

Effect of human chorionic gonadotropin injection before frozen embryo transfer on pregnancy outcomes in endometriosis infertility

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Abstract

Purpose To investigate the effect of hCG in hormone replacement regime for frozen thawed embryo transfer in women with endometriosis. **Methods** We performed a retrospective, database-searched cohort study. The data of endometriosis patients who underwent frozen embryo transfer between 1/1/2009-31/8/2018 were collected. According to the protocols for frozen embryo transfer cycle, these patients were divided into two groups: Control group(n=305), and hCG group(n=362). And clinical pregnancy rate, live birth rate, early abortion rate, late abortion rate and ectopic pregnancy rate were compared between the two groups. **Results** There was a significant increase in clinical pregnancy rate in hCG group (56.6% vs. 48.2%, $p=0.035$) compared to the control group. And the live birth rate in hCG group (43.5% vs. 37.4%, $p=0.113$) also elevated, but the difference is statistically insignificant. **Conclusion** hCG administration in hormone replacement regime for FET increase the pregnancy rate in women with endometriosis.

Introduction

Endometriosis (EM) is a chronic gynecological disease associated with infertility that is characterized by lesion of endometrial-like tissue outside of the uterine cavity [1–2]. Almost half of the women with endometriosis experience infertility [3]. EM affect the outcome of assisted reproductive technology (ART), which compassing a wide sperm of causes, including the poor oocyte, sperm and embryo quality, impaired receptivity of the endometrium and implantation failure [4–5]. Clinically, there can be little doubt that the endometrium of women with endometriosis is less receptive to embryo implantation, and strong evidence exists to suggest that endometrial changes are associated with decreased cycle fecundity as a result of this disease[6]. Endometrial biomarkers are differentially expressed in the endometrium of women with endometriosis compared to normal women [7–8]. Seeking an effective approach to improve endometrial receptivity in endometriosis is a difficult issue in clinical.

Frozen embryo transfer (FET) is recommended for endometriosis in ART. Mohamed suggested that preparation of the endometrium for FET with gonadotropin-releasing–hormone (GnRH) agonists could improve live birth rate in endometriosis, comparing fresh cycles [9]. And recently, Xu found that pregnancy rate, clinical pregnancy rate and birth weight were improved in women with endometriosis who underwent intrauterine injection of human chorionic gonadotropin (hCG) before FET[10]. But these methods are either time-consuming or inconvenient. So we retrospectively analyzed the data of frozen embryo transplantation in patients with endometriosis in an attempt to find a more effective strategy for frozen embryo transplantation.

Materials And Methods

Subjects

The retrospective, database-searched cohort study was conducted in Reproductive Hospital Affiliated Shandong University. This study was reviewed and approved by research ethics committee of our

institution. All patients in the study provided written informed consent for use of their data.

All patients were diagnosed as endometriosis by a laparoscopy, underwent frozen embryo transfer in our hospital during a nine year period (1/1/2009-31/8/2018) were included. Patients older than 42 years at the onset of the cycle, basal FSH > 12 U/L, women with uterine malformation, chromosomal abnormalities, polycystic ovary syndrome, hydrosalpinx, recurrent spontaneous abortion or intrauterine adhesions were all excluded. Finally, 667 women diagnosed with infertility associated with EM were collected. According to whether injection hCG in the protocols for frozen embryo transfer cycle, these patients were divided into two groups : Control group(n = 305) and hCG group(n = 362)□

Endometrial preparation

Patients in control group received hormone replacement (HT) regime for frozen embryo transfer. The protocol was started with oral estradiol valerate (Progynova, Delpharm Lille) at a dose of 4 mg to 8 mg per begin on day 2 or 3 of menstrual cycle. Then the thickness of endometrium was measured by transvaginal ultrasound, and the concentrations of estrogen and LH in serum were measured after about 10 days estradiol valerate treatment. When the endometrial thickness reached at least 7.5 mm, vaginal progestin (Utrogestan; Besins Manufacturing) at dose of 200 mg per day and oral dydrogesterone (Duphaston, Abbott) at dose of 20 mg twice daily was added. When the patients received frozen embryo transfer earlier than 2011, they will be treated with intramuscular injection of progesterone (Progesterone Injection, Zhejiang Xianju Pharmaceutical Co., Ltd) instead. Up to two day 3 cleavage–stage embryos or blastocysts frozen early were thawed and transferred 3 or 5 days, respectively, after the start of progesterone. Women in hCG group received hCG 8000 IU intramuscular injection before progestin administration, and HT regime was the same as control group. Progestin supplementation continued until 12 weeks of pregnancy.

Outcomes

The primary outcome was clinical pregnancy, which was defined as the detection of an intrauterine gestational sac by transvaginal ultrasoundgraphy after 3 weeks embryo transfer. The second outcome was live birth, which was defined as the delivery of any viable neonate who was 28 weeks of gestation or older. The early abortion rate was defined as the percentage of miscarriage early than 12 weeks in the group. Late abortion rate was the proportion of miscarriage in between 12 and 28 weeks in the group. Preterm birth rate was defined as the percentage of birth before 34 weeks in live birth women. Live birth rate was the proportion of women who birth at least one living child in the group.

Statistical analysis

Continuous variables were represented as means and standard deviations; differences in variables were compared by means of Student's t-test. Categorical variables were described as frequencies and percentages, with the between-group difference tested by means of the chi-square test and by means of Fisher's exact test when the number of events was less than 5. Two-sides P value of less than 0.05 were considered to indicate statistical significance.

Results

Patients

The baseline characteristics were similar in control group and hCG group (Table 1). There is no difference in the terms of age, BMI, basal endocrine hormone levels, AMH and the number of oocytes retrieved in fresh cycle between two groups.

Table 1
Basal characteristics of participants

	Control group	HCG group	p value
N	305	362	
Age(Years)	31.85 ± 4.72	31.62 ± 4.42	0.503
BMI(kg/m ²)	22.41 ± 3.96	22.92 ± 3.33	0.221
AMH(ng/ml)	4.52 ± 5.66	4.39 ± 4.16	0.506
Basal FSH(U/L)	6.70 ± 2.30	6.56 ± 1.88	0.380
Basal LH(U/L)	5.81 ± 3.37	5.75 ± 3.43	0.813
Basal E2(pg/ml)	43.50 ± 33.17	48.40 ± 43.04	0.453
No. of oocyte retrieved	14.28 ± 7.95	13.87 ± 7.24	0.485
There were no significant differences between hCG group and control group (P > 0.05) in any of the baseline characteristics.			

Outcomes of FET

The thickness of endometrium, the stage of transferred embryo and the concentration of E2 in serum did not differ significantly among the two groups. However, FET outcomes were improved in hCG group. The pregnancy rate in hCG group (56.6% vs. 48.2%, p = 0.035) significantly increased, comparing the control group (Table 2). And the live birth rate in hCG group (43.5% vs. 37.4%, p = 0.113) also elevated, but the difference is statistically insignificant (Table 2). In addition, there was no significant difference in early abortion rate, late abortion rate, preterm birth rate and ectopic pregnancy rate between control group and hCG group (Table 2).

Table 2
Outcomes of frozen embryo transfer

	Control group	HCG group	p value
Endometrium thickness	0.93 ± 0.17	0.92 ± 0.12	0.236
Transferred embryo stage			0.425
Cleavage stage	22(7.2%)	20(5.5%)	
blastocyte	283(92.8%)	342(94.5%)	
Estrogen	261.79 ± 290.85	302.54 ± 373.58	0.258
LH	18.36 ± 11.51	15.11 ± 13.54	0.029*
Pregnancy rate	48.2%	56.6%	0.035*
Live birth rate	37.4%	43.5%	0.113
Preterm birth rate	4.4%	4.3%	0.601
Early abortion rate	9.2%	10.8%	0.52
Late abortion rate	0%	0.8%	0.254
Ectopic pregnancy rate	1.6%	0.3%	0.098
*means p < 0.05,** means p < 0.001			

Discussion

In our retrospective analysis, we found that the hCG injection could significantly improve pregnancy rate in EM patients undergoing FET. And live birth rate also elevated in hCG group, however, the difference did not reach statically significant.

Several studies have reported that endometriosis affects the endometrium and reduce fertility [11–12]. Reduced implantation, clinical pregnancy rate, ongoing pregnancy and live birth rate was found in women with endometriosis placing sibling oocytes from same donor, comparing women without endometriosis [13]. We also found that higher prevalence of endometrial ployps in infertile patients with endometriosis, implying the special character of eutopic endometrium in endometriosis, which also impair embryo implantation [14]. Animal studies support clinical data suggesting that endometriosis leads to implantation defects, again implicating the endometrium. Induction of endometriosis in animals demonstrates similar phenotypes to human disease [15–17]. And gradual and profound alteration in endometrium over time was found in induction of endometriosis in the baboon, involving the inflammation and immune system changes[18].

The expression of endometrial biomarkers altered in the eutopic endometrium of endometriosis compared to normal women. Lessey reported that endometrial integrins, which is known as cell-surface receptor for extracellular matrix protein, playing important role in embryo implantation, decreased in women with infertility and endometriosis[19]. Reduced integrin expression also associated with reduced IVF outcomes [20]. Integrin β 5 could up-regulated under the influence of hCG in stromal cells from endometriotic lesions in vivo [21]. Other key molecules that are required for normal endometrial receptivity such as HOXA10[22], its expression also reduced in endometriosis, but have been reported to could be induced by hCG[23]. Therefore, hCG injection may improve endometrium receptivity via regulating key molecules related to embryo implantation.

Moreover, endometriosis has been described as a progesterone resistant disease due to the blunted or inadequate response to progesterone of both the eutopic and ectopic endometrial cells and tissue [24–27]. This manifested as low expression of progesterone receptor, blunted expression of progesterone target genes [28–30] and inadequate decidualization response[31]. However, the decidualization is an indispensable process for embryo implantation, thus aberrant decidualization would lead to unfavorable effects on embryo implantation and pregnancy. While it was reported to hCG could regulate progesterone expression via the ERK1/2 pathways [32], and promote human endometrial stromal cell decidualization leading to a significantly stronger induction of decidualization when used in combination with progesterone. [33].

In addition, it has been well established that the immune system of women with endometriosis is dysfunctional. T regulatory (Treg) cells are altered in endometriosis patients and have been suggested to play a role in pathogenesis of endometriosis and its associated infertility [34]. Lower numbers of Treg cells have been detected in the eutopic endometrium of a non-human primate endometriosis model[18]. And it was reported that hCG-producing trophoblasts could attract Treg cell [35], and more importantly, hCG was involved in Treg differentiation [36]. Furthermore, aberrant subset of uNK cells was found in the eutopic endometrium of women with endometriosis associated infertility [37]. Immature uNK cells populations exist in infertile women with endometriosis [38]. And hCG has been reported as a regulator of uNK cell proliferation mediating via the mannose receptor (CD206) [39]. These findings may suggest hCG could improve endometrial receptivity via regulating immune cells in eutopic endometrium of infertility women associated with endometriosis.

In our research, the pregnancy rate significantly elevated after hCG injection in endometriosis, however, the difference of live birth rate could not reach statistical significance. This may be the result of insufficient time or dose of hCG, and may improve by replacing single hCG treatments with a repetitive administration scheme [40]. Since our research is retrospective design, the power of conclusion is lower. Further evidence is needed to clarify the protocol that would lead to beneficial outcomes.

Declarations

Ethics approval and consent to participate: This study was approved by research ethics committee of our institution. All patients in the study have provided written informed consent for use of their data.

Availability of data and materials: The datasets analysed during the current study are not publicly available due to these are all clinical data which needed protect patients identity and privacy, but are available from the corresponding author on reasonable request.

Conflict of Interest: The authors declare that they have no competing interests.

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Authors' contributions: All the authors contributed equally to this manuscript. Rong Tang designed the study; Yanbo Du interpreted the data and drafted the article; Lei Yan revised the manuscript critically and accoute for all aspects of the work; Mei Sun and Yan Sheng collected all the data; Xiufang Li and Zhenhua Feng analysis the data.

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