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Pregnancy outcomes improvement using intrauterine injection of hCG before ET in ICSI cycles

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AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

SUMMARY

Background: Infertility affects about one in six to seven couples globally. Although ARTs (assisted reproductive technologies) have improved, the pregnancy rate is still not sufficient.

Objective: to determine the pregnancy outcomes improvement using Intrauterine Injection of hCG (human chorionic gonadotropin) before ET (embryo transfer) in ICSI Cycles.

Patient and methods: A total of 100 infertile women included in randomized control study which conducted at Repro fertility centre, Alexandria, Egypt, during March 2021 till April 2022, all included women were classified in to, group (I) included 50 infertile women received injection of 500 IU of intrauterine HCG 5 min before embryo transfer (ET) and group (II) included 50 infertile women who did not receive hCG. Demographic data, oocyte performance and pregnancy rate were taken for all studied women.

Results: number of fertilized oocytes was significantly increased among cases group (8.60 ± 2.72) than control group (7.60 ± 2.22), (P=0.047). Also, positive pregnancy test was the most popular among the studied groups 60(60%), with a significant difference (P<0.001). While, there were no significantly differences among the studied groups regarding number mature oocytes, number of retrieved oocytes and number of embryos transferred

Conclusion: Our research suggested that HCG may enhance and improve endometrial receptivity, hence increasing pregnancy rates and implantation rates. HCG administered intrauterinelly had no effect on the likelihood of ovarian hyper-stimulation syndrome or the rate of first-trimester miscarriage. However, the data also brought up another issue that is crucial to the application of ART: an increase in the rate of multiple pregnancies.

Keywords: Clinical Outcomes; ICSI Cycles; Infertile women; Intrauterine Injection

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INTRODUCTION

Infertility affects about one in six to seven couples globally. Although ARTs have improved, the pregnancy rate is still not sufficient [1]. More than half of all pregnancy failures are due to implantation failure, a crucial step of pregnancy that is a difficult procedure. Successful implantation is thought to depend on three factors: embryo quality, endometrial receptivity, and communication between the embryo and the endometrium [2].

hCG is regarded as the most significant autocrine and paracrine factor that controls Embryo-Endometrium Communication [3]. At the two-cell stage, embryos start to release hCG, and this continues until implantation. The endometrial epithelial cells also create hCG during the luteal phase, which operates in an autocrine-juxtracrine manner until it appears in the serum [4]. hCG controls implantation by a variety of processes, including promoting trophoblast invasion, promoting trophoblast apposition and adhesion, and controlling implantation-related proteins [5]. Licht P, et al. [6] suggested that hCG plays a significant role in the angiogenesis, vascularization, and placentation of the endometrium by the ability of intrauterine infusion of hCG to up-regulate vascular endothelial growth factor and matrix metalloproteinase-9, which are essential for tissue remodelling. According to numerous additional researches, hCG can encourage the production of genes that lead to tolerance, receptivity, and implantation [7].

Clinicians are researching the effects of intrauterine hCG administration at the time of embryo transfer on the results of assisted reproductive technology (ART) as a result of hCG's role in the implantation process. The role of intrauterine hCG injection before fresh embryo transfer in ART has been the subject of numerous investigations, although the findings have been conflicting [8]. Therefore, the purpose of this study is to ascertain whether employing intrauterine injection of human chorionic gonadotropin (hCG) before embryo transfer (ET) improves pregnancy outcomes in ICSI Cycles.

PATIENT AND METHODS

A total of 100 infertile women included in randomized control study which conducted at Repro fertility center, Alexandria, Egypt, during March 2021 till April 2022, all included women were classified in to, group (I) included 50 infertile women received injection of 500 IU of intrauterine HCG 5 min before embryo transfer (ET) and

group (II) included 50 infertile women who did not receive hCG.

Ethical consideration

The institutional committee's ethical criteria were followed during all proceedings. The Menoufia University Hospital's Local Medical Ethics Committee approved the study. Following an explanation of the purpose, procedures, and nature of the study to all participants, signed informed consent was obtained from each participant.

Inclusion criteria

Infertile women undergoing ICSI/IVF, aged from 24 till 40 years old.

Exclusion criteria

Women with hydrosalpinges without preceding excision or blockage of the tubal ostia, functional azoospermia, submucous uterine myomas, or previous myomectomy.

Both the day of the embryo transfer and the number and caliber of the embryos were determined in accordance with local protocol.

Before the ET, infertile women in group (I) received 0.1 mL of the tissue culture medium with HCG injected directly into the uterus. Before the ET, 0.01 mL of the tissue culture medium without HCG was administered into the uterus. The time and volume of injected hCG was similar to that used by another study done by Rezaei and his colleagues 20188. Four minutes before ET, the solution was injected using an IUI catheter in both groups I and II.

All of the study's infertile participants were placed in the lithotomy posture. The speculum of Cusco will be used to see the cervix. With a full bladder, the ET catheter was inserted through the cervical Os into the uterine cavity under the guidance of trans-abdominal ultrasound.

After inserting the catheter, embryos were loaded and injected into the cavity at a distance of 0.5 cm from the fundus. At 14 days following ET, a biochemical pregnancy test will be evaluated by evaluating the level of hCG in the woman's serum. A transvaginal ultrasound was performed three weeks after the positive biochemical test if the test result was positive.

The ratio of the number of women who had positive biochemical pregnancy tests to the total number of women enrolled in each group was used to compute the pregnancy rate (PR). When there is evidence of a gestational sac, an embryo, and a fetal heart rate at the time of ultrasound screening, the clinical pregnancy is considered to be viable. The percentage of clinical pregnancies discovered by ultrasound to the ICSI cycles in each group was used to compute the clinical pregnancy rate (cPR).

Statistical analysis

The Statistical Package for the Social Sciences was used to analyze the data (SPSS version 25.0, Armonk, NY: IBM Corp, New York, USA). Additionally, to percentages, means, and standard deviations in descriptive statistics, analytical statistics also featured the chi-square test [2] Student's t-test, independent t-test (t), and correlation coefficient. Statistical significance was defined as a P value 0.05 or lower

RESULTS

When compared to the control group (7.203.28) in the current study, the cases group (9.302.89) had a substantially longer duration of infertility (P=0.001). Additionally, there was a significant difference between the patients and control group in that 30% and 50%, respectively, had previously undergone ICS trials (P=0.041). Age and body mass index did not substantially differ across the groups studied (P>0.05) (**Tab. 1.**).

Also, results in Table 2 shows Compared to the control group (7.602.22), the number of fertilized oocytes was considerably higher in the case group (8.602.72). Although

Tab. 1. Demographic data among cases and control groups.

Variables	Cases (N=50)		Control (N=50)		t	P value	Mean Difference	95% CI	
								Lower	Upper
Age/year									
Mean ± SD	31.70 ± 4.91		30.80 ± 6.48		0.783	0.436	0.9	-1.38	3.18
Range	24-40		24-30						
Median (IR)	32.00 (5.00)		30.00 (9.00)						
BMI (kg/m²)									
Mean ± SD	25.40 ± 4.24		26.50 ± 2.13		1.638	0.105	-1.1	-2.43	0.23
Range	14-30		24-30						
Median (IR)	26 (3.00)		26.00 (3.00)						
Previous ICS trials	**N**	**%**	**N**	**%**	4.167	0.041*	---	---	---
Yes	15	30	25	50					
No	35	70	25	50					
Duration of infertility									
Mean ± SD	9.30 ± 2.89		7.20 ± 3.28		3.393	0.001*	2.1	0.87	3.33
Range	5-16		1-1						
Median (IR)	8.50(2.00)		7.00 (4.00)						

BMI: Body Mass Index; t: independent t-test; X^2: Chi-square test; *Significant; CI: Confidence Interval for Mean

the number of mature oocytes and the number of recovered oocytes did not substantially differ across the groups under study (P>0.05) (**Tab. 2.**).

Also, results in Table 3 shows positive pregnancy test was the most common among the studied groups 60(60%), with a significant difference (P<0.001), (Fig 1). While, number of embryos transferred did not show any significantly differences among the studied groups (P>0.05) (**Tab. 3.**).

Additionally, there was a significant inverse relationship between the number of embryos transferred and pregnancy tests (p0.05), as well as a positive relationship between the duration of infertility, the number of mature oocytes, and the number of fertilized oocytes. While there was a substantial (P 0.001) negative connection between the pregnancy test and the quantity of recovered oocytes. However, there was no connection between BMI and earlier ICS studies that was statistically significant (p<0.05) (**Tab. 4.**).

DISCUSSION

According to a recent Cochrane analysis, giving IU-HCG in fresh cleavage-stage embryo transfer cycles at a dose of 500 IU or more is related with positive pregnancy outcomes [9-15]. The goal of this study is to ascertain whether utilizing intrauterine injections of human chorionic gonadotropin (hCG) prior to embryo transfer (ET) in ICSI cycles improves pregnancy outcomes.

Tab. 2. Oocyte performance among cases and control groups.

Variables	Cases (N=50)	Control (N=50)	t	P value	Mean Difference	95% CI	
						Lower	Upper
Number mature oocytes							
Mean ± SD	12.90 ± 3.54	12.00 ± 2.93	1.385	0.169	0.9	-0.39	2.19
Range	6-17	6-16					
Median (IR)	13.50 (6.00)	12.50 (5.00)					
Number of retrieved oocytes							
Mean ± SD	11.50 ± 3.45	10.40 ± 2.90	1.727	0.087	1.1	-0.16	2.36
Range	5-15	5-15					
Median (IR)	12.50 (6.00)	11.00 (3.00)					
Number of fertilized oocytes							
Mean ± SD	8.60 ± 2.72	7.60 ± 2.22	2.014	0.047*	1	0.01	1.99
Range	03-12	03-10					
Median (IR)	9.50 (3.00)	8.50 (3.00)					

t: Independent t-test; X^2: Chi-square test; *Significant; CI: Confidence Interval for Mean.

Tab. 3. Number of embryos transferred and Pregnancy test among cases and control groups.

Variables	Cases (N=50)		Control (N=50)		t	P value	Mean Difference	95% CI	
								Lower	Upper
Number of embryos transferred									
Mean ± SD	3.30 ± 1.02		3.20 ± 0.76		0.559	0.578	0.1	-0.26	0.46
Range	02-05		02-04						
Median (IQR)	3.50 (2.00)		3.00 (1.00)						
Pregnancy test									
	N	**%**	**N**	**%**	**X^2**	**P value**			
Positive	40	80	20	40	16.67	<0.001*	-	-	-
Negative	10	20	30	60	-	-			

t: Independent t-test; X^2: Chi-square test; *Significant; CI: Confidence interval for Mean.

Tab. 4. Correlation between outcome with the studied parameters.

Variables	Number of embryos transferred		Pregnancy test	
	r	P value	r	P value
Age	-0.557	<0.001*	-0.72	<0.001*
BMI	0.084	0.652	0.092	0.72
Duration of infertility	0.3	0.002*	0.528	<0.001*
Previous ICS trials	-0.103	0.308	-0.167	0.097
Number mature oocytes	0.544	<0.001*	0.734	<0.001*
Number of retrieved oocytes	0.018	0.541	-0.717	<0.001*
Number of fertilized oocytes	0.564	<0.001*	0.745	<0.001*

BMI: Body Mass Index; r: correlation coefficient; *Significant

Our research revealed that the cases group's duration of infertility was much longer than that of the controls. Additionally, there was a substantial difference between the 30% and 50% of patients and control group members who had previously undergone ICS trials. Regarding age and body mass index, there were no appreciable variations among the study groups. Similarly, research by Santibaez, et al. [16], there were no discernible variations in age or body mass index between the tested groups. Mourad MM, et al., [17] discovered that there was no statistically significant variation in demographics between the study and control research groups (age, BMI, duration of infertility). We proposed an intrauterine HCG supplementation 24 hours before ET in the study by Huang P, et al. [18], which reported that following the same rationale of prolonging HCG endometrial exposure period without having negative effects on endometrial receptivity. Unfortunately, no positive impact of this intervention on the course of the pregnancy has been demonstrated. It is hypothesized that altering the time of intrauterine HCG supplementation could cause the release of several mediators involved in implantation and interfere in various ways with the communication between the embryo and the endometrium.

The final finding shows that the effects of the first intrauterine HCG dose on implantation and pregnancy outcomes on the day before BT are negligible. These findings, however, cannot be generalized to other clinical contexts or patient subgroups; they are only applicable to the population of our study. Indeed, a key confounding factor determining the effectiveness of intrauterine HCG therapy could be the clinical characteristics of the individuals receiving it. According to certain studies, people who are younger (under the ages of 38 or 35) or who have experienced repeated implantation failure are more likely to benefit from this treatment. In the study by Liu X, et al., [19] the study population was composed of mainly young women (with a mean age of 32.85 ± 5.10 years). However, his study was marked by a great clinical heterogeneity linked to wide variation in patient's age, history of IVF-ET cycles, aetiology of infertility and the used COH protocols. All these factors can have a clinical impact limiting the intrauterine HCG effectiveness.

In the current study, in comparison to the control group, the number of fertilized oocytes was considerably higher in the case group. The number of mature oocytes and the number of recovered oocytes did not reveal any appreciable variations between the groups under study. Additionally, with a notable difference, the most common response among the study group was a positive pregnancy test. While there were no appreciable differences in the number of embryos transferred between the groups under study. In a recent study, Mostajeran F, et al. [20] discovered that patients who had an intrauterine injection of 700 IU of HCG before to BT had a higher pregnancy rate than the control group, despite the fact that this improvement was not statistically significant. More recently, Liu X, et al., [19] reported Patients with repeated implantation failure treated with 500 IU of HCG 3 days before frozen BT showed a significant improvement in clinical pregnancy rate, implantation rate, and live birth rate when compared to the control group. Contrarily, Hong KH, et al., [21] in a randomized clinical trial, reported for both new IVF cycles and FET cycles, there was no discernible difference in the implantation rate and continued pregnancy rate after BT between the HCG-treated group and the control group. Both a single HCG dose of 500 IU and a double dose, which is equivalent to 1000 IU, had no positive impact on the rates of implantation and pregnancy. This may imply that better results may not always result from increasing the quantity of a missing or deceased cofactor. Our results conflict with earlier research on ET cycles at the cleavage stage that found a beneficial impact of intrauterine HCG application on clinical outcomes, although they are consistent with some reports on BT cycles [22].

In the current study, there was a positive link with the duration of infertility, the number of mature oocytes, and the number of fertilized oocytes, but a significant negative correlation between the number of embryos transferred and pregnancy test. While there was a strong negative association between the pregnancy test and the quantity of recovered oocytes. In the study by Santibañez A, et al., [16] Found no significantly differences among the studied groups regarding number of retrieved oocytes and number of fertilized oocytes.

The advantages of 500 IU intrauterine HCG before embryo transfer. To demonstrate the result, comparative research between two randomized groups was conducted. Different IVF/ICSI failure instances can undoubtedly benefit from these kinds of operations. As is well known, numerous studies have conclusively demonstrated the significance of HCG in these circumstances for implantation, etc. [23]. The majority of pregnancies are lost at the implantation stage, and this loss frequently goes undiagnosed [3]. It is well recognized that HCG has a significant role in the inflammatory response and angiogenesis, both of which favor the implantation process. HCG has a crucial role because it is secreted early in pregnancy. Although there have been some recent developments, the overall pregnancy rate still hovers around 30%. [23].

CONCLUSION

Our research suggested that HCG may enhance and improve endometrial receptivity, hence increasing pregnancy rates and implantation rates. HCG administered intrauterinelly had no effect on the likelihood of ovarian hyper-stimulation syndrome or the rate of first-trimester miscarriage. However, the data also brought up another issue that is crucial to the application of ART: an increase in the rate of multiple pregnancies. This may be advantageous in the modern concept of single embryo transfer.

REFERENCES

1. **Simopoulou M, Sfakianoudis K, Maziotis E, et al.** *Investigating the optimal time for intrauterine human chorionic gonadotropin infusion in order to improve IVF outcome: A systematic review and meta-analysis*. *In vivo*. 2019;33(6):1737-49.
2. **Da Broi MG, Ferriani RA, Navarro PA.** Ethiopathogenic mechanisms of endometriosis-related infertility. *JBRA Assisted Rep.* 2019;23(3):273.
3. **Gridelet V, Perrier d'Hauterive S, Polese B, et al.** Human chorionic gonadotrophin: New pleiotropic functions for an "old" hormone during pregnancy. *Front Immunol.* 2020;11:343.
4. **Zhou C, Yang X, Wang Y, et al.** Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles. *Human Rep.* 2022.
5. **Makrigiannakis A, Makrygiannakis F, Vrekoussis T.** Approaches to improve endometrial receptivity in case of repeated implantation failures. *Front Cell Dev Biol.* 2021;9:613277.
6. **Licht P, Russu V, Wildt L**. On the role of human chorionic gonadotropin (hCG) in the embryo-endometrial microenvironment: implications for differentiation and implantation. *Semin Reprod Med.* 2001.
7. **Fenelon JC, Renfree MB.** The history of the discovery of embryonic diapause in mammals. *Biol Reprod.* 2018;99(1):242-51.
8. **Rezaei M, Frhadifar F, Moradi G, et al.** Evaluation of the impact of 1,000-unit intrauterine injection of human chorionic gonadotropin prior to *in vitro* fertilization on success rate of implantation in infertile women: A double-blind randomized trial. *J South Asian Fed Obstet Gynecol.* 2018;10(1):10-4.
9. **Wong KM, van Wely M, Mol F, et al**. Fresh *vs.* frozen embryo transfers in assisted reproduction. *Cochrane Database Syst Rev.* 2017(3).
10. **Deepika K, Rathore S, Garg N, et al.** Empty follicle syndrome: Successful pregnancy following dual trigger. *J Hum Reprod Sci.* 2015;8(3):170.
11. **Aaleyasin A, Aghahosseini M, Rashidi M, et al.** *In vitro* fertilization outcome following embryo transfer with or without preinstillation of human chorionic gonadotropin into the uterine cavity: A randomized controlled trial. *Gynecol Obstet Invest.* 2015;79(3):201-5.
12. **Firouzabadi RD, Janati S, Razi MH.** The effect of intrauterine human chorionic gonadotropin injection before embryo transfer on the implantation and pregnancy rate in infertile patients: A randomized clinical trial. *Int J Reprod Biomed.* 2016;14(10):657.
13. **Strug MR, Su R, Young JE, et al.** Intrauterine human chorionic gonadotropin infusion in oocyte donors promotes endometrial synchrony and induction of early decidual markers for stromal survival: A randomized clinical trial. *Human Rep*. 2016;31(7):1552-61.
14. **Mansour R, Tawab N, Kamal O, et al.** Intrauterine injection of human chorionic gonadotropin before embryo transfer significantly improves the implantation and pregnancy rates in *in vitro* fertilization/intracytoplasmic sperm injection: A prospective randomized study. *Fertil Steril.* 2011;96(6):1370-4.
15. **Diao LH, Li GG, Zhu YC, et al**. Human chorionic gonadotropin potentially affects pregnancy outcome in women with recurrent implantation failure by regulating the homing preference of regulatory T cells. *Am J Reprod Immunol*. 2017;77(3):e12618.
16. **Santibañez Á, García J, Pashkova O, et al.** Effect of intrauterine injection of human chorionic gonadotropin before embryo transfer on clinical pregnancy rates from *in vitro* fertilisation cycles: A prospective study. *Reprod Biol Endocrinol.* 2014;12(1):1-5.
17. **Mourad MM, Wafa YA, El Awady SA, et al.** Impact of Intrauterine injection of human chorionic gonadotropin at embryo transfer on intra cytoplasmic sperm injection outcome. *Egypt J Hosp Med.* 2019;76(6):4285-91.
18. **Huang P, Wei L, Li X**. A study of intrauterine infusion of human chorionic gonadotropin (hCG) before frozen-thawed embryo transfer after two or more implantation failures. *Gynecol Endocrinol.* 2017;33(1):67-9.
19. **Liu X, Ma D, Wang W, et al.** Intrauterine administration of human chorionic gonadotropin improves the live birth rates of patients with repeated implantation failure in frozen-thawed blastocyst transfer cycles by increasing the percentage of peripheral regulatory T cells. *Arch Gynecol Obstet.* 2019;299(4):1165-72.
20. **Mostajeran F, Godazandeh F, Ahmadi SM, et al.** Effect of intrauterine injection of human chorionic gonadotropin before embryo transfer on pregnancy rate: A prospective randomized study. *J Res Med Sci*. 2017;22.
21. **Hong KH, Forman EJ, Werner MD, et al.** Endometrial infusion of human chorionic gonadotropin at the time of blastocyst embryo transfer does not impact clinical outcomes: A randomized, double-blind, placebo-controlled trial. *Fertil Steril*. 2014;102(6):1591-5.
22. **Huang P, Wei L, Li X.** A study of intrauterine infusion of human chorionic gonadotropin (hCG) before frozen-thawed embryo transfer after two or more implantation failures. *Gynecol Endocrinol*. 2017;33(1):67-9.
23. **Gao M, Jiang X, Li B, et al.** Intrauterine injection of human chorionic gonadotropin before embryo transfer can improve *in vitro* fertilization-embryo transfer outcomes: A meta-analysis of randomized controlled trials. *Fertil Steril*. 2019;112(1):89-97.