Delaying the initiation of progesterone supplementation until the day of fertilization does not compromise cycle outcome in patients receiving donated oocytes: a randomized study

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Objective: To determine whether the initiation of P supplementation as artificial luteal phase support (day −1, day 0, or day +1 of egg donation) in extensive programs of ovum donation influences cycle cancellation, pregnancy outcome, and implantation rate in day 3 embryo transfers.
Design: Prospective randomized trial.
Setting: Oocyte donation program at the Instituto Valenciano de Infertilidad, Valencia, Spain.
Patient(s): Three hundred recipients with normal ovarian function, absence of uterine anomalies, and undergoing their first egg donation were recruited between September 2003 and September 2004.
Intervention(s): A computer-based randomization divided the recipients into three groups when hCG was administered to their matched donors. The first group (group A) started P supplementation the day before oocyte retrieval; the second group (group B) started P supplementation on the day of the oocyte retrieval; and the third group (group C) started P supplementation 1 day after the egg retrieval once fertilization was confirmed.
Main Outcome Measure(s): Implantation, pregnancy, and ongoing pregnancy rates were the primary outcome measures considered. The secondary outcome measure was the cancellation rate, especially due to fertilization failure.
Result(s): Global cancellation rate and cancellation rate due to fertilization failure were significantly higher in group A (12.4% and 8.2%, respectively) than in group C (3.3% and 0%, respectively). Reproductive outcome was similar in all the groups except for a higher biochemical pregnancy rate in group A (12.9%) than in groups B (6.6%) and C (2.3%).
Conclusion(s): Initiation of P on day +1 of embryo development decreases cancellation rates of day 3 embryo transfers in extensive programs of ovum donation without any deleterious effect on pregnancy outcome or implantation rate. (Fertil Steril® 2006;86:92–7. ©2006 by American Society for Reproductive Medicine.)

Key Words: Oocyte donation, initiation of progesterone supplementation, embryo transfer, endometrial receptivity, implantation window

In recent years ovum donation has been considered, on an international level, as the most effective assisted reproduction technology for women whose oocytes are of poor quality or do not produce oocytes. There are varying protocols for donor–recipient synchronization, which are determined mainly by the ovarian function of the recipient, the availability of donors, and recipient demand.

When ovarian function persists, it is viable to prepare the endometrium after a natural cycle or hormonal replacement therapy (estrogen plus P), with or without prior administration of a GnRH agonist (GnRH-a). When ovarian function is nonexistent, hormonal replacement therapy is mandatory (1–3).

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In some egg donation programs, the availability of donors or recipient demand is low. Therefore, a perfect synchronization must be achieved between donor and recipient (one to one) with simultaneous initiation of endometrial preparation of the recipient on the one hand and controlled ovarian hyperstimulation (COH) of the donor on the other (4).

In this way, a perfect synchronization in the dialogue between embryo and endometrium can be obtained, facilitating embryo transfer to the endometrium at the appropriate moment, known as the "implantation window" (5, 6). However, cancellation of the donor due to an inadequate ovarian response, albeit in relatively few cases, is the principal handicap of these protocols.

On the other hand, in large programs with a high number of recipients on the waiting list who are receiving estrogen therapy the main disadvantage is the high cancellation rate (approximately 20%) due to the endometrial bleeding that

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often occurs while waiting for a donor to be found and a transfer performed (7).

This could be avoided with limited E_2 replacement therapy for every recipient undergoing endometrial preparation and with embryo transfer once a healthy endometrial thickness and pattern has been confirmed (8, 9).

This is possible when there is a constant pool of donors available undergoing COH, so that once a recipient is ready, she can be matched immediately with the donor that proves most compatible according to her phenotype and blood group. Following this procedure, recipient "waiting time" after the initiation of estrogen administration tends to be less than 40 days, a period during which endometrial bleeding is unusual (10).

The primary problem with initiating P administration as an artificial luteal phase support on the day of or day before egg donation, as some investigators have described (3, 4), is the significant cancellation rate due to failure to achieve fertilization, mainly due to sperm anomalies or, to a lesser extent, low quality of the oocyte.

A possible solution is to begin P supplementation on the day after egg donation, once fertilization has been confirmed. In this way, when gamete quality is inadequate or fertilization has not occurred, P administration is postponed and recipients continue with estrogen therapy until eggs from another compatible donor or partner/donor sperm sample become available, thereby affording recipients a "second chance."

The only foreseeable handicap of this measure is that cell-stage embryos (on day 2 or 3 of development) could be transferred to an endometrium that is not yet prepared (day 1 or 2 of P supplementation) and, therefore, outside the "implantation window" (11, 12).

The aim of the present randomized study was to determine the effect of P administration (as an artificial luteal phase support) on the pregnancy outcome of day 3 embryo transfers with respect to day of initiation (day −1, day 0, or day +1 of egg donation) and its impact on cycle cancellation as a result of fertilization failure.

MATERIALS AND METHODS

This is a prospective randomized study that was approved by the Institutional Review Board and carried out at the Instituto Valenciano de Infertilidad, Valencia, Spain, between September 2003 and September 2004.

Subject inclusion criteria were oocyte recipients with active ovarian function and showing absence of uterine anomalies, who underwent a day 3 embryo transfer. The following were indications for egg donation: endometriosis, failure of previous assisted reproduction technology attempts, genetic or chromosomal anomalies of maternal origin (including recurrent pregnancy losses), poor oocyte quality, low ovarian response, and advanced age.

Oocyte Donors

In Spain, ovum donation is voluntary and anonymous. Donors are aged between 18 and 35 years and must be healthy, with no family history of chromosomal diseases. They must undergo a complete gynecological examination, karyotype, and screening for infectious diseases such as HIV, hepatitis B and C, gonoccocia, and lues.

The protocol for COH has been described elsewhere (13). In brief, pituitary desensitization with daily SC administration of 1 mg of leuprolide acetate (LA; Procrin, Abbott S.A., Madrid, Spain) or inhaled administration of 800 μg of nafarelin (Synarel, SEID Laboratories, Barcelona, Spain) was initiated in the luteal phase of the menstrual cycle. This dose was continued until ovarian quiescence was confirmed by ultrasound during the subsequent menstruation, at which point the dose of the GnRH-a was halved.

On days 1 and 2 of ovarian stimulation, recombinant FSH (Gonal-F, Serono Laboratories, Madrid, Spain; or Puregon, Organon, Barcelona, Spain) or highly purified hMG (Menopur, Ferring, Madrid, Spain) were administered; the dose varying between 150 and 300 IU/day depending of the age of the donor, body mass index, ovarian pattern, menstrual cycles, basal hormones, and response to previous COH (if any).

From day 3 onward, gonadotropin doses were adjusted every second day according to serum E_2 levels and ovarian appearance as detected by vaginal ultrasound. Human chorionic gonadotropin (Ovitrelle, Serono Laboratories) was administered SC when at least two leading follicles reached a mean diameter of $\geq$18 mm.

Daily GnRH-a and gonadotropin administration were discontinued on the day of hCG administration. Transvaginal oocyte retrieval was scheduled 36 hours later. Donors were matched with recipients according to phenotype and blood group.

Oocyte Recipients

Three hundred recipients with active ovarian function and no uterine anomaly, who had not undergone previous egg donation, were admitted for the study.

Patients underwent ovum donation because of the women's age (47.6%), low response to ovarian stimulation (25.6%), implantation failure (8.5%), severe endometriosis (8.5%), and other causes such as recurrent pregnancy loss, bad oocyte quality, or genetic infertility (9.8%).

The protocol for steroid replacement included pituitary desensitization with a single intramuscular ampule administration of 3.75 mg of triptorelin (Decapeptyl depot 3.75, Ipsen Pharma, Madrid, Spain) in the midluteal phase of the menstrual cycle.

Hormonal replacement therapy was initiated when ultrasound confirmed ovarian quiescence during the following menstruation. Two milligrams of E_2 valerate (Progynova,