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Is human chorionic gonadotropin supplementation beneficial for frozen and thawed embryo transfer in estrogen/progesterone replacement cycles?: A randomized clinical trial

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Abstract

Aim: Human chorionic gonadotropin (hCG) is used frequently for luteal support in fresh in vitro fertilization cycles as it induces progesterone secretion from the ovaries after oocyte retrieval and modulates the endometrium for implantation in fresh cycles. In contrast, hCG is not usually used for the transfer of cryopreserved-thawed embryos in estrogen/progesterone replacement cycles because ovulation is suppressed. However, several studies have shown that luteinizing hormone and hCG receptors are present in the human endometrium and that hCG can directly induce the decidualization of endometrial stromal cells in vitro. Thus, this study evaluated whether hCG supplementation can be beneficial for cryopreserved-thawed embryo transfer in estrogen/progesterone replacement cycles.

Methods: One-hundred-and seventy-three cryopreserved-thawed embryo transfer cycles with estrogen/progesterone replacement were divided randomly into two groups. Transdermal oestradiol was used in combination with vaginal progesterone suppositories for HR. The embryo transfer was performed on day 17 and/or day 20 of the HR therapy cycle in both groups. In Group A, 3000 IU of hCG was administered on days 17, 20, and 23. In Group B, hCG was not used.

Results: There was no significant difference in the average age of the patients, the average number of previous assisted reproductive technology cycles, or the average number of embryo transfers between the two groups. The rates of pregnancy and implantation per embryo were 37.2% and 25.3%, respectively, in Group A and 35.6% and 21.7%, respectively, in Group B. The pregnancy and implantation rates were similar in both groups.

Conclusion: Supplementation with hCG is not beneficial for cryopreserved-thawed embryo transfer in estrogen/progesterone replacement cycles.

KEYWORDS

frozen-thawed embryo transfer, hormone replacement cycle, human chorionic gonadotropin, luteal phase support, randomized clinical trial

1 | INTRODUCTION

Luteal phase support is routinely administered worldwide to women undergoing in vitro fertilization (IVF) treatment.[1] Luteal support is associated with a significantly higher pregnancy rate, compared with the pregnancy rates with no support.[2] The most commonly used types of supplementation include progesterone and/or human chorionic gonadotropin (hCG).[1] It is still unclear whether progesterone alone, hCG alone, or a combination of both will provide the optimal degree of support.[1] It has been reported that hCG supplementation results in higher pregnancy rates[2] and live birth rates,[3] compared to progesterone supplementation. In another prospective randomized study, in which i.m. hCG was compared with i.m. progesterone, luteal phase supplementation with hCG resulted in better conception rates,[4] while other studies reported that hCG administration as a form of luteal supplementation did not have significant benefits in comparison with progesterone supplementation.[5,6] The administration of hCG leads to an increased production of estradiol and progesterone by the corpus luteum.[7] In addition to its classical endocrine role, a series of studies has shown that hCG exerts paracrine effects in the uterine environment.[8,9] It has been reported that stimulating leukemia inhibitory factor (LIF) production by hCG is concentration-dependent, suggesting that the blastocyst might influence its own implantation through hCG.[8] It also has been reported that the specific interaction of blastocyst-derived hCG and the endometrial luteinizing hormone (LH) and hCG receptors constitutes a fundamental component of the molecular dialogue at the materno-fetal interface.[9] Although the controversy that has been raised regarding the expression of the LH and hCG receptors in the human endometrium remains,[10] several studies have shown that the LH and hCG receptors are present in the human endometrium.[11,12] In consideration of these reports, it seems that hCG that is used in luteal support might have a direct effect on the endometrium at implantation. However, hCG is not usually used for the transfer of cryopreserved-thawed embryos with estrogen/progesterone replacement cycles because ovulation is suppressed, there is no corpus luteum formation, and no luteotropic effect is expected. In order to study the direct effect of hCG on the endometrium at implantation, this study evaluated whether hCG supplementation would be beneficial for cryopreserved-thawed embryo transfer with estrogen/progesterone replacement cycles.

2 | MATERIALS AND METHODS

This prospective randomized study was done at a private IVF/intracytoplasmic sperm injection center between April 2003 and March 2004. The trial design was accepted by the center's ethics committee and documented informed consent was received from the patients before their inclusion in the study. One-hundred-and-seventy-three frozen-thawed embryo transfers with estrogen/progesterone replacement cycles were included in this study. For the hormone replacement (HR), transdermal estradiol (Estraderm M; Kissei Pharm, Tokyo, Japan) was used in combination with vaginal progesterone suppositories. Preparation of the endometrium was initiated on day 2 of the HR cycle and was achieved in a step-up regime (2.16-4.32 mg). The administration of the progesterone suppositories (600 mg/day) commenced on day 15. The patients were randomly separated into two groups by using color marble lots that were drawn by a technician who had no access to the patients' information. The 86 patients in Group 1 received hCG supplementation with estrogen and progesterone. The 87 patients in Group 2 received only estrogen and progesterone supplementation. The embryo transfer was performed transcervically, using a φIVF catheter (Fuji Systems, Tokyo, Japan), on day 17 and/or day 20 of the cycle in both groups. In Group 1, 32 patients underwent a frozen-thawed cleavage-stage embryo(s) transfer, 26 patients underwent a frozen-thawed blastocyst(s) transfer, and 28 patients underwent a frozen-thawed two-step consecutive embryo transfer. The two-step consecutive embryo transfer method already has been reported.[13] In Group 2, 26 patients underwent a frozen-thawed cleavage-stage embryo(s) transfer, 21 patients underwent a frozen-thawed blastocyst(s) transfer, and 40 patients underwent a frozen-thawed two-step consecutive embryo transfer. In Group 1, 3000 IU of hCG was administrated on days 17, 20, and 23. In Group 2, hCG was not administered. The patients' backgrounds are summarized in Table 1. There was no difference in the average age, average period of infertility, average number of previous ART cycles, number of early embryo transfer cycles, number of blastocyst transfer cycles, number of two-step consecutive embryo transfer cycles, or average number of transferred embryos. The levels of serum estradiol and progesterone were measured on day 23 of HR. Clinical pregnancy was identified by the development of a gestational sac. The implantation rate was determined by dividing the number of gestational sacs by the number of embryos that had been transferred. The miscarriage rate was determined by dividing the number of miscarriages by the number of clinical pregnancies. Continuous data were expressed as the mean±SD. The two groups were compared by an ANOVA for the continuous variables and Fisher's exact test for the categorical variables. A probability value of $P<.05$ represented statistical significance.

TABLE 1 Baseline characteristics of the patients who were enrolled in the study

Variable	Group 1 (E2/P4/hCG)	Group 2 (E2/P4)
Number of patients	86.0	87.0
Average age (years)	33.7±4.8	33.4±5.3
Average period of infertility (years)	6.2±4.7	5.7±3.6
Average no. of previous ART cycles	2.3±2.3	2.1±2.8
No. of cleavage-stage ETs	32.0	26.0
No. of blastocyst transfers	26.0	21.0
No. of two-step consecutive ETs	28.0	40.0
No. of transferred embryos	2.0±0.8	2.1±0.8

ART, assisted reproduction technology; E2, estradiol; ET, embryo transfer; hCG, human chorionic gonadotropin; P4, progesterone.

TABLE 2 Outcomes of the patients

Variable	Group 1 (E2/P4/hCG)	Group 2 (E2/P4)
Number of patients	86.0	87.0
Average E2 level (pg/mL) on day 23	333.4±148.0	301.9±194.0
Average P4 level (ng/mL) on day 23	7.4±3.2	8.9±5.3
Number of clinical pregnancies	38.0	40.0
Clinical pregnancy rate per ET (%)[a]	44.2	46.0
Number of implanted embryos	50.0	52.0
Implantation rate per embryos (%)[b]	29.4	28.9
Number of miscarriages	5.0	6.0
Miscarriage rate (%)[c]	13.2	15.0

[a]Clinical pregnancy was identified by the development of a gestational sac; [b]the implantation rate was determined by dividing the number of gestational sacs by the number of embryos that had been transferred; [c]the miscarriage rate was determined by dividing the number of miscarriages by the number of clinical pregnancies. E2, estradiol; ET, embryo transfer; hCG, human chorionic gonadotropin; P4, progesterone.

3 | RESULTS

There was no significant difference between groups 1 and 2 in the levels of serum estradiol and progesterone on day 23. The clinical pregnancy rate in Group 1 was 44.2% (38/86) and 46.0% (40/87) in Group 2. There was no significant difference in the clinical pregnancy rate between the two groups. The implantation rates were 29.4% in Group 1 and 28.3% in Group 2. Thus, there also was no significant difference in the implantation rate between the two groups. The percentage of multiple pregnancies was 28.9% in Group 1 and 27.5% in Group 2. Therefore, there was no significant difference in the multiple pregnancy rate between the two groups. The rate of miscarriage was 13.2% in Group 1 and 15.0% in Group 2. There was no significant difference in the rate of miscarriage between the two groups (Table 2).

4 | DISCUSSION

This is the first report to evaluate whether i.m. hCG supplementation is beneficial for cryopreserved-thawed embryo transfers with HR cycles. The results indicate that i.m. hCG supplementation is not beneficial for frozen-thawed embryo transfers with HR cycles. In this study, i.m. hCG injection, rather than intrauterine hCG injection or supplements of hCG that are added to the culture media, was used because the i.m. injection is the only method that has been approved by the Japanese Ministry of Health, Labour, and Welfare. As the half-life of hCG is 24 hours, the administration of hCG three times, on days 17, 20, and 23, was expected to provide longer term benefits, as compared to a single intrauterine injection. Human chorionic gonadotropin is known to have an endocrine role as a luteotropic hormone that is responsible for the maintenance of progesterone production by the maternal corpus luteum. A series of studies has shown that hCG exerts paracrine effects in the uterine environment.[8,9] In fact, it has been shown that hCG administration during the secretory phase significantly modulates several endometrial paracrine parameters that are correlative with endometrial differentiation (eg, insulin-like growth factor-binding protein 1), angiogenesis (eg, vascular endothelial growth factor), implantation (eg, LIF, macrophage colony stimulating factor), and tissue remodeling (eg, matrix metallopeptidase 9).[14] Several studies have shown that the LH and hCG receptors are present in the human endometrium.[11,12] Furthermore, hCG has been detected at various levels in blastocyst culture media.[15,16] The expression of hCG has been documented as beginning at 2 days after fertilization.[17] Therefore, it is likely that the specific interaction of blastocyst-derived hCG and the endometrial LH and hCG receptors constitutes a fundamental component of the molecular dialogue at the materno-fetal interface.[9] However, this study's results did not show the efficacy of hCG supplementation in frozen-thawed embryo transfers with HR cycles. The results might indicate that the amount of hCG that is expressed by the embryo itself at the local implantation site is sufficient to support the molecular dialogue at the materno-fetal interface. Alternatively, hCG itself does not have any role in the molecular dialogue at the materno-fetal interface. In order to determine the role of hCG in the molecular dialogue at the materno-fetal interface, further investigations will be required.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and animal rights*: This article does not contain any experimental study with human or animal participants that was performed by any of the authors.

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