ROLE OF HUMAN CHORIONIC GONADOTROPIN IN FROZEN-THAWED EMBRYO TRANSFER CYCLES FOR SECRETORY TRANSFORMATION: A NARRATIVE REVIEW

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ABSTRACT

The absence of a peak in luteinizing hormone (LH) is the primary distinction between a natural and an artificially manufactured cycle. The LH peak may have clinical significance, and activating LH/hCG receptors in the endometrium may enhance embryo implantation, as these receptors were found to express in human endometrium and experimental evidences also suggested the beneficial role of hCG in embryo implantation. Human chorionic gonadotropin is discussed in this review article for its function in secretory transformation during cycles of frozen-thawed embryo transfer.

Keywords: Human chorionic gonadotropin, Frozen-thawed embryo transfer, Secretory transformation, Luteinizing hormone, *In vitro* fertilization, Hormone Replacement Treatment

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1. INTRODUCTION

Although significant progress has been made in the field of assisted reproductive technology (ART) during the last several decades, up to 70% of frozen-thawed embryo transfer (FET) cycles are still unsuccessful. Embryo implantation is a complicated process that relies on a healthy connection between the endometrium and the embryo. Age of the mother, an increase in hormone levels, embryo quality, and acceptance by the endometrium are all variables that matter here. In FET cycles, preparing the endometrium for implantation has traditionally included the sequential administration of estradiol and progesterone [1].

Non-selective entire embryo cryotransfer (freeze-all ET) involves the temporary freezing of all embryos during *in vitro* fertilization (IVF) or *in vivo* fertilization (ICSI) and their subsequent transfer to the uterus following defrosting during an elective operation. FET may be planned in a variety of different cycles, including those that are natural, modified natural, stimulated, or include hormone replacement treatment (HRT) [2]. The best way to prepare the endometrium for a transfer of a frozen embryo is still up for dispute. The progress of frozen-thawed embryo transfer technology is encouraging notwithstanding the continuing disagreement regarding the efficacy and safety of frozen embryo transfer and fresh embryo transfer. It has the potential to improve patients' cumulative pregnancy rates, enhance endometrial receptivity, buy time for pre-implantation genetic testing, and make fertility preservation easier [3].

Human chorionic gonadotropin (hCG) is one of numerous factors that govern the delicate and complex process of implantation. Primate embryos begin secreting this signal before implantation, making it one of the earliest embryonic signals known [4]. The hormone human chorionic gonadotropin (hCG) has been employed as a trigger in *in vitro* fertilization cycles because it directly acts on LH/hCG receptors in the ovary to drive final oocyte maturation or to encourage corpus luteum development. On the other hand, it was shown that the human endometrium expresses and possesses functioning LH/hCG receptors, with the highest levels occurring during the early-to-mid secretory phase, which coincided with the implantation windows [5].

A natural cycle's luteal-phase increase of luteinizing hormone (LH) has not been replicated in this artificial cycle. hCG, whose receptor is very similar to LH receptor, has been shown to be an effective replacement for LH surge in inducing the processes that control reproduction throughout the natural cycle. In fact, hCG mimics LH roles by binding to LH/hCG

receptors, which are found in the endometrium and ovaries, and then inducing decidualization, endometrial maturation, synchrony promotion, angiogenesis, cytotrophoblast proliferation and invasion, oocyte and corpus luteum maturation, suppression of uterine contractions, and maternal immune regulation [6].

A healthy pregnancy begins with a healthy embryo, and a healthy embryo begins with proper timing of endometrial growth. Despite the advances in ART, implantation failure is still a common clinical occurrence. The ESHRE PGD Consortium found that the implantation rate (IR) for women undergoing PGS was a highly poor 25%. It is a strong indicator that the endometrial receptivity and the two-way street of communication between the endometrium and the embryos are crucial to successful implantation [7]. hCG has been utilized for a long time to hasten the development of the corpus luteum or improve oocyte ultimate maturation by exerting an effect on LH/hCG receptors inside the ovary. However, it was also shown that LH/hCG receptors are produced and functional in human endometrium, with the highest level occurring during the early-mid secretory phase, which coincided with the implantation windows. hCG may have direct effects on the endometrium via acting on the LH/hCG receptor, in addition to its well-known involvement in the ovary [8].

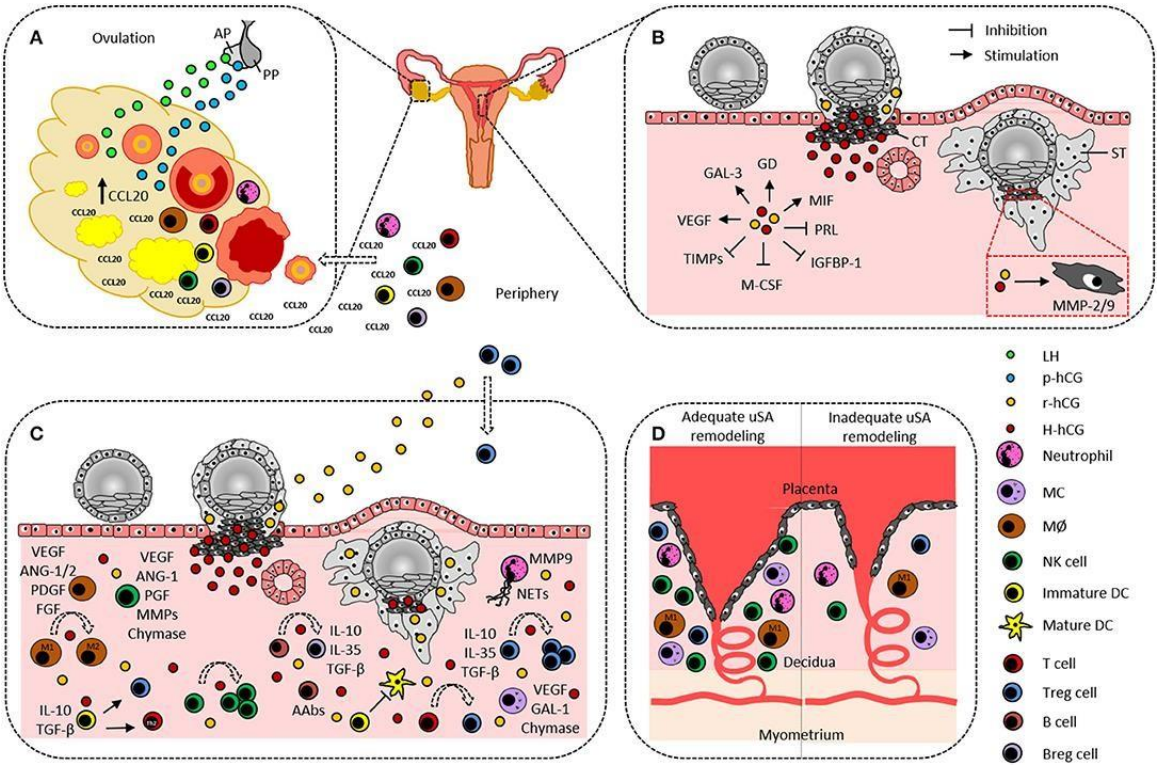

Figure 1. Human Chorionic Gonadotropin-Mediated Embryo Implantation and Placentation.

Most fertility clinics opt for a hormone replacement therapy program to stimulate endometrial growth prior to a frozen embryo transfer cycle. Scientists think that human chorionic gonadotropin helps the ovaries get ready for pregnancy by encouraging follicular maturation and supporting the growth of the corpus luteum. As high estrogen levels hinder follicular growth, very few ART doctors in the center administer hCG prior to endometrial transformation in HRT [9]. However, in an effort to mimic the corpus luteum's maintenance of the endometrium during gestation as closely as possible, some clinicians continue to inject hCG to help pregnant women conceive. It is crucial to perform statistical analysis of the pregnancy rate of patients under different programs of the center and explore its potential significance in order to optimize the selection of clinical programs and verify the clinical value of the application of human chorionic gonadotropin in the process of replacing the endometrial transition of the cycle in the process of freeze-thaw embryo transfer [10].

A luteal phase deficit is common during stimulated *in vitro* fertilization cycles. Supraphysiological quantities of steroids generated by numerous corpora lutea during the early luteal phase directly restrict the LH release through negative feedback mechanisms at the hypothalamic-pituitary level, which is the primary cause of the luteal phase failure in stimulated IVF cycles [11]. The ablation of a high number of granulosa cells during the oocyte extraction process and the use of a GnRH agonist or antagonist to avoid the early LH surge are two additional reasons of the luteal phase abnormality. Because only one follicle typically develops and ovulates in natural cycles, the luteal phase defect often seen in stimulated IVF cycles should not be seen in natural cycle FET. This argument, however, is fraught with diagnostic challenges and debate [12].

Endometrium may be prepared for FET cycles in either a natural or artificial cycle. In most cases, the endometrium is artificially primed by supplementing with estradiol (E_2) and progesterone (P) in a specific order. The absence of an LH peak in intentionally created cycles is the main distinction between them and natural cycles [13]. Stimulation of the LH/hCG receptor within the endometrium can boost embryo implantation, and mid-cycle hCG treatment may restore defective endometrial maturation in individuals with extremely low LH levels. This may be because the LH peak before secretory transition may impact endometrial receptivity. Endometrial epithelium was also shown to release hCG after undergoing a secretory change in response to progesterone at the same time throughout the menstrual cycle [14]. Because of its cheap cost and absence of danger of OHSS, frozen embryo transfer is a crucial part of assisted

reproductive procedures. Factors impacting endometrial acceptance are crucial in enhancing implantation since a healthy and responsive endometrium is required for successful implantation with high-quality embryos. During the implantation window, when the endometrium is most receptive, the embryo must implant successfully. In the range of 50-75% of miscarried pregnancies, this issue is to blame [15].

Although there is no clear evidence to support its significance in natural cycles, luteal phase support is often employed in FET. It is discovered no advantage of hCG in both natural and clomid-induced cycle FET in the retrospective analysis, and previous trial employing vaginal progesterone did not show any improvement in the continuing pregnancy rate of natural cycle FET [16]. However, another retrospective investigation found that the use of progesterone in FET cycles resulted in much higher continuing pregnancy and live-birth rates. Vaginal progesterone usage was linked to a considerably higher continuing pregnancy rate in one randomized study, whereas intramuscular progesterone use resulted in no change in the clinical pregnancy rate compared with the control group despite no placebo being administered in the other study [17].

2. SPECIFIC STUDIES

Asbagh et al. (2023) examined the impact of hCG injections into the muscle on endometrial priming and embryo implantation in women undergoing FET and compared the results to those obtained in a control group. A total of 140 infertile women who had FET were studied in randomized controlled experiment. hCG was injected intramuscularly before the first dosage of progesterone was administered to the intervention group, whereas the control group received no hCG. Cleavage-stage embryos were transplanted in both groups 4 days following progesterone injection. Pregnancy was measured chemically, clinically, and for abortion rates. There was little difference in fundamental data between the two research groups. The intervention group had greater chemical and clinical pregnancy rates than the control group, albeit the higher ratios were only statistically significant for the clinical pregnancy rate. There was no statistically significant difference in abortion rates between the experimental and control groups. Results from this research demonstrated that the success rate of IVF cycles might be increased by injecting 10000

IU of hCG intramuscularly before the endometrial secretory transition period in cleavage-stage embryos [18].

Bilgory et al. (2023) test the impact of increased LH at the time of hCG trigger on LBR and the efficacy of ovulation induction in Ovu-FET cycles. Ovu-FET cycles conducted between August 2016 and April 2021 were included in this retrospective analysis. Both Ovu-FET with an hCG trigger and Ovu-FET without a trigger were studied. The modified group was divided into two subgroups, one receiving hCG before LH doubled to >15 IU/L and the other receiving it after. Neither the modified nor the original Ovu-FET groups, nor the two subgroups of the modified Ovu-FET, those who were triggered either before or after LH increase, differed significantly from one another at baseline. There was no statistically significant change in LBR between original and adjusted Ovu-FET findings (35.4% vs. 32.0%). There was no significant difference in LBR between the modified Ovu-FET groups (31.3%) with respect to hCG trigger time (33.3%). Whether or whether luteinizing hormone was raised during the hCG trigger had no effect on Ovu-FET LBR. These findings provide more comfort with respect to hCG triggering following LH increase [19].

Jahanshahi et al. (2022) analyzed the outcomes of pregnancies after FET those experiencing infertility were involved in this clinical trial research, as did those who had frozen embryos. Before embryo transfer, the intervention group got hCG injection and control group received saline. Biochemical indicators, rates of successful *in vitro* fertilization, miscarriage, transplantation, clinical pregnancy, and other outcomes, as well as demographic data, were compared across the groups. Participants' mean ages ranged from 32.97 to 33.31 years. There were no statistically disparities among the follicle-stimulating hormone, anti-Mullerian hormone, or frozen embryos between the two groups. The percentage of women who got pregnant in the lab was much higher for the intervention group (51% vs. 35%). Significantly more implantations and clinical pregnancies occurred in the intervention group. The researchers found a statistically significant variance in overall pregnancy loss between the intervention group (78.1%) and the control group (86.0%). The findings showed that the success rate of clinical and laboratory pregnancies was boosted by 500 IU of hCG administered prior to ET. But it does little to prevent miscarriages. Therefore, more research on this topic is necessary [20].

Atef et al. (2022) demonstrate the impact of injecting hCG intrauterine on the day of ovum retrieval for patients having a history of unsuccessful intra cytoplasmic sperm injections. One

hundred and ten patients were selected, with half serving as test subjects for intrauterine injection of 500 IU of hCG immediately after ovum extraction in the sham procedure and the other half as controls. Ovarian stimulation utilizing the extended protocol was performed on all subjects. Chemical pregnancies were much more common in the first group, at 39.6%, than in the second group, at 27.8%. In the first group, 28.3% of women became clinically pregnant, but in the second group, only 18.5% did so. The rates of chemical pregnancies and clinical pregnancies were not statistically distinct from one another. Although there seems to be not statistically distinct from one another, intrauterine hCG injection improves the drug and clinical pregnancy rates in women having ICSI trial after failed one or two tries [21].

Deepika et al. (2021) compared the success of GnRHa-triggered FET cycles with those of hCG-triggered FET cycles in treating patients with Asian polycystic ovary syndrome (PCOS). Patients with polycystic ovary syndrome (PCOS) undergoing IVF with an antagonist protocol were randomly allocated to either a GnRHa trigger or an hCG trigger group, and their FET cycles were monitored. GnRHa stimulation results in a much greater cumulative live birth rate each cycle than the hCG trigger. There were 19.1 times as many mature oocytes (14.1) and blastocysts (4.2) available to the GnRHa group than there were to the hCG group (3.26). The cumulative live birth rate of FETs produced during GnRHa-triggered cycles was greater than that of hCG-triggered FETs after transfer. Therefore, GnRHa triggering, whole-embryo vitrification, and FET is recommended for use in PCOS patients undergoing IVF [22].

Du et al. (2020) performed research on the efficacy of hCG for treating endometriosis (EM) after frozen-thawed embryo transfer. Participants in the retrospective cohort research all had endometriosis and had undergone FET. Patients were randomly assigned to either a control group or an hCG group using the FET cycle protocols. Live birth, early abortion, late abortion, clinical pregnancy, and ectopic pregnancy were all measured and compared between the two groups. The hCG group had a significantly greater incidence of clinical pregnancies (57.7%) than the control group (49.0%). However, there was no statistically significant increase in births in the hCG group. Giving hCG to women with Endometriosis during FET, they reasoned, would increase the pregnancy rate [23].

Reichman et al. (2020) determine whether increasing the ongoing pregnancy rate (OPR) in nFETs by injecting hCG intramuscularly 1 day after an LH surge enhances OPR. In a retrospective cohort study, women who underwent natural cycle FET with transfer of a single

euploid blastocyst on days 5 or 6 were split into two groups: those who received hCG 1 day following the LH surge and those who did not. Uterine infertility screenings were not performed on these patients. 529 nFET cycles were run in total. After accounting for possible confounders such embryo shape, the OPR was still considerably higher in the treatment group (69.9%) than in the non-treatment group (57.4%). Patients' ages, BMIs, peak endometrial thicknesses, number of pregnancies, and parities were all taken into account while calculating odds ratios. Current studies imply that patients who get a booster dose of hCG within 1 day after the end of the LH surge have better cycle outcomes than patients who do not receive the booster [24].

Deng et al. (2020) showed that live birth rates was significantly higher in the group of patients who were treated with hCG prior to secretory transition in FET cycles compared to the control group in a retrospective cohort study. The enhancement in LBR due to hCG persisted after taking into account all possible confounding factors. When comparing cycles in which embryos were transferred at the cleavage stage, the rise in LBR after hCG injection was statistically significant [25].

Gao et al. (2019) pooled data from 15 RCTS to draw conclusions on the efficacy of intrauterine injection of hCG prior to embryo transfer. In all, 2,763 people took part in the 15 studies that made up this meta-analysis. Clinical pregnancies were 47.10% higher, live birth rates were 44.89% higher, and the rate of induced pregnancies was 31.64% higher in women who were treated with intrauterine hCG injection prior to ET. The rate of miscarriage was reduced from 18.56% to 12.45% in the treatment group, compared to the rate in the control group. It is also possible that the results of an IVT-ET might change depending on the time and amount of the hCG injection. The best IVF-ET results were seen in women who were given 500 IU of hCG within 15 minutes after ET [26].

Baldini et al. (2018) explored how increasing progesterone levels before injecting hCG affected the success rate of IVF cycles involving embryos in the cleavage phase. This was a retrospective cohort study involving 131 cycles of ovarian stimulation followed by transfers of frozen embryos at the cleavage stage. The first set of women required FET because their ovaries began releasing mature eggs prematurely in response to medically monitored ovarian stimulation. Controls consisted of FET patients whose progesterone levels were typical throughout induction. Progesterone levels were measured on the day hCG was delivered, and the two groups' rates of cleavage, fertilization, clinical pregnancy, implantation, and continued

pregnancy as well as Top-Quality Embryos (TQE) were compared. Neither the number of recovered oocytes nor the total number of oocytes accessible for insemination was significantly affected by the rise in progesterone in Group A patients. Similar rates of fertilization, cleavage, and implantation, as well as clinical pregnancy and sustained pregnancies, were seen in the two groups. Comparing the TQE rates of the two groups yielded nearly the same conclusion. This research found that the success rate of IVF using cleavage-stage embryos stored in frozen storage did not change when progesterone levels were raised on the day hCG was administered. This research provides further evidence that delaying embryo transfer until a subsequent FET cycle unrelated to ovarian stimulation is the optimal strategy for achieving a safe pregnancy in patients with elevated progesterone levels [27].

Lee et al. (2017) hypothesized that does hCG administration during the luteal phase of a natural cycle FET improve the probability of a successful pregnancy. Luteal phase support, whether with hCG or progesterone, has been linked to increased live birth rates in stimulated cycles. A total of 450 female participants were included in this randomized, double-blind controlled experiment. In order to carry out natural cycle FET, women with regular cycles were sought for. Ovulation was timed using serial serum hormonal concentrations, and embryos were transferred at a minimum of Day 2 after cleavage. Patients were assigned to (i) a treatment group that received 1500 IU hCG on the day of FET and (ii) a control group that received normal saline on the same days. Both groups saw comparable rates of implantation and miscarriage. The therapy group had significantly higher blood estradiol levels 6 days post-FET, whereas the progesterone group had similar levels. In comparison, the number of successful embryo transfer cycles was much lower in the control group. There was no significant difference in serum levels of estradiol and progesterone between pregnant and non-pregnant women 6 days after FET. When predicting continuing pregnancy rate following natural cycle FET utilizing multivariate logistic regression, the total quantity of transplanted embryos proved to be the only significant predictor. Results from studies on hCG use in natural cycle FET showed no improvement in pregnancy rates [28].

Groenewoud et al. (2017) demonstrate the potential for embryo-endometrial asynchrony to be induced by ovarian stimulation-induced late follicular phase progesterone elevated levels for *in vitro* fertilization, hence decreasing the chance of successful implantation after the transfer of a fresh embryo. In unstimulated cycles, elevated progesterone levels during the late follicular

phase had little effect on the success rate of frozen-thawed embryo transfer. In a randomized controlled study, 271 women randomly allocated to the modified natural cycle arm had their progesterone and LH levels measured late in the follicular phase. To determine the progesterone threshold associated with an increased likelihood of a successful delivery, a receiver operating characteristic curve was developed. Increased blood progesterone level of 4.6 nmol/l or higher was found in 24.4% of patients, while an increase in progesterone and LH was seen in 44.3% of patients. Clinical results for women with a natural cycle may be improved by monitoring progesterone and LH levels before to a FET, although this yet to be shown [29].

Li et al. (2017) analyzed the impact on clinical pregnancy of intrauterine injection of hCG-activated autologous human PBMC in patients who had FET. For patients with four or more transplant failures, the rates of clinical pregnancy (39.58%), implantation (22.00%), and live birth (33.33%) were all considerably higher than for those with one to three transplant failures. Live birth delivery rate (29.63%) was significantly higher in the PBMC-treated group among patients who underwent RIF and received FET, and among patients with endometrial thickness >7 mm but <8 mm on the day of embryo transfer. These findings demonstrate that intrauterine administration of hCG-activated autologous PBMC is beneficial for individuals with limited endometrial thickness, and that cleavage-stage embryo transfer is the most successful IVF outcome for RIF patients [30].

Aghahosseini et al. (2017) compared the success rate of a frozen cycle to a fresh cycle in achieving a live birth in women whose progesterone levels are high on the day they are supposed to be taking HCG. During this randomized, double-blind clinical research, 72 women having an increased progesterone level on hCG day underwent assisted reproductive technology. The recipients of the embryo transfers were randomly allocated to receive either fresh or frozen embryos. In the end, the clinical pregnancy rate was compared to the live birth rate by the researchers. The implantation rate was 21.51%. In the group that had fresh embryo transfers, 17 out of 36 became pregnant, but only 15 out of 36 became pregnant after receiving frozen embryos. Neither group's birth to term rate was significantly higher than the other. There is no clear winner between fresh and frozen cycles, therefore it is best to make that choice on a patient-by-patient basis. Patients may have additional psychological strain due to the frozen cycle [31].

Huang et al. (2017) evaluated the effect of it-hCG before FET for women with two or more implantation failures (TIFs). Patients undergoing FET with TIFs were the subjects of a randomized, prospective, single-blind trial. ET was performed on 62 women who had received an intrauterine injection of 1000 IU of hCG. Intrauterine injections of physiological saline were used as a placebo in a control group prior to ET. No intrauterine injections were provided to the mothers in the control group. There was a comparison made between the three groups in terms of the prevalence of clinical pregnancy, abortion, and prolonged pregnancy. The clinic saw a 59.68%, 53.06%, and 32.00% pregnancy rate among individuals who took hCG, a placebo, and a control group, respectively. Both the hCG and placebo groups showed statistically significant increases in clinical pregnancy rates as compared to the control group. There was no statistically significant difference in abortion rates between the three groups. Improved pregnancy rates following TIFs were seen when hCG was administered intrauterine before to FET. However, intrauterine perfusion-caused local damage may have a significant role in raising pregnancy rates in the clinic [32].

Ye et al. (2015) compared the success rates of IVF and ICSI before and after the intrauterine administration of hCG prior to embryo transfer. Randomized controlled trials (RCTs) were retrieved by searches of standard medical and pharmaceutical databases. Five randomized controlled trials were included in the meta-analysis. When compared to controls, the biochemical, clinical, and continuing pregnancy rates for women who received intrauterine hCG injections were considerably higher. Neither implantation nor miscarriage rates varied significantly between the two groups. Injecting hCG intrauterinely before ET to females having intracytoplasmic sperm injection or *in vitro* fertilization may benefit from this [33].

Eftekhar et al. (2012) find out whether using hCG during the secretory phase of hormone-prepared cycles for transferring thawed frozen embryos is beneficial. A randomized clinical trial was used in this investigation. In this research, infertile women who were considering a FET were randomly assigned to either the HCG or control group. Both groups used the same endometrial preparation approach, which consisted of daily oral administrations of estradiol valerate beginning on day two of the menstrual cycle, followed by an I.M. injection of progesterone in oil after the endometrial thickness had reached 8 mm. Up to the ninth week of pregnancy, both estradiol and progesterone were given to guarantee a safe birth. HCG was administered at a dose of 5000 IU on the first day of progesterone therapy and transfer day.

Thirty-five couples received HCG, while 65 couples served as controls for a total of 130 participants. The groups did not vary significantly from one another in terms of core characteristics. Implantation, ectopic, clinical, continued, and terminated pregnancies were all about the same in both groups. Although HCG supplementation during the secretory phase of ART cycles has been shown to increase results, this was not the case with frozen cycles [34].

Mansour et al. (2011) observed that injecting 500 IU of hCG intrauterinely before ET may considerably increase implantation and pregnancy rates for IVF/ICSI. Participants were randomly assigned to receive either 100 IU or 200 IU of hCG intrauterine before to ET. A 500 IU hCG intrauterine injection was given to the new study group once the interim analysis was completed. The researchers found that hCG had a positive influence on the implantation window and endometrium since the 500 hCG group had a significantly higher successful implantation and pregnancy rate (41.6% vs. 29.5% in the control group). Injecting 500 IU of hCG intrauterine before to ET has been shown in this research for the first time to dramatically increase implantation and pregnancy rates in IVF/ICSI [35].

Poikkeus et al. (2002) properly evaluate the therapeutic usefulness of a single early HCG test in ART pregnancies, it is necessary to think about the origins of infertility and the methods used to cure them. The hCG concentration in the blood was evaluated on day 12 after embryo transfer, and 774 cycles with a value of 5 IU/l were deemed successful. Overall, 137 frozen embryo transfer rounds and 119 IVF cycles were performed. The concentration of HCG in the serum was measured using a fluoroimmunometric test. Non-viable pregnancies included those that were biochemical, miscarried, ectopic, or molar, whereas viable pregnancies included those with a surviving fetus at 22 weeks of gestation. The data was retrospectively gathered from the past. In healthy pregnancies, the median HCG level was 126 IU/l, but it was only 31 IU/l in those that were not developing normally. In singleton pregnancies, the median HCG level was 115 IU/l, but in multiple pregnancies, it was 201 IU/l. Tubal factor infertility was associated with ectopic pregnancies, while patients with male factor infertility and ICSI therapy had the lowest HCG levels (88 IU/l). The optimal cutoff threshold for predicting a healthy pregnancy was found to be an HCG level of 76 IU/l. The chances of each consequence depending on the HCG level are listed. Planning future follow-up is much easier with only one HCG reading on day 12 following embryo transfer. Low HCG levels in healthy pregnancies are common in cases of male factor infertility and those treated with ICSI [36].

Licht et al. (1998) examined the effects of hCG on human endometrium directly by using an intrauterine microdialysis device to measure intrauterine levels of paracrine mediators *in vivo*. IGFBP-1 and M-CSF were both significantly suppressed after hCG treatment. LIF, VEGF, and MMP-9 were all markedly upregulated. Implantation of an embryo depends on the expression of these substances. hCG enhanced IL-1 responsiveness in endometrial stromal cells, which in turn stimulated VEGF-induced proliferation and migration of human microvascular endothelial cells [37].

3. CONCLUSION

Confounding variables that have an association with pregnancy outcomes, such as maternal age, the total number of embryos transferred, and the proportion of high-quality embryos transferred, may have skewed the results because of the study's retrospective methodology. Multivariate regression analysis was used to account for the aforementioned variations among these parameters, however the difference remained statistically significant. Furthermore, it is conceivable that not all confounding variables, such as the patients' psychological impacts, have been counted in this retrospective analysis.

CONFLICT OF INTEREST

No conflict of interest is declared.

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