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Effects of Intrauterine Human Chorionic Gonadotropin on Endometrial Receptivity in Intracytoplasmic Sperm Injection Cycle

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ABSTRACT

Background: Human chorionic gonadotropin (hCG) is one of the chief embryonic signals in primates. It modifies the uterine environment, encourages uterine receptivity, and plays a key role in embryo implantation.
Objectives: To determine the impact of intrauterine infusion of hCG at day of ovum pickup on the endometrial receptivity using ultrasound measurement of endometrial thickness and sub-endometrial blood flow indices like resistance index (RI), pulsatility index (PI), and systole/diastole (S/D) ratio, and on improvement of intra-cytoplasmic sperm injection (ICSI) outcome.
Materials and methods: This comparative study included 90 infertile females from the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Baghdad, Iraq. The patients were randomly classified into three groups: Group A (30 women received intrauterine insemination of 700 IU hCG); Group B (30 women received 500 IU hCG); and Group C (30 women received no intervention). Ultrasound examination and assessment of plasma hormone level on cycle days 2–3 were done for all patients like follicle stimulating hormone, luteinizing hormone, estradiol E2, prolactin, and thyroid stimulating hormone. Embryo transfer, luteal support, and serum beta-hCG on day 14 after embryo transfer were performed, and the pregnancy rate was registered.
Results: Group A had significantly lower means for the RI, PI, and S/D ratio than groups B and C (P-value = 0.001, 0.002, and 0.027, respectively). Group A had a significantly higher pregnancy rate (P-value = 0.035) than group C. However, there was no significant difference between groups A and B (P-value > 0.05).
Conclusion: Infusion of 700 IU hCG can improve sub-endometrial blood flow by reducing the RI and PI. These effects will improve the pregnancy rate in patients undergoing the ICSI cycle.
Keywords: Implantation; Endometrial receptivity; Human Chorionic Gonadotropin; Intracytoplasmic Sperm Injection Cycle.

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INTRODUCTION

Implantation is a highly organized process that involves an interaction between a receptive uterus and a competent blastocyst. In humans, once the conceptus enters the uterine cavity, the blastocyst must fully hatch from the zona pellucida in order for implantation to take place. Human blastocysts often implant in the endometrium close to the fundus along the uterine wall, either anteriorly or posteriorly [1]. Decidualization occurs when the uterine stromal cells around the spiral arteries change to become bigger, rounder cells to make room for the embryo [2]. The outer trophoblast cells start to differentiate just before implantation, enabling complete implantation to take place in week 2 of development. The processes of adhesion/attachment, invasion, apposition, and immune system control are essential to the implantation process. Implantation window refers to this particular state, which is known for its temporal and spatial uniqueness. It

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often manifests itself on the 20th to 23rd day of the menstrual cycle [3].

The fate of the embryo is largely determined by the expression of endometrial growth factors and cytokines in the mother and the developing embryo. One of the main signals during fetal development in primates is chorionic gonadotropin (CG), which alters the uterine environment and promotes uterine receptivity. CG is the name of a heterodimeric glycoprotein hormone. Numerous investigations have demonstrated the direct involvement of CG on endometrial receptivity via altering the stromal and epithelial cells. It directly regulates α-smooth muscle actin (α-SMA) in stromal cells; this control allows decidualization to occur while halting stromal cell apoptosis [4]. It was proved that the embryo produces its first unique chemical human CG (hCG) as early as the eighth cell stage. hCG ribonucleic acid (RNA) is transcribed, and the blastocyst makes the protein before implantation. The luteinizing hormone/choriogonadotropin receptor (LHCGR), which is found on the surface of the endometrium, binds to hCG in the uterus. This binding increases the synthesis of leukemia inhibitory factor (LIF) and decreases the production of interleukin-6 (IL-6) by endometrial epithelial cells. During the invasion of the uterine endometrium, hCG gives the placenta an appropriate maternal blood supply and optimal embryonic nourishment by inducing angiogenesis and vasculogenesis. The cytokine profile that the endometrium expresses may be affected by the injection of human growth hormone. In endometrial stromal cells, hCG either directly or indirectly affects the genetic expression of several cytokines involved in cell signaling, proliferation, apoptosis, immunological regulation, tissue remodeling, and angiogenesis [5]. Several endometrial, fetal, and embryo transfer technique-related factors affect the rate of embryo implantation. Factors impacting endometrial acceptance are critical to optimizing implantation since a functional and receptive endometrium is necessary for successful implantation. The endometrium expresses several genes that facilitate implantation [6]. hCG interacts with uterine natural killer cells (uNKs), which are involved in the remodeling of spiral arteries, an essential vascular alteration for the placenta's vascularization, which ensures that the fetus will receive an adequate supply. Since these cells (uNKs) do not express LHCGR, hCG would interact with them directly by binding to the mannose receptor, which is expressed by the uNK. Additionally, uNKs release proangiogenic factors like vascular endothelial growth factor (VEGF) family members [7].

Ultrasonography (USG) is a diagnostic and follow-up tool for female infertility. It has grown to be one of the most useful diagnostic techniques in the world of reproductive medicine. It is used not only for follicle monitoring but also for assessing endometrial receptivity [8]. Ultrasonic markers such as endometrial thickness, volume, echo, peristalsis, blood flow, etc. can be used to assess endometrial receptivity [9]. An increasing number of studies have demonstrated the critical role that endometrial blood flow plays in embryo implantation. Not only does blood flow occur within the endometrium, but it also occurs beneath it. It is possible to identify the blood flow through the endometrium and sub-endometrium using a three-dimensional Doppler ultrasound [10].

Assisted reproductive technology (ART) has been widely used since the first child was born in 1778. ART is an essential treatment for many infertile couples to help them become pregnant. ART causes about 40% of pregnancies. Either maternal or embryonic factors can contribute to implantation failure. Thrombophilia, immunological factors, non-receptive endometrium, and anomalies of the uterus' anatomy are examples of maternal factors. Implantation failure due to embryonic causes is associated with genetic flaws or other characteristics of the embryo that affect its capacity to grow in utero, hatch, and implant [11]. Nearly one-third of implantation failures are due to fetal factors, with the other two-thirds being due to endometrial causes. Numerous adjuvant therapies, including immunomodulators, angiogenesis regulators, antioxidants, and hormonal supplements of estradiol, have been used to increase endometrial receptivity. Intrauterine infusions of hCG, autologous peripheral blood mononuclear cells (PBMCs), granulocyte colony-stimulating factor (G-CSF), or platelet-rich plasma (PRP) could be used to treat recurrent implantation failure (RIF), but it's not clear how well they work. These treatments have been demonstrated to enhance embryo implantation and pregnancy outcomes [12]. This study aims to look at how hCG influences endometrial receptivity ultrasonography measurements and prove its beneficial effects on pregnancy and implantation rate.

MATERIALS AND METHODS

This prospective comparative clinical study was conducted between January 2023 and January 2024 at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq. The institute's Local Medical Ethical Committee dated September 9, 2022, with reference number 0701-PF-2022O10, approved the study. Informed consent was obtained from each infertile woman enrolled in the study. Women undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) procedures should possess a grade 1 (G1) embryo, and the age of participants ranged from 18 to 40 years, infertility arose from female factors, including blocked fallopian tubes, lack of ovulation, and unexplained infertility, and male-related factors that contributed to infertility were enrolled in the current study. Additionally, each participant must have at least one embryo of G1 for transfer during a fresh cycle. However, women with chronic systemic conditions (such as diabetes mellitus, hematologic disorders, and thyroid disorders), age $>$ 40 years, endometrioses whether clinically suspected or discovered during laparoscopy, individuals who do not possess G1 embryos, morbid obesity, and congenital abnormalities in the reproductive system were excluded from the study.

The sample size was calculated with this equation: $N = P\ (1\text{-}P)\ Z^2/Me^2$ where P is the prevalence rate of infertile women (12%) according to a previous study [13], Z = 1.96, and Me = 0.05. The required sample size was 162. However, during the studied period, only 119 cases were recruited. Twenty-nine women were excluded; therefore, the remaining studied sample was 90 (Figure 1).

Thirty women were randomly (randomization based on a single sequence of random assignments) assigned to each of the following 3 groups (Figure 1): Group A received intrauterine insemination of 700 IU of urinary hCG (Diclair®-HP) on the day of ova pickup; group B received 500 IU of hCG; and group C received no intervention. Because most previous studies used either a dose of 500 IU [14] or a higher dose of 1000 IU of intrauterine hCG insemination [15], we designed this study to evaluate the effects of two different doses of intrauterine injection of hCG prior to embryo transfer in an IVF or ICSI cycle on the pregnancy rate in comparison with control. A comprehensive medical, surgical, and

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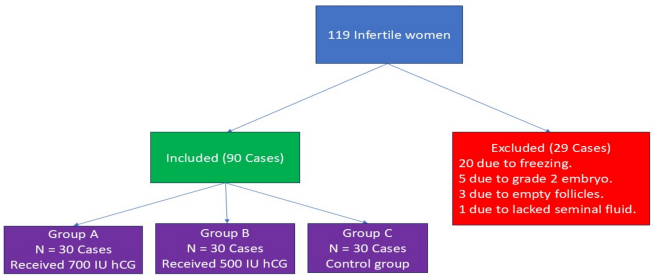

Figure 1. Flow chart of the studied infertile women.

obstetrical history was gathered from couples experiencing infertility. Thorough examinations were conducted on infertile women, encompassing both general and gynecological assessments.

Assessment of plasma hormone level on cycle day 2 or 3 was done on all participants, like follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol E2, prolactin, and thyroid stimulating hormone (TSH). Transvaginal ultrasound, saline infusion sonography (SIS), and hysterosalpingography (HSG) were carried out to evaluate the uterine cavity and confirm tubal patency.

All participants underwent controlled ovarian hyperstimulation using r-FSH (Gonaf-F R, Merk-Serono/Switzerland). The r-FSH administration commenced on the second day of the menstrual cycle, with or without human menopausal gonadotropin (HMG) (Menogone R., Ferring, GmbH/ Germany). The starting dose of GnT was 150 IU-450 IU, depending on age, weight, ovarian reserve, and other factors. A flexible antagonist protocol for ovulation induction was used. Ultrasound assessment of resistance index (RI), pulsatility index (PI), and systole/diastole (S/D) ratio was carried out using the equipment located within the operating theatre of the institute (Versana Balance, gE medical device, China). Each patient was examined twice by the same device and same examiner, first on the day of ova pickup and second exam on the day of embryo transfer. Before the utilization of the ultrasound machine, patients were positioned in the dorsal lithotomy posture with an empty bladder. A comprehensive visualization of the mid-sagittal plane of the uterus was achieved to generate a multiplanar display. After the patient voided her bladder fully, the endometrial thickness of the uterus was assessed as the maximal distance spanning from one basal endometrial interface through the endometrial canal to the opposing endometrial-myometrial interface. A study on blood flow was carried out utilizing a pulsed doppler device in accordance with the B-mode examination. Subendometrial arteries were observed at the perimeter of the endometrium, with instances where they extended towards the endometrial cavity or the hyperechogenic endometrial edge. By activating the pulsed doppler feature and placing the doppler gate on the colored region at zone 2, it became feasible to capture the velocity waveforms of blood flow from the subendometrial arteries [16]. Evaluation of oocytes was performed, and the maturation rate was documented. Fertilization as well as embryo morphology and the number of various embryo grades were determined. Luteal phase support, embryo transfer, and serum beta-hCG performed on day 14 after embryo transfer were all reported.

Height and weight measurements were used to determine body mass index (BMI = Weight per Kg/Height per m^2). The patients were categorized into four groups according to the BMI: Underweight (< 18.5 Kg/m^2), normal-weighted (18.5–24.9 Kg/m^2), over-weighted (> 24.9–< 30 Kg/m^2), and obese (≥ 30 Kg/m^2). According to age, they were subclassified into 3 groups (< 25 years, 25–34 years, and ≥ 35 years).

The data were analyzed using the statistical package for social sciences (SPSS) version 26. Continuous variables were presented as mean, standard deviation, and ranges. Categorical data were presented by frequencies and percentages. An independent t-test and Analysis of Variance (ANOVA) (two-tailed) were used to compare the continuous variables accordingly. A paired t-test was used to compare the continuous variables on pickup day and transfer day. The Chi-square test was used to assess the association between categorical variables, while the Fisher exact test was used instead when the expected frequency was less than 5. A level of P-value less than 0.05 was considered a statistically significant difference.

RESULTS

The mean age of the infertile women was 30.34 ± 5.4 years (age range of 18 to 40 years). The mean of the BMI was 26.9 ± 0.17 Kg/m^2. There were no statistically significant differences (P-value > 0.05) regarding age and BMI among the studied groups (Table 1).

There were no statistically significant differences (P-value > 0.05) among the studied groups regarding all baseline hormonal levels (Table 2).

The mean of the S/D ratio was significantly lower (P-value $= 0.008$) in group C than in groups A and B. There were no statistically significant differences among the studied groups (P-value > 0.05) in the means of all other parameters (Table 3).

The means of RI, PI, and S/D were significantly lower (P-value < 0.05) in group A than those in groups B and C. There were no statistically significant differences in the studied groups (P-value > 0.05) in means of all other parameters (Table 4).

As shown in Table 5, 53.3% of women in Group A got pregnant, while 40% in Group B and 26.7% of women in Group C, and this difference was statistically significant (P-value $=$ 0.035). There were no statistically significant differences in the ICSI cycle outcome (P-value > 0.05) between groups A and B or between groups B and C.

DISCUSSION

A functional and receptive endometrium is necessary for successful implantation, which depends on a number of factors. Key among these are sex steroids that regulate the expression of growth factors, cytokines, and chemokines in the endometrium. Cytokines are very important for implantation. Type 1 cytokines, like IL-17, IL-1β, TNF-α, and INF-γ, cause inflammation, while type 2 cytokines, like IL-10, IL-4, and IL-1ra, balance this response. A physiological balance between these two types of cytokines is essential for successful implantation. The main outcomes of the current study were that hCG improves endometrial receptivity and pregnancy rate in infertile women undergoing ICSI.

There was no significant difference in the mean age between the study groups. In a prospective study like this, it is important to avoid bias in ICSI outcomes that could arise from substantial age differences between the groups. Previous studies have shown that age is a key factor in determining a woman's

Table 1. Distribution of the 90 infertile women according to age and BMI.*

Variable	Study group			Total	P-value*
	A n = 30(%)	B n = 30(%)	C n = 30(%)	n = 90(%)	
Age (Year)					
< 25	5 (16.7)	4 (13.3)	4 (13.3)	13 (14.4)	
25 – 34	17 (56.7)	21 (70.0)	18 (60.0)	56 (62.2)	0.831
≥ 35	8 (26.7)	5 (16.7)	8 (26.7)	21 (23.4)	
BMI Level Kg/m^2					
Normal	4 (13.3)	9 (30.0)	5 (16.7)	18 (20.0)	
Overweight	20 (66.7)	13 (43.3)	18 (60.0)	51 (56.7)	0.386
Obese	6 (20.0)	8 (26.7)	7 (23.3)	21 (23.3)	

* Chi-square test (χ^2) was used, BMI: body mass index.

Table 2. Comparison of baseline hormonal parameters among the studied groups.*

Hormonal parameter	Study group			P-value*
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
FSH (IU/L)	6.13 ± 1.7	6.07 ± 2.8	6.68 ± 2.2	0.521
LH (IU/L)	4.22 ± 2.2	4.64 ± 3.5	4.14 ± 2.3	0.747
TSH (mIU/L)	2.0 ± 0.8	2.23 ± 1.0	2.03 ± 0.6	0.494
Prolactin (μg/L)	19.59 ± 10.3	18.86 ± 9.0	17.81 ± 5.1	0.713
Estradiol (pg/mL)	37.34 ± 12.2	42.99 ± 17.1	33.98 ± 11.5	0.059

* ANOVA test (two-tailed) was used, FSH: follicle stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone.

Table 3. Comparison in means of hormones, ultrasound (US) findings among the studied groups at day of ovum pick-up.*

Variable at day of ovum pick-up	Study group			P-value*
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
Hormonal parameter				
Estradiol (pg/mL)	1097.3 ± 650.8	1249.3 ± 707.3	1056.1 ± 426.0	0.44
Doppler U/S finding				
Endometrial thickness (mm)	8.8 ± 2.0	9.0 ± 1.5	8.62 ± 1.3	0.693
Resistance Index	0.49 ± 0.06	0.51 ± 0.08	0.5 ± 0.05	0.536
Pulsatile Index	0.8 ± 0.14	0.85 ± 0.22	0.79 ± 0.16	0.379
S/D	2.05 ± 0.3	2.3 ± 0.5	2.01 ± 0.3	0.008

* ANOVA test (two tailed) was used, SD, standard deviation, S/D: systole/diastole.

chances of becoming pregnant [17]. Age has long been recognized as one of the most significant predictors of fertility. Reproductive therapy may now be considered by one in six couples, as the average age of conception has increased from 29.4 to 32.8 years. This shift is largely due to factors such as decreased oocyte quality, ovulatory dysfunction, and conditions that affect the reproductive system, including tubal diseases, endometriosis, and leiomyomas. As women age, the number and quality of their oocytes decline, leading to reduced fertility, which in turn impacts the success of IVF in achieving pregnancy [18].

Statistically matching the mean BMI between the three groups is crucial to avoid bias in ICSI outcomes. The lack of significant variation in mean BMI across the groups helps minimize this bias, as BMI is considered an important predictor of pregnancy success in infertile women. High BMI is known to have negative impacts on overall health, and these effects extend to reproduction, potentially causing menstrual disorders and infertility [19]. The reduced fertility observed in obese women is likely due to multiple factors, including disruptions in endocrine and metabolic functions, which can affect follicular growth, implantation, and the ability to achieve pregnancy [20].

This study suggests that hCG may improve endometrial thickness, though the difference is not statistically significant. Group A showed the greatest thickness compared to the other groups. This might be due to the influence of hCG, which has been shown to regulate uNK cell growth in vitro [8]. While

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Table 4. Comparison in means of ultrasound (US) finding among the studied groups at the day of transfer.*

Variables	Study group			P-value*
	A Mean ± SD	B Mean ± SD	C Mean ± SD	
Doppler U/S finding				
Endometrial thickness (mm)	10.72 ± 2.6	10.37 ± 3.4	9.71 ± 1.7	0.338
Resistance Index	0.42 ± 0.07	0.48 ± 0.1	0.5 ± 0.07	0.001
Pulsatile Index	0.64 ± 0.21	0.82 ± 0.25	0.78 ± 0.13	0.002
S/D	1.87 ± 0.3	2.21 ± 0.8	1.92 ± 0.3	0.027

* ANOVA test (two tailed) was used, SD: standard deviation, S/D: systole/diastole.

Table 5. Comparison in the intracytoplasmic sperm injection (ICSI) cycle outcome among the studied groups.*

Study group	ICSI cycle outcome		Total	P-value*
	Pregnant N (%), n = 36	Not pregnant N (%), n = 54	N (%), n = 90	
	n = 28	n = 32	n = 60	
A	16 (53.3)	14 (46.7)	30 (50.0)	0.3
B	12 (40.0)	18 (60.0)	30 (50.0)	
	n = 24	n = 36	n = 60	
A	16 (53.3)	14 (46.7)	30 (50.0)	0.035
C	8 (26.7)	22 (73.3)	30 (50.0)	
	n = 20	n = 40	n = 60	
B	12 (40.0)	18 (60.0)	30 (50.0)	0.273
C	8 (26.7)	22 (73.3)	30 (50.0)	

* Chi-square test (χ^2) was used.

endometrial thickness (EMT) is considered a valuable indicator for predicting pregnancy outcomes, its effectiveness as a predictor remains uncertain. A positive correlation between pregnancy rate and EMT has been observed [21]. According to a prior study, which supports the current study, EMT cannot be used to predict the result of IVF in terms of the occurrence of pregnancy [22]. Using EMT as a tool to decide on cycle cancellation, freezing of all embryos, or refraining from further IVF treatment seems not to be justified based on the current meta-analysis [22]. Further research is needed to investigate the real independent significance of EMT in IVF [23]. The PI and sub-endometrial RI showed no significant differences among all patients on the day of ovum pickup. However, on the day of embryo transfer, group A, which received 700 IU of hCG, had significantly lower sub-endometrial RI and PI compared to groups B and C. Wang et al. (2024) observed that increasing the concentration and exposure duration of hCG improved the viability of endometrial stromal cells (ESCs), supporting the notion that both the level and duration of hCG exposure are crucial factors affecting its activity. After 72 hours of hCG treatment, ESC viability and proliferation were maximized [24]. In the current study, after two to three days of hCG administration, changes in sub-endometrial blood flow were noted. The sub-endometrial RI and PI were significantly lower in group A, which received 700 IU of intrauterine hCG, compared to the other two groups.

The findings of this study also indicate that intrauterine hCG infusion increases pregnancy rates, with rates of 53.3% in group A (700 IU hCG), 40% in group B (500 IU hCG), and 26.7% in group C (control group). A significant statistical difference (P-value = 0.035) was observed between groups A and C. These results align with previous research showing that hCG regulates the continuous production of progesterone in the corpus luteum, which is essential for sustaining pregnancy [25]. Moreover, hCG reduces intrauterine insulin-like growth factor β-1, and increases matrix metalloproteinase, VEGF, and leukocyte inhibition factor, all of which contribute to improved ICSI outcomes [26]. More research is needed on this subject.

The present investigation was limited by its single-center and small sample size, therefore; we were unable to globalize its result. The probability of sampling bias is not uncommon because there is no documented data related to the size of the required population. Notably, another limitation of our study is that a regional bias could not be excluded. The use of various culture media for intrauterine injection across trials may be another limitation.

CONCLUSION

On the day of ova pickup, a selective intrauterine infusion of 700 IU of hCG can enhance sub-endometrial blood flow by lowering the PI and RI. Thus, it will enhance the pregnancy rate in infertile women following the ICSI cycle. However, it is recommended to repeat the study on a larger sample size and from multiple centers to confirm the results of the present study.

ETHICAL DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

The Local Medical Ethical Committee of the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, Baghdad, Iraq (0701-PF-2022O10) issued ethical approval for the current study on September 9, 2022. Informed consent was obtained from each participant.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data generated during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All stated authors contributed significantly, directly, and intellectually to the work and consented to it being published.

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