
EFFECT OF STARTING PROGESTERONE SUPPORT ON THE DAY BEFORE VERSUS THE DAY OF EMBRYO TRANSFER ON THE OUTCOME OF ICSI CYCLES

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ABSTRACT

Objective:: To compare the effect of two different times of onset of luteal phase support on ongoing pregnancy rate in infertile patients undergoing treatment with GnRH down-regulated IVF and embryo transfer (IVF/ET).

Design: prospective randomized trial.

Setting : Assisted reproductive technology program at the shatby university hospital for women , and Madina infertility Private center in Alexandria.

Patients : one hundred and forty patients undergoing IVF-ICSI program.

Intervention: All patients planned to undergo their first IVF treatment cycle were randomly allocated to receive parentral progesterone as luteal support at two different time points, that is, the day before embryo transfer (ET) and at the day of ET. The primary endpoint of this study was ongoing pregnancy rate.

Main outcome Measures: Clinical pregnancy rates.

Results : A total of 140 women were randomized; 70 were allocated to the day before embryo transfer group , and 70 to the group of the day of ET. An ongoing pregnancy rate was 22.7% in the day before embryo transfer group versus 23.6% at the day ET group, respectively.

Conclusion : We could not identify, within the chosen time points and within the sample size, a specific implantation window period in which an optimal endometrial receptivity yields the highest pregnancy rate.

Key words: ICSI, oocytes, fertilization.

INTRODUCTION

The use of GnRH agonists for preventing premature LH surges in controlled ovarian hyperstimulation in IVF/embryo transfer (IVF/ET) has greatly improved the planning of oocyte retrieval (OR). Pituitary function does not resume completely until 2-3weeks after the end of GnRH-agonist characterized by a decline in serum estradiol (E₂) and progesterone 8 days after HCG administration for oocyte maturation⁽¹⁾. This decline in steroids was

thought to have a negative effect on pregnancy rate and exogenous supplementation of progesterone or HCG, i.e. luteal phase support, proved indeed to be mandatory (2, 3).

In all available studies the time of onset of administration of parentral progesterone for luteal phase support ranged randomly from the day before OR to 4 days after ET. Only three randomized studies have been performed to assess the impact of the moment of starting luteal phase support on pregnancy rate in GnRH agonist down-regulated IVF

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cycles. In the first study, a decrease of 12% in pregnancy rate was seen when progesterone was started 12 h before OR compared to 12 h after OR (4). In the second study, a decrease of 24% was seen when progesterone support was delayed until 6 days after OR compared to 3 days after OR (5). In the third study, no difference was found when luteal phase support was started at OR compared to starting at ET (6).

The chosen time points of the start of progesterone support assessed in these randomized studies, however, did not cover the complete implantation window.

The aim of this study, therefore, was to assess the impact of the onset of progesterone support on ongoing pregnancy rate.

We compared administration of parenteral progesterone starting the day before embryo transfer and the day of embryo transfer, in a randomized clinical trial, in infertile patients undergoing treatment with GnRH agonist down-regulated IVF/ET.

MATERIALS & METHODS

The study included 140 women undergoing IVF-ICSI program for both male and female infertility. These women were counseled about the experimental nature of the protocol, and a signed consent was obtained from every patient and her partner to be included in the study. Patients were randomly divided into two equal groups.

After informed consent, patients were assigned to two different luteal phase support groups and received 200 mg parenteral progesterone (prontogest 100mg IBSA) intramuscular (i.m.) starting at the day before embryo transfer or at the day of ET. Parenteral Progesterone treatment was continued until the onset of menstruation, or until 18 days following ET. The randomization was performed at a baseline visit by

fertility doctors by opening a sealed opaque envelope containing the arm of treatment. The envelopes were prepared and numbered by the main investigator.

The IVF treatment was performed according to a local standard protocol described earlier (7). Venous blood samples for serum E_2 (nmol/l) and progesterone (nmol/l) were drawn at OR and on the 3rd, 6th, 9th, 12th and 18th day after OR and were assessed with a radioimmunoassay assay (DPC, Los Angeles, CA, USA) for E_2 and (Orion Diagnostica, Espoo, Finland) for progesterone.

Biochemical pregnancies were defined as an increase in serum HCG >2 IU/ml or a positive pregnancy test assessed at the 18th day after oocyte retrieval (Tandem ICON test; Hybritech, San Diego, CA, USA). Clinical pregnancies were defined as a gestational sac seen by transvaginal ultrasound at the 35th day after oocyte retrieval. Ongoing pregnancies were defined as a positive fetal heartbeat by transvaginal ultrasound 10 weeks after OR.

Statistical Analysis :

Statistical analysis were performed using the χ^2 or t-test as appropriate. All P-values quoted with values < 0.05 indicate statistical significance. Analysis were performed using the SPSS statistical package (SPSS, Inc, Chicago).

RESULTS

The study included 140 women undergoing IVF-ICSI program for male, and/or female infertility. They were randomly divided into two groups : those who received parenteral progesterone the day before embryo transfer (Group I), which included 70 women, and those who received parenteral progesterone on the day of ET (Group II), which also included 70 women. Both groups were homogenous as regards age distribution (33 years \pm 0.4 in Group I, and 32.7 years \pm 0.6 in Group II) and infertility duration (3.5 \pm 1.5 years in Group I and 3.4 \pm 1.4

years in Group II). The mean number of the stimulation days, and the retrieved oocytes were not significantly different as shown in table I.

Also the mean number or quality of transferred embryos or the total number of frozen embryos did not show any significant difference as

shown in the table.

Mean serum E₂ and progesterone levels did not differ between the two groups . Lastly, there were no significant differences between the two groups in biochemical, clinical and ongoing pregnancies or live birth rates.

Table I : Impact of day of onset of luteal support on the success of IVF/ET and ICSI.

	Day before ET (I)	Day of ET (II)	P value
Stimulation days (SD)	9.6 (2.7)	9.8 (2.4)	NS
No. of retrieved oocytes (SD)	10.3 (8.4)	9.7 (6.6)	NS
Number of emb. transfered (SD)	2.1 (0.7)	2.2 (0.7)	NS
Number of frozen embryos (SD)	2.1 (3.9)	1.7 (3.2)	NS
% Biochemical preg.	30% (n = 21)	32% (n = 22)	NS
% Clinical preg	28% (n = 19)	29% (n = 20)	NS
% On going preg	22.7% (n = 15)	23.6% (n = 16)	NS
% Live birth	21.1% (n = 14)	20.5% (n = 14)	NS

* P < 0.05

DISCUSSION

Synchronization of the fertilized egg and the receptivity of the endometrium, i.e. the implantation window, are regarded as essential in the success rate of IVF/ET (8). *In vivo*, a small, but distinct, increase of endogenous progesterone is already seen concurrently with the LH surge. After the LH surge, it takes 36-48h for progesterone to transform the proliferative endometrium into secretory-phase endometrium. The *in vivo* fertilized embryo usually arrives at the uterine cavity 72-96h after ovulation, leaving sufficient time for the completion of the transformation of the endometrium (9). Compared to *in vivo* fertilized embryos, the *in vitro* fertilized embryos arrive earlier in the uterine cavity, i.e. 72h after OR. Starting luteal phase support early in order to achieve a more advanced endometrium seems, therefore, preferable(10). This was also observed in

an oocyte donor programme, where the highest pregnancy rates were found in patients who were pretreated with progesterone for at least 3 days or more (11).

Another method for achieving synchronization between endometrial receptivity and the embryo is varying the day of ET. A Cochrane review showed significantly higher clinical pregnancy rates of day three transferred embryos versus day two transferred embryos(12). Unfortunately, in this review, data concerning the start of luteal phase support was lacking.

The present randomized study aimed to create two different implantation windows by adjusting the luteal phase of an IVF treatment cycle, while the day of ET was fixed on day 3. As luteal support, we used progesterone administered intramuscularly and not HCG, since HCG significantly increases the risk of ovarian hyperstimulation syndrome (Odds Ratio

3.06) (95% CI 1.59-5.86)⁽³⁾ with similar ongoing pregnancy rates.

In conclusion we could not identify, within the chosen time points and within the sample size, a specific implantation window period in which an optimal endometrial receptivity yields the highest pregnancy rate. Further controlled randomized clinical trials are needed to confirm these preliminary data.

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