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ASSISTED REPRODUCTION TECHNOLOGIES

Comparison of daily vaginal progesterone gel plus weekly intramuscular progesterone with daily intramuscular progesterone for luteal phase support in single, autologous euploid frozen-thawed embryo transfers

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Abstract

Purpose To compare outcomes between daily intramuscular progesterone (IMP) and daily vaginal progesterone (VP) gel plus weekly intramuscular hydroxyprogesterone caproate (IMHPC) for luteal phase support (LPS) in single, autologous euploid frozen-thawed blastocyst transfers (FBTs) following artificial endometrial preparation (EP).

Methods The retrospective cohort study included 767 single, autologous FBTs from 731 patients between January 2015 and March 2018. LPS was performed either with IMP (100 mg/day) or with VP gel (90 mg, twice daily) plus IMHPC (250 mg/week). Oral estrogen was prescribed in combination of both regimes. Oral estrogen was discontinued following the visualization of fetal cardiac activity on ultrasound and progesterone at 10 weeks of gestation. The primary outcome was live birth rate. The secondary outcomes included implantation, clinical pregnancy, and multiple pregnancy rates.

Results Patient characteristics did not differ in LPS regimes. Of 767 FBTs, 608 had IMP (100 mg/day) for LPS and 159 had VP gel (90 mg, twice daily) plus IMHPC (250 mg/week) for LPS. The live birth rate was 51.8% and 50.3%, respectively ($p = 0.737$, OR 0.94, 95%CI 0.66–1.33). The implantation rate was 62.7% and 64.2%, respectively ($p = 0.730$, OR 1.06, 95%CI 0.74–1.53). The clinical pregnancy rates were also similar in both groups (59.5% vs. 61.6%, respectively, $p = 0.631$, OR 1.09, 95%CI 0.76–1.56).

Conclusions We did not observe significant differences in the rates of live birth, implantation, and clinical pregnancy between daily IMP and daily VP gel plus weekly IMHPC for LPS in single, autologous euploid FBTs after artificial EP.

Keywords Luteal phase support · Euploid frozen-thawed blastocyst transfers · Vaginal progesterone gel · Intramuscular progesterone · Live birth

Introduction

Improved cryopreservation techniques have led to a significant rise in the utility of frozen-thawed embryo transfers (FETs) over the past years [1, 2]. FETs offer many advantages, such as transfers of surplus embryos, genetic screening of embryos, decreased risks of multifetal gestations and ovarian hyperstimulation syndrome, and deferral of embryo transfer (ET) if needed [1–3]. FETs also render possible to avoid the detrimental effects of controlled ovarian stimulation (COS) protocols on the endometrium [4].

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FETs necessitate an appropriately coordinated endometrium in harmony with the embryo's developmental stage for successful outcomes [5]. Endometrial preparation for FETs is achieved with basically two options: natural and artificial methods. However, no agreement exists to suggest one over another [6–9]. In artificial endometrial preparation (EP) cycles, exogenous estrogen and progesterone are consecutively administered to induce the endometrial development and maturation. Progesterone supplementation is also imperative to maintain early pregnancy as corpus luteum usually does not form in artificial EP cycles secondary to the lack of spontaneous ovulation. Thus, iatrogenic luteal phase defects are the consequence of FETs following artificial EP.

Luteal phase support (LPS) with progesterone plays fundamental roles in optimizing FET outcomes. Various routes of progesterone supplementation are available in clinical use for LPS. Although intramuscular progesterone (IMP) administration can cause local pain, inflammatory reactions and cold abscesses [10, 11], it is the most commonly preferred form of progesterone for LPS. Oral route is associated with an inadequate bioavailability [12]. Vaginal progesterone (VP) administration has been proposed as a delivery route of progesterone to the uterus while avoiding undesirable adverse effects of IMP. VP application is user-friendly, but may cause mild vaginal symptoms and requires daily application [13].

Previous studies have compared different regimes of LPS in cycles using embryos with unknown ploidy status [13–17]. The purpose of our study was to compare the efficacy of daily IMP with that of daily VP plus weekly IMP for LPS in patients undergoing single, autologous frozen-thawed euploid blastocyst transfer (FBTs) following artificial EP.

Materials and methods

This was a retrospective cohort study conducted at the Bahceci Fulya and Umut IVF Centers in Istanbul in Turkey between January 2015 and March 2018. The study was approved by the local review board committee.

We analyzed patients meeting the following inclusion criteria: age of 20-44 years, transfers of single autologous euploid blastocysts, use of IMP in oil alone (100 mg/day) or VP gel (Crinone 8%, 90 mg, BID, Watson Pharmaceuticals, Morristown, NJ) plus 250 mg/week intramuscular hydroxyprogesterone caproate in oil (IMHPC) as LPS and artificial EP. Euploid embryos were obtained from one of the past three COS cycles. The exclusion criteria were as follows: transfer of embryos with unknown ploidy status; double euploid FBTs; patients over the age of 44 or below the age of 20; FETs following natural or modified-natural EP; use of subcutaneous or oral progesterone and/or transdermal estrogen for EP or LPS; and any uncorrected intracavitary structural pathology considered to affect the success of implantation or uterine anomalies including unicornuate, bicornuate, or didelphic uterus. The study did not exclude those undergoing corrective procedures due to structural uterine pathologies or anomalies: endometrial polyps, submucosal fibroids, and uterine septum. Collected data were as follows: age at transfer, body mass index, duration of infertility, number of previous attempts, causes of infertility, endometrial thickness and estrogen and progesterone level on the day of progesterone initiation, and preimplantation genetic testing for aneuploidy (PGT-A) indications and outcomes. Data regarding embryo morphology grading and COS protocols were not analyzed separately since only FBTs were included in the study.

PGT-A technology used was either microarray-based comparative genomic hybridization (aCGH) or next-generation sequencing (NGS) (IGENOMIX S.L, Valencia, Spain). The choice of aCGH or NGS for PGT-A depended on the timing of test performed, as our clinic used aCGH prior to 2016 and NGS thereafter.

Trophectoderm biopsy

After zona pellucida (ZP) opening (approximately 20 μm) on day 3 of embryo development by a non-contact laser system (Octax LaserShot, MTG, Germany), embryos were transferred into new fresh medium and cultured until the day of biopsy. Blastomere biopsies (5–8 cells from each embryo) were performed on only days 5 and 6 hatching blastocysts by the pulling method in a HEPES-buffered media containing Gentamycin (mHTF®, Irvine Scientific, CA, USA). Extracted cells were placed in polymerase chain reaction tubes and later sent to the analysis for PGT-A.

Vitrification and warming of blastocysts

Vitrification and warming were performed by commercial vitrification kits (Vit Kit®-Freeze, 90,133-SO and Vit Kit®-Thaw, 90137-SO, Irvine Scientific, CA, USA) according to the manufacturer's instructions. Embryos were first transferred into 50 μl of equilibration solution (containing 7.5%DMSO, 7.5% EG in a M-199 HEPES-buffered medium) for 6–10 min. They were subsequently transferred and quickly washed in the droplets 50 (μl) of vitrification solution (containing 15% DMSO and 15% EG, 0.5 M sucrose in a M-199 HEPES-buffered medium), immediately placed with a small volume on the embryo carrier device (Cryotech®, Reprolife, Japan) and plunged into liquid nitrogen. For warming, the embryo carrier was taken out of the liquid nitrogen and was instantly placed into the warming solution (1 ml TS, containing 1 M sucrose) for 1 min at 37 °C. Embryos were then sequentially washed by placing them into 50 μl droplets of dilution solution (containing 0.5 M sucrose) for 4 min and then serially washed by transferring them into two 50 μl droplets of washing solution, for 4 min each at room temperature. At the final step, embryos were transferred in continuous single culture medium (CSCM-Complete®, Irvine Scientific, CA, USA) and viability was assessed under the inverted microscope.

Artificial endometrial preparation protocol

Patients were assessed by transvaginal ultrasound (TUS) along with serum estradiol (E2) and progesterone (P4) determinations on the first day of menstruation. Oral E2 (4 mg/day) was initiated in a sequential step-up regime, with a dose increase of 2 mg every 4 days up to a maximum dose of 8 mg/day. Following 12 days of E2 treatment, the patients again had TUS along with serum E2 and P4 levels. Progesterone administration was commenced on those meeting the suitability criteria for embryo transfer (ET): endometrium thickness ≥ 7 mm with trilaminar patterns, lack of dominant follicle, and serum P4 < 1.5 pg/dl. The progesterone form was either IMP (100 mg/day) or VP (90 mg, BID). ETs were carried out on day 6 of progesterone supplementation. IMP (100 mg/day) was continued after ET day. VP (90 mg, BID) was continued with the combination of IMHPC (250 mg/week) after ET day. The first dose of IMHPC was administered just after ET (on ET day).

When the endometrial thickness remained < 7 mm after 12 days of E2 treatment, the assessment with TUS and serum E2 and P4 levels was repeated 3 and 6 days later. The decision to proceed with ET was again made as described above. ET was canceled despite that oral E2 treatment of 18 days failed to result in adequate endometrial appearance on ultrasound. ET was also not performed in those meeting any of the following criteria: presence of heterogeneous endometrial stripe, uncorrected intracavitary structural pathology, or intracavitary fluid collection.

Study groups

The choice of LPS was at the discretion of the managing physicians in our clinic. The initiation time of LPS was on the day of FBT. The patient population was divided into two groups based on the LPS regime used: group 1 (IMP 100 mg/day in oil alone) and group 2 (VP 90 mg BID plus IMHPC in oil 250 mg/week). Daily 8 mg of oral E2 was used in combination with both regimens. Serum beta-human chorionic gonadotropin (β-hCG) level was measured 12 days after ET. LPS was continued in patients with β-hCG level ≥ 5 IU/L. Oral E2 was discontinued after the visualization of fetal heartbeat on ultrasound and progesterone administration at 10 weeks' gestation. The groups were compared in terms of FBT outcomes.

Outcomes

The primary outcome was live birth, which was defined as the delivery of any alive neonate after 24 completed weeks of gestation. The secondary outcomes were biochemical pregnancy, implantation, clinical pregnancy, ectopic pregnancy, and multiple pregnancy. Positive pregnancy test was defined as serum β-hCG level ≥ 5 IU/L 12 days after the transfer. Biochemical pregnancy was defined as no ultrasound evidence of an intrauterine gestational sac despite serum β-hCG level ≥ 5 IU/L. Implantation was defined as ultrasound evidence of an intrauterine gestational sac 4–5 weeks after FBT and clinical pregnancy as ultrasound evidence of intrauterine fetal cardiac activity 6–7 weeks after FBT. Multiple pregnancy was defined as the presence of more than one gestational sac detected on ultrasound 12 weeks after FBT. All outcomes were given per transfer as a ratio of number of a corresponding outcome to number of ETs.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software (IBM version 21.0, USA). Kolmogorov–Smirnov test was used to assess the normality of data. Continuous variables were compared using Mann–Whitney *U* test. Categorical variables were compared using Fisher exact or Pearson's chi-square test. Odds ratio (OR) with 95% confidential interval (CI) was calculated for outcome measures. A two-sided *P* value less than < 0.05 was set as the cutoff for statistical significance. Data are given as median (range) or number (percentage).

Results

A total of 731 patients met the inclusion criteria of the study. The patients' median age, median body mass index, median duration of infertility, and median number of previously transferred embryos (range) were 36 years (20-44), 25 kg/m^2 (18-36), 5 years (2-12 years), and 4 years (1-10), respectively. As a single factor, unexplained infertility was the most common cause of infertility in the study population (19.9%, $n = 145$). However, both partners had at least one of infertility causes (23.5%, $n = 172$). Advanced age alone (≥ 35 years) was the most frequent reason of PGT-A indications (36.7%, $n = 270$). There were more than one PGT-A indications in 24.4% ($n = 178$) of the patient population, 89.3% ($n = 159$) of whom were at advanced age. Overall, the study population had a frequency of 58.7% ($n = 429$) for advanced age. Of 731 patients, 648 (88.6%) was primary infertile and 83 (11.4%) were secondary infertile. The groups did not differ in terms of these parameters ($p > 0.05$ for all parameters, Tables 1 and 2). Both groups also did not significantly differ in endometrial thickness and

Table 1 Comparisons of patient characteristics between two luteal phase support regimes

	Daily IMP ($n = 573$)	Daily VP plus IMHPC ($n = 158$)	p value
Age (years)	36 (20–44)	36 (20–44)	0.887
Age brackets			0.584
< 30	72 (12.6)	23 (14.6)	
30–34	158 (27.5)	36 (22.7)	
35–39	213 (37.2)	58 (36.8)	
> 39	130 (22.7)	41 (25.9)	
Body mass index (kg/m2)	24.3 (18.3–35.2)	26.5 (17–32.1)	0.575
Body mass index brackets			0.351
< 25	278 (48.6)	72 (45.6)	
25–29.9	173 (30.2)	60 (37.9)	
> 30	122 (21.2)	26 (16.5)	
Duration of infertility (years)	5 (2–12)	5 (2–13)	0.138
Number of previous attempts	4 (1–9)	4 (1–10)	0.387
Primary infertility	89 (510)	87.3 (138)	0.559
Day of starting progesterone			
Endometrial thickness (mm)	9.8 (7-13)	10 (7–13)	0.941
Estrogen level (pg/mL)	288 (119–1084)	276 (93–920)	0.412
Progesterone level (ng/mL)	0.17 (0.05–1.23)	0.2 (0.05–1.12)	0.555

Data are given as median (minimum-maximum) or number (percentage). IMP, VP and IMHPC denote intramuscular progesterone, vaginal progesterone, and intramuscular hydroxyprogesterone caproate

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estradiol and progesterone levels on the day of progesterone initiation ($p = 0.941$, $p = 0.412$, and $p = 0.555$, respectively).

Seven hundred thirty-one patients underwent a total of 767 single, autologous euploid FBTs following artificial EP, as 36 women had subsequent transfers due to the negative result of the first transfer. LPS regimes were not changed in the subsequent transfers of these patients. Of 767 single, autologous euploid FBTs, 608 had daily IMP (group 1) and 159 had daily VP plus weekly IMHPC (group 2). The live birth rate was 51.8% in group 1 and 50.3% in group 2, and this difference did not reach statistical significance ($p = 0.737$, OR 0.94, 95%CI 0.66–1.33). The implantation rates were 62.7% and 64.2%, respectively ($p = 730$, OR 1.06, 95%CI 0.74–1.53). The clinical pregnancy rates were 59.5% in group 1 and 61.6% and in group 2 ($p = 631$, OR 1.09, 95%CI 0.76–1.56). The multiple pregnancy rate was 0.7% in group 1 and 1.3% in group 2, respectively ($p = 0.445$). The ectopic pregnancy rates were similar in both groups, too (0.3% and 0.6%, respectively). Table 3 shows FBT outcomes in groups.

Discussion

To the best of our knowledge, this is the first study comparing FBT outcomes between IMP (100 mg/day) alone and VP (90 mg, BID) plus IMHPC (250 mg/week) for LPS in single, autologous euploid FBTs. We did not find the superiority of one regime over the other, with both regimes ensuring similar results in terms of rates of live birth, implantation, and clinical pregnancy. Thus, patient preference may be the priority in choosing one of these LPS regimes in single, autologous euploid FBTs after artificial EP. The regime of daily VP plus weekly IMHPC for LPS appears to be more convenient for patients than daily IMP.

In a retrospective study of day 3 FETs, Kaser et al. found lower clinical and live birth rates in those using VP (90 mg, BID) than in those using IMP (50 mg/day) for LPS [15]. A large randomized trial from China by Wang et al. compared VP (90 mg/day) with IMP (40 mg/day), with the addition of oral dydrogesterone (20 mg/day) to each regime for LPS in FET cycles [17]. Neither the baseline characteristics of the patients nor the clinical outcomes reached statistical differences between the groups. Gibbons et al. concluded that VP (90 mg, BID) resulted in similar clinical and ongoing pregnancy rates to IMP (100 mg/day) in a prospective study using donor eggs [18]. Berger et al. also arrived at the same conclusion in a study of donor oocyte recipients using IMP (50 mg/day) or VP (90 mg, BID) [19]. Silverberg et al. showed significantly higher pregnancy rates in the VP arm (90 mg/day) than in the IMP arm (25 or 50 mg/day) in patients younger than 35 years in a large prospective study of patients undergoing day 3 or 5 ETs in fresh cycles [16]. However, pregnancy rates were similar in those older than 35 years. Kahraman et al. demonstrated comparable pregnancy rates between those

Table 2 Comparisons of causes of infertility and preimplantation genetic screening indications between two luteal phase support regimes

	Daily IMP (n = 573)	Daily VP plus IMHPC (*n* = 158)	*p* value
Causes of infertility			0.164
Tubal factor	87 (15.2)	24 (15.2)	
Ovulatory dysfunction	26 (4.5)	12 (7.6)	
Diminished ovarian reserve	91 (15.9)	17 (10.8)	
Endometrioma	16 (2.8)	2 (1.3)	
Male factor	61 (10.6)	23 (14.6)	
Both couple	142 (24.9)	30 (18.9)	
More than one female factor	42 (7.3)	13 (8.2)	
Unexplained	108 (18.8)	37 (23.4)	
PGT-A indications			0.171
Advanced age (≥ 35 years)	217 (37.9)	53 (33.5)	
Recurrent implantation failure	74 (12.9)	12 (7.6)	
Recurrent pregnancy loss	32 (5.6)	6 (3.8)	
Chromosomal aberrations	13 (2.3)	4 (2.5)	
Single-gene carriers	4 (0.7)	1 (0.6)	
Patient request	105 (18.3)	32 (20.4)	
More than one indication	128 (22.3)	50 (31.6)	

Data are given as number (percentage). IMP, VP, and IMHPC denote intramuscular progesterone, vaginal progesterone, and intramuscular hydroxy-progesterone caproate

PGT-A preimplantation genetic testing for aneuploidy

receiving IMP (100 mg/day) and those receiving VP (90 mg, BID) in a randomized trial of 426 patients undergoing fresh transfers [14]. Another randomized study found no differences in outcomes of fresh cycles between VP (90 mg/day) and IMP (50 mg/day) for LPS, with the former being better tolerated than the latter [13]. Dal Prato et al. did not demonstrate any differences in clinical pregnancy and live birth rates between IMP (50 mg/day) and VP (90 mg/day) and VP (90 mg, BID) in a randomized trial of fresh cycles [20]. Devine et al. reported a lower live birth rate in those receiving daily VP alone (200 mg endometrin) than in those receiving daily VP (200 mg endometrin) plus IMP (50 mg) once every 3 days or daily IMP (50 mg) alone for LPS in a randomized controlled non-inferiority trial of day 5 FETs [21]. Feinberg et al. also showed daily VP alone to be inferior to daily VP plus IMP once every 3 days for LPS in a retrospective study on FETs [22].

As referred above, a vast majority of studies comparing LPS regimes examined patients undergoing cleavage or blastocyst stage ETs with unknown ploidy status in fresh or frozen cycles. However, no study examined LPS regimes on euploid FBTs. That is why, our study is different from the abovementioned studies as it analyzed two different LPS regimes in single euploid FBTs following artificial EP protocol, thereby minimizing the effect of embryo viability as a potential confounding factor. It is clear that controversy regarding the efficacy of VP supplementation on outcomes of frozen and fresh ETs is still continuing. Although VP merits to be considered as a reasonable alternative to IMP, the addition of weekly IMHPC to daily VP may improve FET outcomes.

As is known, the quality of an embryo is the main factor that determines the success of IVF cycles and embryo aneuploidy is likely responsible for the majority of implantation failures [23]. The transfer of euploid blastocysts has been shown to result in an increased pregnancy rate per transfer [24, 25]. FETs have been associated with improved outcomes, as well [26, 27]. Even when only euploid embryos were used, FETs still provided higher ongoing pregnancy rates than did fresh transfers, as shown by a recent randomized study by Coates et al. [28]. The present study includes only euploid embryos, minimizing embryo-related bias, and thus it is a reasonable study design to compare the efficacy of one regime with that of another for LPS. Moreover, since artificial EP was the method of choice in preparing the endometrium, our study represented FBT outcomes of a fairly homogenous patient population. Even though the daily VP group yielded equivalent outcomes compared with daily IMP group, daily VP group also received weekly IMHPC. Thus, it remained unclear if the VP group might have had poorer or similar FBT outcomes if weekly IMHPC had not been given. This needs to be investigated by further studies.

Based on our study, most patients had daily IMP for LPS. This may be explained by the tendency of physicians to more often prefer daily IMP for LPS in euploid ETs. Their tendency may result from an assumption that daily IMP is a more effective way of delivering progesterone to the uterus as the

Table 3 Comparisons of single, autologous frozen-thawed blastocyst transfers between two luteal phase support regimes

	Daily IMP ($n = 608$)	Daily VP plus IMHPC ($n = 159$)	OR (95%CI)	p value
Positive pregnancy test	420 (69.1)	110 (69.2)	1.01 (0.68–1.46)	0.980
Biochemical pregnancy	37 (6.1)	7 (4.4)	0.71 (0.31–1.62)	0.416
Implantation	381 (62.7)	102 (64.2)	1.06 (0.74–1.53)	0.730
Clinical pregnancy	362 (59.5)	98 (61.6)	1.09 (0.76–1.56)	0.631
Live birth	315 (51.8)	80 (50.3)	0.94 (0.66–1.33)	0.737
Ectopic pregnancy	2 (0.3)	1 (0.6)	1.91 (0.17–21.28)	0.590
Multiple pregnancy	4 (0.7)	2 (1.3)	1.92 (0.34–10.59)	0.445

Data are given as number (percentage). IMP, VP, and IMHPC denote intramuscular progesterone, vaginal progesterone, and intramuscular hydroxyprogesterone caproate. OR and CI denote odds ratio and confidential interval

IMP, VP and IMHPC denote intramuscular progesterone, vaginal progesterone and intramuscular hydroxyprogesterone caproate.

OR and CI denote odds ratio and confidential interval

literature has conflicting results regarding the optimum LPS. Although IMP administration is associated with higher serum progesterone levels compared with VP administration, vice versa is true in the tissue progesterone levels because of the direct transport of progesterone from the vagina to the uterus [29, 30]. Currently, the fact that it is not possible to measure the tissue progesterone levels presumably leads physicians to more frequently prefer IMP as the serum progesterone levels are readily measurable if IMP is used. However, it has been shown that the progesterone level monitoring does not provide any benefit in predicting IVF outcomes [31].

The approach for transferring euploid embryos remains to be determined. Studies compared different LPS protocols in different patient populations, which limits the comparisons of our regimes with those used in other studies. Progesterone is the drug of choice for LPS in FET cycles. However, neither the ideal regime for LPS nor the optimal route of progesterone administration has been established in the existing literature. Vaginal application, so far, has provided promising outcomes and is also a pain-free way of administering progesterone for LPS in women undergoing ET. In the era of growing utilization of PGT-A, by which chromosomally abnormal embryos can be excluded, we can illuminate unknown points concerning the optimal regime for LPS in FET cycles. However, other factors (dose and route of estrogen, endometrial receptivity, endometrial thickness, number of embryos transferred and etc.) that possibly affect the success of IVF treatment need to be addressed for certain, as well.

One of the limitations of the study is that it was conducted retrospectively. Another one is that the serum progesterone levels of the patients were not measured on the ET day or during early pregnancy. However, comparing serum progesterone levels between the groups might have caused the misinterpretation of our results as VP administration has a direct effect on the uterus, regardless of serum progesterone levels. In addition, our findings are not generalizable to all FET cycles since we studied only patients undergoing single, autologous euploid FBT in artificial EP cycles. In addition, we did not assess undesirable effects of LPS regimes as an outcome measure. Our study also has some strengths. First, we minimized sampling bias as the study included a relatively large number of patients. Second, we limited selection bias by including a patient population undergoing single, autologous euploid FBT, which eliminated embryo-related bias that would have affected the results. Also, all embryos had been frozen by vitrification technique and were warmed in the same way. Third, the fact that all subjects underwent artificial EP method before ET mitigated bias that would have originated from EP methods.

Combination of daily VP plus weekly IMHPC for LPS appears to yield equivalent outcomes to daily IMP in patients undergoing single, autologous euploid FBT following artificial EP. Weekly IMHPC administration allows 6 days free from injections every week during luteal support. The choice of LPS can be based on patient desire if single, autologous euploid FBT after artificial EP is planned. There is no doubt that future randomized studies are needed to confirm our results and explore the impact of each regimen on outcomes of single, autologous euploid FBTs following artificial EP.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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