SHORT COMMUNICATION

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Trophoblast Persists Despite Lack of Sex-Steroid Support Following Ovum Donation

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INTRODUCTION

It is well established that estrogen (E_2) and progesterone (P) are necessary to prepare and maintain the endometrium for embryo implantation both in natural conception cycles and in assisted reproduction. For this reason, recipients of donated oocytes are typically placed on exogenous hormones prior to embryo transfer. However, the precise hormonal needs and requirements to maintain trophoblastic viability remain unknown. We report persistent growth of trophoblastic tissue in a menopausal woman who had undergone oocyte donation despite discontinuing E_2 and P. The pregnancy, deemed nonviable, eventually required methotrexate and dilation and curettage to terminate.

CASE REPORT

The patient, a 52-year-old gravida 3, para 3003, was discovered to be menopausal 2 years prior to presenting for oocyte donation. She had been actively trying to conceive for 5 years, having undergone three cycles of clomiphene citrate and intrauterine insemination before one unsuccessful attempt at egg donation. Her medical history was unremarkable except for mild osteoporosis confirmed on bone densitometry. Her obstetric history was significant for three births by cesarean sections, in 1974, 1976, and 1980. She was prescribed hormone replacement to ameliorate menopausal symptoms. Her husband had a vasectomy and

a subsequent failed vas reversal. He had undergone an epididymal aspiration and banked spermatozoa.

Her pretransfer evaluation included a normal sonohysterogram, chest x-ray, electrocardiogram, pap smear, and mammogram. She was matched and synchronized to an oocyte donor using a regimen of oral micronized estradiol and intramuscular (im) progesterone. The donor provided nine oocytes, of which four fertilized with intracytoplasmic sperm injection. Two 6-cell and two 8-cell preembryos were transferred transcervically without difficulty 3 days following retrieval. The patient was maintained on micronized estradiol, 4 mg/day, and im progesterone, 100 mg/day.

The recipient returned 9 days posttransfer for pregnancy testing. The serum β -human chorionic gonadotropin (hCG) (day 0) was 9 mIU/ml (2nd IS), rising to 58 mIU/ml 72 hr (day 3) later. However, levels plateaued on day 8 and day 11 (52 and 71 mIU/ml, respectively), at which time her micronized estradiol and P were discontinued. The patient remained asymptomatic, but β -hCG levels continued to rise on day 18, to 95 mIU/ml, in spite of serum E_2 levels less than 20 pg/ml and P a level of 1.1 ng/ml. Transvaginal ultrasound revealed a type-II pattern endometrial strip with a thickness of 12.5 mm. There was no cul-de-sac fluid or adnexal masses. The patient was counseled regarding the abnormal pregnancy and told that she had either a persistent intrauterine pregnancy or an ectopic gestation. Treatment options were discussed and included a dilation and curettage, continued observation, and methotrexate treatment. She elected methotrexate therapy and was given 50 mg im (50 mg/m²).

The patient was contacted daily by telephone and returned to the office on day 22 for repeat serum β -hCG, noted to be 81 mIU/ml. The β -hCG level having failed to fall 15% (75 mIU/ml) from treatment baseline, on day 25 a second injection of methotrexate 50 mg was given im. On day 30 (5 days following her second methotrexate injection), β -hCG levels were still 81 mIU/ml. A third injection of methotrexate was given. On day 33, transvaginal ultrasound revealed a small collection of fluid within the endometrial cavity and a thickness of 13 mm. The β -hCG levels remained 84

mIU/ml. A suction curettage was performed in the office and a fourth injection of methotrexate was administered. Eighteen days following her initial im methotrexate (day 36), her serum β -hCG level finally fell to less than 5 mIU/ml, with an E_2 level of less than 20 pg/ml and a P_4 level of 0.8 ng/ml at castrate levels. Pathology report returned fragments of decidua and chorionic villi. The serum follicle-stimulating hormone and luteinizing hormone levels were 1.0 and 0.7 mIU/ml, respectively, on day +8, rapidly rising to 23.1 and 25.3 mIU/ml 4 days following discontinuation of E_2 and P_4 . No changes in serum DHEA-S, cortisol, and prolactin were noted. Figure 1 displays the post-embryo transfer serum levels of hCG, E_2 , and P_4 .

DISCUSSION

Undoubtedly, complex interactions between maternal, fetal, and placental compartments exist during pregnancy. Trophoblastic rescue of corpus luteal steroidogenesis is believed to be a necessary requirement during the first 4–5 weeks of gestation. Later a "luteoplacental" shift takes place, and the pregnancy may continue without ovarian steroid support. As early as the 6- to 8-cell stage, human embryos appear capable of expressing messenger RNA for hCG and signaling E_2 and P_4 predominantly by the corpus luteum even prior to maternal hCG detection (1).

Trophoblastic hCG production and secretion also appear to effect a complex interaction of sex steroids, cytokines, activin, inhibin, epidermal growth factors, and prostoglandins and, thus, play an autocrine and paracrine role. Gonadotropin-releasing hormone,

which has been localized in the cytotrophoblast, stimulates pulsatile secretion of placental hCG and other peptides including interleukin-1 β (2).

In spite of the importance of sex steroids for maintaining pregnancy, there are reports of successful deliveries in functionally agonadal patients who inadvertently discontinued exogenous E_2 and P_4 following embryo transfer (3,4). Also, unique to recipient cycles, serum follicle-stimulating hormone and luteinizing hormone levels may rapidly rise upon discontinuing exogenous E_2 and P_4 . As a result, rebound ovulation in a perimenopausal woman undergoing ovum donation and methotrexate given for the treatment of an ectopic pregnancy was noted when hormone replacement therapy was discontinued (5).

The persistence of hCG in the absence of sex steroids or rebound ovulation is unique. We hypothesize that other autocrine and paracrine factors including maternal gonadotropin-releasing hormone may continue to stimulate local trophoblastic growth. This seems plausible because complete resolution of serum hCG was seen only following suction extraction. Alternatively, the rapidly rising gonadotropin-releasing hormone secretion resulting from the discontinuation of hormone replacement may have stimulated maternal hCG secretion in a pulsatile fashion in parallel with rising luteinizing hormone levels, which has been reported in postmenopausal women (6).

CONCLUSIONS

A 54-year-old menopausal woman undergoing ovum donation exhibited persistent hCG production

Fig. 1. Summary of serum hormone profiles and interventions.

despite the discontinuation of exogenous steroids and administration of methotrexate. This case underscores the absence of our complete understanding of maternal, placental, and fetal interactions in the maintenance of early pregnancy.

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