluated the recombinant follicle stimulating hormone in world health organization (WHO) group II anovulatory women, and signified ovulation rate after six treatment cycles was 84%, while there were 136 clinical pregnancies (14.4% pregnancies per cycle)(18). Previous studies signified there are different factors influencing treatment outcomes after ovarian stimulation and IUI, such as women's age, ovarian stimulation protocol, semen parameters, method of semen preparation, the number of inseminations, the number of preovulatory follicles, length and cause of infertility as well as a number of prior treatment cycles [10, 15]. In present experience, we evaluated some of these factors, such as the type of infertility, duration of infertility, the cause of infertility and age, while the correlation between these factors and treatment was not significant ($p>0.05$). However, a study by Nikbakht *et al*. (2005) compared two doses of rhCG during ovulation induction in intrauterine insemination cycles and specified that reproductive outcome in the women with infertility < 5 years and BMI < 25 kg/ m2- was more than other women [19] In current study, we did not evaluate the adverse effect of two treatment protocols, which was considered to be the main limitation of this study; therefore, further investigations are recommended regarding adverse effects of rhCG and uhCG in infertile women.

5. Conclusion

Our findings confirmed that rhCG and uhCG did not show the significant difference; however, uhCG was more effective regarding ovulation and pregnancy rates in intrauterine insemination cycles in infertile women. Furthermore, we indicated that age, duration of infertility and cause of infertility did not impact the outcome of treatment.

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7. References

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