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REPRODUCTIVE ENDOCRINOLOGY: ORIGINAL ARTICLE

Comparable Outcomes Using Oral Dydrogesterone Vs. Micronized Vaginal Progesterone in Frozen Embryo Transfer: a Retrospective Cohort Study

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Abstract

This retrospective study was conducted to determine whether using oral dydrogesterone (DYD) instead of micronized vaginal progesterone (MVP) in frozen embryo transfer (FET) cycles affects pregnancy outcomes. Women undergoing autologous FET in an academic fertility center were evaluated. Uses of 10 mg TID oral DYD or MVP for patients treated in FET cycles (artificial and ovulatory cycle, separately) were compared. The main outcome measure was live birth rates in each group. The study analyzed 599 cycles that occurred from January 2018 through December 2019. Chemical and clinical pregnancy rates were comparable between DYD vs. MVP groups (41.6% vs. 38.1%; $P = 0.44$ and 36.7% vs. 31.4%; $P = 0.18$, respectively). The ongoing pregnancy and delivery rates (29% vs. 22%, $P = 0.06$), as well as abortion rate (12.3% vs. 15.8%, $P = 0.2$), were comparable between the two groups. In a case-control sub-analysis of artificial FET cycles, we found comparable results between the two modes of luteal support. Similarly, results were comparable in ovulatory cycles using these medications for luteal support. Chemical and clinical pregnancy rates were comparable with DYD vs. MVP, in artificial FET (33.7% vs. 34.8%; $P = 0.89$ and 27.7% vs. 27.5%; $P = 1$), and in ovulatory FET (46.5% vs. 43.9%; $P = 0.71$ and 42.3% vs. 38.2%; $P = 0.53$), respectively. Our results indicate that in FET, pregnancy outcomes with oral DYD were not inferior to those with MVP.

Keywords Dydrogesterone · Embryo transfer · Luteal phase support · Pregnancy rate

Introduction

The use of frozen embryo transfer (FET) during in vitro fertilization (IVF) procedures has been increasing [1, 2]. Several factors have contributed to this increase, primarily improvements in freezing methods, as vitrification has become the main technique for cryopreservation [3, 4], along with the fact that FET achieves pregnancy rates comparable to those of fresh cycles [5–7]. Other indications for using FET are to avoid hyperstimulation syndrome, avoid multiple gestations, and allow for pre-gestation testing for aneuploidy.

It is accepted that FET cycle outcomes are comparable to those of fresh embryo transfer [8]. However, the preferred protocol for endometrial preparation has not been determined. The most common protocols used are artificial FET (a-FET), natural cycle based on spontaneous ovulation, or modified natural cycle using ovulation induction [9]. All treatment protocols and mainly a-FET use variations of progesterone supplementation for luteal support. Although various progesterone preparations are available, including injectable progesterone or vaginal supplementation consisting of micronized progesterone (MVP), studies have not shown that one is superior to another [10].

Results with MVP vs. injectable progesterone are comparable. However, the ability to avoid painful injections and the ease of vaginal administration has resulted in MVP being the most commonly used medication [11, 12]. MVP are known for being relatively uncomfortable, as they cause vaginal discharge and irritation. To make treatments easier for patients, attempts were made to find an oral progesterone therapy.

In 2017, two randomized controlled trials, known as Lotus I and Lotus II, were conducted to compare dydrogesterone (DYD) and MVP in fresh IVF cycles. In both studies, non-inferiority of oral DYD, as compared with MVP in terms of safety and pregnancy outcomes, was reported [13, 14]. Since then, patients' requests for oral progestin for luteal support in FET have increased.

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To date, no large studies have reported using DYD for luteal phase support (LPS) in artificial and natural FET cycles. This study compared the outcomes of FET cycles using oral DYD vs. MVP in different endometrial preparation protocols. We compared treatment outcomes using DYD vs. MVP for LPS in natural cycle vs. a-FET. Moreover, we compared DYD in natural vs. artificial cycle. We followed the patients until delivery and evaluated pregnancy complications and fetal outcomes.

Material and Methods

Patient Population

This retrospective study was conducted in a single reproductive center. Records of all patients and of the cryopreserved embryos were accessed. Data collected included baseline parameters such as age, body mass index (BMI) in kg/m^2, type and etiology of infertility, parity, and smoking status. Treatment parameters evaluated included number of embryos transferred, hormonal level before transfer, time lapse embryo morphokinetic scoring, and endometrial thickness before transfer.

To reflect the broad range of patients typically encountered in clinical practice, no inclusion/exclusion criteria were applied regarding baseline characteristics. Cycles in which transfers were canceled due to endometrial polyps or premature progesterone elevation or those that involved a donor oocyte were not included.

Ethics Approval

This study was approved by the local Institutional Review Board, number HYMC-20-26. Informed consent was not required due to the retrospective nature of the study.

Embryo Assessment During the Preceding Fresh IVF Cycle

All fertilized oocytes were cultured on EmbryoSlides and incubated in an EmbryoScope™ (Unisense FertiliTech, Aarhus, Denmark) up to 5 days under 5.8% CO_2 at 37 °C and 5% O_2. Images of each embryo were acquired every 10 min in 7 focal planes, starting from the second polar body extraction up to 120 h after fertilization, to precisely determine the timing of cell divisions. On day 3, all embryos were evaluated based on Known Implantation Data (KID) (12, 13) and Alfa ESHRE score (14), as well as the common morphology grade (11, 15, 16). Only top-quality embryos were vitrified and used in this study. Top-quality embryos included the following combinations of KID and Alfa ESHRE scores: 5, 3; 5, 2; 4, 3; or 4, 2, respectively.

Treatment Protocol

All patients scheduled for FET arrived on the second or third day of menstruation for a first ultrasound evaluation. At that point, it was the physician's preference to allocate the patients to a-FET, natural or modified natural cycles. The decision regarding the protocol and medication used was based on the patient's records, previous cycle history, and preferences for DYD 10 mg (Duphastone® Abbott Healthcare Products B.V., Netherlands), Endometrin (Endometrin®, Ferring, Israel), or Crinone® 8% MVP gel, 90 mg daily (Crinone® 8 Merck GmbH, Germany).

Artificial FET Protocol

Estradiol 2 mg TID (Estrofem® Novo Nordisk) was started on day 3 of menstruation for at least 8 days. On day 8, the second visit, endometrial thickness was assessed by transvaginal ultrasound (TVS). When it was more than 8 mm, progesterone was started. The options for progesterone were oral DYD 10 mg TID, MVP as Endometrin 100 mg TID, or Crinone 8% MVP gel, 90 mg daily.

The duration of progesterone administration was based on the age of the embryo. Cleavage stage embryos were transferred after 4 days of progesterone administration and blastocysts were transferred after 6 days [10].

Natural Cycle and Modified Natural Cycle Protocols

Patients who were allocated to natural or modified natural cycles were followed with ultrasound until a dominant follicle reached 18 mm and endometrial thickness was > 7.5 mm. The decision for a fully natural cycle with spontaneous ovulation or induced ovulation by Ovitrelle 250 mcg (Choriogonadotropin alfa; Merck-Serono) was based on timing the transfer to avoid weekends.

Pregnancy Determination

β-hCG was measured 14 days after embryo transfer, and clinical pregnancy and implantation were confirmed when a gestational sac with fetal heartbeat was visible on ultrasound examination 6 weeks after ET.

Demographic data, treatment information and results, and pregnancy outcomes were recorded and followed until delivery.

Statistical Analysis

We analyzed the entire FET cohort, comparing DYD and MVP. We also analyzed a-FET on a case-control basis: for each cycle in the DYD group, we matched 3 cycles from the MVP group. The matching was based on age, BMI, primary

or secondary infertility, and cause of infertility. Statistical analysis was performed using the SPSS software package (SPSS 25 Inc., Chicago, IL). We used Shapiro-Wilks test to evaluate the distribution of the data. Comparisons were analyzed using Student's *t* test or Mann-Whitney *U* test, each as appropriate. Proportions were compared using Chi-square test or Fisher exact test. *P* values less than 0.05 were considered significant. We conducted a forward selection (conditional), a stepwise selection method with entry testing based on the significance of the score statistic (0.05), and removal testing based on the probability of a likelihood-ratio statistic (0.10).

Results

A total of 599 cycles from January 2018 to December 2019 were analyzed. Table 1 presents the entire cohort of FET cycles according to medication used for LPS. While BMI was comparable between groups, the DYD group was significantly younger than the MVP group (34.3 ± 6.1 vs. 35.5 ± 6.4 years, respectively; $P = 0.021$). The mean number of embryos transferred was comparable between the groups (1.2 ± 0.46 vs. 1.22 ± 0.47, respectively; $P = 0.76$). Although the ESHRE morphokinetic score was significantly better in the MVP group for the first transferred embryo and for all available embryos per patient (2.2 ± 0.0.78 vs. 2.5 ± 0.73; $P = 0.04$ and 2.18 ± 0.75 vs. 2.47 ± 0.71; $P = 0.03$, respectively) and the endometrium was significantly thicker in the MVP group on the day of progesterone initiation (9.17 ± 2.2 vs. 8.67 ± 2.1 mm, respectively; $P = 0.017$), the chemical pregnancy rate and the clinical pregnancy rate were comparable between the groups. Maternal complications were comparable and fetal anomalies were not observed in both groups.

Pregnancy outcomes for the entire cohort are presented in Table 2. The ongoing pregnancy and delivery rates (29% vs. 22%), as well as abortion rate of clinical pregnancies (12.3% vs. 15.8%), were comparable between the two groups.

A separate case-control analysis of the a-FET showed similar results, comparable chemical pregnancies (33.7% vs. 34.8%, $P = 0.89$) and clinical pregnancy rate (27.7% vs. 27.5%, $P = 1$) in both groups (Table 3). Pregnancy outcomes between groups were similar, as well (Table 4).

Sub-analysis of the ovulatory cycles revealed the same outcomes as seen previously; chemical (46.5% vs. 43.9%, *P* =

Table 1 Patient characteristics and treatment outcomes in the cohort of FET according to progesterone support

Characteristic	DYD *N* = 226	MVP *N* = 373
BMI (kg/m^2)	25.5 ± 5.2	25.8 ± 5.9
Age (years)*	34.3 ± 6.1	35.5 ± 6.4
Infertility		
Primary	72 (32%)	101 (27%)
Secondary	154 (68%)	272 (73%)
Parity		
No	128 (57%)	199 (53%)
Yes	98 (43%)	174 (47%)
Smoker	38 (20%)	60 (19%)
Alcohol consumption	2 (1%)	5 (2%)
Cause of infertility		
Unexplained	12 (5%)	30 (8%)
Male factor*	123 (54%)	160 (43%)
Anovulation	33 (15%)	74 (20%)
Mechanical factor	42 (19%)	81 (22%)
Endometriosis	4 (2%)	9 (3%)
Number of embryos transferred	1.20 ± 0.43	1.22 ± 0.47
ESHRE score of the first transferred embryo*	2.2 ± 0.78	2.5 ± 0.73
KID score of the first transferred embryo	4.62 ± 0.70	4.73 ± 0.57
Total ESHRE for all transferred embryos*	2.18 ± 0.75	2.47 ± 0.71
Total KID for all transferred embryos	4.62 ± 0.67	4.67 ± 0.58
Endometrial thickness before transfer (mm)*	8.67 ± 2.1	9.17 ± 2.2
Chemical pregnancy per transfer	94/226 (41.6%)	142/373 (38.1%)
Clinical pregnancy per transfer	83/226 (36.7%)	117/373 (31.4%)

DYD oral dydrogesterone; *MVP* micronized vaginal progesterone

Data are presented as mean ± SD or *N* (%); *$P < 0.05$

Table 2 Pregnancy outcomes for all FET cycles

Outcome	DYD $N = 226$	MVP $N = 373$
Ongoing pregnancy rate*	38/226 (17%)	32/373 (8.5%)
Delivery rate	28/226 (12%)	51/373 (14%)
Ongoing pregnancy and delivery rate	66/226 (29%)	83/373 (22%)
Abortion (from clinical pregnancy)	28/226 (12.3%)	59/373 (15.8%)
Ectopic pregnancy	1/226(<1%)	4/373 (1%)
Neonatal weight (grams)	3138 ± 707	3263 ± 570
Pregnancy outcome		
Fetal anomalies	0	0
Pregnancy-induced hypertension	2 (0.9%)	3 (0.8%)
Preterm delivery	1 (0.4%)	2 (0.5%)
Gestational diabetes	3 (1.3%)	3 (0.8%)

DYD oral dydrogesterone; *MVP* micronized vaginal progesterone
*$P < 0.05$

0.7) and clinical pregnancy rates (42.3% vs. 38.2%, $P = 0.53$) were comparable. Results are presented in Tables 5 and 6.

Importantly, both chemical and clinical pregnancy rates were better in the natural cycles than in the artificial cycles.

We used bivariate regression analysis to predict pregnancy outcomes, which included the following variables: BMI, age, endometrial thickness, number of transferred embryos, medication used for LPS, treatment protocol, and embryo quality. We analyzed the parameters in a stepwise selection. When all parameters were included in a univariate model, maternal age, endometrial thickness, and the treatment protocol were the only the parameters that had an effect on pregnancy (Table 7).

In the multivariate model, the adjusted odds ratio revealed that maternal age and embryo quality were the only significant parameters to predict clinical pregnancy, with adjusted odds for maternal age of 0.882, $P = 0.044$; 95% CI 0.78–0.997 and 2.659, $P = 0.041$; 95% CI 1.039–6.804 for embryo quality.

Importantly, we found that the medication used for LPS (DYD or MVP) did not affect the chance to conceive and maintain pregnancy in the univariate model and in the adjusted model.

Discussion

This study evaluated the outcome of FET cycles treated with DYD, as compared with MVP. We assessed treatment results

Table 3 Patient characteristics and treatment outcomes in artificial cycle

Characteristic	DYD $N = 83$	MVP $N = 247$
BMI (kg/m^2)	26.8 ± 5.62	25.8 ± 5.80
Age (years)	35.01 ± 6.0	35.3 ± 6.5
Infertility		
Primary	23 (28%)	70 (28%)
Secondary	60 (72%)	177 (72%)
Parous		
No	44 (53.0%)	140 (56%)
Yes	37 (47.0%)	17 (43%)
Smoke	13 (20%)	42 (20%)
Cause of infertility		
Unexplained	7 (8%)	21 (8.5%)
Male factor	42 (51%)	103 (42%)
Anovulation	19 (23%)	60 (24%)
Mechanical factor	13 (16%)	47 (19%)
Endometriosis	2 (2%)	3 (1%)
Number of transferred embryos	1.20 ± 0.46	1.22 ± 0.47
ESHRE score of the first transferred embryo*	2.1 ± 0.99	2.57 ± 0.71
KID score of the first transferred embryo	4.65 ± 0.71	4.70 ± 0.61
Total ESHRE for all available embryos*	2.13 ± 0.91	2.54 ± 0.70
Total KID for all available embryos	4.65 ± 0.69	4.68 ± 0.59
Endometrial thickness* (mm)	8.27 ± 2.20	9.46 ± 2.18
Chemical pregnancy per transfer	28/83 (33.7%)	86/247 (34.8%)
Clinical pregnancy per transfer	23/83 (27.7%)	68/247 (27.5%)

DYD oral dydrogesterone; *MVP* micronized vaginal progesterone; mean ± SD
*$P < 0.05$

Table 4 Comparable pregnancy outcome for artificial cycles

Outcome	DYD $N = 83$	MVP $N = 247$
Ongoing pregnancy rate	11/83 (13%)	20/247 (8%)
Delivery rate	7/83 (8%)	25/247 (10%)
Ongoing pregnancy and delivery	18/83 (22%)	45/247 (18%)
Abortion rate	10/83 (12%)	41/247 (16.5%)
Ectopic pregnancy	0	2/247 (< 1%)
Fetal weight (grams)	3054 ± 510	3423 ± 485
Pregnancy outcome		
Fetal anomalies	0	0
Pregnancy-induced hypertension	0	1 (0.4%)
Preterm delivery	1 (1%)	0
Gestational diabetes	1 (1%)	2 (1%)

DYD oral dydrogesterone; *MVP* micronized vaginal progesterone

and pregnancy outcomes, including maternal complications and fetal anomalies. We found that although embryo quality was better in the MVP group, the pregnancy outcomes were comparable between the groups. Our study reinforced the findings of non-inferiority that was demonstrated in fresh IVF cycles by previous studies [13–15] and expanded it to include FET cycles both a-FET and natural cycles. Our multivariate regression analysis model demonstrated non-inferiority of DYD over other LPS medications, as well. Although the MVP group had significantly better embryo quality and significantly more embryos were transferred, pregnancy rates and outcomes were comparable between the groups. For a-FET, we demonstrated that although endometrial thickness, number of embryos transferred, and embryo quality were significantly better in the MVP group, the cycle outcomes were comparable between the two groups. In the ovulatory-based cycles, we also found comparable results even though women in the MVP group were older.

DYD is a synthetic progestin, with high affinity for the P receptor [16]. DYD is known for its effectiveness in reproductive disorders, including threatened abortion and recurrent pregnancy loss [17–20]. Several prospective, randomized studies and meta-analyses compared the efficacy, safety, and tolerability of oral DYD with MVP capsules for LPS after fresh IVF. All demonstrated comparable pregnancy and miscarriage rates [15, 21, 22] and concluded that DYD is a possible alternative to MVP capsules. Moreover, the safety profile of oral DYD was similar to that of MVP [15, 22–24].

Table 5 Patient characteristics and treatment outcomes based on ovulation cycles only

Characteristic	DYD $N = 142$	MVP $N = 123$
BMI (kg/m^2)	24.7 ± 4.9	25.8 ± 6.1
Age (years)*	33.9 ± 6.0	36.2 ± 6.1
Infertility		
Primary	49 (34.5%)	30 (24%)
Secondary	93 (65.5%)	93 (76%)
Parous		
No	83 (58.5%)	57 (46%)
Yes	59 (41.5%)	66 (54%)
Smoker	25 (21%)	16 (15%)
Alcohol use	2 (2%)	3 (4%)
Cause of infertility		
Unexplained	5 (3.5%)	8 (7%)
Male factor	80 (56%)	57 (46%)
Anovulation	13 (9%)	13 (11%)
Mechanical factor	29 (20%)	33 (27%)
Endometriosis	2 (1%)	6 (5%)
Last E2, average (range)	215 (136–365)	199 (121–287)
Last progesterone before transfer decision, average (range)	0.85 (0.3–1.5)	0.80 (0.3–1.3)
Total ESHRE for all available embryos	2.21 ± 0.68	2.20 ± 0.72
Total KID for all available embryos	4.60 ± 0.67	4.63 ± 0.57
Number of transferred embryos	1.19 ± 0.41	1.19 ± 0.4+
Endometrial thickness (mm)	8.79 ± 2.1	8.84 ± 2.3
Chemical pregnancy per transfer	66/142 (46.5%)	54/123 (43.9%)
Clinical pregnancy per transfer	60/142 (42.3%)	47/123 (38.2%)

DYD oral dydrogesterone; *MVP* micronized vaginal progesterone; mean ± SD

Table 6 Pregnancy outcomes for ovulation cycles

Outcome	DYD $N = 142$	MVP $N = 123$
Ongoing pregnancy rate*	27/142 (19%)	11/123 (9%)
Delivery rate	21/142 (15%)	26/123 (21%)
Ongoing and delivery rate	48/142 (34%)	37/123 (30%)
Abortion	18/142 (12.6%)	17/123 (13.8%)
Ectopic pregnancy	1/142 (< 1%)	2/123 (1.6%)
Neonatal weight (grams)	3166 ± 772	3123 ± 612
Pregnancy outcome		
Fetal anomalies	0	0
Pregnancy-induced hypertension	2 (1.4%)	2 (1.6%)
Preterm delivery	0	2 (1.6%)
Gestational diabetes	2 (1.4%)	1 (0.8%)

DYD oral dydrogesterone; *MVP* micronized vaginal progesterone

The results of two large-scale, phase III randomized controlled trials, Lotus I [13] and Lotus II [14], were recently published. The first compared 497 patients treated with DYD to 477 patients treated with MVP for LPS in IVF [13]. The DYD group demonstrated non-inferiority with MVP in terms of pregnancy rates (37.6% vs. 33.1%) and live birth rates (34.6% vs. 29.8%, respectively). Lotus II [14] also showed non-inferiority of DYD over MVP, with comparable pregnancy and live birth rates between the groups (38.7% vs. 35.0% and 34.4% vs. 32.5%, respectively). These two large trials [13, 14] and a study by Ganesh et al. [15] demonstrated that DYD used as LPS for fresh IVF cycles was comparable to MVP [13–15] in terms of clinical pregnancy and live birth rates.

Due to its friendly oral administration route, DYD may be a good option for LPS in clinical practice [13]. To the best of our knowledge, very limited information is available regarding the effect of DYD on FET cycles [25, 26]. We used DYD in artificial and natural cycles for endometrial preparation and LPS. This is one of the first studies to show non-inferiority of DYD in clinical pregnancy, abortion, and live birth rates, as compared with MVP.

In terms of a-FET cycles, Rashidi et al. conducted a prospective clinical trial and demonstrated equivalent results with regard to DYD in artificial cycles using various types of luteal progesterone support [25]. Zarei et al. reported significantly lower clinical pregnancy rates with DYD as compared to MVP [26]. Evaluating their study protocols, we noted several differences that could have affected the results. These include the use of 20 mg DYD per day, which is lower than the commonly used dose [13–15, 22, 23, 25], replacing the micronized injectable progesterone after 3 days with either MVP or DYD, and that DYD is a different progesterone compound compared to micronized progesterone [16, 27, 28].

Koren et al. recently questioned the safety of DYD for LPS [29]. They claimed major fetal malformations were associated with DYD use, including hypospadias, cardiovascular anomalies, spina bifida, and hydrocephalus. This paper was criticized for several major methodological issues. They did not validate the data, which was automatically abstracted from an electronic medical record system. They did not have data reflecting actual use of DYD, duration of treatment, or compliance. Moreover, they did not compare DYD with other progesterone supplements given during early pregnancy and for LPS. Ultimately, this paper was retracted.

DYD has been used since the 1960s for various obstetrical conditions related to progesterone insufficiency [30]. To date, no study has doubted the safety of DYD and no congenital malformations have been associated with DYD [31]. Our results did not reveal any birth defects in almost 200 babies. Results using DYD for LPS in all FET cycle protocols were similar to those with MVP [23, 32].

The strengths of our study include the large cohort of 572 cycles, its novelty of implementing DYD in FET cycles, and the long-term follow-up through delivery, including evaluation for prenatal complications. To the best of our knowledge, this is one of the three studies that used DYD only in a-FET cycles. Although the subgroup analysis for a-FET included a relatively small cohort, it added important information regarding the success and safety of a-FET. Despite its strengths, this

Table 7 Adjusted odds ratio for clinical pregnancy rate

Variable	Univariate			Multivariate		
	Odds ratio	*P* value	95% CI	Odds ratio	*P* value	95% CI
BMI (kg/m^2)	0.988	0.39	0.960–1.016	1.078	0.212	0.958–1.212
Age (years)	0.961	*0.002*	0.936–0.985	0.882	*0.044*	0.780–0.997
Endometrial thickness (mm)	1.168	*0.009*	1.040–1.312	0.973	0.874	0.690–1.372
Number of embryos transferred	0.980	0.921	0.661–1.454	0.138	0.118	0.012–1.651
Medication used for luteal support	1.270	0.171	0.902–1.789	1.168	0.849	0.235–5.816
Treatment protocol	1.722	*0.001*	1.249–2.374	2.774	0.233	0.518–14.852
Embryo quality	1.334	0.169	0.884–2.014	2.659	*0.041*	1.039–6.804

The entries in italics were to highlight the parameters that were significantly different between the groups

study was limited by its retrospective nature. Moreover, no differences in terms of fetal anomalies and maternal morbidity during pregnancy were found between the groups. It is important to mention that the prevalence of maternal complications in this cohort was relatively low, which limited our ability to draw any conclusions regarding complications. There were no fetal anomalies.

Conclusion

We found comparable outcomes between using DYD and MVP for LPS in FET cycles, with both natural and artificial treatments. This strengthened the non-inferiority of DYD for LPS in fresh as well as frozen IVF ET cycles, both in natural and artificial cycles. Cycle outcomes, pregnancy and delivery rates, and fetal complications were comparable with both LPS approaches. Owing to the user-friendly aspects of DYD as an oral administration route with reassuring safety profile, DYD may be a good option for LPS in clinical practice and may replace MVP as the standard of care in FET cycles, including a-FET.

Code Availability Not applicable.

Authors' Contributions YA participated in the conception and design, data analysis and interpretation, drafting of the manuscript, and final approval. AB and NA participated in data acquisition and revision of the manuscript and gave final approval. DE and AE were involved in data collection and final revision of the manuscript. ESP was involved in the project conception and design, data analysis and interpretation, and critical revision of the manuscript and gave final approval.

Data Availability Data will be made available upon reasonable request to the corresponding author.

Compliance with Ethical Standards

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

Ethics Approval This was a retrospective study, and ethics approval was granted.

Consent to Participate Informed consent was not required for this retrospective study.

Consent for Publication All authors gave their consent for publication.

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