ORIGINAL ARTICLE

A Study on the Effect of Intrauterine Injection of Human Chorionic Gonadotropin before Embryo Transfer on Clinical Pregnancy Rates in IVF – ICSI Cycles

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Abstract

Introduction: Objective: To investigate the benefits of intrauterine injection of human chorionic gonadotropin (hCG) before embryo transfer on the pregnancy rates in the *in vitro* fertilization intracytoplasmic sperm injection (IVF–ICSI) cycles at a tertiary care center.

Materials and methods: This was a prospective double-blinded randomized control study. All cases of infertile women under the age of 40 years undergoing their first IVF/ICSI frozen embryo transfer (FET) cycles were included in the study. The study group (n = 29) received 500 IU of hCG and the control group (n = 30) received culture media without hCG via intrauterine administration before embryo transfer. The main outcome measures studied were the clinical pregnancy rate (PR) and implantation rate (IR).

Results: The IR and PR were not statistically significant between the 500 hCG group (60.7 and 50% respectively) as compared with the control group (68.6 and 55% respectively).

Conclusion: Intrauterine infusion of hCG before the embryo transfer does not improve implantation and clinical pregnancy rates.

Keywords: Effectiveness, Fertility, Fetal outcome, Infertility and practice.

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Introduction

Within the last 30 years, assisted reproductive technologies (ARTs) have been successfully developed to overcome infertility. The increase in *in vitro* fertilization (IVF) doesn't necessarily mean that couples are dealing with more infertility than before. More likely it's because of women having children later in life, when fertility declines.

The probability of success with IVF relates to several factors, many of which are unfortunately not known until the treatment cycle is well underway or even nearing completion. For *in vitro* fertilization cycles, the cumulative live birth reported in women less than 35 and more than 42 years is 48.6% and 3.4–4.2% respectively.[1] Once the embryo is transferred the process of implantation depends on the embryo quality and the endometrial receptivity. Due to a failure of implantation, approximately 50–75% of pregnancies do not occur.[2] The implantation rate of blastocysts varies from 4.2 to 55.8%, whereas the implantation rate of cleavage-stage embryos vary from 3 to 43.9%.[3]

Three components are considered to be essential for successful implantation, process-embryo quality, endometrial receptivity, and embryo–endometrium communication. Human chorionic gonadotropin (hCG) secreted by embryo is one of the important factors among many regulating the complex processes of implantation. Intrauterine infusion of hCG could upregulate vascular endothelial growth factor and matrix metalloproteinase-9, which are important for tissue remodeling, suggesting that hCG plays a crucial role in angiogenesis, vascularization, and placentation of the endometrium.[4]

Human chorionic gonadotropin is one of the early signals seen before implantation of an embryo, which regulates immune tolerance for the embryo, and starts and controls the existence of hemochorial placentation at the time of implantation. The function of hCG in the implantation process has inspired clinicians to study the effect of intrauterine hCG administration at the time of embryo transfer on ART outcomes.

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Aim of the Study

To determine the effects of intrauterine hCG injection before ET on improving the implantation and pregnancy rates in IVF/ICSI (Intra-Cytoplasmic Sperm Injection) cycles.

Materials and Methods

Patient Population

The research protocol was approved by the institutional ethical board. Patients undergoing IVF/ICSI at our center for treatment of infertility from October 2014 to April 2016 were recruited by

the clinical research team. The inclusion criteria were females age under 40 years old with infertility due to male factors and patients undergoing 1st frozen embryo transfer (FET) cycle. Exclusion criteria were previous IVF/ICSI failures, previous successful IVF cycle, azoospermia, uterine myoma or previous myomectomy, endometriosis, or the presence of hydro-salpinges, D2/3 serum follicle stimulating hormone (FSH) >10 IU, body mass index (BMI) >29 kg/m^2. The patients were counseled and informed consent was taken prior to the study.

Study Design

Patients were recruited voluntarily and randomly assigned by computer-generated program. Allocation concealment was maintained at the level of the patient, primary study researcher and statistician. Patients were allocated into two groups, i.e., groups A and B on the day of starting progesterone for FET. Patient allocation was informed to the embryologist who knew which group was the study or control group.

Procedure

A total number of 76 patients undergoing the IVF–ICSI cycle were recruited for the study. Among 59 infertile patients, who had undergone embryo transfer, 29 cases in the study group were injected with 500 IU of hCG, and 30 cases were considered as control. The rest of the 17 patients were awaiting the embryo transfer.

The preparation of the intrauterine injection of hCG is done by adding 250 µL of embryo culture media to one vial that contains 5000 IU of hCG. The patients in both groups were put in the lithotomy position. The injection was guided by an abdominal ultrasound with a full bladder. The cervix was visualized with a vaginal speculum. Soft catheters were used which were loaded with 25 µL of embryo culture medium that contained 500 IU of hCG, and the tip of the catheter was placed at the internal OS. The embryo culture medium with the hCG preparation included was injected. Finally, embryos were transferred after 2–4 hours of hCG injection. In the control group, the same culture media which was used for embryo transfer but without adding hCG was injected into the uterine cavity. The pregnancy test with biochemical hCG was performed 10 days after the embryo transfer. If the test was positive, then a transvaginal ultrasound was performed 4 weeks later from the day of embryo transfer, to search for signs of pregnancy.

Outcome Measures

The primary outcome measure was the clinical pregnancy rate. The secondary outcome measures were implantation and miscarriage rates. Clinical pregnancy was defined by the presence of a gestational sac with fetal echoes and pulsations. The implantation rate was defined as the number of gestational sacs observed divided by the number of embryos transferred. Chemical pregnancy was defined by a rising hCG level in serum without the detection of a gestational sac. The miscarriage rate was defined as the loss of pregnancy before 20 weeks gestational age.

Statistical Analysis

To detect an absolute increase in the pregnancy rate for the study group, we needed 250 women for a power of 80% as per the Mansour et al.[5] study to get a significance of 0.05. Student's *t*-test and Mann-Whitney test were used. The Chi-square test was used with Fisher's exact test to estimate the odds ratio (OR). The $p < 0.05$ was considered statistically significant.

Results

From October 2014 to April 2016, a total of 59 patients were randomized, out of which 29 patients received intrauterine hCG (hCG group), and 30 patients received the embryo culture media without hCG (control group). Mean age and the demographic characteristics of the study population are given in Table 1. The mean age of the population in the hCG group was 28.90 ± 4.49 years and in the control group was 30.27 ± 2.94 years which was not statistically significant. Similarly, the BMI of the wife, endometrial thickness, FSH, and AMH levels were also not statistically significant. Table 2 summarizes the outcomes. There was no statistical significance in clinical pregnancy rate between the hCG group as compared with the control group (50 vs 55%; $p = 0.695$, OR 0.812, 95% CI (0.286–2.30). There was no statistically significance in implantation rate (34.5 vs 38.9%; $p = 0.623$, OR 0.55, 95% CI (0.166–1.82) biochemical pregnancy rate (60.7 vs 68.6%; $p = 0.514$, OR 0.695, 95% CI (0.23–2.07) between the hCG group as compared with the control group.

Discussion

With improvements in the efficacy, safety, and sophisticated newer treatment of ART, there has been a continued effort to identify

Table 1: Baseline characteristics

	Cases N = 29	*Control N = 30*	*p-value*
Age of the patient	28.90 ± 4.49	30.27 ± 2.94	0.132
Body mass index (BMI)	24.42 ± 3.07	24.87 ± 3.88	0.286
Endometrial thickness	10.06 ± .671	10.2 ± 1.04	0.049
Follicle stimulation hormone (FSH)	7.008 ± 1.61	6.71 ± 2.2	0.303
Anti-müllerian hormone (AMH)	3.52 ± 2.83	3.41 ± 3.4	0.618

Values expressed as mean ± standard deviation

Table 2: Outcome measures

Transfer procedures	*Cases N = 29*	*Controls N = 30*	*p-value*	*Odds ratio 95% CI*
Embryos transferred per patients (mean ± SD)	1.96 ± 0.576	2.03 ± 0.325	0.042*	
Biochemical pregnancy *N* (%)	17 (60.7%)	20 (68.6%)	0.514	0.695 (0.23 – 2.07)
Implantation rate *N* (%)	19 (34.5%)	23 (38.9%)	0.623	0.55 (0.166 – 1.82)
Clinical pregnancy *N* (%)	14 (50%)	16 (55%)	0.695	0.812 (0.286 – 2.30)
Missed abortion *N* (%)	5 (17.8%)	6 (20.6%)	0.786	0.833 (0.222 – 3.11)

Values expressed as mean ± standard deviation, *statistically significant

interventions that optimize IVF outcomes. The applications of extended culture, and time lapse selection of embryos have been shown to enhance selection and improve implantation rates. Pre-implantation genetic screening and pre-implantation genetic diagnosis have further enhanced the selection of euploid embryos to improve the IVF outcome. Embryo glue is used to improve the implantation rate. Despite these interventions, some embryos still fail to implant. Potential causes limiting implantation involve many factors, that may be related to endometrial factors, in particular the cross-talk between embryo/endometrium that occurs during the time of implantation.

This randomized clinical trial has been investigated to evaluate the effects of intrauterine rhCG injection before the embryo transfer on the outcome of the IVF/ICSI cycles. In this preliminary report of a randomized control study, the infusion of 500 IU of hCG at the time of embryo transfer does not significantly improve clinical pregnancy or implantation rates. Based on experimental *in vitro* data, the embryos by morula stage would already be expected to be secreting hCG. It is possible that the additional hCG supplementation at this stage was insufficient to cause an improvement. Additional studies are needed to identify why embryos that otherwise appear optimal fail to implant.

In Cochrane, review results show no substantive differences in live birth among women having blastocyst-stage ET with an IC-hCG (intracavity hCG) dose ≥ 500 IU compared to the women having blastocyst-stage ET without IC-hCG. However, there was an increase in the live birth rate in the subgroup of women undergoing cleavage-stage ET with an IC-hCG dose ≥ 500 IU compared to women having cleavage-stage ET without IC-hCG.[2]

Differences in our study when compared to the other trials are that this study included women who were less than 40 years old with infertility and patients undergoing 1st FET cycle, which was the same as in Mansour et al.[5] and Zarei et al.[6] as in Santibañez et al.[1] and Hong et al.[7] included patients with a history of recurrent miscarriage and implantation failure and hCG was given in both fresh and FET cycles.

The outcomes of implantation and clinical pregnancy rates of the present study are comparable with the Hong et al.[7] study. The results though were in contrast with the other trials i.e., Mansour et al.,[5] Zarei et al.,[6] and Santibañez et al.[1] which showed significant improvement in implantation and clinical pregnancy rates after the intrauterine infusion of hCG. Similarly, a retrospective cohort study by AS Rao, suggests that intrauterine hCG instillation prior to fresh embryo transfer in women over age 35 may enhance implantation and clinical pregnancy rate.[8] However, the review article by Hou W et al. concludes that there is no current evidence for intrauterine injection of hCG before fresh ET in improving clinical pregnancy rate.[4]

Limitations of the study are the small number of patients in the groups. It is difficult to draw any conclusion with the available number of patients. Less number of patients in the study is due to the refusal of consent to be a part of the study. The current findings apply to the population studied and may not be applicable in different clinical settings or patient subgroups. Additionally, the small differences in outcomes between the study and control groups were found as it is a preliminary report of the trial with a smaller number of patients.

Conclusion

In this preliminary report of the trial, intrauterine infusion of 500 IU hCG prior to embryo transfer doesn't improve the IVF outcome.

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