Follicular phase cycle programming using estradiol in oocyte donors—a convenient and effective approach

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Objective: To study the efficacy of estradiol for cycle programming in oocyte donors when administered in the follicular phase only.

Design: Prospective interventional study.

Setting: Single fertility center.

Patient(s): Ninety-three oocyte donors underwent programmed stimulation using estradiol in the follicular phase. Their previous unprogrammed cycles were used as historical controls.

Intervention(s): Donors received 8 mg of estradiol hemihydrate from day 2 till 1 day before the start of stimulation.

Main Outcome Measure(s): The primary outcome measures studied were the number of oocytes retrieved, duration of stimulation, and total gonadotropin dose. The number of mature oocytes, oocyte maturation rate, fertilization rate, blastulation rate, implantation rate, and pregnancy rate were the secondary outcomes.

Result(s): The average number of oocytes retrieved was higher in the study group (36.4 vs. 32.5). The duration of stimulation (9.22 vs. 9.21 days) and the total gonadotropin dose were similar (3,085.5 vs. 3,026 IU) between both groups. The mean number of mature oocytes retrieved was higher in the study group (30.1 vs. 26.3), but the maturation rate was similar (84.6% vs. 81.2%). The fertilization rate (77.8% vs. 78.7%), number of blastocysts, blastulation rate (32.7% vs. 33.2%), implantation rate (59.3% vs. 66.3%), and pregnancy rate (77.3% vs. 77.1%) showed no statistically significant difference.

Conclusion(s): Estradiol usage in the follicular phase alone is an effective and convenient option for cycle programming in oocyte donors. It can yield similar mature oocytes and does not affect the clinical outcomes. Further larger sample-sized studies may be needed to validate its use which can also be extended to routine in vitro fertilization cycles.

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There has been a worldwide increase in the use of in vitro fertilization (IVF) over the years. The number of IVF cycles globally has increased from 1,251,881 in 2007 to 1,858,500 in 2013. The proportion of IVF cycles using donor oocytes has also shown a progressive increase from 71,347 transfers in 2012 to 78,054 transfers in 2013, an increase of 9.4% in 1 year (1).

Gonadotropin-releasing hormone (GnRH) antagonist protocols have become increasingly popular for controlled ovarian hyperstimulation because of their various benefits over agonist protocol. Low gonadotropin consumption and improved safety profile because of a GnRH agonist trigger combined with similar IVF outcomes have led to widespread use in oocyte donor (OD) cycles (2).

An increase in the number of IVF stimulations for both patients and ODs has necessitated many clinics to program cycles. Cycle programming allows busy clinics to have an organized workload with a controlled schedule of oocyte retrievals and avoid overloading the embryology laboratory on certain days (2). Cycle programming has additional challenges in donor oocyte programs. On the one hand, the donor stimulation must be synchronized with the recipient's cycle, while on the other, compliance among donors may be low (3, 4). The IVF cycles using the long protocol were much more flexible and easier to program because the stimulation could be started according

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to the convenience of the clinic. The mandatory start of stimulation once the menstruation commences makes programming a challenge in antagonist cycles.

The commonly used medications for programming in antagonist cycles are oral contraceptive pills (OCP) or vaginal rings, and progestogens all of which have to be started in the preceding menstrual cycle (4, 5). Another method of cycle programming is the use of luteal estradiol in the donor, which is continued across the next menstrual cycle till the stimulation is desired (2, 6). In both cases, the drug used for cycle programming must be started in the previous menstrual cycle, and donors may take them inappropriately, sometimes may not take them at all, or even get the stimulation done at another clinic in the same menstrual cycle. The OCP use may also lead to a suboptimal response to the agonist trigger after the luteinizing hormone suppression (7). The duration of stimulation and the gonadotropin consumption are also found to be higher in the OCP pretreated cycles (8). The use of an antagonist for a few days after menses till the stimulation is initiated has also been attempted (9). Although these can be useful for patients undergoing self-cycles, there is a need for a more efficient and straightforward method in ODs.

Studying the efficacy of a cycle-programming agent in ODs provides an opportunity to exclusively evaluate its effect on stimulation while ignoring the endometrial effects. Although various investigators have used estradiol for cycle programming by starting it in the luteal phase of the previous cycle and then continuing it in the follicular phase (2, 6), its efficacy for cycle programming, if administered in the follicular phase alone, has been unexplored.

This novel study was designed to explore the efficacy of estradiol hemihydrate for suppressing follicular recruitment, starting in the follicular phase till the suitable time for IVF stimulation of the OD is finalized, according to the recipient's menstrual cycle. To our knowledge, this is the first prospective study in ODs where estradiol is used for cycle programming from the onset of the menstrual period and continued till the stimulation is desired, unlike the previously advocated luteo-follicular use.

The present study aimed to prospectively evaluate the outcomes of OD IVF cycles programmed with estradiol hemihydrate and compare these outcomes with historical control data obtained from the previous unprogrammed IVF cycles in the same cohort of donors.

MATERIAL AND METHODS

This was a prospective interventional study on ODs, using paired historical control data from the previous cycles of the same donors. The study included all ODs who were planned for stimulation at Nova IVF Fertility, Ahmedabad, India, between September 2020 and February 2021, and who had previously undergone an unprogrammed cycle within the past year with the same stimulation protocol as used in the present study. Donors without a previous unprogrammed cycle at our center were excluded from the study.

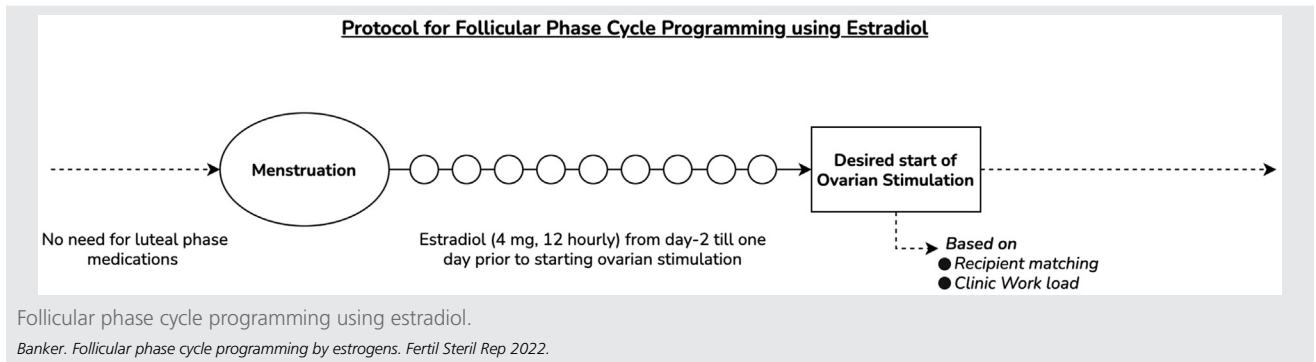All ODs complied with the national (Indian Council of Medical Research) guidelines for oocyte donation (10).

Routine screening according to the Institution's policy was performed before recruitment. Each donor was appropriately counseled by the clinic's counselor, and informed consent was obtained.

All enrolled donors were given estradiol for cycle programming as described below (study group). The outcomes of these cycles were compared with the outcomes of their previous unprogrammed cycle, which acted as paired historical controls (control group). Data pertaining to their previous unprogrammed cycles and their outcome variables were retrieved from the electronic medical records of our hospital. The study was approved by the local Ethics Committee before the recruitment of subjects (Care Institute of Medical Sciences, Ref No EC/206/Inst/GJ/RR20). The study was registered with the Clinical Trials Registry of India (CTRI/2020/09/027815).

For the study, transvaginal sonography was performed on the second day of the spontaneous menstrual cycle to assess the baseline status of the ovaries and the uterus and a requisite blood test evaluation for oocyte donation was performed. In addition, baseline serum estradiol and follicle-stimulating hormone (FSH) levels were measured. Estradiol hemihydrate was administered in a dose of 4 mg 12-hourly from day 2 till the initial day of the IVF stimulation for which was decided based on the onset of the recipient's menstrual cycle (Fig. 1). Serum estradiol and FSH levels were measured, and transvaginal sonography was repeated on the initial day of the stimulation. The donors were screened for COVID-19 (real-time reverse transcription-polymerase chain reaction) before the stimulation initiation and on the day of trigger. Oocyte donors underwent the standard IVF stimulation on the GnRH antagonist protocol with gonadotropins (recombinant human-FSH [Follitropin alfa], Folisurge [Intas, India] with or without additional human menopausal gonadotropin [Bharat Serums and Vaccines Limited, India]) beginning 1 day after the last intake of estradiol hemihydrate. The stimulation was started with the same dose as in the previous unprogrammed cycle of that donor. The donors were reviewed for a follicular response after 5 days of initial stimulation, and the administration of an injectable antagonist cetrorelix (0.25 mg) (Asporelix, Bharat Serums, India) was added when the lead follicle was ≥ 14 mm. Injectable triptorelin (0.2 mg) (Decapeptyl, Ferring Pharmaceuticals, India) was administered for triggering the follicular maturation when ≥ 3 follicles were ≥ 17 mm in mean diameter. Transvaginal oocyte retrieval was performed 35 hours later. All the metaphase II oocytes were inseminated using intracytoplasmic sperm injection and cultured till the blastocyst stage. All good-quality blastocysts were either used for embryo transfer (ET) or vitrified. One or two embryos were transferred per ET. The stimulation record and the IVF outcome of all cycles of the study group were noted electronically and compared with the unprogrammed control cycle. For calculating the implantation rate and pregnancy rate, only the first ET cycle was considered.

The primary outcome parameters included the number of oocytes retrieved, duration of stimulation (in days), and total dosage of gonadotropins (International Units, IU). The secondary outcome parameters studied were the number of

FIGURE 1

Protocol for Follicular Phase Cycle Programming using Estradiol

Menstruation

Desired start of Ovarian Stimulation

No need for luteal phase medications

Estradiol (4 mg, 12 hourly) from day-2 till one day prior to starting ovarian stimulation

Based on
● *Recipient matching*
● *Clinic Work load*

Follicular phase cycle programming using estradiol.

Banker. Follicular phase cycle programming by estrogens. Fertil Steril Rep 2022.

mature oocytes and maturation rate, number of fertilized oocytes and fertilization rate, number of blastocysts and blastulation rate, implantation rate, and pregnancy rate (11). The minimum required sample size was calculated using the number of oocytes and the duration of stimulation as the primary objective. Using the duration of stimulation from a previous study (12) (mean SD, 10.1 and 9.2), the sample size required for the study was 43, with a level of significance (α) fixed at 0.05 or 5% and power (1-β) at 0.80 or 80%. Using the number of oocytes, with an assumed effect size of 0.5, the sample size was 34 with the same α and β.

After checking for normality using the Shapiro-Wilk's test, for the continuous variables that followed a normal distribution, the paired t test was used to find if the means of the two paired measurements were significantly different. For the

parameters that did not follow the normal distribution, the Wilcoxon's signed rank test was used to find if the mean and median of the two paired measurements were significantly different. Dichotomous variables were compared using a χ^2 test. A P value $<.05$ was considered statistically significant.

RESULTS

A total of 98 ODs who fit the study criteria were recruited for this study. Of these, 5 were excluded because their cycle was canceled for medical/personal reasons. A total of 93 donors were enrolled, and their estradiol-programmed cycles were compared with their historical control cycle for the primary and secondary outcomes.
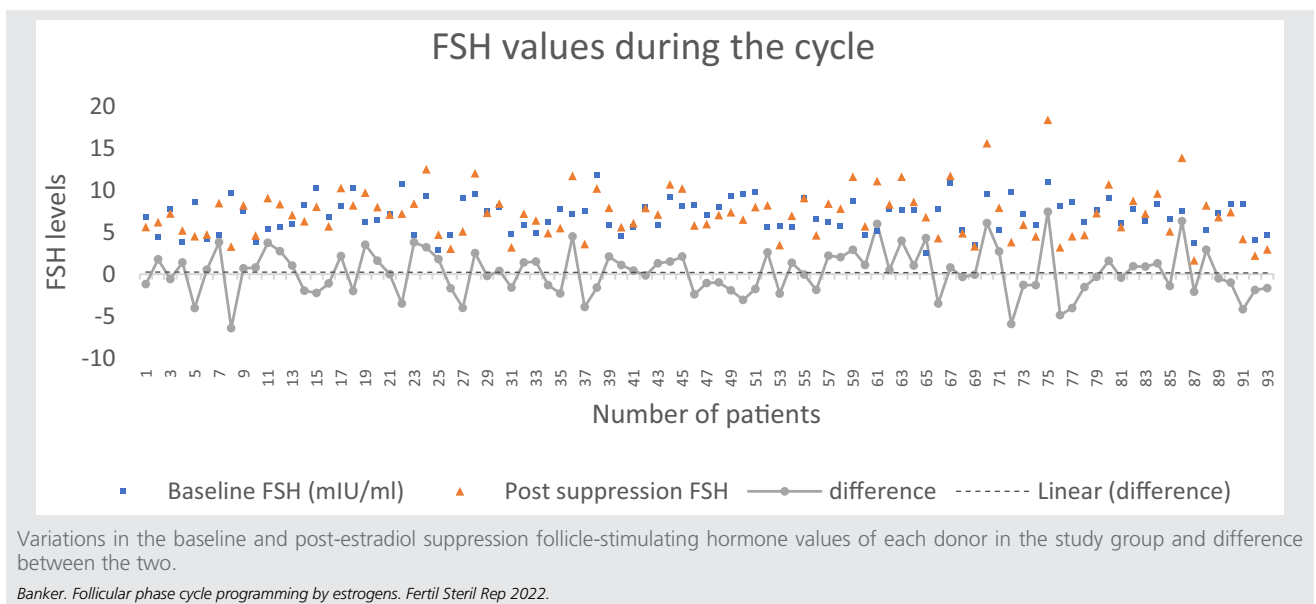
FIGURE 2

Variations in the baseline and post-estradiol suppression follicle-stimulating hormone values of each donor in the study group and difference between the two.

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TABLE 1

Comparison of the number of oocytes retrieved, duration of stimulation, and gonadotropin dose among the two groups.

Characteristics	Study group	Control group	P value
Oocytes retrieved			
Mean ± SD	36.4 ± 18.1	32.5 ± 14.2	.02
Duration of stimulation (d)			
Mean ± SD	9.22 ± 0.5	9.21 ± 0.6	.84
Gonadotropin dose (IU)			
Mean ± SD	3085.5 ± 369.2	3026.3 ± 379.2	.06

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The FSH and estradiol levels were measured in the study group before and after estradiol administration. The baseline FSH ranged between 2.5 and 11.8 mIU/mL with a mean of 7 ± 2.01 mIU/mL. The baseline estradiol ranged between 18.2 and 139 pg/mL with a mean of 44.9 ± 19.18 pg/mL. The minimum and maximum duration of estradiol administration were 2 and 10 days, respectively, with a mean duration of 5.65 days $\pm$ 1.64 days. The FSH values on the initial day of the stimulation ranged between 1.65 and 18.38 mIU/mL with an average of 7.2 ± 2.92 mIU/mL. The change in FSH levels with estradiol programming ranged from -6.4 to 0.4 mIU/mL, with a mean of 0.2 ± 2.7 mIU/mL (Fig. 2), and showed no statistical change with increasing duration of estradiol administration. The estradiol values on the initial day of the stimulation ranged between 17.3 and 664.5 pg/mL with an average of 194.95 ± 122.5 pg/mL (Supplemental Fig. 1, available online). The stimulation records and embryological outcomes of 186 stimulation cycles (93 in each study and control group) were analyzed.

The mean number of oocytes retrieved in the study group was higher than the controls (36.4 vs. 32.5; $P=.02$). The mean duration of the stimulation was 9.22 days in the study group and 9.21 days in the control group, which was statistically not significant ($P=.8$). There was a similar total gonadotropin consumption in both groups (3085.5 vs. 3026.3 IU; $P=.06$) (Table 1).

There was a statistically significant increase in the number of metaphase II oocytes in the study group than the controls (30.1 ± 15.7 vs. 26.3 ± 11.6, $P=.001$), but the maturation rates were similar in both the groups ($82.9\% \pm 9.3\%$ in the study vs. $81.6\% \pm 8.5\%$ in the control group). Although the study group had more fertilized oocytes (23.4 ± 12.7 vs. 20.7 ± 9.6, $P=.001$), the fertilization rate was similar among the two groups (77.8% vs. 78.7%, $P=.23$). No statistically significant difference was noted among the two groups when comparing the total blastocysts (7.4 vs. 6.8; $P=.10$) and the blastulation rate (32.7% vs. 33.2%; $P=.50$) (Table 2).

There were 181 and 163 recipients in the study and control groups, respectively. Supplemental Table 1 depicts the characteristics of the recipients in the two groups with respect to age, body mass index, and the average number of embryos transferred, which were comparable.

The implantation rates in the study and control groups were 59.3% and 66.3% ($P=.17$), respectively, which were also

TABLE 2

Embryological and clinical outcomes in the study and control groups.

Characteristics	Study group	Control group	P value
Maturation rate (%)			
Mean ± SD	82.9 ± 9.3	81.6 ± 8.5	.31
Median (range)	84.6 (57.1–100)	81.2 (59.2–100)	
Fertilization rate (%)			
Mean ± SD	77.8 ± 7.9	78.7 ± 9.6	.23
Median (range)	77.8 (58.9–100)	80.6 (37.5–100)	
Blastulation rate (%)			
Mean ± SD	32.7 ± 12.1	33.2 ± 11.5	.50
Median (range)	33.3 (12.5–100)	32.0 (16.7–100)	
Implantation rate (%)			
Mean± SD	59.3 ± 34.1	66.3 ± 33.1	.17
Median (range)	50 (0–100)	60 (0–200)	
Pregnancy rate (%)			
Mean ± SD	77.3 ± 56.6	77. ± 32.3%	.5
Median (range)	100 (0–100)	100 (0–100)	

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comparable. Similarly, the pregnancy rates were also comparable among the two groups (77.3% vs. 77.1%; $P=$ .5).

DISCUSSION

Based on the findings of this prospective study, the estradiol-programmed cycles had similar duration of stimulation, total gonadotropin dose, maturation rate, fertilization rate, blastulation rate, implantation rate, and pregnancy rate compared with the historical non-programmed cycles in ODs. Further, there was a significant increase in the number of retrieved oocytes, mature oocytes, and fertilized oocytes in the estradiol-programmed cycles.

An ideal agent for routine cycle programming should not interfere with follicular recruitment, have no adverse effects on the endometrium, and be patient-friendly. The effect of the agent on the duration and the dose of stimulation should be minimal, and the oocyte and embryo quality should not be affected. Scheduling the cycles of ODs has different challenges as it needs to be simpler, and on the other hand, the effect on the endometrium is of no significance. A common issue noted with the use of cycle programming in the previous cycle is compliance, with instances of donors leaving the program midway. Hence, in these women, the therapeutic modality should be simpler, convenient, requiring a shorter duration, and with minimal side effects. It has been shown that a reduced burden of treatment makes it more patient-friendly, less stressful, and might help minimize dropouts; the same should apply to donor compliance as well ([13], [14]). The follicular phase cycle programming using estradiol is a novel way to schedule the stimulation in ODs with ease and compliance while giving superior cycle start flexibility.

Estradiol was used for cycle programming way back in 1999 by de Ziegler et al. ([15]) who advocated its use to program the onset of new menstrual cycles solely by delaying the intercycle FSH elevation (the actual onset of new cycles) without postponing menses (the end of the previous cycle). Luteal estradiol also reduces the size discrepancies of the small antral follicles of the early follicular phase. Hence, its usage may yield a synchronized follicular cohort and be more physiological than the pretreatment with OCP or a GnRH agonist ([16]). Estradiol suppresses the endogenous FSH during the follicular phase, and extending the usage beyond the menstrual period does not have a detrimental effect on the IVF outcome ([17]).

In the studies by Hauzman et al. ([2]) and Nestour et al. ([18]), estradiol has been continued until the desired day of stimulation or even beyond the menstrual period, and its negative effect on the FSH rise during the luteal-follicular transition aids in cycle programming. The FSH suppression is modest compared to that of OCP and progestogen, with a quicker recovery to basal levels within 3 days ([19]).

We extrapolated the effect of estradiol on FSH suppression for its utility in cycle programming in ODs in the follicular phase until the day of stimulation was decided. Oocyte donors are young with a good ovarian reserve and have a continuous cohort of follicles in the follicular phase and thus may not require estradiol in the luteal phase. The luteo-follicular transition in FSH leading to early recruitment in the luteal phase may not be critical in ODs; hence, usage of estradiol for a shorter period in the follicular phase may be as efficacious for cycle programming as the luteal estradiol and may ensure higher compliance. The loss of recruitment of a few follicles by their atresia using estradiol on the follicular phase may be compensated by recruitment of other follicles in the next wave during the programming phase.

Baerwald et al. ([20]) shared insights on various theories of ovarian follicular waves based on >70 years of information. The three distinct theories mentioned are the continuous recruitment theory, which suggests a continuous availability of antral follicles and selection of a cohort based on the available FSH; a follicular wave theory, which means cohorts of follicles arising at 2 or 3 phases in a cycle and selection based on the hormone levels, and a third cyclic recruitment theory, which suggests only one wave of follicular recruitment. The initial two theories have helped formulate newer stimulation protocols like the "DUOSTIM" protocol, but it has been less explored for cycle programming. Our study found a similar number of oocytes retrieved, which also supports this theory of continuous recruitment.

Our study reports that the FSH levels did not fluctuate significantly (range, -6.4 to 0.4 mIU/mL; mean, 0.2 ± 2.7 mIU/mL during the programming phase, indicating that the follicular recruitment had not occurred ([Fig. 2]). The duration of the estradiol usage also did not affect the FSH levels indicating that recruitment can be halted for longer periods. This is further confirmed by the fact that the duration of the stimulation and the gonadotropin usage were similar in both groups. In addition, retrieval of significantly higher mature oocytes among the programmed cycles could be explained by a better-synchronized cohort during stimulation and avoiding discordant follicles at the trigger. The number of fertilized oocytes was significantly higher in the study group (22.9 vs. 20.8), explained by the higher number of mature oocytes (30.1 vs. 26.3). However, this did not translate into a clinically discernible effect because the fertilization and blastulation rates were similar, with no significant differences in the implantation and pregnancy rates.

A similar protocol was used in a retrospective Turkish study by Aslan et al. ([12]). They compared two different cohorts, one with estradiol programming in the follicular phase and the other with unprogrammed cycles, and each cohort had 35 patients undergoing IVF. They reported similar gonadotropin dosage, number of retrieved oocytes, mature oocytes, maturation rates, fertilization rates, implantation rates, and pregnancy rates. Our study was a prospective interventional study on ODs, with both the study and control groups consisting of the same subjects, thus, eliminating any bias due to patient characteristics. Further, the power of this study with a final sample size of 93 donors was 0.951, meaning that the chance of finding a statistically significant difference when such a difference exists was 95.1%.

Our study is novel because it prospectively evaluates the efficacy of estradiol for cycle programming of donors in the follicular phase so that the duration of pill intake is shorter, can be started after the onset on menses, and, hence, is more convenient and allows easier synchronization with the

recipient. At the same time, the outcomes of such programmed cycles were not found to be different from the unprogrammed ones in terms of the convenience to the donor (total duration of stimulation) and the IVF clinic (gonadotropin cost and the embryological outcome).

Although our study is limited by its small size, its strength is its prospective nature and matched controls. It is a pilot study to prospectively evaluate its usage for cycle programming in the follicular phase in ODs. It can also be used in patients who have an intolerance or any contraindication for OCP usage due to its progesterone component. Its short duration of requirement makes it more cost effective than other agents like the daily administration of GnRH antagonists. This can be especially convenient for the ODs, because they will have to take the medicine only for a few days in the treatment cycle instead of the regular OCPs for a month. Its utility can be extrapolated to the program routine cycles in the IVF clinics to space out the oocyte retrievals, avoid weekend retrievals, or plan a batch IVF. Cycle programming with estradiol also gives a window to patients who are still deciding on starting treatment in the current cycle. However, the effects of estradiol programming on the endometrial receptivity for a fresh ET are still to be studied and, at present, may be advocated in all-freeze cycles only. We recommend further randomized prospective studies with a larger sample size to be conducted to substantiate these findings.

CONCLUSION

Follicular phase estradiol is an effective alternative for programming cycles in ODs. This method can give equally good results and is more convenient for the donor as well as the clinic. Further prospective, controlled, and blinded trials will help provide more information to recommend its use for programming in routine practice.

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