Luteal phase progesterone increases live birth rate after frozen embryo transfer

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Objective: To see if progesterone support has a beneficial effect on live birth rate after frozen embryo transfer in natural cycles.
Design: Prospective randomized controlled trial.
Setting: University-based hospital.
Subject(s): Four hundred thirty-five women undergoing embryo transfer in natural cycles.
Intervention(s): The women received either vaginal progesterone, 400 mg twice a day from the day of embryo transfer in natural cycles, or no progesterone support.
Main Outcome Measure(s): Live birth rate, biochemical pregnancy rate, pregnancy rate, and spontaneous abortion rate.
Result(s): Live birth rate were significantly greater in women receiving vaginal progesterone as luteal phase support after frozen–thawed embryo transfer in natural cycles compared with those who did not take progesterone. There were no differences in biochemical pregnancy rate, pregnancy rate, or spontaneous abortion rate.
Conclusion(s): Progesterone supplementation improves live birth rate after embryo transfer in natural cycles. (Fertil Steril® 2011;95:534–7. ©2011 by American Society for Reproductive Medicine.)

Key Words: Progesterone, pregnancy rate, live birth rate, frozen embryo transfer, natural menstrual cycle

Single-embryo transfer has become standard procedure to avoid multiple pregnancies in in vitro fertilization (IVF) and embryo transfer. Recently, it was shown that single-embryo transfer in combination with cryopreservation is more effective as regards cumulative birth rate, more cost-effective, and results in a lower number of twins than double-embryo transfer (1). Furthermore, the receptiveness of the endometrium is seriously compromised by controlled ovarian stimulation protocols (2). Therefore, transfer of frozen–thawed embryos in natural cycles is a preferred choice for women with normal ovulatory menstrual cycles.

Progesterone is a prerequisite for development of the endometrium and implantation of an embryo. Transformation of the endometrium to a receptive phase depends on adequate progesterone exposure in addition to preceding estrogen priming (3). Low levels of circulating progesterone during early pregnancy may result in miscarriage (4). In women with proven fertility, production of progesterone from the corpus luteum is sufficient to support the endometrium and facilitate implantation. There is little controlled data regarding the need of progesterone supplementation if an embryo is transferred during a natural cycle to an infertile woman, and there is no consensus about the possible benefits of progesterone supplementation.

There are varying practices among clinics; some offer supplementation with progesterone after embryo transfer in natural cycles, whereas others do not. Generally, there is a belief that endogenous production of progesterone is sufficient to support implantation in a natural cycle. Beneficial effects of high doses of progesterone after frozen embryo transfer in artificial cycles were shown by Orvieto et al. (5). In another report, after fresh embryo transfer there was no effect on pregnancy and implantation rates among women receiving micronized progesterone as luteal phase supplementation (6). Frozen–thawed embryo transfer in a natural cycle is a different situation. The women involved are often subfertile, and they may have suboptimal endometria during their natural cycles.

In view of the above, we designed a prospective randomized study to investigate if pregnancy rates could be improved with vaginal progesterone supplementation during the luteal phase and early pregnancy after frozen–thawed embryo transfer.

MATERIALS AND METHODS

Subjects

Women scheduled for frozen embryo transfer were asked to participate in the study. Four hundred thirty-five women agreed to participate, and were randomized to either vaginal micronized progesterone supplementation (n = 219) or to no supplementation (n = 216). The women included had been initially diagnosed with unexplained infertility, tubal factor infertility, or male factor infertility.

Ethics

The Ethics Committee at Karolinska Institutet approved the study. There is no institutional review board at Karolinska Institutet. None of the investigators had any conflict of interest in relation to this study. Informed oral and written consent was obtained from all participating women.

Study Design

The study was designed as a prospective randomized controlled trial. At the day of embryo transfer, the women were asked to participate in the study. They were randomly allocated to either the progesterone or the no-progesterone group. Allocation was performed by using opaque sealed

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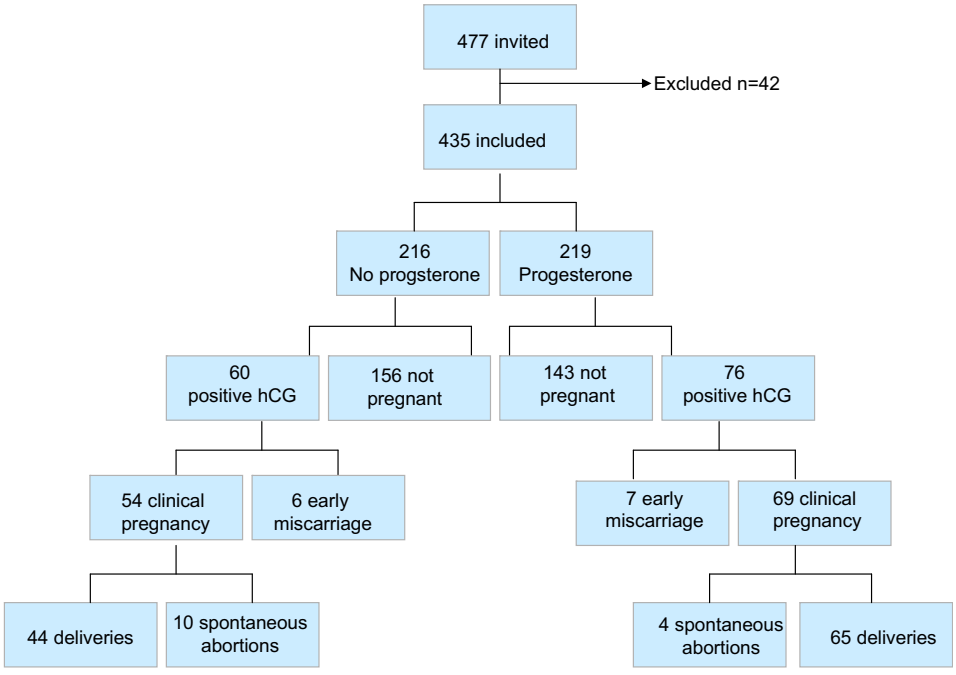
FIGURE 1

The number of women included in the study, and the numbers of positive hCG test results, early miscarriages, clinical pregnancies, spontaneous abortions, and deliveries are shown.



Bjuresten. Progesterone and live birth rate. Fertil Steril 2011.

envelopes. The study was an open trial, because it was not possible to obtain a placebo alternative to micronized progesterone. The study was not supported by any pharmaceutical company, and the hospital pharmacy could not produce the placebo needed. Power calculation showed that 213 subjects in each group were needed to detect a difference of 15% at the 80% level and an α value of 0.05.

Treatment

The control women did not receive any hormone supplementation. The treated women received vaginal micronized progesterone, 400 mg twice a day, starting from the evening of the day of embryo transfer. A vaginal ultrasonographic scan was performed once for each woman included in the study, on cycle days 10 to 14. The ovaries were visualized and the diameter of the leading follicle was measured. On the day the leading follicle had reached 16 mm in diameter, the women started daily urine tests in the morning to detect the LH surge, using Clearblue digital ovulation tests (Swiss Precision Diagnostics GmbH, Bedford, UK). Three days after the LH surge, the embryo/embryos were thawed and embryo transfer was performed. Embryo transfer was performed using either a Sidney K-jets-7019 SIVF catheter (COOK, Queensland, Australia) or an Emtrac 4219 Delphin catheter (Gynétics Medical products N.V., Hamont-Achel, Belgium). One midwife (K.B.) transferred all the embryos.

Outcome Measures

The main outcome measures were positive pregnancy test results, indicated as measurable serum human chorionic gonadotropin (hCG) concentrations, early miscarriage rate, clinical pregnancy rate, spontaneous abortions, and live birth rate.

Statistics

Statistical evaluation was performed by using a chi-square test, with SPSS software (SPSS, Chicago, IL, USA).

Definitions

The quality of embryos transferred was evaluated as either grade A, with all blastomeres intact, or grade B, with between 50% and 100% of blastomeres intact. Lower quality embryos were not transferred.

Pregnancy was confirmed by a positive result in a urine hCG test conducted 18 days after frozen embryo transfer. The positive hCG rate was determined as the ratio between the number of positive hCG tests and the total number of transfers. The clinical pregnancy rate was defined as the number of cases with evidence of at least one gestational sac, divided by the number of transfers. The early miscarriage rate was defined as the number of early pregnancy losses divided by the total number of transfers. The clinical abortion rate was defined as the number of clinical pregnancy losses before the 20th week of gestation divided by the number of transfers. The live birth rate was the ratio of live births to embryo transfers.

RESULTS

Study Subjects

Of the initial 477 women invited to participate, 435 were included in the study. Forty-two women were excluded for the following reasons: 34 did not want to participate, 3 presented with ovarian dysfunction, 2 received a donated oocyte, 1 had cancer, 1 had rheumatoid arthritis, and 1 was excluded because she was already included in another study (Fig. 1). Women who were later found to have endometriosis were included in the data analysis. The distribution of diagnoses was similar in the two groups (Table 1).

The women who did not want to participate in the study had negative experiences of previous use of progesterone. The mean age of the women in the progesterone group was 35.0 $\pm$ 3.68 years, and the mean age of the women in the no-progesterone group was 34.2 $\pm$ 3.56 years.

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