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ARTICLE

Individualized luteal phase support using additional oral dydrogesterone in artificially prepared frozen embryo transfer cycles: is it beneficial?

BIOGRAPHY

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KEY MESSAGE

Additional supplementation with oral dydrogesterone in patients with low serum progesterone concentrations at the moment of transfer showed comparable reproductive outcomes to those with normal serum progesterone. This could have the potential to rescue outcomes in low progesterone HRT–FET cycles, but this field remains hampered by the absence of randomized controlled trials.

ABSTRACT

Research question: Does additional supplementation with oral dydrogesterone improve reproductive outcomes in patients with low serum progesterone concentrations on the day of frozen embryo transfer (FET) after artificial (HRT) endometrial preparation?

Design: Retrospective, single-centre cohort study including 694 unique patients performing single blastocyst transfer in an HRT cycle. For luteal phase support, intravaginal micronized vaginal progesterone (MVP, 400 mg twice daily) was administered. Serum progesterone concentrations were assessed prior to FET and outco-mes were compared among patients with normal serum progesterone (≥8.8 ng/ml) continuing the routine protocol and patients with low serum progesterone (<8.8 ng/ml) who received additional oral dydrogesterone supplementation (10 mg three times daily) from the day after FET onwards. Primary outcome was live birth rate (LBR), with a multivariate regression model correcting for relevant confounders.

Results: Normal serum progesterone concentrations were observed in 547/694 (78.8%) of patients who continued only MVP as planned, whereas low (<8.8 ng/ml) serum progesterone concentrations were detected in 147/694 (21.2%) patients who received additional oral dydrogesterone supplementation on top of MVP from the day after FET onwards. LBR was comparable between both groups: 37.8% for MVP-only versus 38.8% for MVP+OD ($P = 0.84$). The multivariate logistic regression model indicated that LBR was not significantly associated with the investigated approaches (adjusted odds ratio 1.01, 95% confidence interval 0.69–1.47, $P = 0.97$).

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KEYWORDS

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Conclusions: The current findings suggest that additional oral dydrogesterone supplementation in patients with low serum progesterone concentrations at the moment of transfer could have the potential to rescue reproductive outcomes in HRT–FET cycles. This field of research, however, remains hampered by the absence of randomized controlled trials.

INTRODUCTION

Several studies have suggested that low serum progesterone concentrations around the moment of frozen embryo transfer (FET) in artificially prepared (HRT) cycles are associated with increased rates of early pregnancy loss (EPL) and decreased chances of reaching a live birth (*Melo et al., 2021*). The first landmark paper by *Labarta et al. (2017)* determined that a serum progesterone concentration <9.2 ng/ml on the day of FET was significantly associated with a lower ongoing pregnancy rate (OPR). This initial study only included women who became pregnant after oocyte donation. A subsequent study by the same research group took into account autologous and donated oocyte cycles and confirmed that the OPR remained lower when serum progesterone concentrations were below a certain threshold, in this study more specifically calculated at 8.8 ng/ml (*Labarta et al., 2021*).

Likewise, *Gaggiotti-Marre et al. (2019)* concluded that the serum progesterone concentration measured on the day before FET of euploid blastocysts had a significant impact on the success rates following HRT–FET. Indeed, the EPL rate appears to be higher in patients with a serum progesterone concentration below 10.6 ng/ml the day before FET, with a further clear impact on the resulting LBR. Interestingly, the same group provided evidence of a potential 'rescue' of HRT–FET cycles with low serum progesterone on the day prior to FET as they retrospectively demonstrated that additional s.c. progesterone supplementation in this low progesterone group results in comparable reproductive outcomes as when normal serum progesterone concentrations were measured (i.e. >10.6 ng/ml) (*Álvarez et al., 2021*).

Analysis of reproductive outcomes in women who have low serum progesterone concentrations on the day of FET in a HRT cycle and who receive additional progesterone supplementation with oral dydrogesterone instead of s.c. progesterone as a rescue strategy has not previously been performed.

Dydrogesterone is a stereoisomer of progesterone with the major advantage that, thanks to the curved isomer structure, it has a high bioavailability when compared to orally administered micronized progesterone, the latter being severely affected by the hepatic first-pass effect lowering its efficiency via this route (*Griesinger et al., 2019*). As bioavailability is higher for oral dydrogesterone, a lower dose is required for luteal phase support (LPS) in comparison to micronized vaginal progesterone (MVP). Indeed, the Lotus I and II studies, international phase 3 randomized controlled trials, demonstrated a similar safety profile and non-inferiority in terms of reproductive outcomes between oral dydrogesterone and MVP administered for LPS in fresh IVF cycles (*Griesinger et al., 2018*; *Tournaye et al., 2017*). Moreover, an individual patient data meta-analysis suggested that patients who received oral dydrogesterone had a significantly higher OPR at 12 weeks and a higher LBR than the group who received MVP for fresh embryo transfer (*Griesinger et al., 2020*). For HRT–FET, studies on the efficacy of oral dydrogesterone as a single LPS agent are currently still ongoing and so far only a limited number of data have been published, which are reassuring as long as oral dydrogesterone is dosed adequately (*Atzmon et al., 2021*; *Pabuccu et al., 2022*; *Rashidi et al., 2016*; *Zarei et al., 2017*). Furthermore, safety data on the use of dydrogesterone in early pregnancy are reassuring (*Katalinic et al., 2022*; *Queisser-Luft, 2009*). The current analysis investigated whether progesterone supplementation with oral dydrogesterone in addition to MVP can rescue the LBR in patients with serum progesterone concentrations below 8.8 ng/ml on the day of FET in a HRT cycle, exploring a patient-friendly, low-cost alternative for individualized LPS (iLPS).

MATERIALS AND METHODS

Ethical approval and quality assurance

The study was approved by the Ethical Committee of the Universitair Ziekenhuis Brussel (BUN 1432021000518, 23 June 2021) and performed in accordance with the endorsed guidelines.

Study design and population

This retrospective, single-centre cohort study was conducted on patients attending between 1 June 2020 and 1 May 2021 at Brussels IVF, the Centre for Reproductive Medicine of Universitair Ziekenhuis, Belgium. All patients performing a single blastocyst FET in a HRT cycle were selected from the electronic database and included once in the analysis. Excluded from the analysis were patients with a history of recurrent miscarriage as defined by the ESHRE guidelines (*Kolte et al., 2015*), a uterine anatomical distorsion (polyp, fibroid or Mullerian anomaly), oocyte recipients, patients with FET following oocyte in-vitro maturation (IVM) and preimplantation genetic testing (PGT) cycles (PGT-M, PGT-SR and PGT-A) and patients with incomplete data in their electronic records.

Endometrial preparation protocol

After confirmation of basal serum hormonal values, oral oestrogen administration with oestradiol valerate (Progynova®, Bayer-Schering Pharma AD, Berlin, Germany) was started to induce endometrial proliferation. More specifically, oestradiol valerate was started on cycle day 2 at a dose of 2 mg three times daily for at least 10 days. Patients had their first follow-up visit planned between day 10 and day 14 of the endometrial preparation protocol. During this visit serum oestradiol concentrations, progesterone, LH and FSH were determined and a vaginal ultrasound scan was performed to assess the endometrial thickness and to exclude follicular growth despite the oestradiol valerate feedback mechanism. If serum progesterone was ≥1.5 ng/ml, the cycle was cancelled. If the vaginal ultrasound scans showed an endometrial thickness of <6.5 mm, a step-up protocol was prescribed to the patients in which additional vaginal oestradiol valerate was administered at a dose of 2 mg three times daily. If the endometrial thickness was still <6.5 mm on day 21 of oestradiol valerate, the cycle was cancelled and excluded for analysis. When an optimal endometrial thickness of ≥6.5 mm was achieved with a serum progesterone concentration <1.5 ng/ml, MVP (Utrogestan®, Besins Healthcare, UK or Amelgen®, Gedeon Richter, Benelux) was started to induce the secretory phase

according to the standard protocol at a dose of 400 mg twice daily. The dose of oestradiol valerate was 2 mg three times daily for all patients as of the start of MVP.

FET was performed on the 6th day of MVP administration. Transfers were systematically performed under ultrasound guidance by a trained gynaecologist according to the centre's standard operating procedures. Serum progesterone concentrations were assessed just prior to FET using a validated electrochemiluminescence immunoassay (Cobas 6000®, Generation II, Roche, Basel, Switzerland). Patients with normal serum progesterone on the day of FET (defined as ≥8.8 ng/ml) continued the routine medication protocol consisting of oestradiol valerate and MVP only, while patients with low serum progesterone on the day of FET (defined as <8.8 ng/ml) continued oestradiol valerate and MVP but were additionally prescribed oral dydrogesterone at a dose of 10 mg three times daily (Duphaston®, Abbott, Switzerland). All medication was continued until the first human chorionic gonadotrophin (HCG) pregnancy test, about 10–12 days post-FET. If the test was positive (HCG >5 mIU/ml), all medication was continued until the 8th week of gestation, after which a gradual decrease was proposed with a medication stop at week 9 of gestation.

Outcome measures and statistical analysis

The patients were divided into two groups depending on whether additional oral dydrogesterone supplementation was used, based on the serum progesterone concentration measured on the day of FET as described above. Data related to patient and cycle characteristics were retrieved as well as reproductive outcomes following the HRT–FET. For continuous variables, the distribution of the observations was examined. In case of normal distribution (Shapiro–Wilk test), the mean values and SD within each group of interest was used. Categorical variables are presented as number of cases or percentages, including nominator and denominator values. Continuous variables were compared using the Mann–Whitney *U*-test. Categorical variables were compared using the chi-squared test. A *P*-value of less than 0.05 was considered statistically significant..The primary outcome of this study was LBR (*Zegers-Hochschild et al., 2017*), while the secondary outcome was EPL rate, calculated as the sum of biochemical pregnancy losses (given only HRT cycles were included, all positive HCG tests were taken into account) + early clinical miscarriages (until 10 weeks' gestation, *Kolte et al., 2015*) divided by the total number of embryo transfers performed. To identify characteristics that may be associated with the LBR, multivariable logistic regression analysis was performed, with the LBR as the dependent variable and LPS protocol (oral dydrogesterone supplementation or not) as the main independent variable. The potential predictors considered for the analysis were maternal age at oocyte retrieval, body mass index (BMI), endometrial thickness prior to luteal phase induction, embryo quality score and day of blastocyst vitrification (day 5 or day 6). All variables were simultaneously entered into the logistic regression model. The likelihood of LBR-based oral dydrogesterone supplementation is presented as an adjusted odds ratio (aOR) with 95% confidence interval (CI). All statistical tests used a two-tailed alpha of 0.05. All analyses were performed using STATA 13 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 694 unique patients were included, all performing a single blastocyst transfer in an HRT cycle. A normal serum progesterone concentration (≥8.8 ng/ml) was observed in 547 patients (78.8%), whereas a low (<8.8 ng/ml) serum progesterone concentration was detected in 147 patients (21.2%). Thus, as planned, 547 patients continued MVP only (MVP-only group), while 147 patients received additional oral dydrogesterone supplementation alongside MVP from the day following FET onwards (MVP+OD group).

TABLE 1 shows the baseline patient and cycle characteristics. The mean age in the MVP-only group versus the MVP+OD group was 34.6 ± 4.2 and 33.6 ± 4.3 years, respectively ($P = 0.01$). For BMI, a mean of 24.2 ± 4.4 kg/m^2 was observed in the MVP-only group versus a mean of 24.9 ± 4.7 kg/m^2 in the MVP+OD group ($P = 0.06$). The mean endometrial thickness for both groups was 8.4 ± 1.7 mm. The mean serum progesterone concentration on the day of FET was 14.6 ± 5.8 ng/ml in the MVP-only group and 7.0 ± 1.8 ng/ml in the MVP+OD group ($P < 0.001$). For serum oestradiol concentration on the day of FET the mean values were 201.8 ± 75.7 pg/ml for the MVP-only group versus 208.5 ± 81.8 pg/ml in the MVP+OD group ($P = 0.55$).

The reproductive outcomes are reported in TABLE 2. Overall, 390 patients (56.2%) had a positive pregnancy test following the FET; 301/547 patients, i.e. a biochemical pregnancy rate (BPR) of 55.0% in the MVP-only group versus 89/147, i.e. a BPR of 60.5% in the MVP+OD group ($P = 0.23$). In the MVP-only group, 87/547 patients experienced an EPL (15.9%) while in the MVP+OD group this was 29/147 (19.7%) ($P = 0.27$). The LBR was 207/547 (37.8%) for the MVP-only group versus 57/147 (38.8%) for the MVP+OD group ($P = 0.84$). The multivariate logistic regression model (TABLE 3) indicated that LBR was not significantly associated with the LPS supplementation protocol (aOR 1.01, 95% CI 0.69–1.47, $P = 0.97$). The only variable significantly associated with LBR was embryo quality (aOR 2.60, 95% CI 1.27–5.33, $P = 0.009$), with higher quality associated with increased odds of a live birth.

DISCUSSION

This retrospective study evaluated the effect of enhanced LPS through the addition of oral dydrogesterone to the MVP regimen in patients with low serum progesterone concentrations on the day of FET in HRT cycles. It was observed that the study group (MVP+OD) had a LBR comparable to the group with normal progesterone concentrations (≥8.8 ng/ml) (MVP-only; 38.8% and 37.8%, respectively), and as expected in a cohort with a single blastocyst FET without specific age limits or routinely performed PGT-A. Additionally, the multivariate logistic regression model confirmed that the LBR was not significantly associated with LPS supplementation protocol and showed that the parameter most predictive of reaching an ongoing pregnancy was the embryo quality of the warmed blastocyst at the moment of transfer. These data suggest that additional oral dydrogesterone supplementation on top of routine MVP indeed results in favourable clinical outcomes and may correct the previously observed suboptimal outcomes in women who have low serum progesterone concentrations on the day of FET when they receive a standard FET–HRT regimen with MVP.

TABLE 1 BASELINE PATIENT AND CYCLE CHARACTERISTICS

Baseline characteristic	MVP-only Serum progesterone ≥8.8 ng/ml (*n* = 547)	MVP+OD Serum progesterone <8.8 ng/ml (*n* = 147)	*P*-value
Maternal age at oocyte retrieval (years)	34.6 ± 4.2	33.6 ± 4.3	0.01[a]
BMI (kg/m^2)	24.2 ± 4.4	24.9 ± 4.7	0.06[a]
Endometrial thickness (prior to starting LPS) (mm)	8.4 ± 1.7	8.4 ± 1.7	0.99[a]
Serum oestradiol concentration on day of FET (pg/ml)	201.8 ± 75.7	208.5 ± 81.8	0.55[a]
Serum progesterone concentration on day of FET (ng/ml)	14.6 ± 5.8	7.0 ± 1.8	<0.001[a]
Quality score of blastocyst transferred[c] (*n*, %)			
1–2	505 ± 92.3	139 ± 94.6	0.35[b]
3–4	42 ± 7.7	8 ± 5.4	

Data are presented as mean ± SD) unless otherwise stated.

BMI = body mass index; FET = frozen embryo transfer; LPS = luteal phase support; MVP = micronized vaginal progesterone; OD = oral dydrogesterone.

[a] Mann–Whitney *U*-test.

[b] Pearson's chi-squared test.

[c] Embryo quality scoring system is given in **Supplementary Table 1**.

The current findings are in line with previous research in the field demonstrating that an iLPS in artificially prepared FET cycles improves pregnancy outcomes (*Álvarez et al., 2021*; *Labarta et al., 2022*). Both previous studies individualized the LPS by adding a daily injection of 25 mg of s.c. progesterone to routine MVP. This is the first study indicating that oral dydrogesterone, a more patient-friendly and less expensive compound at a dose of 10 mg three times a day, can also be considered in this setting. However, to date all three available studies are limited by their retrospective design and risk for bias due to unmeasured confounding. The outcomes presented here, as well as the data reported by *Labarta et al. (2022)*, were analysed in a multivariate logistic regression model correcting for the most relevant confounders; the study by *Álvarez et al. (2021)* did not perform a logistic regression, but created a homogeneous population by including only patients undergoing euploid transfers. In an ideal research setting, patients with low serum progesterone concentrations around the moment of FET–HRT should be randomized into one group that continues the MVP-only protocol as planned versus a second group receiving iLPS. Nevertheless, from a clinical and ethical point of view, such a randomized trial would be difficult to conduct given the convincing retrospective data showing that low serum progesterone concentrations may have a negative impact on pregnancy outcomes (*Gaggiotti-Mare et al., 2019*; *Labarta et al., 2017*, *2021a*). However, several questions concerning the use of serum progesterone concentrations in daily clinical practice are currently still unanswered.

TABLE 2 CRUDE REPRODUCTIVE OUTCOMES

Outcome	MVP-only Serum progesterone ≥8.8 ng/ml (*n* = 547)	MVP+OD Serum progesterone <8.8 ng/ml (*n* = 147)	*P*-value
Biochemical pregnancy rate[a]	301 (55.0)	89 (60.5)	0.23[b]
Early pregnancy loss rate (= biochemical pregnancy losses + early clinical miscarriages)	87 (15.9)	29 (19.7)	0.27[b]
Biochemical pregnancy loss rate	34 (6.2)	11 (7.5)	0.58[b]
Early clinical miscarriage rate	53 (9.7)	18 (12.2)	0.36[b]
Ongoing pregnancy rate	211 (38.6)	58 (39.5)	0.85[b]
Live birth rate	207 (37.8)	57 (38.8)	0.84[b]

Data are presented as *n* (%).

From the data beyond biochemical pregnancy rate, in the MVP-only group there were three ectopic pregnancies and four terminations of pregnancies (one voluntary abortion, one polymalformation, one exencephaly and one trisomy 21), and in the MVP+OD group there were two ectopic pregnancies and one termination of pregnancy (for a monochorial triamniotic triplet).

HCG = human chorionic gonadotrophin; MVP = micronized vaginal progesterone; OD = oral dydrogesterone.

[a] As only artificially prepared cycles were included in this study and as no exogeneous HCG was administered, all HCG values >5 mIU/ml were considered as a positive pregnancy test.

[b] Pearson's chi-squared test.

TABLE 3 MULTIVARIATE LOGISTIC REGRESSION MODEL FOR THE PRIMARY OUTCOME OF LIVE BIRTH RATE

Live birth rate	aOR	95% CI	*P*-value
Investigated Individualized LPS approach			
MVP-only (ref)	1	–	
MVP+OD	1.01	0.69–1.47	0.97
Maternal age at oocyte retrieval	0.97	0.94–1.01	0.16
BMI	0.97	0.94–1.01	0.11
Endometrial thickness	1.05	0.95–1.15	0.32
Quality score of blastocyst transferred[a]			
3–4 (ref)	1	–	
1–2	2.60	1.27–5.33	0.009
Day of blastocyst vitrification			
Day 5 (ref)	1		
Day 6	0.75	0.51–1.10	0.14

The potential confounders considered for the analysis were maternal age at oocyte retrieval, BMI, endometrial thickness prior to luteal phase induction, embryo quality score and day of blastocyst vitrification (day 5 or day 6). All variables were simultaneously entered into the logistic regression model.

aOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; FET = frozen embryo transfer; MVP = micronized vaginal progesterone; OD = oral dydrogesterone; ref = reference.

[a] Embryo quality scoring system is given in **Supplementary Table 1**.

A first element for debate is the absence of a relationship between serum and endometrial progesterone concentrations (*Labarta et al., 2021b*). This observation could frame into the hypothesis that serum progesterone concentrations are mainly important to sustain implantation rather than to induce receptivity. Indeed, when comparing a historical cohort with low serum progesterone concentrations and no iLPS versus low serum progesterone concentrations with iLPS, the BPR was not significantly different between both groups, whereas the OPR and LBR were (*Labarta et al., 2021a*). Nevertheless, these data need to be interpreted with caution as they are crude, non-adjusted outcomes. In light of this, the observed EPL rate in the current study deserves attention in this discussion. Although not reaching significance, according to the current data, patients with low serum progesterone concentrations measured at the moment of FET–HRT may have a slightly higher risk for EPL despite additional oral dydrogesterone supplementation. Specifically, when evaluating the EPL rate using HCG-positive patients as a denominator instead of the entire cohort, fairly high rates of 28.9% (87/301 for MVP-only) versus 32.6% (29/89 for MVP+OD) were calculated for both arms. Prospective studies are therefore required to further investigate EPL rate following FET–HRT in larger datasets and eventually after PGT-A. Of note in this context is the large multicentre cohort study recently published by *Vinsonneau et al. (2022)* reporting that in FET, HRT cycles were significantly associated with higher EPL rates compared with stimulated or natural cycles.

Another point that merits consideration are the specific factors associated with serum progesterone concentrations, such as age, BMI and the timing of blood sampling in relation to the last MVP dosing (*Bellver et al., 2022*; *Gonzalez-Foruria et al., 2020*; *Maignien et al., 2022*). It is noteworthy that age and BMI were used as potential confounders in the analysis, but there was no detailed information on when patients administered the last dose of MVP prior to the endocrine blood sampling performed just before FET. Given that in the study centre transfers are performed throughout the day (from 10:00 until 16:00 h) and that patients were given instructions to administer 400 mg of MVP twice a day (morning and evening dose), this variation in timing is thought to be a drawback of the current study.

A third point to mention is the recommended lower threshold and the associated incidence of patients detected as insufficiently supplemented with MVP alone. Different studies, although all evaluating HRT–FET with MVP as routine LPS but in different dosages, have proposed different cut-off levels (<9.2 ng/ml by *Labarta et al., 2017*; 10.6 ng/ml by *Gaggiotti-Mare et al., 2019*; <10 ng/ml by *Cédrin-Durnerin et al., 2019*; 8.8 ng/ml by Labarta et al., 2021). Using the 8.8 ng/ml limit for a dosage of 400 mg MVP twice a day, about one in five patients (21.2%) were found to benefit from additional oral dydrogesterone supplementation in the current study. In the current setting, this percentage is rather smaller than one-third, as previously published (*Labarta et al., 2017*, 2021), an observation that probably supports the recommendation that each clinic should determine its own clinically relevant cut-off. Furthermore, the rather limited number of patients with low serum progesterone concentrations when using MVP alone sets into a more critical perspective the routinely combined LPS strategies (*Vuong et al., 2021*).

Finally, when looking at the future of FET preparation protocols, two important topics should not be overlooked. The first is the potential rise in the use of oral dydrogesterone as a single LPS agent in HRT cycles given the patient-friendliness, reduced costs and data supporting the molecule's efficacy as well as safety, not only in fresh but also in FET cycles (*Griesinger et al., 2020*; *Pabuccu et al., 2022*; *Queisser-Luft, 2009*). Of note, in the current study, not a single malformation was reported in the MVP+OD group. Nonetheless, a relevant side note in the context of iLPS and oral dydrogesterone is that neither dydrogesterone nor its active metabolite 20α-dihydrodydrogesterone can be detected by the currently available clinically applicable serum hormone assays. In a prospective cohort study, Griesinger and colleagues used liquid chromatography/tandem mass spectroscopy (LC-MS/MS) to analyse plasma concentrations of both molecules in HRT–FET cycles using only oral dydrogesterone LPS and showed that patients in the lowest quarter on the day of FET had a reduced OPR (*Neumann et al., 2022*). Commercially available kits to measure dydrogesterone could therefore be of interest as iLPS continues to gain more ground. A second ongoing trend in FET preparation protocols is the back-to-nature approach in which NC-FET becomes the first-line treatment as the corpus luteum function has been consistently shown to be protective for obstetrical complications such as

hypertensive disorders of pregnancy/pre-eclampsia and large for gestational age infants (*Pereira et al., 2021*; *Roelens and Blockeel, 2022*; *Roelens et al., 2022*). However, in this context suboptimal endogenous serum progesterone concentrations have also been associated with lower reproductive outcomes and additional supplementation is worth considering (*Gaggiotti-Mare et al., 2020*; Roelens et al., in preparation; *Wanggren et al., 2022*).

In summary, this is the first study to evaluate additional oral dydrogesterone supplementation on top of MVP as a rescue strategy when low serum progesterone concentrations are detected at the moment of FET in HRT cycles. The data show that additional oral dydrogesterone supplementation in this context gives rise to comparable LBR as observed in patients with normal progesterone concentrations. Future studies should attempt to conduct randomized controlled trials to more robustly investigate the actual impact of different iLPS strategies on the outcomes of FET cycles.

AUTHOR ROLES

SM, CB and MDV were responsible for the concept and study design. FP and SA performed the data collection. PD performed the statistical analyses. SM, FP and SA drafted the manuscript. All authors contributed to the interpretation, discussion and editing of the manuscript, and approved the final version.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2023.02.007.

DATA AVAILABILITY

Data will be made available on request.

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