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ORIGINAL

Comparing the effect of three trigger methods (human HCG, combination of recombinant HCG with GnRH agonist, and double recombinant HCG) on the fertility outcome of patients with poor ovarian response in ovulation stimulation cycle (IVF/ICSI)

Comparación del efecto de tres métodos desencadenantes (HCG humana, combinación de HCG recombinante con agonista de GnRH y HCG recombinante doble) en el resultado de la fertilidad de pacientes con respuesta ovárica deficiente en el ciclo de estimulación de la ovulación (FIV/ICSI)

Hatav Ghasemi Tehrani[1], Nasrin Heidari[2], Farahnaz Mardanian[3], Ferdous Mehrabian[2], Elham Naghshineh[3], Narges Motamedi[4]

1. Department of Obstetrics & Gynecology, School of Medicine, Al-Zahra Hospital, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, Iran. 2. Department of Obstetrics & Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. 3. Department of Obstetrics & Gynecology, School of Medicine, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, Iran. 4. Isfahan University of Medical Sciences, Isfahan, Iran

Corresponding author
Elham Naghshineh
E-mail: naghshineh@med.mui.ac.ir

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Abstract

Aim: The aim of this study is comparing the effect of three trigger methods (human HCG, combination of recombinant HCG with GnRH agonist, and double recombinant HCG) on the fertility outcome of patients with in poor ovarian response in ovulation stimulation cycle (IVF/ICSI).

Methods: In this double-blind randomized clinical trial study, 158 patients with low ovarian reserve were divided to three groups: Group 1: Two doses of recombinant HCG (Ovitrelle) at a dose of 250 µg at 12 hour intervals, Group 2: HCG trigger (KARMA) alone at a dose of 10,000 units, and Group 3: 250 µg of recombinant HCG+ GNRH agonist. Collected data includes age, BMI, AMH, type of transferred embryo (Fresh or Freez), number of embryos, and results of pregnancy (clinical pregnancy rate/ongoing pregnancy rate/ implantation rate). Three groups is statistically similar in terms of age and BMI, AMH, and AFC.

Results: In groups 1 and 3, the number of oocytes, the number of M2 oocytes and the number of 2PN embryos was higher than group 2 after ovulation. The percentage of empty follicle syndrome was low in the two groups 1 and 3. Three groups had no significant difference in term of fertilization rate, the number of embryos A, B, and C, chemical pregnancy, clinical pregnancy, ongoing pregnancy, and implantation rate.

Conclusion: Dual trigger treatment with recombinant hCG and GNRH agonist and double recombinant hCG can improve fertility outcome patients with poor response in ovulation stimulation cycle. However, there were no significant differences among three groups regarding pregnancy results.

Keywords: recombinant HCG, GnRH agonist, Fertility, Pregnancy, Ovulation.

Resumen

Objetivo: El objetivo de este estudio es comparar el efecto de tres métodos desencadenantes (HCG humana, combinación de HCG recombinante con agonista de GnRH y HCG recombinante doble) sobre el resultado de fertilidad de pacientes con respuesta ovárica deficiente en el ciclo de estimulación de la ovulación (FIV/ ICSI).

Metodología: En este ensayo clínico aleatorio doble ciego, 158 pacientes con baja reserva ovárica se dividieron en tres grupos: Grupo 1: Dos dosis de HCG recombinante (Ovitrelle) a una dosis de 250 µg a intervalos de 12 horas, Grupo 2: HCG desencadenante (KARMA) solo a una dosis de 10.000 unidades, y Grupo 3: 250 µg de agonista de HCG+ GNRH recombinante. Los datos recopilados incluyen edad, IMC, AMH, tipo de embrión transferido (fresco o congelado), número de embriones y resultados del embarazo (tasa de embarazo clínico/tasa de embarazo en curso/tasa de implantación). Los tres grupos son estadísticamente similares en términos de edad e IMC, AMH y AFC.

Resultados: En los grupos 1 y 3, el número de ovocitos, el número de ovocitos M2 y el número de embriones 2PN fue mayor que el grupo 2 después de la ovulación. El porcentaje de síndrome de folículo vacío fue bajo en los dos grupos 1 y 3. Los tres grupos no tuvieron diferencias significativas en términos de tasa de fertilización, número de embriones A, B y C, embarazo químico, embarazo clínico, embarazo en curso y tasa de implantación.

Conclusiones: El tratamiento de activación dual con hCG recombinante y agonista de GNRH y hCG recombinante doble puede mejorar los resultados de fertilidad en pacientes con una respuesta deficiente en el ciclo de estimulación de la ovulación. Sin embargo, no hubo diferencias significativas entre los tres grupos con respecto a los resultados del embarazo.

Palabras clave: HCG recombinante, agonista de GnRH, Fertilidad, Embarazo, Ovulación.

Introduction

People with poor ovarian response in ovulation stimulation cycle are identified according to the Blogna criteria[1]. According to these criteria, individuals who meet two of the following three criteria may be considered poor responders to ovarian stimulation:

1. Age over 40 years or risk factors for reducing ovarian reserve, such as a history of surgery on the ovary, etc.
2. History of previous poor response to IVF (less than 3 oocytes in the previous cycle)
3. Abnormal ovarian reserve test AFC (antral follicle count) (less than 5 to 7) or AMH (anti-Müllerian hormone) less than 1.1[1]

During various studies, different treatment strategies (such as stimulating ovulation, vitamin supplements, various trigger methods, and etc.) have been stated to increase the response of infertile patients in the IVF cycle with poor response[2-6]. None of these strategies has been stated as the main protocol yet, due to the sensitivity of these patients and the small amount of ovarian reserve[6]. So, more research is still needed in this field. In the IVF cycle, when the size of the follicle reaches the appropriate amount, the HCG hormone is used to resume meiosis and enter the oocyte into meiosis II due to its structural similarity with the LH hormone. Ovulation is carried out under ultrasound guidance after 36 hours. In studies in patients with poor ovulation response in the IVF cycle, changes in this hormone have been applied. In a number of studies, the combination of HCG with GNRH agonist has been used in patients with low reserve, and the rate of pregnancy results is higher than HCG alone for triggering in the IVF cycle. According to a hypothesis, in a study, two injections of newly synthesized HCG have been used in the IVF cycle of patients with low reserve, with the mechanism that the second dose of HCG at an interval of 12 hours can release the cumulus mass and attached oocyte to the follicle wall, and prevent from the empty follicle syndrome. Zhang et al. comprised HCG trigger method with or without GNRH in IVF patients with poor response. This group showed that there was a higher number of oocytes in the combined treatment group, but there was no difference between the two groups in terms of fertility results[7]. In similar study, Eftekhar et al. showed no difference in the number of oocytes and fertility results in HCG trigger method with or without GNRH in IVF patients with poor response[8]. Lin et al.[9] and Maged et al.[10] indicated that HCG trigger method along with GNRH can enhance both number of oocytes and fertility results. Tesarik et al. used recombinant HCG in IVF patients with poor response. This groups showed that the follicles had oocytes in the new cycle after treatment[11]. So, based on limited studies with various results, in our study, we comprised three trigger methods (human HCG, combination of recombinant HCG with GNRH agonist, and double recombinant HCG) on the fertility outcome of patients with poor response in ovulation stimulation cycle (IVF/ICSI).

Materials and methods

This is a double-blind randomized clinical trial study. Patients under the age of 43 with two bologna criteria were included in study:

1. Age over 40 years or risk factors for reducing ovarian reserve, such as a history of surgery on the ovary, etc.
2. History of previous poor response to IVF (less than 3 oocytes in the previous cycle)
3. Abnormal ovarian reserve test: Antral Follicle Count (AFC) less than 5 to 7 or anti-Müllerian hormone (AMH) less than 1.1.

Patients with azoospermia, history of surgery on the uterus, endocrine disorders such as diabetes, history of repeated abortions, repeated failure of implantation more than equal to 3 times in the history, and BMI>30 were not entered to study.

Patients who get infected with corona virus during the cycle, patients who did not respond properly to the ovulation stimulation cycle, and patients who have taken drugs incorrectly during the cycle were excluded from study. In the third day of menstruation cycle day, selected patients were administrated with combined 150IU units recombinant FSH (CINALF brand Iran) and 150 UI hMG (KARMA brand Iran). When a follicle was seen on TVS above 14 mm, 0.25 mg of GnRH antagonist (Cetrorelix) was given daily up to oocyte triggering. Then, after observing at least two or three follicles, patients were divided to three groups:

Group 1: Two doses of recombinant HCG (Ovitrelle) at a dose of 250 µg at 12 hour intervals.
Group 2: HCG trigger (KARMA) alone at a dose of 10,000 units.
Group 3: 250 µg of recombinant HCG+ GNRH agonist

COVID-19 polymerase chain reaction (PCR) test were checked for all patients before oocyte reteieval. Oocytes were retrieved under anesthesia and with vaginal ultrasound guidance (voluson E6 brand) 36 hours after triggering. On the same day, a sperm sample was taken from the wife and prepared by a laboratory process, and microinjection was performed by an embryologist. Three days after the preparation of embryos, their quality was determined by the embryologist based on the degree of fragmentation, and embryos with quality a, b were candidates for transfer Then in morula or blastocyst stage under sonographic guidance (voluson E6 brand) maximum two embryos was transferred with LABOTEK catheter. After embryo transfer, luteal phase support with progesterone (50 mg) twice a day intramuscularly from the day of ovulation and continues until 12 weeks of IM pregnancy. βhCG test was requested two weeks after embryo transfer and vaginal sonography was performed one week later to prove the presence of

pregnancy. Collected data includes age, BMI, AMH, type of transferred embryo (Fresh or Freeze), number of embryos, and results of pregnancy (clinical pregnancy rate/ongoing pregnancy rate/ implantation rate).

Data analysis was done by SPSS version 24. ANOVA test was used to compare the average number of M2 oocytes and the number of 2PN, A, B, C obtained embryos after ovulation in the three studied groups. Chi-square test was used to compare the frequency of chemical pregnancy, the frequency of implantation rate (the gestational sac in ultrasound number of embryo transferred), the frequency of clinical pregnancy (fetal heart activity in ultrasound per transfer), and the frequency of ongoing pregnancy (pregnancy continuing until the 12th week of pregnancy per transfer) in the three study groups. P<0.05 was considered significant. In the statistical analysis, v1 is the ratio of the number of oocytes to the number of follicles above 14. v2 is the number of gestational sacs, and its number divided by the number of transferred embryos represents the implantation rate. W12 is the number of gestational sacs with a heart at 12 weeks of pregnancy divided by the number of transferred cycles and is used to obtain the ongoing pregnancy rate.

Results

In this study, 158 patients with low ovarian reserve according to Blogna criteria were included. Eight patients were excluded from the study: Two patients due to a positive corona test, three patients due to non-acceptance of medication, and three patients due to the wrong use of medication. Three groups is statistically similar in terms of age and BMI, AMH, and AFC. There was no significant difference in term of progesterone and estradiol levels before the trigger among three groups. Three groups did not differ in terms of the total dose of gonadotropin and the duration of gonadotropin treatment and the number of follicles above 14 mm. In groups 1 and 3, the number of oocytes, the number of M2 oocytes and the number of 2PN embryos was higher than group 2 after ovulation. The percentage of empty follicle syndrome was low in the two groups 1 and 3 (**Table I**). Three groups had no significant difference in term of fertilization rate, the number of embryos A, B, and C, chemical pregnancy, clinical pregnancy, ongoing pregnancy, and implantation rate. In the statistical analysis, there is no significant difference among three groups in term of v1, v2, and v3 variables (**Table II**).

Discussion

In this study, we compared and evaluated the IVF/ICSI results of three methods, human HCG, combination of recombinant HCG with GNRH agonist, and double recombinant HCG. Acquired results showed that in groups with combination of recombinant HCG with GNRH agonist, and double recombinant HCG had higher number of oocytes, the number of M2 oocytes and the number of 2PN embryos than human HCG. The percentage of empty follicle syndrome was also lower in in groups with combination of recombinant HCG with GNRH agonist, and double recombinant HCG alone. In previous studies, similar results was reported. In these studies, dual-trigger using GnRH agonist and hCG was introduced as the best strategy. However, we used recombinant hCG in this dual-trigger method. More studies showed no significant differences between dual-trigger and hCG alone. In dual triggering, we used recombinant HCG. Eftekhar et al showed that recombinant HCG is as effective as urine HCG. This group indicated that the numbers of retrieved oocyte,

Table I: Comparison of demographic data among three groups.

	Trigger with 12 hour		Trigger with 2 hCG		Trigger with 2 deka and oitrel		p-value
	mean	SD	mean	SD	mean	SD	
Age	35.74	3.95	34.74	3.53	35.86	4.05	0.283
BMI	24.60	1.22	24.54	0.64	24.56	1.24	0.961
Amn	0.77	0.34	0.80	0.29	0.79	0.28	0.887
AFC	3.76	1.04	3.68	1.11	3.48	1.01	0.397
Basal fsh	7.39	1.38	7.15	1.46	7.34	1.23	0.654
Fertilizat rat	78.40	27.01	75.30	34.54	79.80	26.47	0.739
No_2PN	2.34	1.20	1.86*	1.21	2.56	1.16	0.31
Duration of stimulate day	10.06	1.83	10.22	1.56	10.16	1.60	0.890
Total_Dose_of_gonadotrop	1832.40	278.83	1808.50	240.77	1777.40	242.18	0.557
Serum_E2	931.90	385.20	883.40	388.28	880.34	427.01	0.771
Serum_pr	0.88	0.43	0.73	0.37	0.79	0.38	0.187
No_Follicle	4.04	1.41	4.00	1.17	4.26	1.44	0.585
No_Total_oocyte	3.40	1.47	2.54*	1.72	3.50	1.63	0.006
No_Muture_oocyte	2.52	1.35	1.46*	1.31	2.62	1.41	0.001
Empty follicle syndrome	17.56	3.08	40.66*	4.82	21.33	3.18	0.001
Total embryo	1.86	1.38	1.82	1.56	1.96	1.21	0.875
Embryo grade A	0.64	0.13	0.46	0.10	0.56	0.11	0.559
Embryo grade B	1.14	0.13	1.14	0.16	1.24	0.14	0.859
Embryo grade C	0.42	0.11	0.20	0.08	0.52	0.11	0.085
Total No embryo_transfer	1.26	1.02	0.94	0.99	1.36	0.87	0.08

Table II: Comparison of pregnancy-related data among three groups.

	Trigger with 12 hour		Trigger with 2 hCG		Trigger with 2 deka and oitrel		p-value
	number	%	number	%	number	%	
Previus_IVF_attempt							
0	35	70	27	54	40	80	0.066
1	13	26	18	36	9	18	
2	2	4	5	10	1	2	
IVF_indicator							
T	18	36	15	30	14	28	0.066
U	27	54	27	54	23	46	
M	5	19	8	16	8	16	
C	0	0	0	0	5	10	
Cancelation_rate							
BAD ANDOMETER	6	12	7	14	7	14	0.403
ABSENCE EMBRYO	9	18	11	22	6	12	
ABSENCE OVUM	2	4	6	12	2	4	
NO CANCEL	33	66	26	52	35	70	
No_embryo_grade_A							
0	32	64	34	68	32	64	0.499
1	6	12	9	18	8	16	
2	10	20	7	14	10	20	
3	2	4	0	0	0	0	
No_embryo_grade_B							
0	17	34	22	44	17	34	0.165
1	10	20	7	14	7	14	
2	22	44	14	28	24	48	
3	1	2	6	12	1	2	
4	0	0	1	2	1	2	
No_embryo_grade_C							
0	47	94	44	88	44	88	0.783
1	2	4	3	6	4	8	
2	1	2	2	4	2	4	
4	0	0	1	2	0	0	
No_transfer_grade_A							
0	38	76	44	88	33	66	0.148
1	4	8	2	4	8	16	
2	7	14	4	8	9	18	
3	1	2	0	0	0	0	
No_transfer_grade_B							
0	25	50	31	62	27	54	0.794
1	9	18	7	14	5	10	
2	15	30	11	22	17	34	
3	1	2	1	2	1	2	
No_transfer_grade_C							
0	50	100	47	94	50	100	0.190
1	0	0	1	2	0	0	
2	0	0	2	4	0	0	
Result_pregnancy							
NO	38	76	39	78	39	78	0.963
YES	12	24	11	22	11	22	
V1	0.82	0.21	0.59*	0.34	0.78	0.22	0.001
V2							
0	42	84	43	86	42	84	0.950
1	8	16	7	14	8	16	
V3							
0	44	88	45	90	44	88	0.936
1	6	12	5	10	6	12	
W12							
0	45	90	45	90	46	92	0.924
1	5	10	5	10	4	8	
Implementation rate							
	8/63	12.6	7/47	14.89	8/68	11.76	0.884

maturation rates, and fertilization and clinical pregnancy rates are similar in both recombinant and urine HCG[12]. Based on similar studies, increases of the number of oocyte, mature oocytes and the number of zygotes can improve the IVF outcome[9,13,14]. In current study, these increases is more in dual triggering than HCG alone. On the other hand, these increases is more in triggering with recombinant than urine HCG. Beck-Fruchter et al[15] and Castillo et al[16] mentioned that combination of HCG with GNRH agonist can used for treatment of recurrent empty follicle syndrome. Based on our results, the percentage of empty follicle syndrome was lower in dual triggering than HCG alone. Based on Humaidan et al study, administration of hCG either 12 or 35 hours after GnRH agonist trigger can lead to rescue of corpus luteum function[17]. This condition reduce the pregnancy loss rate. Lin et al also showed that dual triggering can increase ongoing pregnancy rates and clinical pregnancy rate[9]. In our study, number of oocyte is also better values in dual triggering than urine HCG alone group. However, these difference but result of pregnancy is not statistically significant in our study. Based on a Meta-analysis study (2021), seven studies data showed that dual trigger treatment by HCG and GNRH agonist had significant effects on clinical pregnancy rate compared with HCG trigger alone[18]. This data is not compatible with our study. We showed that there is no significant difference among three groups in term of clinical pregnancy rate. Our data is compatible with Eftekhar et al. study[8]. Similar to our study, Hu el in Meta-analysis study showed that dual trigger treatment was associated with a significant increase in the number of oocytes, maturate oocytes, and empty follicle syndrome[18]. There are conflicting results regarding the effect of dual trigger treatment and hCG alone treatment on implantation and clinical pregnancy rates[19-22]. These conflicting results can be because most of the reported studies are retrospective. In these studies, potential confounding factors can limit data. Our study showed that in some variable (total oocyte, mature oocyte, and empty follicle syndrome), dual trigger and double trigger treatment has more significant effect than hCG alone treatment. In another variables, especially implementation rate, clinical pregnancy rate, and ongoing pregnancy rate, there was no significant difference. In a pilot study, Tesarik et al. also used double HCG trigger (HCG ovulation trigger 36.5 hours before ovarian puncture and second HCG trigger 12.5 hours later) in women with a paucifollicular response to ovarian stimulation. This group showed that a double HCG trigger appears to improve the rate of oocyte recovery[11]. Similar to Tesarik et al., we showed similar data by application of same double HCG trigger procedure. Our data also showed that dual trigger treatment can improve the number of oocytes, maturate oocytes, and empty follicle syndrome. Similar to Tesarik et al. suggestion, the addition of a second injection of HCG at 12 hour intervals can improve pregnancy in patients with poor ovarian response. Moreover, we showed that application of combination method (recombinant HCG+ GnRH agonist) also improve pregnancy rates.

Conclusion

In conclusion, our study showed that dual trigger treatment with recombinant hCG and GNRH agonist and double recombinant hCG can improve fertility outcome patients with poor response in ovulation stimulation cycle. However, there were no significant differences among three groups regarding pregnancy results. It's recommended that a study with larger populations design and comprise the live birth rates. It is necessary to study the pregnancy results of frozen embryos in these patients. Further studies are also required to identify the specific characteristics of women to help the fertility specialist's counseling based on patient's characteristics.

Conflict of Interest

The authors declare that no competing interests exist.

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