RESEARCH PAPER

Impact of Intrauterine Injection of Human Chorionic Gonadotropin vs Intrauterine Infusion of Autologous Platelet Rich Plasma vs Endometrial Scratch on Pregnancy Rates as Management of Unexplained Recurrent Implantation Failure

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Abstract

Background and Objective: Several types of treatment include intrauterine human chorionic gonadotropin (HCG) injection, platelet-rich plasma (PRP) infusion, and endometrial scratching, are being studied to help women who have recurrent implantation failure (RIF) that cannot be explained have better pregnancy outcomes. The purpose of this study was to examine and compare the impact of intrauterine HCG injection before embryo transfer (ET) in an in vitro fertilization (IVF) cycle, intrauterine infusion of autologous PRP, and endometrial scratch on the clinical pregnancy rate in managing cases of unexplained recurrent implantation failure (RIF).

Methods: This prospective comparative study was carried out on 90 female patients aged <35 years old, with unexplained RIF. Patients were divided into three equal groups: Group A: had HCG injected into their endometrial cavities, Group B: performed endometrial damage or scratching and Group C: received treatment by intrauterine injection of autologous PRP.

Results: Basic hormonal profile, AFC, number of follicles >16 mm during induction, endometrial thickness at day of HGG triggering, number of oocyte retrieval, fertilized, ET, duration of stimulation and cumulative pregnancy rates were insignificantly different between studied groups.

Conclusions: When comparing biochemical pregnancy rates, medical pregnancy, spontaneous abortion, and miscarriage amongst the three methods, we did not find any significant differences.

Keywords: Endometrial Scratch, Human Chorionic Gonadotropin, Platelet Rich Plasma, , Recurrent Implantation Failure

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Highlights:

Several types of treatments are being studied for recurrent implantation failure (RIF), including intrauterine HCG injection, platelet-rich plasma (PRP) infusion, and endometrial scratching.

The study aimed to compare the impact of these treatments on clinical pregnancy rates in unexplained RIF cases.

A total of 90 female patients aged <35 years with unexplained RIF participated in the study.

No significant differences were observed between groups in basic hormonal profiles, AFC, number of follicles >16 mm, endometrial thickness, oocyte retrieval, fertilization rates, embryo transfer (ET), stimulation duration, or cumulative pregnancy rates.

When comparing biochemical pregnancy rates, medical pregnancy, spontaneous abortion, and miscarriage, no significant differences were found among the three methods.

Introduction:

The struggle of infertility is one of the most frequent issues faced by couples everywhere. When other treatments have failed, such as those for tubal blockage or significant male factor or low ovarian reserve or infertility of extended duration, in vitro fertilization (IVF) is the therapy of choice (1).

A vital physiological phenomenon for both IVF and pregnancy is implantation. It describes how the embryo adheres to the uterine endometrial luminal surface (2).

One of the most challenging problems with assisted reproductive technology (ART) is recurrent implantation failure (RIF). The failure to conceive after transferring three or more high-quality embryos through IVF is known as infertility (3).

The process of implantation is multifactorial, meaning that a number of factors influence whether it is successful or not. Fifty to seventy percent of failed pregnancies are caused by RIF(4).

Small submucous fibroids or polyps, intrauterine syncheia, cervical enlargement, and concealed endometriosis are among uterine pathological disorders that contribute to RIF. Women undergoing IVF have a reported 40% higher risk of uterine disease than the general population (5, 6).

Since occult endometriosis is linked to elevated aromatase expression and decreased integrin expression, it is thought to be a potential cause of RIF. Reproductive failure is associated with chronic

endometritis (CE), which is primarily linked to older mothers and repeated miscarriages (7).

Patients undergoing IVF cycle have ongoing all infertility profile for complete evaluation including hormonal profile, semen analysis, thyroid function tests and ultrasonography HSG, SIS, and hysteroscopy are all valid methods for assessing the endometrial cavity before ET is performed (8).

Recent years have seen a proliferation of RIF management techniques. To increase the success rate of IVF, some doctors have tried injecting HGG directly into the uterus just before embryo transfer (ET). Strug et al. (9) observed that HGG instillation enhanced implantation rates by boosting endometrial expression of estrogen and progesterone receptors.

It has been proposed that intrauterine infusion of PRP is an effective method for treating thin endometrium. It is used to increase the endometrial thickness and vascularity of women with less-than-ideal conditions, making it easier for embryos to implant (10).

Endometrial injury or “scratch”. Patients with a history of unsuccessful transfers are benefiting from endometrial injury treatments (11).

The aim of this work was to assess and evaluate the effect of intrauterine injection of HCG before ET of IVF cycle versus intrauterine infusion of autologous PRP versus the endometrial scratch on CPR as a management of the cases who were suffering from unexplained RIF.

Materials and Methods

This prospective comparative study was carried out on 90 female patients aged <35 years old, with at least two implantation failures following IVF cycle and a high level of ovarian reserve (anti-mullerian hormone (AMH) > 1 ng/ml). The study was done from October 2020 to October 2023 after approval from the Ethical Committee. An informed written consent was obtained from the patients.

The exclusion criteria were patients with ovarian disorders: polycystic ovarian syndrome (PCOS), endometrioma or ovarian cyst, anatomical uterine pathology (uterine septum, polyp, arcuate uterus or bicornate uterus), diabetes mellitus, high blood pressure, autoimmune illnesses, suspected or confirmed hydrosalpinx, inherited, acquired thrombophilia, thyroid dysfunctions, and female genital tract infections are common reasons of implantation failure.

Patients were divided into three equal groups: Group A: subjected to instillation of the endometrial cavity with HCG. Intra-cavitary instillation of HGG was mediated immediately before ET in a dose of HGG (≤ 500 international unit). A HGG ampoule included 5000 international units, it was estimated for 500 international unit via the ET media (1 mL of tissue culture media) in the laboratory, Group B: had an endometrial scrape or damage. In the cycle before ET, the endometrium was scratched once, on day 21 of the menstrual cycle. The cervical OS was used to introduce a Novak curette, which was used to gently scrape the anterior and posterior endometrial walls and Group C: treated by intrauterine infusion of autologous PRP. Preparation of PRP was an office procedure that involved withdrawal of venous blood, preparation of the PRP, and then injection it intrauterine through ET catheter 48h before ET under ultrasound guidance.

A complete medical history, general and abdominal examination, along with a series of laboratory investigations (complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid stimulating hormone (TSH), prolactin, AMH, human chorionic gonadotropin (HCG), and gonadotropin-releasing hormone (GnRH)), and radiological investigations (ultrasound (US)) were performed on all patients.

All patients in all three groups were given 2 mg of Estradiol Valerate ("the white pills") (Cycloprogenova, Bayer Schering Pharma) daily from day 2 of menstrual flow until a positive pregnancy test was achieved at 12 weeks gestation in anticipation of ET. Pregnancy tests were given two weeks after ET, and if they were positive, an ultrasound was performed three weeks later to check for the presence of gestational sacs and confirm the heartbeat of the developing fetus.

Mechanism of intrauterine injection of human chorionic gonadotropin

It was done through the ET step of the whole procedure. One vial of HGG (Epifasi,5000 IU, EIPICO), the powder of the vial was presented in 1ml of culture media then incubated for several hours to be suitable for the embryo (one ample was enough for ten cases). ml of the culture media containing the HGG was taken through Insulin syringe connected to intrauterine insemination catheter. The intrauterine insemination (IUI) catheter was used for injection of the medication just before ET completed the whole procedure.

Preparation of PRP

It had been prepared as follows: the patient's arm was pricked, and 15-50 ml of venous blood was collected into an anticoagulant-containing tube. Platelet activation during blood centrifugation may be avoided by keeping the processing temperature between 21 and 24 degrees Celsius. Blood was centrifuged at 1200 rpm for 10 minutes to separate the red blood cells from the plasma. Again, centrifuging the fluid at 3300 rpm for 5 minutes yielded the plasma used to make the PRP, which has a platelet concentration around four to five times that of whole blood. It was time to inject the PRP. Roughly 3–5 milliliters (ml) of PRP may be extracted from almost 30 ml (ml) of venous blood; this is a concentration of platelets that is about 4-5 times greater than that seen in normal blood. The ET

catheter was used to inject around 0.5-1 ml of PRP directly into the uterus. The ET catheter was linked to the syringe containing the PRP, and the PRP was injected. After that, the remaining PRP was pushed in with the use of an air-filled syringe. When ultrasonography was performed, the air pockets were verified.

Procedure of the endometrial scratch

The scraping was performed in the middle of the luteal phase of a natural or hormonally controlled cycle. Scratching happened on the day that coincided with the LH surge as determined by urine ovulation tests (LH plus 5-8 day), the cycle day (5-10 days before the anticipated next menstruation), or the desired termination day of contraceptive treatment (5-10 days before the expected withdrawal bleeding). The patient was put in lithotomic position. A Casco speculum was used to examine the cervix. Vaginal and cervix hygiene were attended to using sterile saline. Then Novak curette was introduced through the cervical internal os up to the uterine cavity, about 1,5 cm below the fundus. Scratching the fundus and anterior wall then rotate it posterior for scratching the posterior wall by the serrated sharp border under guidance of ultrasonography.

In vitro fertilization cycle: GnRH agonist usage as standard practice (Initially, controlled ovarian stimulation causes the pituitary gland to produce follicle stimulating hormone (FSH) and LH, but with continued administration, the GnRH receptors are downregulated, resulting in little FSH and LH production and no LH surge.) Subcutaneous injections of (Decapeptyl 0.1mg/ml amp, Ferring) were started on day 21 of the menstrual cycle and continued daily until the HGG trigger day. By the time of the second day of menstruation, pituitary down regulation had been secured after GnRh agonist had been discontinued. The next menstrual cycles gonadotrophin therapy began on day two and lasted until the HGG trigger. At day 2 of menstrual cycle, ultrasonography done for assurance of absence of ovarian cyst and checking of endometrial thickness less than 6 mm). For criteria of pituitary suppression, LH<5 IU, FSH<5 IU and E2: 50-80. If down regulation of pituitary gland was not achieved, treatment was continued. And once down regulation was achieved injection of Decapeptyl decreased to the half dose and recombinant FSH (r-FSH) (GONAL-f, Merk-Sereno) was started.) Ovarian stimulation with urinary human menopausal gonadotropin (u-hMG) (Merional , IBSA) 75 IU ,and /or recombinant human follicle stimulating hormone hormone (r-hMG) (Gonal F , Merck) 75 IU , Adjustments to the stimulation dose were made based on the ovarian response, which was tracked via serum E2 levels and ultrasound of the antral follicular count (AFC) on day 6, until the criteria for HCG administration were reached. Every other day, ovulation was monitored through serum E2 analysis and transvaginal ultrasound to assess the thickness of the endometrium. Ovulation was triggered through aadministration of HGG (Choriomon, IBSA) 5,000-10,000 IU intramuscular (IM.) injection or (r-HCG) as (ovitrelle,serono) subcutaneous When there were 2 or more follicles greater than 18 mm in diameter.

Oocyte retrieval: Single lumen catheter oocyte extraction under general anesthesia and transvaginal ultrasound guidance was conducted 34:36 hours following HGG injection. Oocytes were retrieved, then treated with 5% co2 at 37 c for 3-4 hours, after which Metaphase II oocytes were examined. The ICSI method was used. The presence of two pronucleiad two polar bodies was used to determine fertilization 16 to 18 hours after ICSI. The score was used as a means of judging the quality of the embryos.

The patient was positioned in lithotomy for the embryo transfer. The cervix was exposed using Cusco's speculum, and mucus from the cervical canal was cleared with fresh gauze. A dummy embryo transfer was conducted with a rigid yet flexible catheter (Cook IVF). After the catheter passed through the internal cervical os, embryos were transferred into the uterine cavity under ultrasound guidance. The vaginal speculum was maintained for about 5 minutes, gently pressing on the cervix, before it was removed.

The primary outcomes were evaluation of serum estradiol level, day of HGG inducing endometrial thickening, >16mm follicle count, oocytes retrieved each cycle, number of oocytes fertilized, instances of ET and stimulation time period. The secondary outcomes were evaluation of CPR, OPR and MR.

Statistical analysis

The statistical analysis was performed using SPSS version 25 (IBM Inc., Chicago, IL, USA). The distribution of quantitative data was examined using the Shapiro-Wilks normality test and histograms to decide if parametric or nonparametric testing was needed. For comparing the three groups, the F test was utilized, with post hoc Tukey tests for pairwise comparisons. Parametric variables (e.g., age) were reported as a means with standard deviations. The paired T test was used to compare two independent variables within the same set of subjects. The Chi-square test calculated frequencies and percentages for categorical factors like gender. A P value below 0.05 was considered statistically significant.

Results:

Demographic data, clinical characters and basic hormonal profile were insignificantly different between studied groups. **Table 1**

Parameters used for following up during the duration of induction and IVF/ET cycle were insignificantly different between studied groups. **Table 2**

Cumulative pregnancy rates were insignificantly different between studied groups. **Table 3**

Discussion

Over the last two decades, researchers have looked at many strategies for improving pregnancy outcomes in instances of unexplained infertility (12).

In group A, the average duration of infertility was 4.04; in group B, it was 5.01; and in group C, it was 5.8. This time frame allowed for the completion of all standard infertility diagnostics, resulting in the diagnosis of unexplained implantation failure for these ladies. Our research classified cases of infertility into many categories. Group A women were found to have a 57% incidence of initial infertility and a 43% incidence of secondary infertility. There was no statistically significant difference between Group B and Group C, where 33% of couples had primary infertility and 67% experienced secondary infertility, respectively. Researchers, Safdarian et al. (13) found no significant differences between the groups.

None of the three groups showed a significant difference in the number of follicles larger than 16 mm as measured by AFC. Nonetheless, two to six follicles were seen throughout the board. The research also found no significant difference in the total number of oocyte retrievals performed among the three groups. In all three groups, the number of oocytes ranged from two to three.

There was no significant difference in endometrial thickness between the groups one day after HGG triggering. In addition, there was no discernible difference between the two therapies on a statistical level. This corroborated the findings of Ershadi et al. (14) found no significant differences in Endometrial thickness across the groups.

Group (A) had a 100% OPR after using intrauterine injections of 500 B-HCG, with a biochemical pregnancy rate of 63.3%, a CPR of 66.6%, and a 100% OPR (60 percent). When compared to previous studies, we discovered some consonance as well as some discordance. Like our study, Mansour et al. (15) found that both the CPR and the implantation rate were significantly greater in the HGG 500 group compared to the control group. Our findings are higher than the overall pregnancy rate, the biochemical pregnancy rate and the CPR.

In our study, 500 IU of HGG was given into patients after being diluted in normal saline. However, they used 105 examples, whereas we only had 10. (30 cases). Unlike our findings, their dose was inserted three days prior to embryo implantation. In our study, the dosage was implanted at the time of ET. Compared to the control group, the HCG group had a considerably higher CPR, implantation rate, and live birth rate. However, there was no change in the abortion rate, which was unexpected. Both the OPR and MR were 60%, while the biochemical pregnancy rate was 63% and the CPR was 66%, according to our findings (16).

Intrauterine injection of HGG prior to ET has been shown to improve IVF-ET outcomes, according to a review by MingXia Gao et al. (17) started with 500 IU instead of the whole range of 500, 700, and 1000 IU that was examined. Their OPR was 48.0%, whereas ours was 60%; their biochemical pregnancy rate was 31.64%, while ours was 63.33%. Additionally, Renwei Su et al. (9) showed that it did not have a major effect on endometrial receptivity, but did cause the expression of pre-decidual markers.

However, prospective clinical research assessing the effect of the B HGG injection on the incidence of clinical pregnancies was reported by Santibaez et al. (18) found a greater prevalence of clinical pregnancies and a lower percentage of biochemical pregnancies. The difference might be because of insufficient sample sizes. Pinxiu Huang et al. (19) found that the RIF case biochemical pregnancy rate was 49.02 percent, whereas ours was 63.3%. Their CPR rate was 48.05 percent, while ours was 48.9 percent.

Intrauterine injection of HGG with more than 500IU in certain groups and less than 500IU in other groups was discussed in a review study by Craciunas L et al. (20) for infertile women undergoing assisted reproduction.

In group (B), where a single endometrial scratch was performed on day 21 of the menstrual cycle prior to ET, we observed a biochemical pregnancy rate of 23.3%, a CPR of 20%, an OPR rate of 20%, and a miscarriage rate of 16.66%. Similarities and discrepancies between our study and previous research were noted. Consistent with our results, from an examination of medical records, Bernard et al. (21) showed that the time of the menstrual cycle in which endometrial injury is performed does not significantly impact the implantation rate. Implantation rates are significantly decreased when endometrial injuries exist at the time of oocyte retrieval, according to one study. In addition, Barash et al. (22) found that chemical pregnancy rate was 27%, their CPR was 66%, and their MR was 20%. Twenty-three-point three percent, twenty-point zero percent, and sixteen-point six percent were the variations observed in our research.

Performing an endometrial biopsy before to ART did not improve treatment results for individuals who were not pre-selected, according to a 2014 study by L. Polanski et al. (23) found that There was no significant difference between CPR groups in the rates of biochemical pregnancy and miscarriage in the first trimester. In addition, Cohen A et al. (24) employed a Novak curette, endometrial damage was conducted in the cycle before the index IVF cycle using an endometrial biopsy catheter. Clinical and OPR rates were similar across the two investigations (28% vs. 34% vs. 20%), with the researchers drawing this conclusion after analyzing the data.

Group (C) was treated with intrauterine injections of PRP to enhance endometrial implantation, as determined by our findings. PRP was prepared 48 hours before ET and injected intrauterine via the ET catheter under ultrasound guidance. The trial's outcomes were positive: 43.3% of pregnancies were confirmed biochemically, 30% were confirmed clinically, 30% were OPRs, and 33.3% of pregnancies ended in miscarriage.

During implantation, endometrial epithelial and stromal cells produce cytokines and GFs in response to HGG produced by pre-implantation embryos. These cytokines and GFs act locally to influence mechanisms like inflammation, invasion, differentiation, proliferation, and cell adhesion, as described by Srivastava et al. (25) PRP stimulation results in the production of a variety of cytokines and GFs that improve endometrial receptivity and, by extension, implantation rates. It is vital for the implantation process to maintain a balance between the inflammatory and anti-inflammatory responses, since an imbalance in either direction may result in disorders like RIF. Thus, it seems that anti-inflammatory chemicals like HGF may play a role in how PRP influences endometrial receptivity.

There was no significant difference between the frequency of chemical pregnancies in the experimental group (40%) and the frequency of chemical pregnancies in the control group (27%), according to a randomized clinical trial conducted by Ershadi et al. (14) found that the prevalence of clinical pregnancy did not vary significantly between the two groups, with 33% in the experimental group and 24% in the control group. Among the study's experimental participants, 31.25 percent had abortions, whereas only 10.75 percent of the control group did (8.33 percent). Basirat et al. (26) found that their chemical, clinical, and OPR rates were 13.35%, 3.3%, and 3.3%, respectively, while ours were 23.33%, 205, and 20%.

Refractory thin endometrium is a common problem throughout the frozen ET cycle, and Kim et al. (27) found that there were no significant differences in the number of high-quality embryos and the general population in terms of age, body mass index, or the number of embryo transplants

Limitations of the study included that the sample size is rather modest. Because it was conducted at only one location, the findings may not generalize. We left out randomized controlled trials.

Conclusions:

When comparing biochemical pregnancy rates, medical pregnancy, spontaneous abortion, and miscarriage amongst the three methods, we did not find any significant differences.

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Table 1: Demographic data, clinical characters and basic hormonal profile of the studied groups

		Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P
Age (years)		31.9± 2.24	30.93 ±2.58	31.56 ±2.11	0.264
BMI (Kg/m²)		27.02 ±2.2	27.8± 1.35	26.95 ±1.23	0.092
Duration of infertility (years)		2-10	3-8	2-9	0.069
Type of infertility N (%)	**Primary**	17(57.0%)	15(50.0%)	10(33.0%)	0.175
	Secondary	13(43.0%)	15(50.0%)	20(67.0%)	
Basic hormonal profile					
AMH (ng/ml)		2.20± 0.40	2.01± 0.56	1.98± 0.49	0.172
FSH (mIU/ml)		7.39± 1.62	7.21± 1.48	7.72± 1.37	0.407
LH (mIU/ml)		7.94± 2.70	7.59± 2.53	8.22± 2.26	0.31
E2(Basal) (pg/ml)		33.4± 9.56	36.53 ±8.35	33.52 ±6.86	0.905
TSH (mIU/ml)		1.95± 0.605	2.293 ±0.70	2.8±0.58	0.259
Prolactin (ng/ml)		13.56 ±4.14	12.16 ±3.82	11.51 ±3.71	0.120

Data are presented as mean ± SD or frequency (%) or range. BMI: body mass index, AMH: anti-mullerian hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, TSH: thyroid stimulating hormone.

Table 2: Parameters used for following up of the patient during the duration of induction and IVF/ET cycle

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P
Duration of induction				
AFC	11.5±0.86	11.96±1.58	11.96±1.79	0.368
Number of follicles >16 mm during induction (for both ovaries)	8.03±0.85	8.67±0.84	8.47±1.46	0.076
Endometrial thickness at day of HGG triggering (mm)	8.67±0.46	8.8±0.81	8.73±0.87	0.790
IVF/ET cycle				
Number of oocyte retrieval	7.17±0.83	7.43±0.5	7.17±0.95	0.320
Number of oocytes fertilized	6.1±0.99	6.37±0.85	6.2±1.1	0.5728
Number of ET	2.03±0.18	1.87±0.35	1.87±0.35	0.062
Duration of stimulation (days)	11.37±1	11.27±1.17	11.47±1.11	0.779

Data are presented as mean ± SD. AFC: antral follicular count, HGG: human chorionic gonadotropin, IVF: in vitro fertilization, ET: embryo transfer.

Table 3: Cumulative pregnancy rates in the three studied groups

		Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P
Biochemical Pregnancy rate	**Positive**	9(30.0%)	9(30.0%)	11(36.5%)	0.815
	Negative	21(70.0%)	21(70.0%)	19(63.5%)	
CPR	**Positive**	7(23.3%)	6(30.0%)	10(33.33%)	0.468
	Negative	23(76.66%)	24(30.0%)	20(66.66%)	
Ongoing pregnancy rate	**Positive**	6(30.0%)	4(13.33%)	7(23.3%)	0.601
	Negative	24(80.0%)	26(86.66%)	23(76.66%)	
Miscarriage rate (related to clinical rate)	**Positive**	1(3.33%)	1(3.33%)	2(6.66%)	0.952
	Negative	6(30.0%)	5(16.66%)	8(26.66%)	

Data is presented as frequency (%). CPR: clinical pregnancy rate.