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Effect of estradiol on oocyte development

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Abstract

Objective—To determine whether elevated serum estradiol (E₂) concentrations in oocyte donors affect assisted reproduction outcome.

Method—In a retrospective cohort study of 58 consecutive oocyte donation cycles, donors were stratified into 2 groups according to E₂ concentration, group 1 (n=32; E₂≤2000 pg/mL [range 456–2000 pg/mL]) and group 2 (n=27; E₂>2000 pg/mL [range, 2062–6957 pg/mL]). Data were analyzed using the *t* test and χ^2 test.

Results—Donors in group 1 produced significantly less oocytes than donors in group 2 (19.3±1.7 vs 12.0±1.4; *P*<0.001), and recipients of oocytes from group 1 had significantly fewer numbers of embryos available for transfer (10.4±1.1 vs 6.4±0.8; *P*=0.003). However, the mean number (3.3) of embryos transferred and the pregnancy rate were the same in both groups.

Conclusion—Elevated estradiol concentration in oocyte donors did not affect pregnancy outcome, suggesting that estradiol levels in donors do not affect oocyte development.

Keywords

Oocyte donation; Estradiol (E₂); In vitro fertilization; Oocyte biology

1. Introduction

Assisted reproductive technologies (ART) aim at stimulating the ovaries to produce a large number of oocytes and maximize the chances of pregnancy. The effect of supraphysiologic estradiol (E₂) concentration on ART outcome is controversial [1–6]. Recently, it has been suggested that elevated estradiol concentrations may have adverse effects, not only on the endometrium but also on the oocyte and/or embryo [5,6]. More generally, the success of oocyte donation is influenced by multiple factors such as donor age, oocyte and embryo quality, and the recipient's endometrial receptivity [7–9].

In oocyte donation, the donor's gametogenesis and ovarian steroidogenesis are dissociated from the recipient's endometrial development and receptivity, allowing the effects of elevated estradiol concentrations on the embryo to be distinguished from those on the endometrium. One study of oocyte donation cycles that examined the effects of elevated E₂ peak concentrations in donors found a detrimental effect on endometrial receptivity; however, the lack of donor uniformity was certainly a limitation, with recipients receiving supernumerary oocytes from infertile donors who themselves were undergoing in vitro

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fertilization and embryo transfer [5]. Other studies, as well as the present study, used a protocol where each recipient received all the oocytes retrieved from a designated donor, and oocytes from infertile women were not included [1].

To differentiate the effects of elevated estradiol concentration in the donor on the oocyte from the effects of elevated estradiol concentration in the recipient on the latter's endometrium in oocyte donation cycles, we examined the relationships between ART outcome and donor estradiol concentration, quantity of oocytes, and quantity of embryos.

2. Materials and methods

We conducted a retrospective cohort study of 58 consecutive oocyte donation cycles from January 2000 to December 2002 within the framework of the Yale University Oocyte Donation and Surrogacy Program. Specifically, we examined the relationship between cycle characteristics and ART outcomes. Inclusion criteria for oocyte donors were age less than 35 years; serum levels of follicle stimulating hormone less than 10 IU/mL and serum levels of E₂ less than 50 pg/mL on day 3 of the cycle; no history of infertility; and no significant ongoing medical problems. None of the men had severe oligospermia (sperm count <10 × 10⁶/mL). All transfers were made on day 3 of the cycle with embryos of more than 7 cells. The donors were stratified into 2 groups based on their peak estradiol level, group 1 (n=32; E₂ ≤ 2000 pg/mL [range 456–2000 pg/mL]) and group 2 (n=27; E₂ > 2000 pg/mL [range, 2062–6957 pg/mL]). Oocytes from infertile women were excluded. The outcomes examined in each group were number of oocytes, number of embryos, clinical pregnancy rates, and live birth rates.

A standard synchronization regimen was used for oocyte donor and recipient, as previously described [10–12]. Each recipient underwent a mock cycle followed with an endometrial biopsy, and all the oocytes retrieved from a designated donor were available to her. Recipients with gonadal function first underwent pituitary downregulation with leuprolide acetate. In all cases, recipient and donor were synchronized by taking oral micronized E₂ approximately 5 days before the donor was administered human chorionic gonadotrophin (hCG) to provoke ovulation. The recipient started taking progesterone twice daily on the morning of the day before the donor underwent oocyte retrieval, and continued the treatment thereafter. All embryos were transferred 72 hours following oocyte retrieval. Peak donor E₂ serum levels were measured on the morning of hCG administration. Before transfer, the embryos were graded from 1 to 5 according to established criteria [13].

A serum pregnancy test was done 12 to 14 days after treatment, but clinical pregnancy was confirmed by the presence of a gestational sac on ultrasound. Chemical pregnancy was defined as the presence of the beta subunit of hCG without any evidence of a gestational sac. Abortion was defined as a pregnancy loss prior to 20 weeks of gestation, with fetal heartbeat previously documented. Serum levels of E₂ were measured by chemiluminescent enzyme immunoassays (Immulite; Diagnostic Products, Los Angeles, CA, USA). Intra-assay and interassay coefficients of variation did not exceed 9.3% and 10.5%, respectively. The protocol was approved by the Yale University School of Medicine institutional review board. Statistical analyses were performed using the *t* test or the χ^2 test, as indicated. *P* < 0.05 was considered significant.

3. Results

The relevant baseline characteristics of the 2 groups are outlined in Table 1. As expected, the donors' population was younger than the recipients' (27.9 years [range, 21–34 years] vs

42.5 years [range, 31– 55 years]). The percentage of recipients undergoing intracytoplasmic sperm injection was 24.4%.

Significantly more oocytes were retrieved from donors with E₂ levels higher than 2000 pg/mL than from donors with E₂ values of 2000 pg/mL or less (19.3±1.7 vs 12.0±1.4; $P<0.001$). Similarly, more embryos were produced with oocytes from donors with peak E₂ levels higher than 2000 pg/mL than those with E₂ values of 2000 pg/mL or less (10.4±1.1 vs 6.4±0.8; $P<0.001$) (Table 2).

However, the mean number of embryos transferred in each group was the same, 3.3, and all embryos comprised more than 7 cells on day 3, with no differences in embryo quality (ie, cell number or grade). Moreover, there were no differences in clinical pregnancy rates (58.1% [18/31] vs 59.2% [16/27]; $P=0.93$) or live birth rates (54.8% [17/31] vs. 55.6% [15/27]; $P=0.95$) between the 2 groups (Table 2). The study had more than 80% power to detect a difference in pregnancy rates greater than 15%.

There were 6 chemical pregnancies, 3 spontaneous abortions, and 28 clinical pregnancies for which we were able to obtain complete obstetric outcomes. The mean±SD gestational age at delivery was 36.7±3.1; 53.5% of the pregnancies were multiple; 25% were spontaneous vaginal deliveries and 75% were cesarean deliveries. No differences in gestational age at delivery or mode of delivery were found between the 2 groups.

4. Discussion

The success of oocyte donation is influenced by multiple factors, including donor age, embryo quality, and the recipient's endometrial receptivity. Elevated E₂ levels have been thought to inhibit implantation in animals and humans [14–16]. Oocytes (and thus, the embryos) obtained from young donors may have superior potential compared with oocytes obtained from patients with impaired fertility who are undergoing in vitro fertilization and embryo transfer [2,8]. It has been postulated that increased implantation rates in oocyte donation resulted from a more physiologic hormonal milieu that uncoupled endometrial receptivity from oocyte production [16]. Previous reports comparing natural cycles with ovarian stimulation cycles found a higher incidence of dys-synchrony between endometrial glands and stroma in the ovarian stimulation cycles [17]. There is evidence of a significant reduction in nuclear receptors for progesterone and estrogen in both gland and stroma after ovarian stimulation. Implantation could be affected if these endometrial responses to ovarian stimulation changed the endometrial morphology and affected the window of receptivity [6,18,19]. In contrast, a large amount of evidence suggests that high levels of estradiol are not detrimental to oocyte quality, fertilization, and embryo cleavage [1,3,8,20–22].

To discern the impact of estradiol levels on folliculogenesis and endometrial receptivity is difficult in conventional in vitro fertilization cycles. However, the oocyte donation model allows to study isolated parameters that may affect outcome, and compare their effects on embryo quality and endometrium receptivity [23].

In the present study, the donors were typically young, healthy, not infertile—a more homogeneous cohort than infertile populations. Similarly, endometrial receptivity was relatively constant in the recipients because the uniform artificial preparation, as confirmed by endometrial biopsy in a mock cycle.

As expected, our study demonstrated that greater numbers of oocytes, and therefore greater numbers of embryos, were obtained when donors had higher levels of estradiol. Other studies also indicate that high peak E₂ levels are not detrimental to oocyte quality, fertilization, and embryo cleavage; and that to the contrary, elevated E₂ levels result in a

greater number of oocytes and embryos for selection at the time of embryo transfer or cryopreservation [1,3,14,20,21]. These findings are in agreement with observations for high responder (those with peak $E_2 > 2000$) undergoing conventional in vitro fertilization. The lesser embryo implantation rates must therefore be imputed to an endometrial effect rather than to egg quality [3,14,20–22].

In conclusion, elevated E_2 levels in donors were not found to affect pregnancy outcome in oocyte donation cycles. This suggests elevated E_2 levels do not compromise oocyte quality or embryo development in vitro, but that elevated E_2 levels may diminish endometrial receptivity.

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Table 1Relevant characteristics of donors and recipients ^a

Characteristic	Value
Donor group (n=77)	
Age, y	27.9 (21–34)
Recipient group (n=90)	
Age, y	42.5 (31–55)
Body mass index ^b	23.8 (18.5–43.7)
Parity	0.48 (0–3)

^aValues are given as mean (range).^bCalculated as weight in kilograms divided by height in meters squared.

Table 2Assisted reproduction outcomes according to donor E₂ level ^a

Outcome	Donor E2 level ≤2000 pg/mL	Donor E2 level >2000 pg/mL	P value
No. of oocytes retrieved	12.0±1.4	19.3±1.7	<i>P</i> <0.001
No. of embryos obtained	6.4±0.8	10.4±1.1	<i>P</i> <0.001
Clinical pregnancy rate	59.2 (16/27)	58.1 (18/31)	<i>P</i> =0.93
Live birth rate	55.6 (15/27)	54.8 (17/31)	<i>P</i> =0.95

^aValues are given as mean ± SD or percentage unless otherwise indicated.