

Value of Intrauterine Injection of HCG (Human Chorionic Gonadotropin) before Fresh Embryo Transfer on Clinical Pregnancy Rate in Women with Previous Failed One or Two ICSI (Intra Cytoplasmic Sperm Injection) Trials

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ABSTRACT

The human endometrium is a complex, multicellular tissue that is regulated by steroid hormones (estrogens, progesterone, androgens, and glucocorticoids) and has different characteristics in the various phases of the menstrual cycle. HCG plays a major role in endometrial receptivity via modulation of the production of various cytokines and chemokines.

Aim of the Work: The study aimed to show the effect of intrauterine injection of Human Chorionic Gonadotropin (HCG) on the day of ovum pickup in patients with a history of one or two failed Intra Cytoplasmic Sperm injections (ICSI). **Patients, and Methods:** A sample of 110 patients was obtained, half of them were candidates for intrauterine injection of 500 units of HCG immediately after ovum retrieval during the mock, while the other half were controls. All patients underwent controlled ovarian stimulation using the long protocol. The study was conducted at the Assisted reproduction unit of Obstetrics and Gynecology Hospital, Faculty of Medicine, Cairo University, between December 2019 and November 2021. **Results:** The rate of chemical pregnancy was 39.6 % in the first group and 27.8% in the second group. The clinical pregnancy rate was 28.3% in the first group and 18.5% in the second group. There was no significant difference between the two studied groups regarding the proportion of chemical pregnancies (P-value 0.195) and the proportion of clinical pregnancies (P-value 0.232).

Conclusion: Although intrauterine injection of HCG improves chemical and clinical pregnancy rates in patients undergoing ICSI trial after failed one or two trials, statistically seems with no differences.

Keywords: HCG injection; Endometrial receptivity; Infertility; In vitro fertilization; ICSI failure.

INTRODUCTION

The embryonic syncytiotrophoblastic cells generate the glycoprotein hormone known as human chorionic gonadotropin (HCG) largely during pregnancy. To continue the pregnancy, the hormone induces the corpus luteum to generate progesterone ⁽¹⁾. Before the embryo enters the uterine cavity on days 5 and 6 as a blastocyst, HCG has already started the embryo-endometrial conversation ⁽²⁾.

HCG has been linked to T cell regulation, and it has been discovered that embryonic HCG release is related to morphological grading in the blastocyst stage and embryos with significant implantation potential on day 3. In a recent study, **Schumacher *et al*** employed migration experiments to show that trophoblasts that produced HCG attracted regulatory T cells (Treg) ⁽³⁾. More importantly, new reports indicate that HCG plays a role in Treg differentiation ⁽⁴⁾.

The endometrium is crucial for implantation, therefore its thickness has long been seen as a sign of quality ⁽⁵⁾, particularly in assisted reproduction, where the chosen embryos should ideally be put into a receptive environment. Poor pregnancy outcomes have also been linked to thin endometrium, which has been documented in 5 percent of women under 40 and 25 percent of women between 41 and 45 years old ⁽⁶⁾.

The exposure of the endometrium to higher levels of sex steroid during IVF treatment make it thicker than during a natural cycle. However, the rate of implantation is still low when compared to natural conception cycles, indicating that it is not only

endometrial thickness that might ensure implantation. One explanation for this discrepancy may be that endometrial histology during IVF is considerably aberrant when compared to the histological picture of the endometrium during normal cycles ⁽⁷⁾.

IVF patients, particularly those who transfer blastocysts, do not experience HCG's effects on the uterus before embryo transfer. In the early stages of embryo development, IVF reduces HCG signaling to the endometrium, which may explain the comparatively low implantation rate ⁽⁸⁾. Since the beginning of IVF, additives like progesterone supplementation have been used in the luteal phase to boost endometrial thickness and receptivity. This increases receptivity and improves pregnancy success ⁽⁹⁾.

Before embryo transfer, intrauterine HCG injection was expected to significantly boost the rates of clinical pregnancy and embryo implantation in IVF ⁽¹⁰⁾. We conducted this study to assess the impact of intrauterine hCG administration on clinical pregnancy rates and live birth rates following a fresh embryo transfer in ICSI cycles.

PATIENTS AND METHODS

Study design and setting:

We conducted a prospective single-blind randomized controlled trial on patients with previous failed one or two ICSI trials at the Assisted reproduction unit of Obstetrics and Gynecology Hospital, Faculty of Medicine, Cairo University, between December 2019 and November 2021.

Ethical considerations:

The study was carried out following the World Health Organization's ethical standards for human studies and the Helsinki Declaration. The Research Ethics Committee of Cairo university Kasr Alainy approved the study protocol (IRB: MD-72-2019), and all women were given a clear and lay Arabic explanation of the study before enrolment, and all participants gave their informed consent.

Study population:

Women with primary or secondary infertility, aged between 20 years to 35 years with an average body mass index ranging from 18.5 to 25, with good ovarian reserve, previous one or two failed ICSI trials, and fresh cycle transfer were included in the study. We excluded women with active cervical or pelvic infection, poor ovarian reserve, and women whose husbands had azoospermia.

During the period of the study, we examined 205 infertile couples who were undergoing ICSI cycles after previous failed one or two ICSI trials for eligibility. 36 couples were excluded due to the presence of azoospermia, 22 women not matching the included BMI, 18 women not matching age, 12 women with hydrosalpinx, and 7 with poor ovarian reserve. The remaining 110 women were divided randomly into two groups

Group 1: 55 women were scheduled for intrauterine HCG administration after ovum pickup during the mock.

Group2: 55 patients were scheduled to undergo an ICSI cycle without intrauterine HCG injection.

Study measurements:

All patients were subjected to history taking including the history of their previous trial of ICSI (the protocol of induction, number of ova retrieved, number of embryos transferred, timing of the transfer, and if there were frozen embryos). General examination including vital signs, measuring BMI, and breast examination. Local examination: per vaginal and bimanual examination for any tenderness, discharge, detection of the size of the uterus, cervical mobility and any cervical or adnexal masses or tenderness, speculum examination for inspection of the cervix, and visualization of the discharge. Investigations as hormonal profile: FSH, LH, E₂, TSH, prolactin, and AMH were done for all patients in the cycle preceding the ICSI cycle, and vaginal ultrasonography was performed using a Mindray dp-5 ultrasound machine on day 2 or day 3 of the cycle. The uterus was scanned in the sagittal plane for detection of any endometrial abnormality and the antral follicular count was performed which is defined as the number of antral follicles measuring 2 to 10 mm in its widest dimensions in both ovaries and office hysteroscope for assessment of uterine cavity to exclude any abnormality causing failure of ICSI cycles. Semen analysis was done for the

male partner in the period preceding the ICSI cycle not more than three months.

Induction of ovulation: All eligible women were subjected to the Long protocol for induction by inducing mid-luteal down-regulation by GnRH agonist (Triptofem 0.1mg, IBSA) subcutaneously given till the day of trigger, and stimulation by HMG (Fostimon 150-300 IU, IBSA) intramuscularly given after confirmation of down-regulation by serum E₂ <50pg/ml and ultrasound endometrial thickness <5mm and after transvaginal ultrasound examination to exclude any ovarian cysts on day 2 or 3 of the cycle. The dose of gonadotropin was decided by the staff round meeting of the IVF unit according to the patient history, age, BMI and AFC then tailored to each woman according to their response to stimulation by folliculometry. Triggering ovulation by HCG (Choriomon5000 IU, IBSA) intramuscular route when we found more than 2 follicles reaching a diameter of 17mm or more. Ovum pick-up was done under deep sedation after 34 hours and before 36 hours after HCG administration using ultrasound-guided transvaginal sonography (Mindray DP5). Ovum pickup was done by an IVF unit specialist according to the unit standard protocol. Simple randomization was used with a 1:1 ratio within both groups.

-The study group: received 0.2 ml of 500 IU of HCG (ChoriomonTM 5000IU, EBSA) immediately prepared in the IVF Lap, injected by soft embryo transfer cannula (WallaceTM classic) during mock immediately following ovum pickup.

-The control group, mock was done without receiving HCG. Both groups were blind to the procedure.

All women were subsequently submitted to transfer of 2 to 3 embryos grade A or B, on day 3 by soft embryo transfer cannula (WallaceTM classic). Luteal phase support by 400 mg of progesterone suppository (ProntogestTM 400mg vaginal suppositories, Marcyrl) twice daily was given to all participants until pregnancy test becomes positive (a couple of weeks after ET).

Chemical pregnancy was considered positive by a rising titer of HCG level in serum (positive pregnancy test HCG more than 5miu/ml) a couple of weeks after ET.

Clinical pregnancy was confirmed by the presence of an intrauterine gestational sac with a fetal pulsating heart by ultrasonography.

Sample size:

The comparison of the chemical pregnancy rate in women having IVF cycles treated with intrauterine HCG and non-treated matched women served as the primary outcome for sample size calculation. In a prospective study, the Chi test was used to compare two proportions from separate samples; the 0.05 -error level was fixed, the power was set at 80%, and the intervention group's ratio was set at 1. According to a prior study ⁽²⁾, the chemical pregnancy rate in the intrauterine HCG group was 29.2%, compared to 19.4%

in the untreated group. In light of this, 50 people in each group should make up the minimum and maximum sample sizes. With the MS Windows version 3.1.2 of the G*Power software, sample size calculations were performed. Kiel University's Franz Faul, Germany.

Statistical methods

Data were statistically described in terms of mean \pm standard deviation (\pm SD), median and range, or frequencies (number of cases) and percentages when appropriate. Student *t*-test was used for comparison of numerical variables between the study groups. For comparing categorical data, Chi-square (χ^2) test was selected. The exact test was performed instead when the expected frequency is less than 5. Two-sided *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using the computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS

Among 200 patients who were undergoing ICSI cycles after previous failed one or two ICSI trials, 90 patients were excluded as they did not fulfill our inclusion and exclusion criteria: 38 cases were excluded as their BMI was more than 32, 21 cases were excluded as their husbands had a severe male factor, 17 cases were excluded due to poor ovarian reserve, 9 cases were excluded due to presence of hydrosalpinx and 5 cases were excluded as they were older than 40 years.

The rest of the patients were divided randomly into two groups; Group 1: 55 patients were scheduled to undergo intrauterine injection of HCG after ovum pickup during mock in the preceding ICSI cycle, and Group 2: 55 patients were scheduled to undergo an ICSI cycle without intrauterine HCG injection.

The demographic information for both groups is shown in **Table 1**. Regarding age, body mass index, length or type of infertility, and the proportion of patients with primary or secondary infertility, there were no significant variations between the two groups.

Table 1: Demographic data of studied groups

	Cases (n = 55)		Controls (n = 55)		P-value
	Mean	SD	Mean	SD	
Age	30.36	5.424	29.35	5.261	0.320
BMI	26.749	3.7489	27.962	3.8095	0.095
Type of infertility	Number of cases	%	Number of cases	%	0.446
1ry infertility	25	45.5%	29	52.7%	
2ry infertility	30	54.5%	26	47.3%	

BMI: body mass index SD: standard deviation, $P < 0.05$ is statistically significant.

Table 2 shows lab results, hormonal profile, and antral follicle count in both groups with no significant difference regarding this data.

Table 2: Lab results, hormonal profile, and US assessment among studied groups

	Cases (n = 55)		Controls (n = 55)		P-value
	Mean	SD	Mean	SD	
FSH	6.65	1.355	6.61	1.378	0.931
LH	5.157	.0731	6.123	1.6439	0.090
TSH	2.063	0.29	3.481	0.255	0.331
E2	47.688	3.6143	50.145	2.4461	0.653
PRL	15.821	3.8914	14.725	3.8025	0.494
AMH	2.794	0.028	2.321	0.379	0.171
AFC	14.16	3.849	14.15	3.356	0.986

FSH: follicle-stimulating hormone, LH: luteinizing hormone, TSH: thyroid-stimulating hormone, E2: estradiol, PRL: prolactin, AMH: anti-Müllerian hormone, AFC: antral follicle count. SD: standard deviation, $P < 0.05$ is statistically significant.

Figure (1) demonstrates the ovarian reserve among the studied groups as represented by serum AMH and basal Antral Follicle Count with no significant statistical difference.

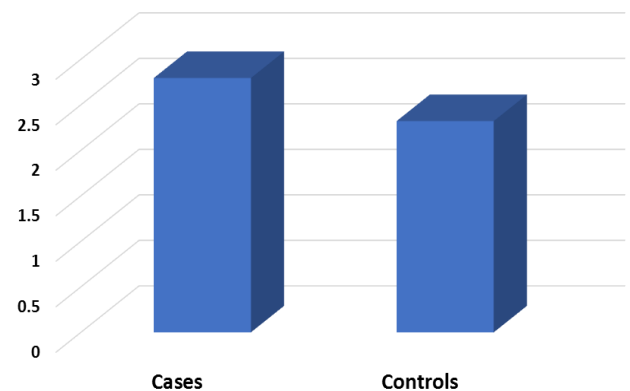


Figure (1): Mean AMH (ng/ml) between cases and control groups

Regarding the causes of infertility and the number of previous ICSI trials in both groups, there were no statistical differences between both cases and control groups except that for polycystic ovarian syndrome which was 30.9% in cases and 14.5% in control with 0.041 as the *p*-value as shown in **Table 3**.

Table 3: Causes of infertility and previous ICSI trials in cases and control groups

	Cases (n = 55)		Controls (n = 55)		p-value
	No of cases	%	No. of cases	%	
PCO	17	30.9%	8	14.5%	0.041
Tubal	13	23.6%	12	21.8%	0.820
Male	43	78.2%	49	89.1%	0.122
Endometriosis	4	7.3%	3	5.5%	0.696
Unexplained	5	9.1%	5	9.1%	1.000
	Mean	SD	Mean	SD	
ICSI trials	1.42	0.498	1.27	0.449	0.111

PCO: polycystic ovary, ICSI: Intracytoplasmic sperm injection. $P < 0.05$ is statistically significant, SD: standard deviation. No= Number.

Table 4 shows the number of retrieved oocytes and transferred embryos between the study group and the control group which shows no significant difference. Two cases were canceled in the study group because of failure of fertilization.

Table 4: Number of retrieved oocytes and number of transferred embryos among the studied groups

	Cases (n = 55)		Controls (n = 55)		p-value
	Mean	SD	Mean	SD	
M1	1.44	1.151	1.25	1.075	0.394
M2	10.49	5.821	11.85	4.836	0.184
GV	1.60	1.949	1.25	1.236	0.269
no. of ETs	2.64	0.522	2.78	0.534	0.170

M: metaphase, GV: germinal vesicle, ETs: embryo transfer
P<0.05 is statistically significant, SD: standard deviation

As regards both chemical and clinical pregnancy rates representing our primary and secondary outcomes in both groups, adding HCG increased the percent of both chemical pregnancy and clinical pregnancy rates between the study and control respectively (39.6% - 27.8%) (28.3%- 18.5%) but with no significant statistical differences as demonstrated by **Figure (2)**.

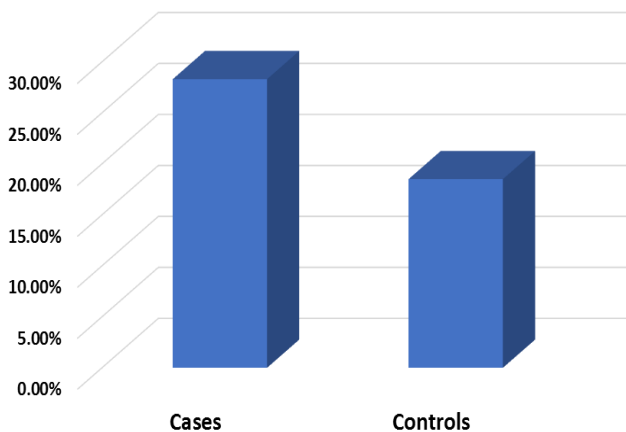


Figure (2): Percentage of clinical pregnancy rate between both groups

DISCUSSION

The blastocyst produces HCG, a heterodimeric placental hormone, both before and following embryo implantation. IVF patients, especially those transferring blastocysts, do not experience HCG's uterine lining impact. In the early stages of embryo development, IVF reduces HCG signaling to the endometrium, which may explain the comparatively low implantation rate ⁽⁸⁾. It was hypothesized that intrauterine injection of HCG prior to embryo transfer could greatly increase rates of clinical pregnancy and embryo implantation in IVF ⁽¹⁰⁾.

Regarding the demographic data of the two groups, there were non-significant differences between them. As in age, BMI also hormonal profile, and AFC, there were no significant differences between the two groups which illustrate the matching of our cases between the two groups and non-biased selection.

The causes of infertility in our study were different. However, mostly male-factor was the most common; 43 in the study group and 49 in the control group with a non-significant difference. The 2nd common cause in our study was PCO with a significant difference between the two groups. This is because our age group was selected between 20 -35 years and in this age group PCO contributes higher incidence as an ovarian cause of infertility. The remaining cases had a tubal factor, endometriosis, and unexplained infertility.

In our study, we found that intrauterine HCG injection during mock after ovum retrieval in patients with previous failed one or two ICSI trials increased both chemical and clinical pregnancy rates as it was (39.6%-27.8%) (28.3%-18.5%) respectively but with no statistical significance.

Other studies discovered a pattern where study cases had a higher pregnancy rate than control cases, even though this difference was statistically insignificant. The pregnancy rate in the **Mostajeran F et al.** trial following 700 UI of intrauterine HCG injection before embryo transfer was not substantially different from the control group, although it was more than twice as high in the HCG group (28.6 percent vs 12.5 percent). These results and those of earlier studies demonstrated that a straightforward approach like the intrauterine infusion of HCG before embryo transfer can be helpful to increase conception rates ⁽¹¹⁾.

Osman et al in Egypt concluded that there was no sufficient evidence favoring the use of intrauterine HCG injection before ET after reviewing eight RCTs. Among 3087 women who had IVF/ICSI in total (intrauterine HCG group: 1614; control group: 1473), there were no appreciable differences in the spontaneous abortion rate or the live birth rate ⁽¹²⁾.

Similar to our work, Assuit University conducted a study on 181 women who underwent IVF/ICSI with the intrauterine injection of 500 units of HCG in 0.1 ml culture media 4 minutes prior to ET (whether fresh or vitrified-warmed embryo). HCG intrauterine injection before embryo transfer did not increase live birth rates in women having IVF, with clinical pregnancy rates in the study and control groups being 24 percent versus 19 percent, respectively ⁽¹³⁾.

The results of our study were consistent with those of other studies that were done on patients who had ICSI trials in a randomized control study with 126 women, 15 (27.3 percent) of the case group and 14 (25.5 percent) of the control group experienced positive chemical pregnancy after intrauterine injection of 1000 units of HCG immediately following oocyte retrieval. The clinical or chemical pregnancy rates did not differ significantly between the groups ⁽¹⁴⁾.

Another randomized trial from Iran analyzed 159 patients who underwent intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF) using an antagonist strategy. 53 patients were split up into three groups. The control group had ET without receiving an intrauterine injection of HCG beforehand, while groups 1 and 2 received 500, 1000, and 2000 IU of HCG

respectively. Their findings showed that there was no real difference between the groups. Clinical pregnancy rates were 31.4 percent, 32.1 percent, and 35.3 percent, respectively, while the rates for chemical pregnancies were 34 percent, 32.1 percent, and 35.3 percent ⁽¹⁵⁾.

The meta-analysis also included results from another fresh embryo transfer (ET) clinical trial conducted in China. 2759 women underwent fresh ET in total (1429 in the HCG group and 1330 in the control group). In comparison to controls, intrauterine HCG injection significantly raised the frequencies of biochemical pregnancy (RR 1.61) and continuing pregnancy (RR 1.58). Nevertheless, there were no appreciable variations in a clinical pregnancy (RR 1.11), and they advised against using HCG intrauterine in ART ⁽¹⁶⁾.

An intrauterine injection of 500 units of HCG 15 minutes before embryo transfer in a randomized trial on 196 infertile women revealed a significant difference in the chemical pregnancy rate between the study and control groups (30.92 percent vs 18.18 percent). In terms of clinical pregnancy, no significant difference was discovered ⁽¹⁷⁾, and they advise high sample size studies.

On the other hand, in a 2011 study, injections of 100, 200, and 500 IU of HCG were contrasted with one another and with a control group seven minutes before the ET. While the pregnancy rate did not vary in the groups receiving 100 and 200 IU of HCG, it significantly increased after receiving 500 IU. The injection was carried out on the day of the transfer and just before the embryo's placement into the endometrial cavity ⁽¹⁸⁾. The difference between our study and that of **Mansour et al** may be due to the exclusion of cases of prior ICSI failure, the injection of HCG 15 minutes before embryo transfer on the day of transfer, and the use of diluted HCG in the culture medium.

Additionally, prospective cohort research was carried out to assess the effect of intrauterine HCG injection on pregnancy outcomes in FET cycles in repeated implantation failure patients. Three days before embryo transfer, the treatment group (n=153, 152 cycles) received an injection of 500 IU of diluted HCG in normal saline. In the control group (n=152, 151 cycles), embryo transfer was performed after an intrauterine injection of sterile saline that did not contain HCG. Clinical pregnancy rates and implantation rates were considerably higher in the HCG-treated patients' group (37.5% vs. 25.17%) and (29.19% vs. 19.4%), respectively ⁽²⁾. Their study differs from ours in that it calls for larger sample sizes because their number of cases is three times bigger than ours.

In two settings in China, a prospective randomized trial was carried out. Two days prior to blastocyst transfer, HCG application was carried out on cohort A. Just before the embryo transfer on day 5 in batch B, HCG was administered. Patients from both cohorts were randomly assigned to receive intrauterine HCG administration or culture medium as part of the control group. After intrauterine HCG treatment on days 3

(cohort A) and 5 (cohort B), there was no change in the clinical outcome ⁽¹⁹⁾.

CONCLUSION

In conclusion, from our study results, we can conclude that adding intrauterine HCG with the dose of 500 IU/dl on the day of ovum pickup during mock may benefit patients undergoing ICSI cycle after previous failed one or two ICSI trials compared to non-giving - despite being statistically insignificant- as regarding both chemical and clinical pregnancy. However, because of the notable discrepancies in research and the paucity of thorough exploration for endometrial disease in these populations, the clinical usefulness of intrauterine injection of hCG on the outcome of IVF/ET remains debatable. Therefore, additional research in this area is required.

Declaration of conflicting interests

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