Another option for cycle programming: follicular start estradiol in oocyte donation cycles

Oocyte donation has become an increasingly prevalent and successful mechanism for achieving pregnancy in women of advanced reproductive age experiencing a decline in oocyte quantity and quality. The logistics of planning oocyte donation cycles can be difficult, particularly when donors are traveling from a distance or when synchronization with a recipient's cycle is necessary for a fresh embryo transfer. Cycle programming with combined hormonal contraceptive pills has been used to overcome this challenge; however, combined hormonal contraception has been associated with longer stimulations and higher gonadotropin dose requirements (1).

Banker et al. (2) set out to provide a second option for cycle programming in oocyte donation cycles using oral estradiol to program the start of a donor stimulation cycle in the follicular phase. In this study, they demonstrated that 8-mg estradiol hemihydrate (comparable with micronized estradiol) initiated on the second day of a menstrual cycle and continued for 2–10 days with gonadotropin initiation 1 day after the final dose of estradiol was associated with clinical outcomes similar to the same donor's previous unprogrammed donation cycle.

Notably, the investigators studied 8-mg estradiol hemihydrate, raising the question of relative ovarian suppression achieved compared with the 30-μg ethinyl estradiol in a standard combined hormonal contraceptive pill. In a prior study, oral contraceptive pills were found to result in suppressed follicle-stimulating hormone levels for up to 5 days after discontinuation, whereas a 4-mg daily dose of estradiol before treatment in the luteal phase resulted in poorly suppressed follicle-stimulating hormone on the day after discontinuation, with maximal follicle-stimulating hormone rebound 3 days after discontinuation (3). In the study by Banker et al. (2), the stimulation was initiated 1 day after the last estradiol hemihydrate dose, whereas stimulation is generally initiated 4–5 days after the last combined hormonal contraceptive pill. Although one might hypothesize that the recent daily dose of 8-mg estradiol hemihydrate might result in undue ovarian suppression, prolonging stimulation, and total gonadotropin requirement, the investigators did not find a statistically significant increase in gonadotropin dose or in the days of stimulation compared with the donors' unprogrammed historical control cycle.

Although the investigators demonstrate an increased mature oocyte yield with estradiol before treatment, there was no difference in maturation, fertilization, blastulation, implantation, or pregnancy rates compared with that in the unprogrammed cycles. Additionally, the total number of available blastocysts was not different from the control cycle. As a result, the investigators conclude that high-dose estradiol can be employed from the follicular phase in a similar fashion to combined hormonal contraception with similar clinical outcomes to an unprogrammed cycle. The investigators suggest that estradiol may be used for a shorter duration than combined hormonal contraception (2–10 days in this study) and, therefore, be associated with improved compliance. Compliance was not, however, assessed, and the comparator group was the donor's index cycle without hormonal pretreatment rather than combined hormonal contraceptive pretreatment. It may be worthwhile to pursue a prospective randomized trial to identify any difference in outcomes between follicular estradiol and combined hormonal contraception administered for a similar duration, particularly if this protocol is to be introduced in the greater population of patients with infertility beyond the good prognosis group of oocyte donors.

Although oral contraceptive pills may continue to be the most commonly selected method for programming oocyte donation cycles, it is helpful to have alternatives. The combined hormonal contraceptive ring has been used in a similar fashion with acceptable outcomes—and, although not studied, may be associated with higher compliance due to the avoidance of the need for daily medication (4). Additionally, it is common to find patients who have a history of side effects from combined hormonal contraceptives that may be attributed to the progestin component. An estradiol-only approach to program cycles may put these patients at ease and promote individualization of care.

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