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ORIGINAL ARTICLE

Letrozole versus artificial hormonal endometrial preparation for vitrified–warmed embryos transfer cycles

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KEYWORDS

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Abstract *Objective:* To evaluate the efficacy of letrozole in the endometrial preparation of vitrified–warmed embryo transfer cycles and to compare it to the hormonal preparation with estradiol valerate and progesterone study. *Design:* Retrospective observational study. *Methods:* We analyzed 197 cycles of endometrial preparation for vitrified–warmed embryo transfer from January 2013 to August 2014. A final 94 cycles of letrozole were compared to 96 cycles of hormonal preparation. *Results:* Pregnancy rate was non significantly higher in the letrozole group (53.2%) than in the hormonaly prepared group (40.6%) while the ongoing pregnancy rate was significantly higher in the letrozole group 47.9% v 32.3% (P value 0.02). The abortion rate was non significantly lower in the letrozole group 5.3% v 8.3%. The mean endometrial thickness in the hormonaly prepared group was significantly higher than the letrozole 9.9 mm ± 1.7 and 9.1 mm ± 1.6 respectively. *Conclusion:* Endometrial preparation for vitrified-warmed embryo transfer using the aromatase inhibitor letrozole has a significantly higher ongoing pregnancy rate than that of the hormonal preparation.

1. Introduction

Frozen–thawed embryo transfer (FET) enables the excess embryos generated by IVF and ICSI to be stored and utilized at a later date. This can increase the cumulative pregnancy rate of IVF/ICSI treatment (1).

The number of FET cycles has been increased due to the trend toward transferring fewer embryos after a fresh IVF cycle and as a result of improved laboratory techniques (2–5).

In contrast to the complex stimulation protocols employed to stimulate multiple follicular growth for IVF, FET protocols are simpler, with the primary aim limited to adequate preparation of the endometrium to receive the thawed transferred embryo(s).

Furthermore, FET results in similar live birth rates to fresh cycles when frozen top quality embryos are transferred (6).

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However, despite the growing importance of vitrified–warmed ET in the treatment of sub-fertility there is little consensus on the best method for endometrial preparation in ovulatory women (3,7).

In order to optimize pregnancy rates, the development of embryo and endometrium should be synchronized. This can be achieved in various ways. The simplest method of endometrial preparation is represented by natural cycle FET (NC-FET), in which the endocrine preparation of the endometrium is achieved by endogenous sex steroid production from a developing follicle. Timing of embryo transfer is determined by detecting the spontaneous LH surge or by administering hCG to initiate luteinization (8,9).

A frequently employed alternative approach is represented by artificial cycle protocols in which estrogen and progesterone are administered in a sequential regimen which aims to mimic the endocrine exposure of the endometrium in the normal cycle. Initially, estradiol is given in order to cause proliferation of the endometrium, while suppressing the development of the dominant follicle. This is continued until the endometrium is observed to be 7–9 mm thick on ultrasound, at which time progesterone is added to initiate secretory changes (10,11).

Letrozole, a selective aromatase inhibitor, prevents the conversion of androgens to estrogen in the granulosa cells, thus releasing the hypothalamo-pituitary axis from the negative feedback of estrogen, resulting in an increase of FSH secretion from the anterior pituitary. In addition, the accumulated androgens in the ovary further increase follicular sensitivity to FSH (12).

Letrozole has a relatively short half-life (±2 days) compared with CC (±2 weeks), so estrogen target tissues (e.g., endometrium and cervix) are spared anti-estrogenic adverse effects. Because of these mechanisms, it was postulated that Letrozole may have superior ovulation induction properties in terms of follicular growth and endometrium development, which is important for embryo implantation (13).

Letrozole does not block hypothalamic estrogen receptors and, therefore, the negative feedback mechanism remains intact. This enables regulation of the FSH discharge when estrogen is produced and should reduce the prevalence of multiple follicles development (14,15).

So, the use of letrozole typically results in mono-ovulation and this reduces the effect of supraphysiological levels of estrogen (of multiple growing follicles) on the endometrium and embryo (7).

Considering these advantages, letrozole could be an optimal choice for endometrial preparation for vitrified–warmed ET.

This study is a retrospective one comparing the results of two different protocols of endometrial preparation before vitrified–warmed ET. In the first protocol, artificial hormonal preparation with estradiol valerate and progesterone was used while in the second one letrozole was used to induce ovulation and hence prepare the endometrium for vitrified–warmed ET.

2. Participants and methods

This is a retrospective study, which was performed in Al-Banoon fertility center in Zagazig city between 2013 and 2014.

Vitrified–warmed embryos transfer cycles were grouped as artificial cycles (group 1) and letrozole cycles (group 2), based on endometrial preparation method used.

2.1. Artificial cycle

Ultrasound evaluation of the patients was performed to confirm ovarian quiescence then estradiol valerate 2 mg three times daily was started from day 2 or 3 of the cycle (without prior pituitary suppression by GnRH) for endometrial preparation.

The patients were evaluated after 10–15 days, by TVS, to assess the endometrial thickness. When the endometrium reached a minimum thickness of 7–9 mm, progesterone was started vaginally (Cyclogest vaginal pessaries 400 mg twice/day) as a luteal phase support. Vitrified–warmed ET was scheduled 3–4 days after starting progesterone (according to the day of embryos vitrification).

If the endometrium had not reached a thickness of 7 mm, the estradiol valerate was continued for another 5–7 days with increasing the dose to 4 mg twice daily. If the endometrium did not reach 7 mm thickness after 21 days of estradiol supplementation the cycle was canceled.

The same doses of estrogen and progesterone were continued until 14 days after vitrified–warmed ET when a serum hCG level was measured. If the pregnancy test was positive, the estradiol was continued till 8 weeks and progesterone till the end of first trimester.

2.2. Letrozole cycle

Letrozole was used to induce follicular growth and, hence, endometrial preparation by natural hormones derived from the growing follicles.

Following initial TVS (to exclude ovarian cysts), Letrozole (Femara) 2.5 mg/day was started from day 3 of the menstrual cycle and continued for five consecutive days.

Ultrasonographic (TVS) folliculometry and endometrial evaluation was started on the 8th day of the cycle and follow-up was scheduled according to the response.

When the follicle reached $\geqslant$17 mm and the endometrium $\geqslant$7 mm, hCG was given in a dose of 10.000 IU to trigger ovulation. Progesterone was started vaginally (Cyclogest vaginal pessary 400 mg twice/day) as a luteal phase support. Vitrified–warmed ET was scheduled 3–4 days after starting progesterone (according to the day of embryos vitrification).

Vaginal progesterone supplementation was continued until 14 days after vitrified–warmed ET when a serum hCG level was measured. If the pregnancy test was positive, progesterone supplementation was continued till the end of first trimester.

Warming of vitrified embryos was done on the day of ET or the day before it. Embryos were transferred if at least >50% of their blastomeres were survived.

The primary outcome was the clinical pregnancy rate per vitrified–warmed ET, which was defined as the presence of gestational sac on ultrasound conducted 4 weeks after ET.

The secondary outcomes were ongoing pregnancy and first trimester abortion rates. Ongoing pregnancy was defined as pregnancy beyond 12th week of gestation.

This study was approved by the ethical committee of AlBanoon fertility center.

3. Statistical analysis

Analysis was performed using IBM Statistical Package for Social Science software (SPSS statistics version 19.0).