Estrogen-suppressed in vitro maturation: a novel approach to in vitro maturation

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Objective: To evaluate the laboratory and clinical outcomes of estrogen-suppressed in vitro maturation (ES-IVM), a novel IVM protocol that eliminates the need for FSH stimulation and cycle monitoring.
Design: Case series.
Setting: Academic infertility center.
Patient(s): Eighteen infertile couples undergoing ES-IVM (n = 20). Eligible candidates included women ≤38 years old with either polycystic ovarian syndrome, antral follicle count ≥15, and/or history of ovarian hyperstimulation syndrome.
Intervention(s): ES-IVM.
Main Outcomes Measure(s): Oocyte yield, maturation, fertilization, embryo quality, implantation, clinical pregnancy, and live-birth rate were analyzed.
Result(s): The average number of oocytes retrieved was 16.7 ± 5.9, with a 52.1% maturation rate and a 58% fertilization rate by intracytoplasmic sperm injection. The average number of embryos transferred was 2.85 ± 0.6. The implantation rate was 17.5%, the clinical pregnancy rate was 40%, and the live-birth rate was 40%.
Conclusion(s): The efficiency of ES-IVM appears to be similar to natural cycle and low-stimulation IVM protocols with respect to laboratory and clinical outcomes, while eliminating the need for FSH stimulation and cycle monitoring. (Fertil Steril® 2013;99: 1886–90. ©2013 by American Society for Reproductive Medicine.)
Key Words: In vitro maturation, immature oocytes, polycystic ovarian syndrome

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In vitro maturation (IVM) involves the retrieval of immature oocytes from small antral follicles with minimal or no gonadotropin stimulation followed by maturation and fertilization in the laboratory. By reducing or eliminating gonadotropin stimulation, IVM offers select infertile couples a safe and convenient alternative to conventional IVF, although clinical pregnancy and live-birth rates may be lower when compared with IVF (1–3).

The majority of IVM protocols use low-dose gonadotropin or the subject's natural cycle. However, the data suggest that these cycles shorten the follicular phase, thereby decreasing the likelihood of implantation (4, 5). Estrogen-suppressed IVM (ES-IVM) is a novel protocol that initiates suppressive doses of oral E_2 on cycle day 3 to suppress dominant follicle development and ovulation while maintaining a uniform cohort of small antral follicles. In addition, the exogenous E_2 facilitates endometrial development in preparation for ET. ES-IVM eliminates the need for FSH stimulation, which reduces the cost, side effects, and risks associated with the low-dose stimulation IVM protocols. Given the predictable response to the suppressive dose of E_2, the need for monitoring by laboratory and/or transvaginal ultrasound evaluation is eliminated, which further reduces the cost and allows for advanced scheduling of the day of oocyte retrieval, unlike natural cycle and low-dose stimulation IVM protocols.

While the reduced cost, convenience, and lower risk of ES-IVM are appealing to eligible infertile couples, the clinical pregnancy and live-birth rates must be comparable to reported IVM outcomes to justify the benefits

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of this novel IVM protocol. The aim of this research is to report the laboratory and clinical outcomes of the first 20 cycles of ES-IVM.

MATERIALS AND METHODS

Patients

Consecutive patients (n = 18) undergoing ES-IVM at the Center for Reproduction and Infertility in Providence, Rhode Island, from 2008 to 2010 were included in the analysis. Eligible candidates for ES-IVM include women ≤38 years old with either polycystic ovarian syndrome (PCOS), antral follicle count (AFC) ≥ 15, and/or history of ovarian hyperstimulation syndrome (OHSS). Two patients completed repeat ES-IVM cycles, which were included in the analysis. Approval was obtained from the Women and Infants Hospital Institutional Review Board.

ES-IVM Protocol

After a spontaneous menses or P-induced withdrawal bleed, patients initiated oral E_2 2 mg 3 times a day (Estrace; Warner Chilcott) on cycle day 3 (Fig. 1). Monitoring by laboratory or ultrasound evaluation for the development of a dominant follicle was not necessary given the suppressive dose of E_2. On cycle day 14, patients administered recombinant hCG 250 μg SC (Ovidrel; EMD Serono) and underwent an IVM retrieval 36 hours later. This uterine preparation was based on our long-standing and successful frozen ET protocol. At the time of oocyte retrieval, the ovary was examined for dominant follicles and endometrial thickness was assessed. Immature oocytes were aspirated from small antral follicles using transvaginal ultrasound guidance and a 19-g single lumen needle (Cook Medical) with an aspiration pressure of 80 mmHg. Curettage of each aspirated follicle was performed. To avoid clotting, the needle was removed from the vagina and flushed with 2 mL of embryo wash media every five follicles. Patients initiated vaginal P 100 μg 3 times a day (Endometrin; Ferring Pharmaceuticals) 36 hours after retrieval. In accordance with the American Society of Reproductive Medicine guidelines, the number of embryos transferred was determined by the patient's age. However, given that IVM embryos are considered to have lower implantation rates, the number of embryos transferred was determined by the guidelines for "less than favorable prognostic characteristics" (3, 6). A serum hCG was evaluated 12–14 days after ET. If the patient was pregnant, a transvaginal ultrasound was performed at 6 weeks' gestational age to detect fetal heart activity and vaginal P was continued until 8 weeks' gestation.

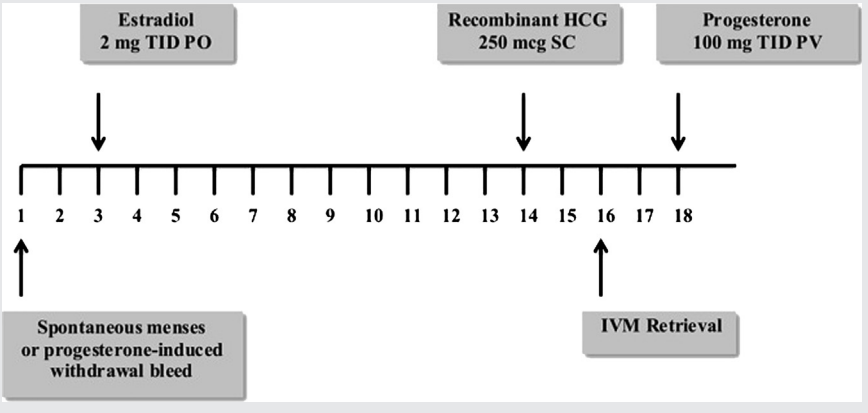
Oocyte and Embryo Culture and Assessment

Immature oocytes enclosed in cumulus cells were cultured in IVM media (Sage) supplemented with 75 IU of human menotropins (Repronex; Ferring Pharmaceuticals). Oocytes were assessed for nuclear maturation at 24 hours by minimally stripping the cumulus, and meiosis II (MII) oocytes were inseminated by intracytoplasmic sperm injection (ICSI). Exposing the oocytes to <1 minute of hyaluronidase (80 IU/mL) and then minimally stripping <20% of the cumulus with a 250 μm stripper tip (Origio) allows for identification of the presence or absence of the polar body. Immature oocytes were cultured for an additional 24 hours and reassessed for maturation at 48 hours. Additional MII oocytes at 48 hours were inseminated by ICSI. Embryos were assessed for cell number, fragmentation, and symmetry on day 2 and day 3 postinsemination. ET was performed on day 3 postinsemination. Suitable supernumerary embryos were cultured for cryopreservation at the blastocyst stage on day 5 or 6 postinsemination.

Outcomes and Analysis

Laboratory outcomes were defined as oocyte yield, maturation rate (number of MII oocytes/total number of oocytes retrieved) at 24 and 48 hours, fertilization rate (number of two-pronuclei [2PN] zygotes divided by number of mature oocytes) at 24 and 48 hours, and embryo quality (assessed by cell number, fragmentation, and symmetry). Clinical outcomes were defined as implantation rate, clinical

FIGURE 1



ES-IVM protocol. TID = 3 times a day; PO = by mouth; PV = via the vagina.

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