Does high estrogen level negatively affect pregnancy success in frozen embryo transfer?

Ayşe Zehra Özdemir¹, Pervin Karli², Çağrı Gülümser³

¹Faculty of Medicine, IVF Center, Ondokuz Mayıs University, Samsun, Turkey
²Department of Obstetrics and Gynecology, Faculty of Medicine, Amasya University, Sabucuoğlu Şefeddin Research Hospital, Amasya, Turkey
³Department of Obstetrics and Gynecology, Faculty of Medicine, Başkent University, Ankara, Turkey

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Abstract

Introduction: High estrogen levels could reduce pregnancy rates by disrupting the implantation of the embryo into the endometrium in patients treated with fresh cycles of in vitro fertilization (IVF) [1, 2].

Frozen embryo transfer is currently preferred to prevent the negative effects of high estrogen levels in IVF cycle induction on the endometrium, prevent IVF complications such as ovarian hyperstimulation syndrome (OHSS), and increase cumulative pregnancy rates. However, there may be elevated estrogen levels in frozen cycles [3–5]. Estrogen

Conclusions: In autologous frozen embryo transfer with HRT, estrogen levels did not have a significant effect on the pregnancy or abortion rate. Therefore, estrogen levels do not need to be monitored in frozen embryo transfer with HRT.

Key words: estradiol, frozen embryo transfer, pregnancy rate.

Introduction

High estrogen levels could reduce pregnancy rates by disrupting the implantation of the embryo into the endometrium in patients treated with fresh cycles of in vitro fertilization (IVF) [1, 2].

Frozen embryo transfer is currently preferred to prevent the negative effects of high estrogen levels in IVF cycle induction on the endometrium, prevent IVF complications such as ovarian hyperstimulation syndrome (OHSS), and increase cumulative pregnancy rates. However, there may be elevated estrogen levels in frozen cycles [3–5]. Estrogen
endometrial thickness of less than 7 mm on day 11 were excluded from the study. Four patients with endometrial thickness of less than 7 mm on day 11 were also excluded from the study. Patients older than 18–40 were included in the study. All patients had frozen embryos from the previous IVF cycle. A total of 204 patients aged 18–40 were included in the study. The study protocol was approved by the Ethical Committee of the Medical Faculty of Ondokuz Mayis University (No: OMU-KAEK 2018/475). All frozen autologous embryos transferred from January 2016 to January 2018 at the IVF center of Ondokuz Mayis University were retrospectively screened.

Inclusion criteria: Only patients with endometrial HRT and day 5 embryo transfer were included in the study. All patients had frozen embryos from a previous IVF cycle. A total of 204 patients aged 18–40 were included in the study.

Exclusion criteria: Patients with a history of more than 3 failed transfers and with an endometrial thickness of less than 7 mm on day 11 were excluded from the study. Patients older than 40 years old and younger than 18 were also excluded from the study.

A total of 204 patients aged 18–40 were included in the study. Four patients with endometrial thickness less than 7 mm on day 11 were also excluded from the study.

Endometrial preparation was initiated on day 2–3 of the cycle following transvaginal ultrasound with oral estradiol hemihydrate (2 mg Estrofem; Novo Nordisk, Bagsvaerd, Denmark). The endometrial preparation protocol began with 4 mg/day Estrofem on days 1–4, 6 mg/day Estrofem on days 5–8, and 8 mg/day Estrofem from day 9 onwards. A second transvaginal ultrasound was performed after 10 days of estrogen treatment. Embryo transfer was scheduled if the endometrial thickness was at least 7 mm. Progesterone was administered intramuscularly (50 mg Progestan; Koçak, Istanbul, Turkey) at a dose of 100 mg for 5 days prior to embryo transfer (day of progesterone). One or two embryos were transferred depending on the patient’s age and the quality and number of embryos. All of them were 5-day embryos. All transfers were performed without anesthesia using ultrasonography by the same reproductive endocrinologist.

Serum samples were taken to determine estrogen levels on day 2 or 3 of the cycle and on the day of progesterone (when progesterone treatment was initiated). The level on day 2 or 3 of the cycle was indicated as e2, and the level on the day of progesterone was indicated as e1.

Human chorionic gonadotropin (β-hCG) positivity, which was examined on day 14 after the transfer, was used to evaluate biochemical pregnancy. Abortion was defined as the termination of pregnancy before the 20th gestational week.

Progesterone was given intramuscularly (Progestan 50 mg; Koçak, Turkey) and estrogen (Estrofem 2 mg; Novo Nordisk, Denmark) was given orally as luteal support until 12 weeks of pregnancy.

Material and methods

The study protocol was approved by the Ethical Committee of the Medical Faculty of Ondokuz Mayis University (No: OMU-KAEK 2018/475). All frozen autologous embryos transferred from January 2016 to January 2018 at the IVF center of Ondokuz Mayis University were retrospectively screened.

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Table I. Demographic details

| Parameter                        | Pregnant $n = 89$ | Nonpregnant $n = 115$ | $P$-value |
|----------------------------------|-------------------|-----------------------|-----------|
| Patient groups, $n:$             |                   |                       |           |
| Unexplained infertility          | 58                | 72                    | $\chi^2 = 0.5453, p = 0.7613$ |
| Poor ovarian reserve             | 4                 | 16                    |           |
| Male factor                      | 27                | 27                    |           |
| FSH levels on day 2–3 [mIU/ml]   | 8.348 ±2.080      | 7.179 ±2.919          | 0.0809    |
| Antral follicle count            | 16.09 ±3.988      | 14.36 ±5.144          | 0.2793    |
| Patients’ age [years]            | 30.65 ±4.996      | 31.21 ±4.654          | 0.5680    |
| Endometrium thickness [mm]       | 10.22 ±1.536      | 9.643 ±1.311          | 0.1606    |

FSH – follicle-stimulating hormone.

The median level was 208.5 pg/ml for non-pregnant women and 202 pg/ml for pregnant women (Table II). The median e1 level was 21.5 pg/ml for patients who had an abortion and 37 pg/ml for those who did not have an abortion, which did not show a statistically significant difference ($p = 0.117$) (Figure 3). Similarly, there was no statistically significant difference between e2 levels according to the abortion rate ($p = 0.722$) (Figure 4). The median level was 205 pg/ml for patients who did not have an abortion and 216.5 pg/ml for patients who had an abortion (Table III).

Discussion

In a normal menstrual cycle, progesterone and estrogen in the endometrium in the follicular phase are required for endometrium maturation [12]. However, estrogen should increase within a certain limit as high estrogen levels may impair implantation [3]. High estrogen levels could reduce uterine vascularization, inhibit the invasion of trophoblasts, and suppress the expression of genes needed for implantation [13]. Estrogen levels in natural cycles gradually increase and remain above 200 pg/ml for at least 50 h, and an luteinizing hormone (LH) surge is triggered. Subsequently, estrogen levels decrease after reaching 300–400 pg/ml in the ovulation phase. We mimicked this natural cycle by using a step-up regimen in HRT cycles in...
our clinic; however, the estrogen decrease after ovulation in natural cycles was not observed in HRT cycles, and estrogen levels in the follicular phase were occasionally above physiological levels. It has been suggested that high estrogen levels in HRT cycles before the day of progesterone may inhibit implantation by disrupting embryo-endometrium synchronization. Niu et al. demonstrated that e2 levels on the progesterone day in frozen embryo transfer with HRT did not affect the results of the pregnancy or implantation rate [5]. Banz et al. reported that estrogen levels did not affect the results of pregnancy when the endometrium was 7–15 mm in frozen HRT cycles with estrogen patch and vaginal progesterone [14]. Remohi et al. conducted a study of oocyte donation cycles using oral estrogen after GnRH agonist induction and reported that there was no relationship between the estrogen levels on the progesterone day and the implantation or pregnancy rate [15]. Similar to our study, various studies have found that estrogen levels do not affect the results of pregnancy [16–18]. Estrogen and progesterone are necessary for the preparation of the endometrium for pregnancy. However, even very low levels of estrogen do not reduce pregnancy rates [15].

Consistently, the present study and other studies indicated that high estrogen levels would not have a negative effect on the results of pregnancy. For pregnancy there is a wide range of estrogen levels. This suggests that estrogen exerts an effect on the endometrium through cytokines and adhesion molecules [18]. Therefore, changes in estrogen levels would not affect implantation. Interestingly, Fritz et al. reported that the maximum estrogen levels were not different between pregnant and non-pregnant women; however, patients with lower e2 levels had higher rates of pregnancy. Unlike our study, estrogen levels were examined four times in each cycle in the study by Fritz et al. In addition, the study used intramuscular and transdermal e2. On the other hand, in our study, oral estrogen was used. Oral estrogen is a weaker estrogen, which is transformed into estrone during the first transition in the liver and intestine. This first transition effect is reduced for intramuscular and transdermal e2. On the other hand, in our study, oral estrogen was used. Oral estrogen is a weaker estrogen, which is transformed into estrone during the first transition in the liver and intestine. This first transition effect is reduced for intramuscular and transdermal e2. On the other hand, in our study, oral estrogen was used. Oral estrogen is a weaker estrogen, which is transformed into estrone during the first transition in the liver and intestine. However, although Banz et al. used transdermal estrogen in their study, their results were similar to ours. A limitation of the present study is that it is a retrospective study with a first-pass effect. However, all patients followed the same protocol, which is a strength of the study. The results of our study demonstrated that estrogen levels in frozen embryo transfer with HRT did not affect pregnancy results and that estrogen monitoring was not necessary. Further prospective studies are needed to confirm the findings.

There are limited studies about the effect of estrogen levels on frozen embryo transfer, and this study is important because we found that it is not necessary to monitor estradiol levels in HRT cycles.
Conflicts of interest

The authors declare no conflict of interest.

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