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Effect of intrauterine flushing of human chorionic gonadotropin prior to intrauterine insemination in sub fertile women on clinical pregnancy rate, comparative study

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Abstract
Background: Intrauterine Insemination (IUI) that is the simplest form of ART remains widely used and affordable treatment for infertility among the populations of developing countries. However, implantation still plays an important role which determines the success rates of IUI or IVF cycles. Implantation outcome is dependent on quality of the embryo, quality of the endometrium, and quality at the level of maternal-fetal interface. To improve implantation and therefore subsequently the CPR various strategies have been investigated including targeting of different local embryonal signals. For example, implantation has been studied with the help of autologous platelet-rich plasma (PRP) that is introduced via intrauterine infusion (IUIF). There is perhaps no other signal as important and as widely acknowledged as hCG or human chorionic gonadotropin.
Aim of study: The objective of this study was to assess if the use of hCG with a concentration of 1000 IU in the process of flushing before the IUI procedure will improve the pregnancy rate in sub fertile women who are candidates for IUI treatment.
Material and Methods: In the period from November 2020 to May 2022, an empirical research was performed among 140 women with infertility problems and receiving treatment in a private clinic. These women agreed to be subjected into ovarian stimulation according to their response and were booked for intrauterine insemination (IUI) treatment at the clinic. It was possible to monitor the follicles using a special ultrasound and as soon as the largest follicle considered to be 17-19 mm, subcutaneous hCG was prescribed to encourage ovulation. The ladies of both groups underwent IUI treatment 36-38 hours after the hCG injection; ultrasound confirmed that ovulation had occurred. The women of study included in this analysis received either hCG 1000 IU gently flushed (for 3-5 minutes) through the IUI catheter for 70 of the women or no intervention for the control population.
Results: The results of the study suggest that there were no significant variations in the initial traits, reasons for undergoing IUI, fundamental menstrual cycle traits, and ovarian stimulation traits between the study group and the control group. However, there was a significant distinction between the two groups in terms of the causes of infertility, progesterone levels on the day of trigger, as well as the biochemical and clinical pregnancy rates.
Conclusion: The application of human chorionic gonadotropin (hCG) directly into the endometrial lining within 3-5 minutes before intrauterine insemination (IUI) can increase both biochemical and clinical pregnancy rates in IUI cycles, according to research.

Keywords: IUI, hCG, endometrial flushing, pregnancy rate, infertility

Introduction
Intrauterine Insemination (IUI) is the simplest procedure and affordable to couples facing infertility in developing nations. Just like IVF, ICSI is an ART that can be employed wherever there are male and female factor infertility problems. It is suggested when the male partner suffers from low sperm count or poor sperm quality, ejaculation failure or even when the female partner may suffer from cervical hostility, endometriosis or unexplained subfertility [1].
The available evidence shows that the rate of IUI and IVF cycles is limited by the implantation process. Some of the factors include the quality of an embryo, receptivity of the endometrium and contact that is afforded between the endometrium and the embryo during the implantation process. A process known as implantation that include hatching, attachment,

adhesion, penetration and finally invasion of the synchronized endometrium by blastocyst. These steps are mediated by ovarian steroid hormones, fetal derived factors, local autocrine paracrine factors [1, 2, 3, 4, 5]. These signals act in concert during a distinct period that is referred to as the window of implantation which is the time at which the endometrial environment is well-suited to supporting efficient blastocyst implantation [6, 7].

Clinically the implantation and pregnancy success rate has been pursued employing various techniques by manipulating the cues regulating implantation and embryonal signals in the surrounding microenvironment. Among these, one of them was the intrauterine injection of freshly prepared, autologous platelet rich plasma (PRP) into the patients during IUI cycles [8]. The embryo's main signals materials before implantation is known as human chorionic gonadotropin or hCG. Endometrial microdialysis was used by Licht *et al*., by giving intrauterine small doses of hCG (500 IU) to the endometrium during the luteal phase for the first effectiveness record in 1998 [9,10]. The previous studies have shown that hCG enhances implantation through a direct effect to the endometrium. In order to achieve this, it is possible to promote trophoblast invasion and also induced endometrial stromal decidual cells to stimulate the growth of uterine natural killer cells, changes immune response at the fetomaternal crosstalk and caused change that brought about angiogenesis of uterine endometrium and most importantly ensure the secretion of progesterone by the corpus luteum [11, 12, 13].

During the two-cell stage before implantation to the uterus, embryos emit the hormone hCG. The endometrial epithelial cells secrete hCG also during the luteal phase. There is a correlation between the structure of the embryo and the amount of hCG production. Small amounts of hCG produced by early poor-quality embryos affect endometrial cells' capability to be attracted or 'pulled' to the blastocyst [3].

In IVF cycles, the implantation and clinical pregnancy can be enhanced by hCG administration to the endometrium before the transfer of embryos at the cleavage stage, as reported by researches of Mansour, Santibaez, and Zarei [1, 14, 15]. On the other hand, the direct administration of hCG to the uterus before the transfer of blastocysts, was reported by Hong *et al.*, and Wireline *et al*., to have no additional added benefits [16,17].

The only window through which hCG could influence the endometrium before implantation could be of no additional benefit through injection facilitating poor implantation before blastocyst transfer. To address this limitation, Navali *et al*., attempted to determine the consequences of administering hCG intra-uterine after oocyte retrieval in IVF cycles. Which revealed results that both implantation rate and CPRs had significantly risen (clinical pregnancy rates) [18].

The purpose of this work was: to evaluate whether the positive outcome of administration of intrauterine hCG in IVF cycles expected that it would be similarly effective in IUI cycles. It was also projected that intrauterine hCG before IUI may have similar favorable effect to that of implantation as evidenced by IVF cycles.

Aims of Study

This Study sought to evaluate the effect of giving intrauterine hCG before IUI on the CPR.

Patients, Materials and Methods

This study was conducted as a randomized prospective clinical trial comparative study at a private clinic in Waist, over the time period from November 2020 to May 2022.

In this study, 140 sub fertile couples who were enrolled for IUI at the private clinic in Waist were included. All the couples who were experiencing infertility underwent a comprehensive assessment, which included obtaining a complete medical history, conducting general and gynecological examinations, and performing a full range of infertility investigations. In these investigations, the husband's semen was examined for quality, hormonal profile information from the early follicular phase was collected, trans-vaginal ultrasound was performed, hysterosalpingography was done to evaluate the uterine cavity and the patency of the fallopian tubes, and laparoscopy was done to evaluate tubal patency and rule out any pelvic abnormalities.

All the patients in the research were given counselling and were required to provide written consent before they were included in the study based on their agreement and meeting the inclusion criteria.

To be eligible for enrolment in the study, female participants had to be between the ages of 18 and 44, have at least one patent fallopian tube, and have a BMI between 18 and 40 kg/m2. Male partners were also included in the study if they had a normal or subnormal semen analysis. Additionally, female participants were required to have normal thyroid function test results and normal blood sugar levels.

The 140 females who were experiencing infertility were randomly selected and divided into two groups, as illustrated in Figure 1.

- **Group A:** The control group included 70 infertile women who had IUI without flushing human chorionic gonadotropin into the endometrium and received routine ovarian stimulation with letrozole and/or gonadotropins.
- **Group B:** The research group included 70 infertile women who had IUI with the flushing of human chorionic gonadotropin into the endometrium and received routine ovarian stimulation with letrozole and/or gonadotropins. Three to five minutes prior to the IUI process, a 1000 IU dosage of human chorionic gonadotropin flushing was administered.

Starting on the third day of the menstrual cycle, Letrozole tablets (Letro-Denk; Denk Pharma, Germany) were administered twice per day for a period of five days. Recombinant FSH from Folisurge-PFS by INTAS, India, was administered from the fifth day of the menstrual cycle at a dosage of 75 IU per vial, which was adjusted depending on the patient's response. Transvaginal scanning using the Philips iU22 ultrasound machine, scans were used to measure the number, size of follicles, and to track the development of follicles and thickness of the endometrial lining. To trigger ovulation, a dose of 5000 IU/vial of highly purified human chorionic gonadotropin (hCG) (Ovunal SC 5000; INTAS, India) was administered subcutaneously on day 12 or 13, when at least one follicle had reached a size of 17 mm, with the dominant follicle size between 17-23 mm.

During IUI, women in group B were positioned in a lithotomy posture, and the uterine cervix was visualized using a vaginal speculum. Without using a volusellum, an intrauterine insemination cannula was introduced into the

uterine cavity through the cervical canal after excess vaginal and cervical secretions had been wiped away with sterile gauze. Afterwards, without using any medicine, 0.5 mL of hCG solution containing 1000 IU of hCG was injected intrauterine through the cannula. This solution was created by diluting a 5000 IU hCG vial with 2.5 mL of sterile saline. 3-5 minutes following the endometrial hCG flush, the females were then ready for IUI. The luteal phase was supported post-IUI with vaginal progesterone suppositories (400 mg twice daily). A serum ß-HCG test was performed on day 14 after IUI**.** For the woman who later had a positive result, an ultrasound was done to objectively determine if there were 1 or 2 gestational sacs, which are indicative of clinical pregnancy [19]. The data was analyzed by the Statistical Package for Social Sciences (SPSS) version 22.0. ANOVA, independent sample t-tests, chi square and Fishers exact tests. The findings were considered statistically significant whenever the *p* value was equal or less than 0.05.

Results

The demographic characteristics of the study participants in the control Group (A) and the trial Group (B) were compared, and it was found that there were no significant differences between the two groups, except for the causes of subfertility (as indicated in Table 1).

The mean age was (30.85 ±5.80;31.8± 6.26) years for group A and B respectively with (p=0.883). The mean body mass index was (26.07± 3.74 ; 26.34 ± 3.40) for group A and B respectively with (p= 0.758) as shown in (table 1).

The percentage of primary infertility were (30 (43%); 42 (60.0%)) for group A and B respectively, while for secondary subfertility were (40 (57%);28 (40.0%)) for group A and B respectively with(p=0.156) as shown in (table 1).

The mean duration of infertility was (6.37±3.29; 6.86±3.84) in group A and B respectively with (p= 0.572) as shown in (table 1).

Regarding the reasons of infertility, there were substantial variations between the two groups of women. As shown in Table 1, the male and combined factors were greater in group A than B, whereas the female and unexplained factors were higher in group B (p=0.043).

The number of prior IUI cycles among the women in the two groups did not significantly differ from one another (*p*=0.366), as can be seen in (table 2).

When comparing the basal hormonal levels between the two groups (A and B), there were no significant differences found. This included levels of E2, P4, LH, and FSH, with p-values of 0.782, 0.802, 0.473, and 0.050, respectively, as indicated in Table 3.

According to the data presented in table 4, although there were no significant differences between the women in groups A and B, the most commonly used drug for ovulation induction was letrozole. The p-value for the comparison between the two groups was 0.463.

Table 5 shows that there were no significant differences in the intrauterine cycle characteristics between the control group (A) and the trial group (B), except for the progesterone hormone level on the day of trigger.

The hormonal levels at the day of trigger, which included E2 and P4, were compared between the women in group A and group B. The results showed that there were no significant differences in the E2 level between the two groups, with a p-value of 0.696. However, there was a significant difference in the P4 level between the two groups, with a p-value of 0.003, as shown in table 5.

The number and size of dominant follicles at the day of trigger showed no significant differences between Group A and Group B. The p-values for the number and size of dominant follicles were 0.508 and 0.068, respectively, as shown in Table 5.

There were no significant differences in the endometrial thickness at the day of trigger between group A and group B with a p-value of 0.391, as indicated in table 5.

When comparing the two groups for outcomes after intrauterine flushing with hCG, it was found that the biochemical pregnancy rate and clinical pregnancy rate were significantly higher in Group B (who received intrauterine hCG before IUI) compared to the control Group A (11.43% versus 34.3%, P = 0.023) as shown in Table 6 and Figure 2. The miscarriage rate, multiple pregnancy rate, and ectopic pregnancy rate were all zero as shown in Table 6.

Table 1: Comparison of Demographic characteristics of the study participants between the control Group (A) and the trial Group (B)

Parameter		Group A	Group B	*P*-value
Age (years) Mean ± SD		30.85 ±5.80	31.8± 6.26	0.883
Body Mass Index (BMI) (kg/m2) Mean ± SD		26.07± 3.74	26.34 ± 3.40	0.758
Type of infertility Number (%)	Primary	30 (43%)	42 (60.0%)	0.156
	Secondary	40 (57%)	28 (40.0%)	
Duration of Infertility (years) Mean ± SD		6.37±3.29	6.86±3.84	0.572
Causes of Infertility Number (%)	Male	36 (51.42%)	22 (31.42%)	0.043*
	Female	6 (8.57%)	30 (42.85%)	
	Combined	22 (31.42%)	10 (14.28%)	
	Unexplained	6 (8.57%)	8 (11.42%)	
SD; Standard deviation, BMI; Body mass index, *; Significant P value<0.05				

Table 2: Comparison of number of IUI cycles of the study participants between the control Group (A) and the trial Group (B)

Number of IUI cycles	Group A Number (%)	Group B Number (%)	*P* value
First	50 (71%)	(74.3%)*52*	0.366
Previous 1 IUI	12 (17%)	14 (20.0%)	
Previous 2 IUI	4 (6%)	4 (5.7%)	
Previous 2 IUI+ 1ivf	2 (3%)	0 (0.0%)	
Previous 1 IUI + 2 IVF	2 (3%)	0 (0.0%)	
IUI; Intrauterine insemination, Significant *P* value<0.05			

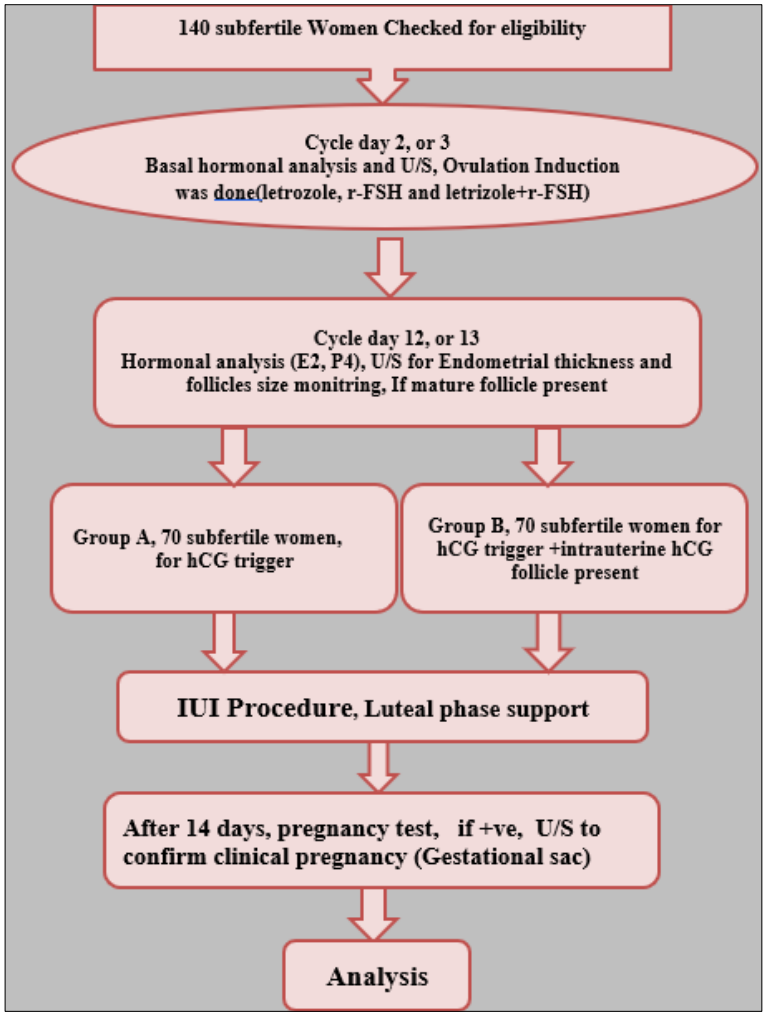

Fig 1: Study Design

Table 3: Comparison of the Basal Hormonal level of the study participants between the control Group (A) and the trial Group (B)

Basal hormonal level	Group A Mean ± SD	Group B Mean ± SD	P value
Estradiol (pg/ml)	54.04±25.00	55.82±28.51	0.782
Progesterone(ng/ml)	0.51±0.21	0.50±0.21	0.802
LH(IU/L)	5.62±2.45	5.24±1.83	0.473
FSH(IU/L)	7.83±2.74	6.66±2.10	0.050
FSH; Follicle-stimulating hormone, LH; Luteinizing hormone, Significant *P* value<0.05			

Table 4: Comparison of Ovarian Stimulation Drugs used in IUI cycle stimulation for the study participants between the control Group (A) and the trial Group (B)

Ovarian Stimulation Drugs	Group A Number (%)	Group B Number (%)	P value
Letrozole	40(57%)	46 (65.7%)	0.463
r-FSH	14 (20%)	12 (17.1%)	
Letrozole + r-FSH	16 (23%)	12 (17.1%)	
r-FSH; Recombinant follicular FSH=Follicle-stimulating hormone, Significant *P* value<0.05			

Table 5: Comparison of the intrauterine cycle characteristics of the study participants between the control Group (A) and the trial Group (B)

Parameters		Group A	Group B	*P*-value
Day of Trigger hormonal level Mean ± SD	Estradiol(pg/ml)	256.46±60.12	263.46±92.05	0.696
	Progesterone(ng/ml)	2.30±0.99	1.68±0.60	0.003*
Number of dominant follicles Mean ± SD		1.46±0.51	1.49±0.51	0.508
Dominant Follicle Size at day of trigger (mm) Mean ± SD		19.17±1.79	18.42±1.62	0.068
Endometrial Thickness at day of Trigger (mm) Mean ± SD		9.96±3.86	9.27±2.69	0.391
SD; Standard deviation, *; Significant *P* value<0.05				

Table 6: Comparison of Outcomes after intrauterine Flushing with hCG between study groups

Parameters	Group A	Group B	*P* value
Biochemical Pregnancy	8 (11.43 %)	24 (34.3%)	0.023*
Clinical Pregnancy	8 (11.43%)	24 (34.3 %)	0.023*
Miscarriage Rate	0 (0%)	0 (0%)	Non estimated
Multiple Pregnancy	0 (0%)	0 (0%)	Non estimated
Ectopic Pregnancy	0 (0%)	0 (0%)	Non estimated
IUI intrauterine insemination, *; $P < 0.05$ (Significant)			

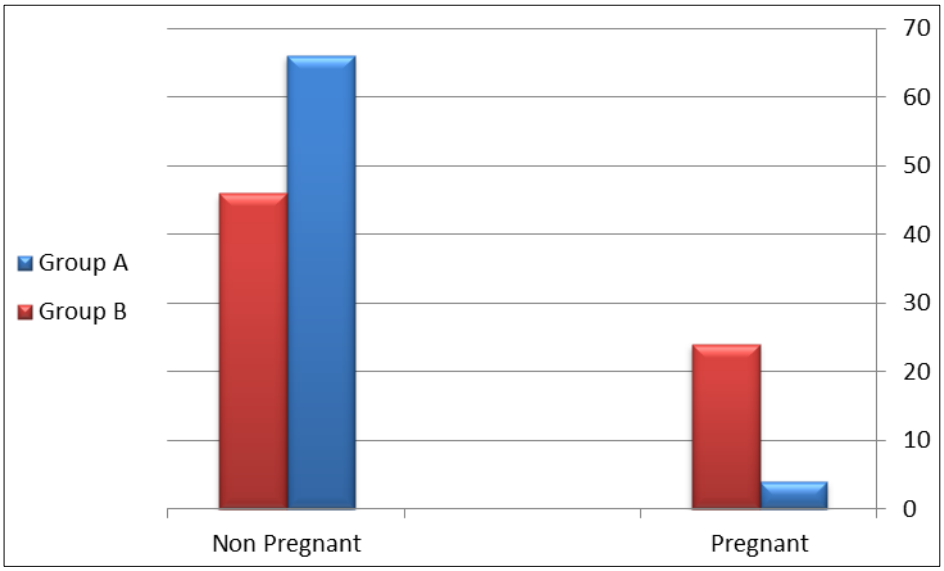

Fig 2: Comparison of the Pregnant and Non pregnant number of the study participants between the control Group (A) and the trial Group (B)

Discussion

In the last 40 years, significant efforts have been made to improve the success rates of IUI and IVF by creating new treatments. These researches have included a variety of techniques, such as metabolomics, that aim to improve the laboratory performance of IUI and IVF. Successful implantation needs good embryos quality, receptive endometrium, and embryo–endometrium cross talk [20]. Implantation is synchronized by many elements and the most important element was human Chorionic Gonadotropin (hCG) [21]. The purpose of this study was to determine whether intrauterine hCG flushing, which is thought to have a comparable beneficial impact to intrauterine hCG injection in IVF cycles, may enhance the results of IUI in women.

The comparison was done between control and study groups concerning demographic parameters**,** basal hormonal level, number of IUI cycles, drugs used for ovulation induction, IUI cycle characteristics, and outcomes of IUI after flushing. The statistical analysis revealed no significant difference in age, BMI, type and duration of infertility and this is mandatory from statistical perspective as it is essential in such a randomized controlled study to ensure absence of any factors that possibly affects positively or negatively the pregnancy outcomes. The significant differences in causes of infertility due to random allocation of cases with the highest female factor in group B. The basal hormonal level and cycle number of IUI show no significant differences and again this is mandatory to decrease bias in the study. The ovarian stimulation protocol used for each case varied based on their individual cycle characteristics, and there was no significant difference in the type of stimulation protocol used. Also the IUI cycle characteristics show no significant differences except for progesterone level at day of trigger which was significantly different between the study groups with the higher mean level in group A. During the implantation period, the endometrium experiences a series of changes in both function and structure, which are influenced by the ovarian steroid hormones. These changes are necessary to facilitate the attachment of the blastocyst. Progesterone and estrogens are the primary hormonal regulators of endometrial development, with progesterone playing a critical role in implantation events and pregnancy maintenance across all mammals, while the requirement for estrogen is specific to each species [22]. The study shows the beneficial effect of intrauterine flushing of hCG which improve the endometrial receptivity. The lack of significance of other factors act to decrease the effect on implantation rate and so pregnancy rate.

Women who received intrauterine hCG flushing (group B) had significantly higher rates of biochemical and clinical pregnancy compared to women in group A. None of the women in either group experienced miscarriage, multiple pregnancy or ectopic pregnancy. The technique of intrauterine hCG flushing was initially developed for IVF cycles by Mansour and colleagues. They found that flushing 1 mL of culture media containing 500 IU of hCG into the uterine cavity 7 minutes before embryo transfer improved pregnancy rates [23].

However, there are several differences in studies involving intrauterine administration of hCG prior to blastocyst transfer or early embryo transfer, the type of hCG used was either urinary or recombinant, and hCG was used at many different concentrations and time points earlier than embryo transfer [24].

Numerous studies have reported that administering hCG infusion at various doses and times prior to embryo transfer (ET) has improved the outcomes of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (Zarei *et*

al., [25]; Santibañez *et al*., [26]; Ye *et al*., [27]; Craciunas *et al*., [28]; Hosseini *et al*., [29], Gao *et al*., [30]; Tan *et al*., [31] and very recently Asbagh *et al*., [32]. Navali *et al*., suggested that administering 500 IU of hCG through intrauterine flushing after oocyte pick up under general anesthesia can significantly increase both the implantation rate and pregnancy rate [33].

Contrary to our research, other studies by Wirleitner *et al*. [34], Hou *et al*. [20], Firouzabadi *et al*. [21], and Osman *et al*. [35] found various findings and came to the conclusion that intrauterine hCG flushing prior to embryo transfer (ET) did not improve the results of ICSI. Moreover, intrauterine hCG flushing was shown by Volovsky *et al*. to have detrimental impacts on clinical pregnancy rates [36].

In current study the selection of a dose of 1000 IU hCG coincides with [37] and Firouzabadi [21]. Study shown a significant increase in the implantation rate among subfertile women who received more than 500 IU intrauterine hCG [31]. In the current study, the chosen volume for intrauterine flushing which was 0.5 ml is the same as in the previous study which supposed that by directing this volume, the volume will reach more surface area of the endometrium and triggering the receptive pathway without affecting IUI outcome [25].

Our study's timing of hCG injection was planned to be 2-3 days prior to the embryo's natural hCG production, which is consistent with the Wadhwa study's timing of hCG administration [38]. By administering hCG early, the goal was to mimic the natural process and set off the critical processes for implantation, optimizing the environment for successful implantation.

It is clear that hCG medications have a range of immune-modulating effects [39]. Nevertheless, the exact mechanism by which hCG supports the immune system in its role in enhancing embryo implantation and placentation is still not fully comprehended. The involvement of immune cells in pregnancy-related processes does not only begin during pregnancy, but rather starts during the menstrual cycle prior to ovulation [40].

According to data from earlier research, the use of HCG medications in the uterine cavity prior to embryo transfer has grown in favor over the last 20 years. Several investigations have demonstrated that HCG is produced as early as the 8-cell embryo stage and is engaged in the first interactions between the fetus and the maternal decidua [12,13]. When implantation continues, cytotrophoblasts separate from syncytiotrophoblasts, and the normal HCG molecule is transformed into the hyperglycosylated HCG isoform (H-HCG), which encourages extra-villous trophoblast proliferation and invasion [14,15]. HCG stimulates the release of leukemia inhibitory factor, vascular endothelial growth factor, and matrix metalloproteinase-9 while suppressing insulin-like growth factor binding protein-1 and macrophage colony stimulating factor. Moreover, it inhibits oxidative stress and apoptosis in endometrial stromal cells [16]. Several studies have reported a positive impact of intrauterine hCG administration on improving fertility outcomes [17].

This sentence describes the different functions of hCG/LH receptors in various tissues during pregnancy. The corpus luteal cells' hCG/LH receptors stimulate progesterone secretion. The receptors in the decidua are involved in the initial contact between the blastocyst and the uterus. The receptors on the myometrium help synchronize growth between the fetus and uterus. The receptors on umbilical cord tissue support growth, while the receptors on uterine vasculature help with angiogenesis. The receptors on cytotrophoblast cells aid in differentiation, and the receptors in various fetal organs contribute to both growth and differentiation [41].

The presence of LH/hCG receptors in the epithelial cells of the uterus explain the ability of hCG to improve the endometrial quality and stromal fibroblast function and hence endometrial receptivity [42] and also the beneficial effect of hCG to the uterine angiogenesis and the inflammatory process [43].

Added to the previous mentioned effect, the effect of hCG on the sperms that is found in the semen suspension which are flushed into the uterine cavity.

After ovulation, the sperms detach from the epithelial cells of the fallopian tubes and begin to travel towards the released oocyte in the ampulla for fertilization. It appears that the secretions of fallopian tubal cells are required for the hyperactivation and motility of sperms [44]. Epithelial cells in the fallopian tubes secrete hCG which may have a beneficial effect on the hyperactivated motility of sperm and facilitate fertilization [45].

The presence of hCG/LH receptors has been observed in human sperm as well as in the fallopian tubes through the expression of mRNA and demonstration of receptor actions. Although the role of hCG/LH receptors in human sperm is unclear, it may be associated with fertility. LH hormone may regulate hCG/LH receptors in the fallopian tubes, which could relax them in preparation for fertilization [46].

One possible explanation suggests that the effects of hCG may be more extensive than previously believed, due to the abundant distribution of hCG receptors in reproductive tissues, particularly in the gonads, such as the ovary and testis, as well as in extra-gonadal reproductive organs like the uterus, the fallopian tubes [42], and even in human sperm [47].

The hormone hCG, also known as the "hormone of pregnancy," appears to have more therapeutic uses and applications than previously believed [48]. It is hoped that future research will discover even more potential uses for this hormone.

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References

1. Mansour R, Tawab N, Kamal O, El-Faissal Y, Serour A, Aboulghar M, *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.e1.
2. Banerjee P, Fazleabas AT. Extragonadal actions of chorionic gonadotropin. Rev Endocr Metab Disord. 2011;12(4):323-332.

3. Cole LA. Biological functions of hCG and hCG-related molecules. Reprod Biol Endocrinol. 2010;8:102.
4. Cole LA. HCG, the wonder of today's science. Reprod Biol Endocrinol. 2012;10:24.
5. Diedrich K, Fauser BC, Devroey P, Griesinger G; Evian Annual Reproduction (EVAR) Workshop Group. The role of the endometrium and embryo in human implantation. Hum Reprod Update. 2007;13(4):365-377.
6. Palomino WA, Argandoña F, Azúa R, Kohen P, Devoto L. Complement C3 and decay-accelerating factor expression levels are modulated by human chorionic gonadotropin in endometrial compartments during the implantation window. Reprod Sci. 2013;20(10):1103-1110.
7. Racicot KE, Wünsche V, Auerbach B, Aldo P, Silasi M, Mor G. Human chorionic gonadotropin enhances trophoblast-epithelial interaction in an in vitro model of human implantation. Reprod Sci. 2014;21(10):1274-1280.
8. Abaid WA, Al-Obiadi MT, Abood MS. Intrauterine infusion of autologous platelet-rich plasma affects the endometrial thickness, epidermal growth factor and pregnancy outcome in patients undergoing IUI. Iraqi J Embryos Infertility Res. 2019;9(2):18-38. DOI: 10.28969/IJEIR.v9.i2.r2.
9. Licht P, Fluhr H, Neuwinger J, Wallwiener D, Wildt L. Is human chorionic gonadotropin directly involved in the regulation of human implantation? Mol Cell Endocrinol. 2007;269(1):85-92.
10. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY, editors. Implantation, Embryogenesis, and Placental Development: Secretory or Post Ovulatory Endometrial Phase. USA: McGraw-Hill; 2010. p. 48.
11. Bourdiec A, Shao R, Rao CV, Akoum A. Human chorionic gonadotropin triggers angiogenesis via the modulation of endometrial stromal cell responsiveness to interleukin 1: A new possible mechanism underlying embryo implantation. Biol Reprod. 2012;87(3):66.
12. Harvey MB, Leco KJ, Arcellana-Panlilio MY, Zhang X, Edwards DR, Schultz GA. Role of growth factors during peri-implantation development. Hum Reprod. 1995;10(6):712-718.
13. Kayisli UA, Selam B, Guzeloglu-Kayisli O, Demir R, Arici A. Human chorionic gonadotropin contributes to maternal immunotolerance and endometrial apoptosis by regulating Fas-Fas ligand system. J Immunol. 2003;171(5):2305-2313.
14. Santibañez A, García J, Pashkova O, Colín O, Castellanos G, Sánchez AP, *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;12:1-5.
15. Zarei A, Parsanezhad ME, Younesi M, Alborzi S, Zolghadri J, Samsami A, *et al*. Intrauterine administration of recombinant human chorionic gonadotropin before embryo transfer on outcome of in vitro fertilization/intracytoplasmic sperm injection: A randomized clinical trial. Iran J Reprod Med. 2014;12(1):1-6.
16. Hong KH, Forman EJ, Werner MD, Upham KM, Gumeny CL, Winslow AD, *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):1591-1595.
17. Wirleitner B, Schuff M, Vanderzwalmen P, Stecher A, Okhowat J, Hradecký L, *et al*. Intrauterine administration of human chorionic gonadotropin does not improve pregnancy and life birth rates independently of blastocyst quality: A randomized prospective study. Reprod Biol Endocrinol. 2015;13:70.
18. Navali N, Ghassemzadeh A, Farzadi L, Abdollahi S, Nouri M, Hamdi K, *et al*. Intrauterine administration of hCG immediately after oocyte retrieval and the outcome of ICSI: A randomized controlled trial. Hum Reprod. 2016;31(12):2520-2526.
19. Murugan VA, Murphy BO, Dupuis C, Goldstein A, Kim YH. Role of ultrasound in the evaluation of first-trimester pregnancies in the acute setting. Ultrasonography. 2020 Apr;39(2):178-89. DOI: 10.14366/usg.19043.
20. Hou W, Shi G, Cai B, Ding C, Song J, Zhang X, *et al*. Effect of intrauterine injection of human chorionic gonadotropin before fresh embryo transfer on IVF and ICSI outcomes: A meta-analysis. Arch Gynecol Obstet. 2018;298(5):1061–1069.
21. Firouzabadi DR, 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):657–664.
22. Marquardt RM, Kim TH, Shin JH, Jeong JW. Progesterone and estrogen signaling in the endometrium: What goes wrong in endometriosis? Int J Mol Sci. 2019 Aug 5;20(15):3822. DOI: 10.3390/ijms20153822.
23. Mansour R, Tawab N, Kamal O, El-Faissal Y, Serour A, Aboulghar M, *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):1370-1374.e1.
24. Makrigiannakis A, Vrekoussis T, Zoumakis E, Kalantaridou SN, Jeschke U. The role of HCG in implantation: A mini-review of molecular and clinical evidence. Int J Mol Sci. 2017;18(6):1305.
25. Zarei A, Parsanezhad ME, Younesi M, Alborzi S, Zolghadri J, Samsami A, *et al*. Intrauterine administration of recombinant human chorionic gonadotropin before embryo transfer on outcome of in vitro fertilization/intracytoplasmic sperm injection: A randomized clinical trial. Iran J Reprod Med. 2014;12:1–6.
26. Santibañez A, García J, Pashkova O, Colín O, Castellanos G, Sánchez AP, *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(9).
27. Ye H, Hu J, He W, Zhang Y, Li C. The efficacy of intrauterine injection of human chorionic gonadotropin

before embryo transfer in assisted reproductive cycles: Meta-analysis. J Int Med Res. 2015;43:738–746.
28. Craciunas L, Tsampras N, Coomarasamy A, Raine-Fenning N. Intrauterine administration of human chorionic gonadotropin (hCG) for subfertile women undergoing assisted reproduction. Cochrane Database Syst Rev. 2016;20(5)
29. Hosseini RS, Farzadi L, Abdollahi S, Nouri M, Ghasemzadeh A, Hamdi K, *et al*. Effect of intrauterine injection of human chorionic gonadotropin before frozen-thawed; c2021.

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