# Luteal phase support for patients undergoing frozen-thawed embryo transfer cycles - the required progesterone dose

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**Summary**

*Objective:* With the recent trend toward single-embryo transfer (ET), cryopreservation of extraneous embryos is becoming increasingly prevalent. Several replacement protocols for frozen-thawed ET exist, with no consensus regarding the dosage or delivery mode of progesterone.

*Patients and methods:* Hormonal replacement with only estrogen and progesterone is the most frequently used protocol in women with and without functioning ovaries in our unit. Since August 2005, we have doubled the usual daily dose of progesterone for luteal support due to a high prevalence of patients experiencing withdrawal bleeding 11-13 days after ET. We compared the outcome of frozen-thawed ET cycles using different doses of progesterone for luteal support.

*Results:* While the prevalence of embryos that survived the thawing process was significantly higher in the earlier (69%) as compared to the later period (58%), positive b-hCG pregnancy rates (17.5% vs 44.8%, respectively) and clinical pregnancy rates per transfer (7.9% vs 41.4%, respectively) were significantly higher in the later period.

*Conclusion:* We conclude that high-dose progesterone supplementation in the luteal phase of frozen-thawed ET cycles results in a significantly higher clinical pregnancy rate.

*Key words:* Luteal phase support; Progesterone; Pregnancy; IVF; Cryopreservation.

## Introduction

With the recent trend toward single embryo transfer (ET) in an attempt to reduce the risk of multiple pregnancy [1-3], the remaining extra embryos are cryopreserved providing further possibilities for conception after the initial fresh transfer. There are several currently employed replacement protocols for frozen-thawed ET [4], all are based on understanding the physiology of human endometrial development after exogenous administration of estrogen and progesterone [5]. Moreover, their success requires that the embryonic stage at thawing be synchronized with the date of the endometrium within the endometrial preparation cycle [6]. While there is a consensus regarding the duration, route of delivery and dosage of estrogen supplementation, and the optimal ultrasonographic endometrial appearance and thickness, the effect of the different modes of progesterone delivery or doses remains unclear [7, 8].

In our practice, we observed that patients undergoing frozen-thawed ET cycles reported a relatively high rate of withdrawal bleeding 11-13 days after ET with a consequent low pregnancy rate. Therefore, beginning August 2005 and continuing to date, we doubled the usual progesterone dose supplementation in the luteal phase. We present here the comparison of our frozen-thawed ET cycle outcomes from this period with those of the preceding 2.5 years.

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## Materials and Methods

From January 2003 to July 2005, 83 patients underwent frozen-thawed ET cycles in our IVF unit. Endometrial preparation included 6 mg micronized 17-β-estradiol (Estrofem, Novo Nordisk, Denmark) or estradiol valerate (Progynova, Schering Pharmaceuticals, Germany) starting on the second day of the menstrual cycle. After ten days of estrogen exposure the patients were asked to attend the clinic, and from this point they were monitored by serial ultrasound scanning for endometrial thickness and serum estradiol and progesterone levels. Progesterone supplementation was added whenever a triple-line pattern endometrium reached 8 mm thickness concomitant with a follicular level of plasma progesterone. The dose of progesterone was 50 mg IM daily (Gestone, Ferring-Lapidot), or 100 mg bid of progesterone vaginal tablets (Endometrin, Ferring- Lapidot).

From August 2005, 31 patients underwent frozen-thawed ET cycles in our IVF unit. During this period, we used the same endometrial preparation protocol with a higher progesterone supplementation. Luteal support consisted of 100 mg of progesterone IM daily, or 200 mg bid of progesterone vaginal tablets.

The clinical outcomes of the frozen-thawed ET cycles were compared between the two periods. The only difference between the two periods was the raising of the dose of progesterone. Clinical pregnancy was defined as visualization of a gestational sac and fetal cardiac activity on transvaginal ultrasound.

Statistical analysis was performed with the Student's t-test and/Chi square, as appropriate. Results are presented as means ± standard deviations; $p < 0.05$ was considered significant.

## Results

Table 1 details the clinical outcome of the frozen-thawed ET cycles in the two periods. While the prevalence of embryos that survived the thawing process was higher in the earlier period ($p < 0.04$), positive β-hCG pregnancy rates and clinical pregnancy rates per transfer were significantly higher during the later period using the higher progesterone dose.

Table 1. — *Clinical outcomes of the frozen thawed ET cycles during the two periods.*

| Characteristics | Jan 2003-Jul 2005 | Aug 2005-Feb 2006 | Significance |
|---|---|---|---|
| No. of patients | 83 | 31 | |
| Mean patient age (y) | 30.6 ± 5.0 | 30.9 ± 5.5 | ns |
| No. of ET cycles/ no. of initiated cycle (%) | 63/83 (76%) | 29/31 (93.5%) | ns |
| No. of embryos thawed | 196 | 112 | |
| No. of surviving embryos/ no. of embryos thawed (%) | 136 (69%) | 65 (58%) | 0.04 |
| No. of embryos transferred per cycle | 1.86 ± 1.1 | 2.2 ± 0.8 | ns |
| No. of positive β-hCG/ no. of ET cycles (%) | 11/63 (17.5%) | 13/29 (44.8%) | < 0.01 |
| No. of clinical pregnancy/ no. of ET cycles (%) | 5/63 (7.9%) | 12/29 (41.4%) | < 0.001 |

## Discussion

Perinatal morbidity following IVF cycles are mainly attributed to the high incidence of multiple births, which relates to the number of embryos transferred. Thurin et al. [1] showed that transferring one fresh embryo and then, if needed, one frozen-and-thawed embryo dramatically reduces the rate of multiple births while achieving a rate of live births that is not substantially lower than the rate that is achievable with a double-embryo transfer. This trend toward single-embryo transfer results in the cryopresevation of more extra embryos for future replacement.

While studies dealing with parameters that predict the implantation rate of thawed embryos have usually examined embryologic parameters during different cooling/thawing protocols, the use of assisted hatching or previous IVF cycle outcome [9, 10], most studies found no statistically significant difference in outcome according to the method of endometrial preparation used [4]. Moreover, in a systematic review on luteal phase support in infertility treatment, Pritts and Atwood [7] concluded that the question of which dose of progesterone supplementation or which type of drug formulation to use is presently unanswered.

In the present study we clearly observed a significantly higher clinical pregnancy rate with the use of high-dose progesterone supplementation in the luteal phase of frozen-thawed ET cycles, using an endometrial preparation with estrogen and progesterone. These higher doses are apparently necessary and in accordance with the absence of corpora lutea in this protocol, which has actually been modeled on the natural menstrual cycle [11].

The choice of an endometrial preparation protocol for frozen-thawed ET cycles depends on the individual woman's ovarian function and convenience of the method, as well as on the experience gained with the method by the team. Regardless of the protocol used, we suggest increasing the progesterone luteal support to levels we have suggested in order to increase clinical pregnancy rates.

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