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*Original Research*

# Randomized Clinical Trial Comparing Oral Dydrogesterone to Micronized Vaginal Progesterone for Endometrial Preparation in Frozen-Thawed Embryo Transfer Cycle

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**Abstract**

**Background**: The objective was to compare the use of micronized vaginal progesterone 800 mg daily and oral dydrogesterone 40 mg daily in the endometrial preparation for frozen-thawed embryo transfer (FET). **Methods**: Prospective randomized study with women undergoing FET along with hormone replacement therapy for endometrial preparation, between September 2019 and February 2021. A total of 73 patients were randomly selected and orally received 40 mg/day dydrogesterone (DYD group, n = 36) or 800 mg/day micronized vaginal progesterone (MVP group, n = 37) after endometrial preparation with transdermal estradiol. The main outcome was a viable ongoing pregnancy with 12 weeks of gestation. Biochemical pregnancy, clinical pregnancy and live birth rates were the secondary outcome. **Results**: The reproductive outcomes in FET cycles were similar, with pregnancy and Live birth rates in the didrogesterone and MVP treatment groups being respectively: Biochemistry (38.9%/37.8%; $p$ = 0.189 [95% confidence interval (CI) = –23.4–21.2]), Clinical (33.3%/35.1%; $p$ = 0.192 [95% CI = –20.0–23.6]); 12 Weeks Pregnancy (33.3%/32.4%; $p$ = 0.196 [95% CI = –22.4–20.6]); Live birth (33.3%/32.4%; $p$ = 0.196 [95% CI = –22.4–20.6]). **Conclusions**: 40 mg/day dydrogesterone and 800 mg/day MVP revealed similar reproductive results in FET cycles. The use of oral dydrogesterone is a reasonable option, may be more accepted by patients in terms of ease of use and lower cost. **Clinical Trial Registration**: U1111-1247-1845.

**Keywords:** dydrogesterone; embryo transfer; hormonal replacement therapy; *in vitro* fertilization; infertility

## 1. Introduction

There has been a progressive increased the use of frozen-thawed embryo transfer (FET) over the past decade [1]. Using a protocol with an antagonist and triggering the final follicular maturation with an agonist, followed by a "freeze-all" strategy and embryo transfer in a subsequent cycle, is an effective option for preventing the ovarian hyperstimulation syndrome (OHS) and leads to high rates of live births [2].

Other advantages and the applicability of FET are: multiple pregnancy risk prevention by the elective transfer of one or a few fresh embryos, thereby allowing for the cryopreservation surpluses [3,4] and carrying out a preimplantation genetic study; cryopreservation of embryos as a strategy for transfer to a more appropriate endometrium with a prospect of increasing rates of live births and cumulative pregnancy [4,5]. Further, randomized multicenter clinical trials found that the rate of live births did not differ significantly between groups that performed either fresh or thawed embryo transfers [6,7].

The methods of endometrial preparation for FET can be divided into natural and medicated (artificial) cycles. During the natural cycle, participants were only monitored, without receiving any pharmacological intervention before ovulation. In the medicated cycle, on the other hand, estrogen was administered to achieve endometrial proliferation and suppression of follicular growth. When endometrial thickness is greater than or equal to 7 mm and a trilaminar pattern, progesterone is introduced to induce secretory changes. The time to thaw and transfer the embryo is determined according to the onset of progesterone support and the stage of development at which the embryo was frozen. Hormone supplementation continues until the day of $\beta$-HCG test and, in the event of pregnancy, it should be continued until the 9th to 12th week of gestation, due to the beginning of the placental function after this gestational age [8].

Progesterone can be administered via oral, vaginal, rectal, subcutaneous, or intramuscular routes. All of these forms of administration appear to have similar efficacy [9,10]. One explanation for this is that the vaginal route does not involve the first hepatic passage and also provides higher and sustained serum concentrations than does the oral route [11]. Nevertheless, all forms of progesterone administration can have side effects, such as drowsiness and headache by the oral route; vaginal administration may be

associated with vaginal irritation, discharge, and bleeding [12]; the intramuscular route has the inconvenience of daily injections, and can have adverse effects such as local pain, infections, abscess [10,13].

The oral route would be an option for luteal phase support and for endometrial preparation for the transfer of thawed embryos. Since micronized progesterone does not have good intestinal absorption, dydrogesterone appears to be a better option [14]. It is a retro-steroid with good oral bioavailability and high selectivity for progesterone receptors. It can be used at lower oral doses to mimic the luteal phase due to its better bioavailability and the progestogenic activity of its metabolites [15]. The use of this medication is considered safe during pregnancy, with no evidence of congenital malformations associated with it [16].

Prospective studies on the support for the luteal phase in IVF (*in vitro* fertilization) with fresh embryo transfer have shown that oral dydrogesterone is as effective as micronized vaginal progesterone (MVP), with better patient satisfaction rates [17,18]. In addition, a recent meta-analysis based, systematic review comparing the efficacy of oral dydrogesterone (20 to 40 mg/day) with MVP (600 to 800 mg/day) or 8% MVP gel (90 mg/day) in IVF cycles with fresh embryo transfer have shown that oral dydrogesterone was associated to significantly higher rates of pregnancy and live births than MVP. Safety results were similar between both groups (oral DYD versus MVP) in the maternal and fetal/neonatal populations [19].

Hence, there is a need for an effective, well-tolerated and safe treatment that could improve patient satisfaction in addition to the outcomes of assisted reproduction techniques with increased rates of pregnancy and live births. As the treatment can be long, oral administration is often preferred over the vaginal route [20].

Nevertheless, the vast majority of studies have been carried out with IVF cycles using fresh embryo transfer, whereas those using frozen embryos remain scarce. Hence, as the dydrogesterone tablets are readily available in our country with a reasonable cost, we were interested in comparing micronized vaginal progesterone and oral dydrogesterone in the endometrial preparation for the transfer of frozen-thawed embryos.

## 2. Materials and Methods

This was a randomized-controlled, parallel, open clinical trial, with two groups of women undergoing frozen-thawed embryo transfer along with hormone replacement therapy for endometrial preparation, at the Assisted Reproduction Service at Hospital Pérola Byington, in partnership with the Santa Casa de Sao Paulo School of Medical Sciences, conducted between September 2019 and February 2021.

The research was approved by Plataforma Brasil (Brazil's national and unified database of research records involving human beings), having received its CAAE (acronym for Certificado de apresentação para Apreciação Ética, i.e., Submission Certificate for Ethical Appreciation) number: 13189119.7.0000.0069, and Document Number: 3.453.065, Rapporteurship on 07/13/2019, and Brazilian Registry of Clinical Trials (ReBEC). UTN (Universal Trial Number): U1111-1247-1845, date: 03/31/2020. All participants signed the Voluntary and Informed Consent Form, according to item IV of Resolution/CNS (acronym for Conselho Nacional de Saúde, i.e., Brazil's National Health Council) No. 196/96, as required by the service's protocol.

Patients' characteristics such as age, body mass index (BMI), as calculated by the formula weight/height$^2$ (kg/m$^2$) and categorized based on the criteria defined by World Health Organization [21], referral for assisted reproduction techniques (ART), such as endometriosis, ovulatory factors, tubal, male, unexplained. Decreased ovarian reserve (anti-Müllerian hormone (AMH) $<$1 ng/mL or antral follicle count $<$7), endometrial thickness after 10–12 days of estrogen use, number of embryos transferred, embryonic stage and quality, biochemical pregnancy (positive $\beta$-HCG test), clinical pregnancy (visualization of fetal heartbeat by ultrasound at 6 weeks of gestational age), pregnancy at 12 weeks of gestation and live births were input into our database.

The women were randomly divided into two groups: one group used oral dydrogesterone 40 mg daily whereas the other used micronized vaginal progesterone 800 mg daily (Fig. 1). The computer program used to randomize the patients into two groups was the R-Project. Participants received the study drugs through the institutional pharmacy, as required by the service's protocol.

### *2.1 Inclusion Criteria*

Women undergoing embryo cryopreservation and frozen-thawed embryo transfer due to risk of ovarian hyperstimulation syndrome, surplus embryos following failed pregnancy after fresh transfer, absence of transfer due to an inappropriate endometrium, or patients who underwent preimplantation genetic diagnosis.

### *2.2 Exclusion Criteria*

Patients with an endometrium thinner than 7 mm after endometrial preparation with estrogen; recurrent miscarriages (history of $\geq$3 spontaneous miscarriages); severe male factor; uterine diseases (for example, myomas, polyps, previously diagnosed Müllerian abnormalities); unilateral or bilateral hydrosalpinx; and those who had a dominant follicle even after estrogen administration.

### *2.3 Endometrial Preparation Protocol*

Estradiol administration was initiated transdermally (Oestrogel® Besins Healthcare, Drogenbos, Belgium) at a 6 mg/day dose (3 pumps twice a day) on the 2nd day of the menstrual cycle. After 10–12 days of estrogen therapy, a blood sample was collected and a transvaginal ultra-

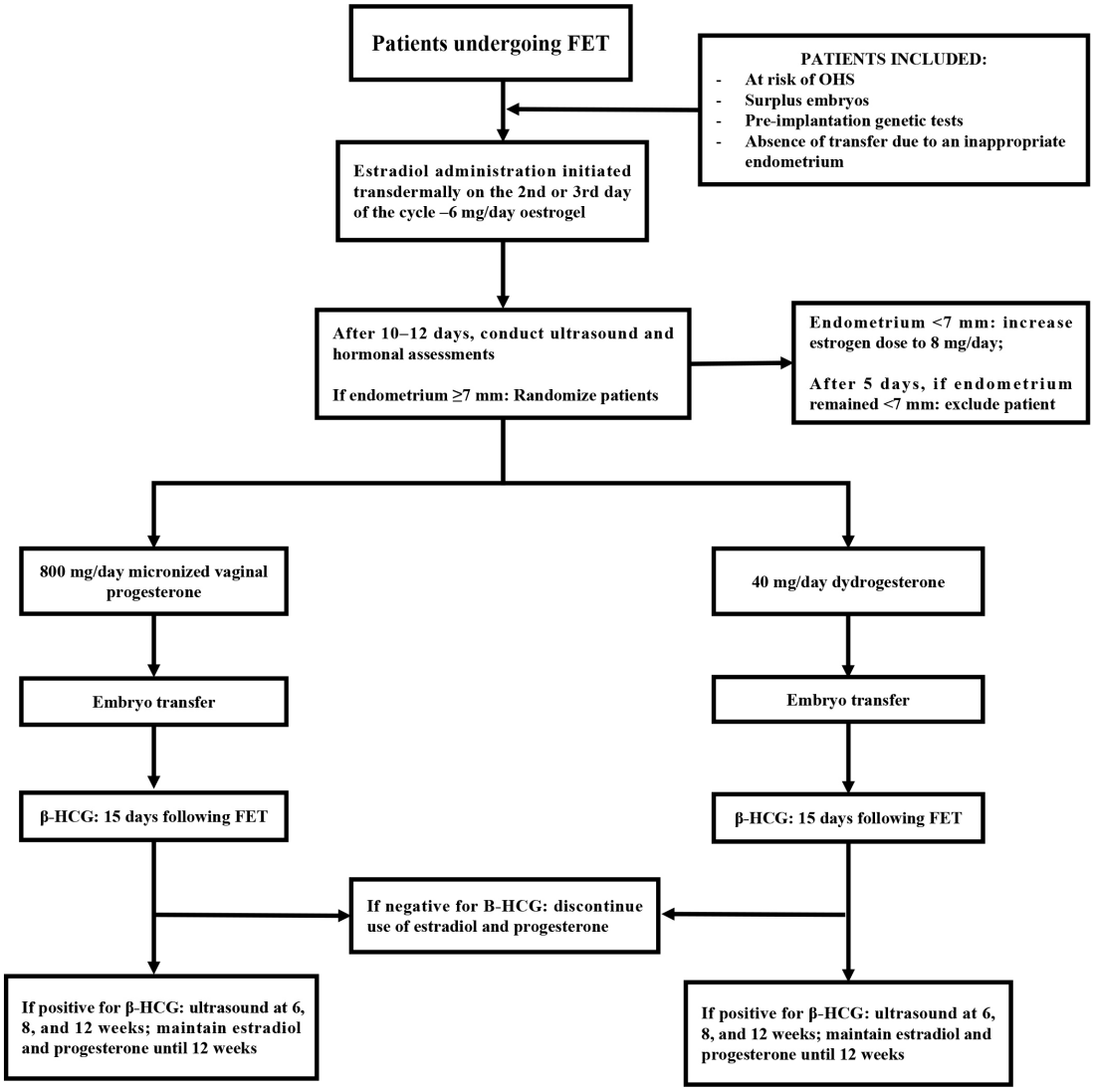


**Fig. 1. Research protocol flowchart**. TET, frozen-thawed embryos transfer; OHS, ovarian hyperstimulation syndrome; B-HCG, human chorionic gonadotropin hormone; US, ultrasound.

sound was performed to assess the progesterone, LH, estradiol levels and endometrial thickness. If the endometrium was <7 mm, the estrogen dose was increased to 8 mg/day for an additional five days. When a 7 mm thick, triple-line endometrium was observed, with serum progesterone concentrations <1.5 ng/mL, we started administering micronized vaginal progesterone 800 mg/day, 400 mg twice a day (Utrogestan® 200 mg, Besins Healthcare, Drogenbos, Belgium) in one of the groups; in the other group, 40 mg/day, 20 mg twice a day (Duphaston® 10 mg; Abbott BV, Olst, Netherlands) dydrogesterone was given orally, while maintaining estradiol administration. Embryo transfer was performed after progesterone administration on day 3 for Day 3 embryos and on day 5 for blastocysts.

Supplementation with estrogen and progestogen was continued at the same dose until the pregnancy test, performed 15 days after embryo transfer. This support was continued up to 10–12 weeks in viable pregnancies and discontinued in patients who did not become pregnant.

Ultrasonography was performed during the sixth week of amenorrhea to assess the presence and number of gestational sacs with embryos showing a heartbeat. Ultrasonography was also performed at 8 and 12 weeks of gestation.

### *2.4 Embryo Transfer*

Embryos were obtained from *in vitro* fertilization cycles or intracytoplasmic sperm injection (ICSI), vitrified and heated on Day 3 or at the blastocyst stage. All embryo transfers were performed with ultrasound guidance. Were recorded the stage, number and quality of embryos transferred. If at least one good quality embryo was transferred, quality was classified as Q +. The criteria for Q + quality was the same as those for Day 3 embryos: 6 to 10 cells with less than 20% fragmentation according to the Holte classi-

fication [22]; whereas for blastocysts: expanded to hatched blastocysts with internal cell mass and trophectoderm A or B quality (from 4B upwards) according to the Gardner classification [23].

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### *2.5 Sample-Size Calculation and Statistical Analysis*

For calculating sample size, the comparison of proportions was considered; the reference values were those from LOTUS I [18]. A difference of 0.281 was adopted, with a significance level of 5%, and Test power of 80%. In this case, we found n = 36 per group.

Initially, the sample was characterized as a whole, that is, summary measures (means, standard deviations, medians and so on) were obtained for quantitative variables and absolute (n) and relative (%) frequencies for the qualitative variables collected. This step aimed to present a profile of the research participants.

For the bivariate analysis, a proportion comparison was performed by using the Normal approximation method with a significance level = 0.05; 95% Confidence Intervals were constructed for proportion differences.

The computer software used for creating the database and conducting the statistical analysis was SPSS (Statistical Package for the Social Sciences) version 13.0 for Windows (IBM Corp., Chicago, IL, USA).

## 3. Results

A total of 111 cycles of patients who were to undergo frozen-thawed embryos transfer with hormone replacement therapy for endometrial preparation were randomized into one of the treatment groups. In general, 65.8% (73/111) reached the end of the study after exclusion criteria were applied, 37 of whom were in the MVP group and 36 in the dydrogesterone group (Fig. 2).

The patients' characteristics were similar between the two treatment groups and are summarized in Table 1. The patients' age ranged from 23 to 40 years, with a mean of 33.2 years (±4.4): in the dydrogesterone group, it was 34.1 (±4.4) years; and in the MVP group, it was 32.3 (±4.3) years.

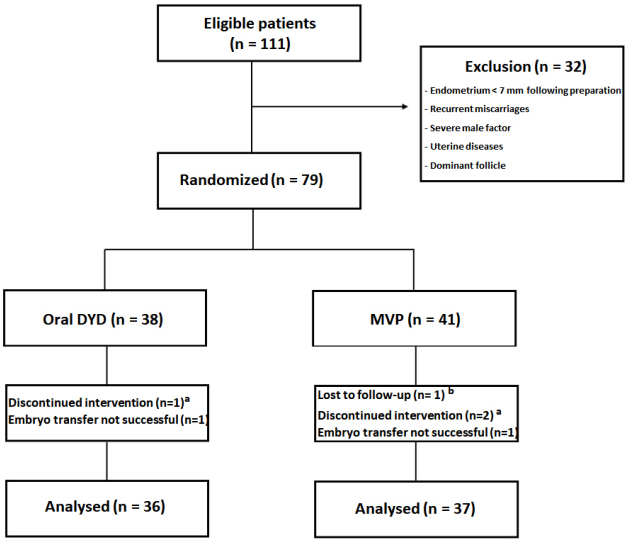


**Fig. 2. Patient distribution flowchart as determined by inclusion/exclusion criteria.** DYD, dydrogesterone; MVP, micronized vaginal progesterone.

Most patients did not have comorbidities. In relation to BMI, 64.4% of them had a BMI lower than 30 kg/m$^2$, with an average of 25.8 kg/m$^2$ (overweight). In the dydrogesterone and MVP groups, respectively, 3 (10.3%) and 4 (16.0%) patients were obese. Hypothyroidism, with appropriate treatment, was described in 8.1% (n = 3) of the individuals in the MVP group versus 11.4% (n = 4) in the dydrogesterone group.

Among the infertility factors found, those with the highest frequency were: Tubal Factor (46.6%), Male Factor (32.9%), and Polycystic Ovary Syndrome (26.0%), with some patients having more than one factor. In both the dydrogesterone and MVP groups, the tubal factor prevailed as the main infertility factor.

The reasons for cryopreserving the embryos were mainly due to the risk of Ovarian Hyperstimulation Syndrome (39.7%) and the presence of Surplus Embryos (31.5%). The number of cases in each group was similar, 15 with OHS and 11 with surplus embryos in the MVP group, and 14 with OHS and 12 with surplus embryos in the dydrogesterone group.

The overall mean endometrial thickness on the day that progesterone was administered was 9.1 mm (±1.7): in the MVP group, it was 9.2 mm (±1.6), whereas in the dydrogesterone group, it was 9.0 mm (±1.7). Of the 111 cycles initially selected for the study, 13 patients had an endometrium <7.0 mm. After increasing the transdermal estradiol dose, 9 patients reached an endometrium ≥7.0 mm, and 4 patients were excluded from the study due to inappropriate endometrial thickness.

The number of embryos transferred was also similar between the two treatment groups. Of the total number of cycles in the DYD group, one single embryo was transferred in 47.2% (n = 17), two embryos were transferred in

**Table 1. Patients' characteristics and treatment results.**

| | Oral DYD (36) | MVP (37) | Total (N = 73) |
|---|---|---|---|
| Mean Age, years (SD) | 34.1 (4.4) | 32.3 (4.3) | 33.2 (4.4) |
| Age n (%) | | | |
| <35 years | 17 (43.5) | 22 (56.4) | 39 (53.4) |
| ≥35 years | 19 (55.8) | 15 (44.1) | 34 (46.6) |
| Mean BMI, kg/m$^2$ (DP) | 25.2 (5.0) | 26.5 (5.7) | 25.8 (5.3) |
| Mean endometrial thickness on the day that progesterone was administered (mm) | 9.0 (1.7) | 9.2 (1.6) | 9.1 (1.7) |
| Embryonic stage n (%) | | | |
| D3 | 14 (38.9) | 16 (43.2) | 30 (41.1) |
| Blastocyst | 22 (61.1) | 21 (56.8) | 43 (58.9) |
| No. of embryos transferred n (%) | | | |
| 1 | 17 (47.2) | 16 (43.2) | 33 (45.2) |
| 2 | 16 (44.4) | 19 (51.4) | 35 (47.9) |
| >2 | 3 (8.3) | 2 (5.4) | 5 (6.8) |
| Embryonic quality n (%) | | | |
| Q+ | 27 (77.1) | 26 (70.3) | 53 (73.6) |
| Q– | 8 (22.9) | 11 (29.7) | 19 (26.4) |

SD, standard deviation; DYD, dydrogesterone; MVP, micronized vaginal progesterone; BMI, body mass index.

**Table 2. Pregnancy rates after treatment in the two study groups.**

| *Pregnancy* | % (n/N) | | Difference in pregnancy rate (Oral DYD – MVP) | 95% CI |
|---|---|---|---|---|
| | Oral DYD | MVP | | |
| Pregnancy rate | | | | |
| Biochemical pregnancy n (%) | 38.9 (14/36) | 37.8 (14/37) | 1.1 | [–23.4; 21.2] |
| Clinical pregnancy n (%) | 33.3 (12/36) | 35.1 (13/37) | 1.8 | [–20.0; 23.6] |
| Pregnancy at 12 weeks n (%) | 33.3 (12/36) | 32.4 (12/37) | 0.9 | [–22.4; 20.6] |
| Live Birth n (%) | 33.3 (12/36) | 32.4 (12/37) | 0.9 | [–22.4; 20.6] |

Clinical Pregnancy, 6 weeks of gestational age; DYD, dydrogesterone; MVP, micronized vaginal progesterone; CI, confidence interval. Biochemical Pregnancy, positive $\beta$-HCG test 2 weeks after embryo transfer.

44.4% (n = 16), and three embryos were transferred in 8.3 % (n = 3). In the MVP group, one single embryo was transferred in 43.2% (n = 16), two embryos were transferred in 51.4% (n = 19), and three embryos were transferred in 5.4% (n = 2).

There was a greater number of embryos that were transferred in the blastocyst stage as compared to D3. Transfer in the blastocyst stage was performed in 61.1% (n = 22) in the DYD group and in 56.8% (n = 21) in the MVP group. In most cycles (73.6%), at least one good quality (Q +) embryo was transferred; this was similar in the two groups (77.1% in the VP group and 70.3% in the dydrogesterone group).

The reproductive outcomes in FET cycles were similar with the two progesterone supplementation methods (oral dydrogesterone versus vaginal progesterone), as demonstrated by the pregnancy rate at 12 weeks of gestation (Table 2). Pregnancy rates in the dydrogesterone and MVP treatment groups were, respectively: Biochemistry (38.9%/37.8%; $p$ = 0.189 [95% CI = –23.4–21.2]), Clinical (33.3%/35.1%; $p$ = 0.192 [95% CI = –20.0–23.6]); 12 Weeks Pregnancy (33.3%/32.4%; $p$ = 0.196 [95% CI = –22.4–20.6]); Live birth (33.3%/32.4%; $p$ = 0.196 [95% CI = –22.4–20.6]). The rate of pregnancy loss in the first trimester was similar in the groups, with 2 cases having been observed in each group.

## 4. Discussion

The reproductive outcomes in frozen-thawed embryo transfer (FET) cycles were similar with the two methods of progesterone supplementation (oral dydrogesterone versus vaginal progesterone) with regard to the study's primary objective, which is the rate of ongoing pregnancies, and its secondary objectives, which are the biochemical pregnancy, clinical pregnancy and live birth rates. Accordingly, we can provide supporting evidence for the use of oral dydrogesterone in FET, similarly to the results already established in the literature with respect to fresh embryo transfer.

Studies have shown oral dydrogesterone as an alternative to micronized vaginal progesterone to support the luteal phase in IVF cycles when using fresh embryo transfer [10,17,19,24–32]. Among these, the randomized, double-blind, multicenter phase III clinical trial (LOTUS I) for luteal phase support has notably demostrated that oral dydrogesterone is as effective as micronized vaginal progesterone (MVP), as determined by pregnancy rates at 12 weeks of gestation [18].

It is important to highlight the relevance of our results, since there are several Randomized Clinical Trials (RCTs) showing that oral dydrogesterone is an alternative to micronized vaginal progesterone (MVP) to support the luteal phase when using fresh embryo transfer. Nevertheless, there is a lack of studies comparing the efficacy of these two types of progestogens in FET cycles, which would probably be the most effective way to assess the two types of treatment. In addition, considering the progressively increasing use of TED [1] and its advantages and applicability, such as possibility to preserve the fertility freezing embryo in case of diagnosis of malignancies, fertility sparing treatments, pre-implantation genetic study, OHS prevention [4,5], it is important to conduct further research on existing progestogens and their different routes of administration in cycles with TED.

Our results are also supported by ample evidence from a meta-analysis comparing oral dydrogesterone with micronized vaginal progesterone for supporting the luteal phase in women undergoing *in vitro* fertilization with transfer of fresh and/or frozen-thawed embryos, showing similar reproductive outcomes with the two progestogens [33]. However, this study did not determine the clinical differences that may exist due to endocrinological changes between both IVF protocols in cycles with either fresh embryo transfer or FET, such as the presence or absence of a corpus luteum [19,34]. To reduce this bias, in our study, we only evaluated FET cycles and exclude patients who had a dominant follicle after estrogen administration.

Our findings with frozen-thawed embryo transfer cycles are corroborated by the results described by Rashidi *et al*. [35], who conducted a randomized, controlled, single-blind study with 180 women undergoing FET. Their results showed that oral didrogesterone is as effective as intramuscular and vaginal progesterone [35].

Was observed similar rates of ongoing pregnancies and live births in the two research groups, and no patient discontinued treatment due to side effects or intolerance to the progestogens used. The 40 mg dydrogesterone dose (the highest dose safely used in other studies) was chosen based on data disclosed in the literature and on recommendations from IVF specialists and took into consideration that no corpus luteum would be present in these FET cycles [19,35].

The findings of this research are strengthened by the selection of an appropriate sample size comprising 73 randomized individuals, the fact that both treatment arms are well balanced, and the use of broad eligibility criteria. Yet, with a larger sample size, we could have obtained more robust evidence. Hence, there is a need for further work comparing the effectiveness of these two types of progestogens in FET cycles.

## 5. Conclusions

Oral dydrogesterone (40 mg/day) and micronized vaginal progesterone (800 mg/day) revealed similar reproductive results in FET cycles. The use of oral dydrogesterone is a reasonable option, may be more accepted by patients in terms of ease of use and lower cost.

In this way, it is important to conduct further research on existing progestogens and their different routes of administration in cycles with FET, for choosing either of them should be based not only on effectiveness and safety, but also on availability, cost, side effects and patient tolerance, thereby improving their satisfaction with Assisted Reproduction treatments.

## Availability of Data and Materials

Data is available in our physical database.

## Author Contributions

Authors LCGMM and ARR contributed with data acquisition. Authors LCGMM, MCN, AD, ARR and SMRRL contributed with data interpretation. Authors LCGMM, MCN, AD and SMRRL contributed with the conception and design of the study, writing and revision of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

The research was approved by Plataforma Brasil (Brazil's national and unified database of research records involving human beings), having received its CAAE (acronym for Certificado de apresentação para Apreciação Ética, i.e., Submission Certificate for Ethical Appreciation) number: 13189119.7.0000.0069, and Document Number: 3.453.065, Rapporteurship on 07/13/2019, and Brazilian Registry of Clinical Trials (ReBEC, acronym for Registro Brasileiro de Ensaios Clínicos) UTN (Universal Trial Number): U1111-1247-1845, date: 03/31/2020. All participants signed the Voluntary and Informed Consent Form, according to item IV of Resolution/CNS (acronym for Conselho Nacional de Saúde, i.e., Brazil's National Health Council) No. 196/96, as required by the service's protocol.

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## Conflict of Interest

The authors declare no conflict of interest.

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