Evaluation of the Impact of 1,000-unit Intrauterine Injection of Human Chorionic Gonadotropin prior to \textit{in vitro} Fertilization on Success Rate of Implantation in Infertile Women: A Double-blind Randomized Trial

Masomeh Rezaei, Friba Frhadifar, Ghobad Moradi, Ilnaz Khalatbari

ABSTRACT

Aim: Studies have shown that intrauterine injection of human chorionic gonadotropin (hCG) prior to embryo transfer causes success in pregnancy. This study has been done to determine the effect of 1,000-unit intrauterine injection of hCG prior to \textit{in vitro} fertilization (IVF) on success rate of implantation in infertile women.

Materials and methods: This double-blind clinical trial study has been done on two intervention groups (n = 40) and control group (n = 40), who were randomly selected. For the intervention group cases, soft catheter penetrated the uterus and 0.3 cc of liquid fetus culture media with 0.2 cc (1000 unit) of hCG was injected into the uterus. After 7 minutes, the fetus was transferred into the uterus with a soft catheter. In the control group, 0.5 cc of liquid fetus culture media was injected into the uterus and after 7 minutes embryo was transferred into the uterus with another soft catheter. In both groups, the speculum was removed after 3 minutes.

Results: The results of this study showed that pregnancy success was the same in both intervention and control groups and it was in eight cases (20%). In this study, 38 cases (95%) of the agonistic cycle type were in the intervention group and 33 (82.5%) cases were in the control group (p > 0.05). On assessment of the situation of pregnancy of each person according to the ultrasound results, the size of right and left ovary in two groups showed no significant differences (p > 0.05).

Conclusion: The pregnancy success during the IVF process is related to the quality of the blastocyst in the secretion of many cytokines and hormones in the early days of egg cell implantation, such as interleukin 1 and hCG, and increased level of these hormones and mediators causes disruption of the process of making proteins needed for implantation at the start of the initial development.

Keywords: Clinical trial, Human chorionic gonadotropin, \textit{in vitro} fertilization, Intrauterine, Successful implantation.

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INTRODUCTION

Infertility is defined as failure to conceive after 12 months or more of regular sexual intercourse without contraception. It is estimated that 15% of couples are infertile in developing countries.\(^1\) Evaluation and treatment of infertility during the last three decades have changed considerably and IVF and assisted reproductive technologies (ART) are the most helpful methods including all the methods with direct manipulation of oocytes outside the body. The first and most common form of ART is IVF.\(^2\)

In many cases with failure of ART, aiming the replacement of the human embryo according to cross-reactions between endometrium and blastocyst at the correct time can lead to a successful pregnancy.\(^3\) Replacement of the embryo consists of three phases: apposition, adhesion, and invasion between efficient blastocyst and receptive endometrium occurs in a short period of time, about 6 or 7 days after fertilization. This shows repeated unsuccessful replacement may be due to embryonic factors, the uterus of the recipient, or both attributed. Thus, any intervention leading to reduced receptive endometrium, such as immune therapies, can affect significantly the results of IVF. In addition, some reports cannot explain the previous unsuccessful IVF and suggest the existence of an autoimmune mechanism theory.\(^4,5\) Numerous reports...
have shown annual live birth rate in IVF procedures is about 40.1% in women younger than 35 years and 29.6% in older than 40 years.

The process of implantation after IVF and embryo transfer depends on embryo quality, its cytokines and hormone secretion, and endometrial receptivity, and it is estimated that 50 to 75% of pregnancies are lost because of the failure of implantation. Human chorionic gonadotropin is one of the most important factors. Human chorionic gonadotropin is a heterodynamic glycoprotein hormone that is needed to maintain pregnancy; hCG is one of the first hormones secreted by the egg cell before implantation, which secretes 6 to 8 days after fertilization by binding to its endometrial receptor; hCG hormones directly prompt vessel growth and cause angiogenesis by producing vascular endothelial growth factor.

Intrauterine injection of hCG (500 IU/mL) before transferring the embryo increased rate of pregnancy in IVF/intracytoplasmic sperm injection. This effect of intrauterine injection of hCG has been shown in several studies. This study aimed to determine the effect of intrauterine injection of 1,000 units hCG prior to embryo transfer on IVF’s success rate in infertile women.

**MATERIALS AND METHODS**

The study was done by double-blind clinical trial on the two groups (n = 40) and control group (n = 40) who were randomly selected. The main criteria for doing this study concern women with background of maternal infertility who had come to the Be’sat Hospital of Sanandaj for the first IVF. Also, patients over 45 years old, patients with a previous pregnancy, patients with structural abnormalities of the uterus, those with a history of uterine surgery or endometriosis, and those with azoospermia in partner were excluded. Informed consent forms for patients were completed and conditions of study, plan, and no harmful effect of hCG were explained to the patients. Patients were selected randomly and double blind so that the injection was given by the nurse of infertility unit and patients and doctors who were tasked with the responsibility of reviewing the results of the injection were not informed. In the cases, soft catheter penetrated the uterus and 0.3 cc of liquid fetus culture media with 0.2 cc (1,000 IU) of hCG was injected into the uterus. After 7 minutes, embryo was transferred into the uterus by another catheter.

In the control group, 0.5 cc of liquid embryo culture media was injected into the uterus and after 7 minutes with another catheter embryo was transferred into the uterus. In both groups, speculum was removed after 3 minutes. Reproductive outcomes, including biochemical pregnancy rates and clinical pregnancy rates, were compared between the two groups (Flow Chart 1). Qualitative descriptive purposes and the ratio will be calculated as well as the confidence interval.

In one-variant analysis for the purposes of quantitative and qualitative analysis, in case of normality, t-test, chi-square, and Fisher’s exact test were used for calculation. In this study, the significance level was p < 0.05, and data analysis was performed using Stata 12 software.

**RESULTS**

This study was effectuated on two groups of 40 people. Results showed that age, body mass index (BMI), duration of infertility, ovarian size, and type of cycles in both intervention and control groups showed no significant difference (p > 0.05). But endometrial thickness was different between the two groups: in the intervention group it was 9.9 ± 1.4 and in the control group 9.4 ± 0.91 (p = 0.043). In this study, concerning the type of cycles, 38 cases (95%) of the agonistic cycle were in the intervention group and 33 cases (82.5%) were in the control group (p > 0.05; Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.1 ± 4.5a</td>
<td>31.1 ± 3.6</td>
<td>0.373</td>
</tr>
<tr>
<td>BMI</td>
<td>25.5 ± 3.5</td>
<td>24.4 ± 3.4</td>
<td>0.140</td>
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<tr>
<td>Infertility duration</td>
<td>8.4 ± 5.2</td>
<td>7.8 ± 6.5</td>
<td>0.529</td>
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<tr>
<td>Right ovary size</td>
<td>19.4 ± 4.7</td>
<td>20.8 ± 1.8</td>
<td>0.070</td>
</tr>
<tr>
<td>Left ovary size</td>
<td>19.6 ± 4.5</td>
<td>17.7 ± 5.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>9.9 ± 1.4</td>
<td>9.4 ± 0.91</td>
<td>0.043</td>
</tr>
<tr>
<td>Cycle type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonistic</td>
<td>38 (95%)</td>
<td>33 (82.5%)</td>
<td>0.077</td>
</tr>
<tr>
<td>Antagonistic</td>
<td>2 (5%)</td>
<td>7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

*aMean ± standard deviation*
The results showed that the success of pregnancy in both groups was the same in 8 cases (20%). In reviewing the results in terms of successful pregnancy by ultrasound, the right and left ovary size in the two groups showed no significant difference. Pregnancy in women with agonistic cycle type was equal in both groups and did not show a statistically significant difference (Table 2).

**DISCUSSION**

Oocyte maturation requires simultaneous events in nucleus and other parts of the oocyte and that gives the egg cell this potential to successfully pass the initial period of the embryo formation. Successful implantation requires receptive endometrium and an appropriate blastocyst at the same time. The best period of reception is limited to days 20 to 24 of the cycle. Cytokines and hormones released by blastocyst can influence the endometrial receptivity and the endometrium responds by producing factors increasing blastocyst products leading to more invasion.

Despite the nuclear maturation in culture media, the oocytes are not able to do cytoplasmic maturation because the culture media is unable to signal oocyte and there is no association between somatic and egg cell maturation and implantation. Therefore, this clinical trial evaluated the injection of 1,000 units of intrauterine hCG prior to IVF on implantation success rate in infertile women. Several studies have been done on the effect of hCG hormone injection, and results of these studies have shown hCG hormone injection is helpful to patients undergoing hormone injection, and results of these studies have shown hCG hormone injection of 1,000 units of intrauterine hCG prior to IVF is limited to days 20 to 24 of the cycle. Cytokines and hormones released by blastocyst can influence the endometrial receptivity and the endometrium responds by producing factors increasing blastocyst products leading to more invasion.

Also, endometrial thickness was different between two groups, which was 9.9 ± 1.4 in the intervention group and 9.4 ± 0.91 in the control group (p = 0.043). Concerning the type of cycles, 38 cases (95%) of the agonistic cycle were in the intervention group and 33 cases (82.5%) were in the control group (p > 0.05). The results showed that the success of pregnancy in the two groups was the same, in 8 cases (20%). In reviewing the results in terms of successful pregnancy by ultrasound, the right and left ovary size in both groups showed no significant difference, which is compatible with the results of Wirleitner et al. In general, hCG hormone regulates local immune tolerance via cellular apoptosis. It regulates balance of Th1/Th2 and influences endometrial reception by increasing intrauterine natural killer cells. Also, the successful implantation of the embryo requires an adequate coordination between the egg cell and the implantation environment.

The underlying mechanism of improvement in implantation and pregnancy outcome after intrauterine injection of hCG hormone can be attributed to the pharmacological effects of this hormone. Bourdiec et al. showed that the hCG hormone increases endometrial cell proliferation and migration. The hCG hormone plays a key role in the process of implantation due to the fact that the hormone is secreted form trophoblastic cells (TE), so hCG hormone secretion depends on blastocyst quality and grade of TE. Therefore, the quality of TE plays a decisive role in the success of the implantation. In addition, endometrial thickness has been associated with reproductive success and studies showed that fertility increases with greater endometrial thickness per each cycle and is consistent with estradiol concentrations, and cycles in which the endometrial thickness is less than borderline, usually less than 7 mm, chance of pregnancy is low. We can say that the higher concentration of hCG reduces the coordination between the nuclear and cytoplasmic maturation and reception of endometrium, which can be due to a disturbance in the process of making proteins needed for attachment and invasion to the endometrium and influence fertilization in the initial stage of development.

**CONCLUSION**

According to the findings of this study, reproductive success did not show a significant relation with increasing the volume of hCG. Pregnancy success during the process of IVF depends on the quality of the blastocyst in the secretion of this hormone in the first days after the egg cell implantation, and increased level of this hormone causes disruption in the process of making proteins needed for implantation at the start of the initial development.

**ACKNOWLEDGMENT**

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**Table 2: Comparison of pregnancy in the two study groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Intervention</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
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<tr>
<td>Pregnancy result</td>
<td>8 (20%)</td>
<td>8 (20%)</td>
<td>1</td>
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<tr>
<td>Ultrasound result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ovary size</td>
<td>17.2 ± 7.1</td>
<td>21.1 ± 1.6</td>
<td>0.154</td>
</tr>
<tr>
<td>Left ovary size</td>
<td>18.9 ± 2.06*</td>
<td>20.8 ± 1.9</td>
<td>0.075</td>
</tr>
<tr>
<td>Cycle type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonistic</td>
<td>8 (50%)</td>
<td>8 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>Antagonistic</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation
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