Case Report: Pregnancies Established by Gamete Intrafallopian Transfer and Pronuclear-Stage Transfer in Patients with Premature Ovarian Failure Using Donated Oocytes and Low-Dose Oral Micronized Estradiol and Progesterone

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This report describes both gamete intrafallopian transfer (GIFT) and pronuclear-stage transfer (PROST) of donated oocytes to patients with premature ovarian failure (POF), using micronized oral progesterone (P₄) and low-dose micronized estradiol (E₂) for endometrial preparation and maintenance. Patient A, with POF of 15 years' duration, received four donated oocytes for GIFT and subsequently delivered a normal, term, female infant. Patient B was diagnosed as POF 3 years ago. She received four donated oocytes, which were subsequently fertilized in vitro with husband's sperm. The following day, four pronuclear-stage embryos were transferred to her fallopian tubes. She recently delivered twin, healthy female infants. These procedures, along with exogenous hormonal development of the endometrium, provide a simplified means to establish and maintain pregnancy in POF patients. Both patients were maintained on low-dose oral micronized estradiol prior to their procedure. Patient A on 3 mg E₂ per day cyclically and Patient B on 0.5 mg E₂ continuously. Micronized oral P₄ was used to maintain pregnancy.

KEY WORDS: gamete intrafallopian transfer (GIFT); pronuclear-stage transfer (PROST); premature ovarian failure (POF); micronized steroids; pronuclear.

INTRODUCTION

The use of donated oocytes was first reported in 1983 (1), with the first delivery reported in 1984 (2). This early success led to the possibility of establishing pregnancy in anovulatory women suffering from premature ovarian failure (POF). This group of patients has been estimated to comprise 85% of women requiring donor oocytes (3). The use of controlled ovarian hyperstimulation for in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) has provided the opportunity for oocyte donation when cryopreservation of excess embryos is not desired. Additionally, in most reports of successful oocyte donation with POF patients, the authors have utilized intramuscular injections of progesterone or intravaginal progesterone suppositories to maintain pregnancy (4–6).

The following is a report of two cases of oocyte donation to patients with premature ovarian failure, one patient undergoing GIFT simultaneously with the donor and the other undergoing pronuclear-stage transfer (PROST) the day after donor oocyte retrieval. Both individuals were maintained on low-dose oral micronized estradiol and oral micronized progesterone for endometrial development and maintenance of pregnancy.

MATERIALS AND METHODS

Patient A. This patient, age 33 years, was diagnosed at age 18 years as premature ovarian failure. Since April 1, 1985, she has been treated with 3.75 mg of conjugated estrogens daily (Premarin, Wyeth-Ayerst, Philadelphia, PA) and with medroxyproges-
terone acetate (MPA) cyclically. On the day corresponding to cycle day 1, the patient began taking micronized estradiol-17B (Estrace, Mead-Johnson, Evansville, IN), 3 mg per day in divided doses. The oocyte donor received clomiphene citrate (CC; Serophene, Serono, Inc., Randolph, MA), 100 mg per day from cycle day 2 through cycle day 6, and human menopausal gonadotropin (hMG; Pergonal, Serono Inc., Randolph, MA), 150 IU from cycle day 2 through cycle day 9. The oocyte recipient began taking micronized progesterone (P4) capsules (400 mg every 8 hr) the day prior to GIFT and continued Estrace at a dosage of 3 mg per day. These dosages were judged adequate by endometrial biopsy 2 months previous and by peripheral hormone levels measured by radioimmunoassay.

At oocyte aspiration, seven mature oocytes were retrieved. Three were transferred to the fallopian tubes of the donor, along with $5 \times 10^4$ motile spermatozoa/oocyte from the donor’s husband. Four oocytes were transferred to the fallopian tubes of the recipient along with $5 \times 10^4$ motile spermatozoa/oocyte from the recipient’s husband.

All oocyte culturing, spermatozoal washing, swim-up, and gamete transfer were performed with Ham’s F10 (GIBCO, Grand Island, NY) combined with 7.5% (v/v) heat-inactivated maternal serum.

**Patient A**. This patient, age 30 years, was diagnosed at age 27 years as premature ovarian failure. The patient had been treated with conjugated estrogens and progestagens. In August 1987, the patient was placed on micronized estradiol-17B (Estrace, Mead-Johnson, Evansville, IN) at a dosage of 1 mg per day continuously and medroxyprogesterone acetate (MPA), 10 mg per day for calendar days 1–5, in order to maintain the endometrium for possible oocyte donation. In May 1988, Estrace was lowered to 0.5 mg daily, cycle days 1–30, due to prolonged bleeding following MPA. The patient continued on this dosage until the prospect of donor oocytes became eminent. The oocyte donor was undergoing a GIFT cycle. The donor received CC (100 mg per day) on cycle days 2 through 6 and hMG (150 IU per day) on cycle days 2 through 10. She received hCG (10,000 IU) on cycle day 11. At laparoscopy, 36 hr later, eight mature oocytes were retrieved. Two hours after oocyte retrieval, the recipient was given estradiol cypionate, 4 mg intramuscularly (im), and progesterone, 25 mg in oil, im. The Estrace dosage was increased to 1 mg three times a day and she began taking micronized P4 capsules, 200 mg every 6 hr. The donor received four mature oocytes and $5 \times 10^4$ motile spermatozoa/oocyte into each fallopian tube. Four mature oocytes were donated to Patient B. These oocytes were inseminated in vitro with $5 \times 10^4$ motile spermatozoa/oocyte from the recipient’s husband. The next morning (18 hr postinsemination), inspection of the oocytes revealed four pronuclear stage embryos. Pronuclear-stage transfer with two zygotes transferred to each fallopian tube was performed 21 hr postinsemination, 27 hr postretrieval.

Beginning the fifth day after oocyte retrieval, the Estrace dosage was increased to 4 mg per day.

**RESULTS**

Ten days post-GIFT, Patient A presented with thin, red spotting. The Estrace dosage was increased to 8 mg per day and P4 was increased to 1600 mg per day at this time. Five days later, 15 days post-GIFT, a quantitative serum hCG level of 704 mIU/ml was obtained. At this time, her serum P4 level was 3953 ng/dl and her serum estradiol (E2) level was 328 pg/ml. Estrace dosage was maintained at 8 mg per day and P4 was maintained at 1600 mg per day. Serum P4 was 10,473 and 7332 ng/dl at 4 and 6 weeks post-GIFT, while E2 was 895 and 842 pg/ml. At 9 weeks post-GIFT, the Estrace dosage was decreased to 6 mg per day and P4 was decreased to 1200 mg per day. At 12 weeks post-GIFT, E2 was discontinued with a serum level of 6320 ng/dl. The patient was transferred for routine obstetric care at 18 weeks and P4 was discontinued at this time (serum level, >3000 ng/dl). Her pregnancy was uneventful, and she gave birth to a normal, healthy, 3300-g female by elective cesarean section. The oocyte donor did not conceive.

Eleven days after PROST, Patient B complained of a slight blood-tinged discharge. Her serum P4 was 1604 ng/dl and her serum E2 was 557 pg/ml. A quantitative serum hCG level of 155 mIU/ml was measured at this time. The P4 dosage was increased to 1200 mg per day. Five days later, serum P4 was 3538 ng/dl, and serum E2 was 621 pg/ml. Serum hCG had increased to 1737 mIU/ml. The following day bright red vaginal bleeding was noticed by the patient, and the P4 dosage was further increased to 1600 mg per day, while the Estrace dosage was increased to 8 mg per day. Intermittent bleeding continued for ap-