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ORAL DYDROGESTERONE VERSUS MICRONIZED VAGINAL PROGESTERONE FOR LUTEAL PHASE SUPPORT FOLLOWING INVITRO FERTILIZATION (IVF): A PROSPECTIVE MULTICENTER RANDOMIZED CONTROLLED STUDY IN ENUGU, SOUTH-EASTERN NIGERIA

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ABSTRACT

Background: Infertility is a major reproductive health problem, and in vitro fertilization (IVF) is an important treatment option. Adequate luteal phase support (LPS) is essential following IVF because controlled ovarian stimulation may impair endogenous luteal function. Micronized vaginal progesterone (MVP) is widely used, but its vaginal route may be inconvenient and associated with local adverse effects. Oral dydrogesterone (OD) offers a potentially more convenient alternative. However, comparative evidence remains inconsistent, particularly in African populations.

Objective: To compare the efficacy, safety and tolerability of oral dydrogesterone with micronized vaginal progesterone for LPS among women undergoing IVF in selected fertility centres in Enugu, South-Eastern Nigeria.

Methods: This prospective, multicentre, single-blind randomized controlled study involved 112 women undergoing IVF, randomized equally into two groups. Group A received oral dydrogesterone 30 mg daily with vaginal placebo, while Group B received MVP 100 mg twice daily with oral placebo, commencing on the day of oocyte retrieval. Embryo transfer occurred between Days 2 and 5. Pregnancy outcomes, uterine contractions, vaginal bleeding, miscarriage, additional intervention and treatment-emergent adverse effects were assessed. Data were analysed using Student's t-test, chi-square or Fisher's exact test, with significance set at $p \leq 0.05$.

Results: Baseline characteristics were comparable. Positive pregnancy tests occurred in 33.9% of the dydrogesterone group versus 37.5% of the MVP group, while clinical pregnancy rates were 30.4% and 33.9%, respectively. Pregnancy continuation to 14 weeks occurred in 25.0% and 28.6%, respectively. These differences were not statistically significant. Miscarriage rates were also not significantly different (8.9% vs. 3.6%; $p = 0.219$). However, uterine contractions (66.1% vs. 39.2%; $p = 0.004$), vaginal bleeding (64.3% vs. 23.2%; $p < 0.001$) and additional intervention (66.1% vs. 30.4%; $p < 0.001$) were significantly more frequent with dydrogesterone.

Conclusion: OD and MVP produced comparable pregnancy and miscarriage outcomes. However, MVP was associated with fewer symptomatic events and less need for additional intervention. Larger randomized trials are recommended to further evaluate their comparative efficacy, safety, tolerability and cost-effectiveness.

Keywords: Infertility; In Vitro Fertilization; Luteal Phase Support; Oral Dydrogesterone; Micronized Vaginal Progesterone; Pregnancy Outcome; Miscarriage; Nigeria.

1 INTRODUCTION

The World Health Organization (WHO) estimates that approximately one in six people experience infertility during their reproductive lifetime, corresponding to a global lifetime prevalence of about 17.5%. The burden is comparable between high income and low and middle-income countries, emphasizing the need for accessible, effective and safe fertility treatment. Assisted reproductive technologies (ART), particularly in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have consequently become important treatment options for couples with infertility (World Health Organization, 2023; Garg et al., 2024).

The success of IVF depends on several interconnected processes, including adequate ovarian response, oocyte and embryo quality, endometrial receptivity, embryo-endometrial synchrony and appropriate hormonal support during the luteal phase. During a natural menstrual cycle, progesterone secreted by the corpus luteum induces secretory transformation of the endometrium, facilitates implantation and contributes to the maintenance of early pregnancy. However, controlled ovarian stimulation used during IVF produces supraphysiological concentrations of ovarian steroids and may interfere with normal hypothalamic-pituitary-ovarian function and corpus luteum activity. Follicular aspiration, multiple corpora lutea, suppression of endogenous luteinizing hormone (LH) secretion and the type of ovulation trigger can all contribute to luteal dysfunction following stimulated IVF cycles (Garg et al., 2024; The ESHRE Guideline Group on Ovarian Stimulation et al., 2026; van der Linden et al., 2015).

Luteal phase support (LPS) is therefore routinely used following IVF/ICSI to compensate for impaired endogenous luteal function and to optimize endometrial receptivity. Progesterone is the principal agent used for LPS, although considerable variation exists regarding its formulation, route, dose, timing and duration. The 2025 European Society of Human Reproduction and Embryology (ESHRE) guideline recommends progesterone for luteal phase support following IVF/ICSI and states that dydrogesterone is probably recommended for this purpose. Natural progesterone may be administered by several non-oral routes, including vaginal, intramuscular and subcutaneous administration, while oral dydrogesterone represents a synthetic progestogen option (The ESHRE Guideline Group on Ovarian Stimulation et al., 2026).

Micronized vaginal progesterone (MVP) has traditionally been one of the most widely used methods of luteal phase support. Vaginal administration has the theoretical advantage of providing high local exposure to the endometrium while avoiding extensive hepatic first-pass metabolism. Several preparations are available, including vaginal capsules, pessaries and gels. Nevertheless, vaginal progesterone has practical disadvantages. Repeated vaginal administration may be associated with vaginal discharge, irritation, itching and discomfort, and some women may find the route inconvenient or unacceptable during the period surrounding embryo transfer and early pregnancy. Surveys of fertility specialists have demonstrated that vaginal progesterone remains the preferred route of LPS, although oral progestogens have increasingly been incorporated into clinical practice (Di Guardo et al., 2020; Garg et al., 2024).

Dydrogesterone is an orally active synthetic progestogen with high oral bioavailability and selective activity at the progesterone receptor. Its oral administration provides a potentially more convenient alternative to vaginal progesterone and may improve patient acceptability and adherence. Interest in dydrogesterone for IVF luteal support has increased following randomized trials demonstrating reproductive outcomes comparable to those obtained with vaginal micronized progesterone (Tournaye et al., 2017; Griesinger et al., 2018). The LOTUS I randomized controlled trial compared oral dydrogesterone with micronized vaginal progesterone and demonstrated non-inferiority of dydrogesterone for ongoing pregnancy at 12 weeks. Similarly, the LOTUS II trial found oral dydrogesterone to be non-inferior to micronized vaginal progesterone gel with respect to pregnancy outcomes (Tournaye et al., 2017; Griesinger et al., 2018).

A systematic review and individual-participant-data meta-analysis published in 2020 further strengthened the evidence supporting dydrogesterone as an alternative to vaginal progesterone. The analysis included nine eligible studies and found that, among participants with individual-level data, oral dydrogesterone was associated with higher odds of ongoing pregnancy at 12 weeks and live birth compared with micronized vaginal progesterone. However, the authors also recognized limitations in the evidence base and the need for further evaluation in different populations and clinical settings (Griesinger et al., 2020).

Evidence from subsequent studies has remained somewhat heterogeneous. A randomized controlled trial conducted in Nigeria compared oral dydrogesterone with micronized vaginal progesterone pessaries among 162 women undergoing IVF. Positive pregnancy test rates, clinical pregnancy rates, ongoing pregnancy rates and miscarriage rates were statistically similar between the groups. Importantly, vaginal itching occurred significantly more frequently among women receiving vaginal progesterone, suggesting a potential tolerability advantage for oral dydrogesterone. The Nigerian study is particularly relevant because it demonstrates that the two treatment strategies can produce comparable reproductive outcomes within an African clinical setting (Ikechebelu et al., 2023).

Conversely, evidence has not been uniformly supportive of dydrogesterone. A randomized clinical trial involving 207 women reported a higher live-birth rate in the vaginal micronized progesterone group than in the oral dydrogesterone group (Atarieh et al., 2024 [retracted]). Other studies have reported similar outcomes between oral dydrogesterone and vaginal progesterone. For example, a randomized pilot study evaluating oral dydrogesterone, vaginal progesterone gel and intramuscular progesterone found no statistically significant differences in ongoing pregnancy or live birth rates between treatment groups (Tomic et al., 2015; Pabuccu et al., 2022). These divergent findings indicate that the question of whether oral dydrogesterone is genuinely equivalent or superior to micronized vaginal progesterone cannot be regarded as completely settled.

Recent evidence has also examined combination regimens. In a 2024 prospective randomized study involving 620 IVF patients, oral dydrogesterone combined with vaginal micronized progesterone did not significantly improve clinical pregnancy, implantation or live birth rates compared with vaginal micronized progesterone alone. Live birth occurred in 30.6% of women receiving vaginal progesterone alone compared with 29.2% receiving the combination regimen (Rinaldi et al., 2024). Similarly, observational evidence from women receiving donated oocytes has suggested that oral dydrogesterone may provide outcomes comparable to micronized vaginal progesterone, although differences in study design and concomitant progesterone administration limit the strength of conclusions (Lorillon et al., 2024).

Safety is another important consideration. Because luteal support may continue into early pregnancy, the safety of progestational agents is clinically important. Concerns have previously been raised regarding a possible association between first-trimester dydrogesterone exposure and congenital anomalies. However, a 2022 critical appraisal found no convincing evidence supporting an increased risk of fetal abnormalities, while a 2024 systematic review and meta-analysis involving randomized and observational studies concluded that dydrogesterone exposure was not associated with a relevant additional risk of congenital anomalies. Nevertheless, the authors graded the certainty of evidence as low and emphasized limitations in the available studies (Katalinic et al., 2022; Katalinic et al., 2024).

The wider literature also demonstrates that the optimal form of luteal phase support remains uncertain. A 2021 systematic review and network meta-analysis involving 89 randomized controlled trials and 29,625 women found that several active LPS strategies were more effective than placebo or no treatment for ongoing pregnancy, while differences between active treatment regimens were generally small and uncertain (Wu et al., 2021). A contemporary review published in *Nature Reviews Endocrinology* similarly emphasized that important uncertainties remain regarding the optimal timing, dose, route and duration of luteal phase support (Garg et al., 2024).

More recently, a 2026 network meta-analysis of 24 randomized controlled trials examining progestogen routes in fresh embryo-transfer IVF cycles reported that oral administration was the only route associated with a statistically significant increase in clinical pregnancy compared with placebo, while oral and intramuscular routes were associated with statistically significant improvements in live birth compared with placebo. However, overlapping confidence intervals between active interventions indicate that clinically meaningful superiority of one route over another remains uncertain (Griesinger et al., 2026).

The issue is particularly relevant in Nigeria, where access to ART remains constrained by the high cost of treatment. Studies from Nigeria demonstrate increasing utilization of IVF but also indicate substantial room for improvement in clinical pregnancy and live-birth outcomes. In a large review from a tertiary hospital in southwestern Nigeria, approximately 23.7% of women undergoing ART achieved clinical pregnancy, highlighting the continuing importance of optimizing every component of IVF treatment (Ottun et al., 2023). Furthermore, the high cost of ART has been identified as a major barrier to utilization in Nigeria (Ezeome, Akintola and Jegede, 2023). In this context, an oral luteal-support medication that provides reproductive outcomes comparable to vaginal progesterone, while potentially offering improved convenience and tolerability, could have meaningful clinical implications. However, because existing

studies have produced mixed findings and differ in patient characteristics, ovarian stimulation protocols, embryo-transfer strategies, progesterone formulations and outcome measures, additional comparative research remains justified.

Therefore, direct evaluation of oral dydrogesterone versus micronized vaginal progesterone with respect to efficacy, safety and tolerability is warranted. Such evidence may help clinicians select an LPS regimen that provides optimal reproductive outcomes while minimizing treatment-related discomfort and improving patient acceptability.

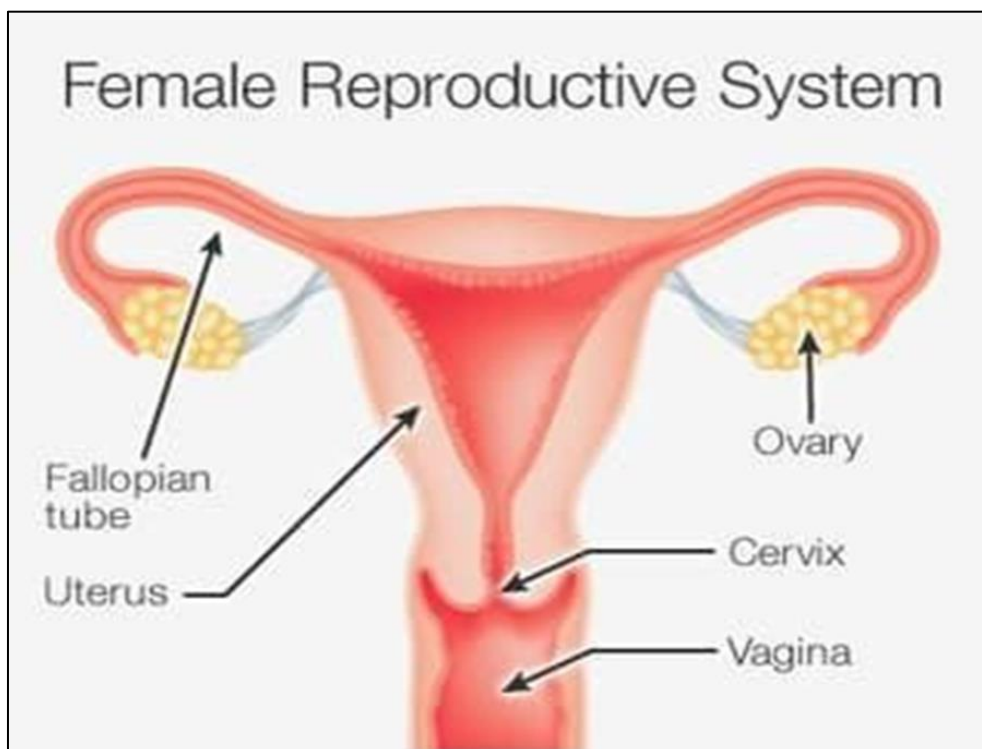


Figure 1: Female Reproductive Tract



Figure 2: Micronized Vaginal Progesterone (Endometrin)

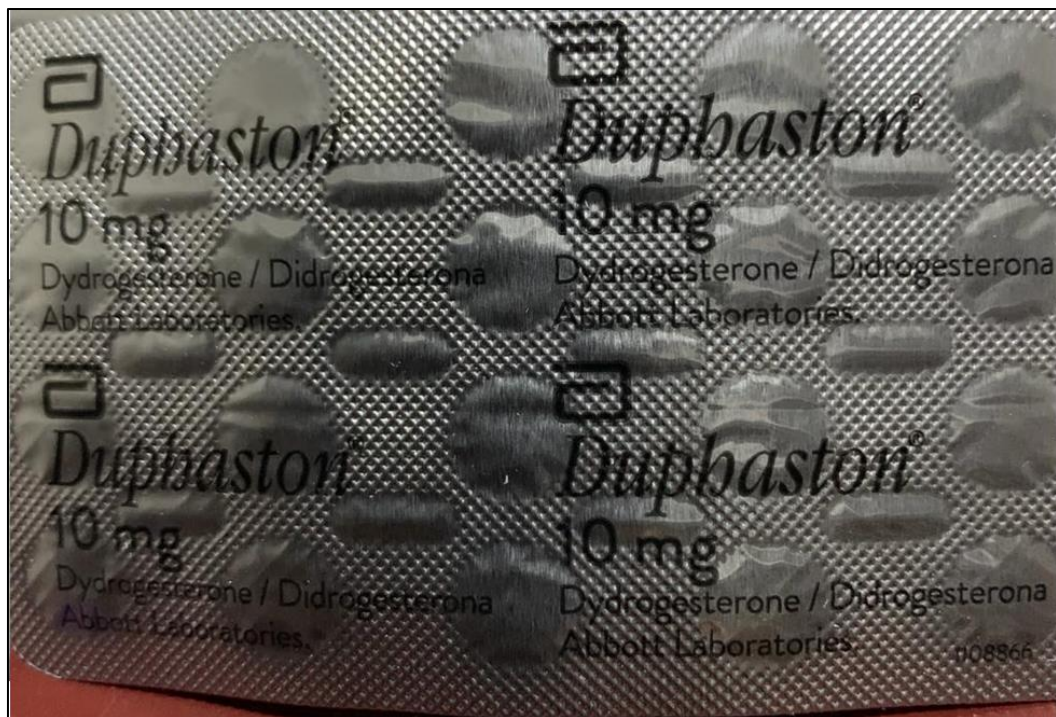


Figure 3: Oral Dydrogesterone (duphaston)



Figure 4: Front covers of the study drugs

2 MATERIALS AND METHODS

2.1 Study design and setting

This was a prospective, multicentre, randomized controlled trial conducted at four fertility centres in Enugu, South-Eastern Nigeria: Freedom Fertility and Reproduction Centre, Pink-Petal Fertility Centre, Kenechukwu Fertility Centre, and Maternal Health Fertility Centre.

Freedom Fertility and Reproduction Centre and Pink-Petal Fertility Centre are located in Independence Layout, Enugu. Kenechukwu Fertility Centre is located in Thinkers Corner, while Maternal Health Fertility Centre is located in GRA, Enugu. The centres provide fertility and assisted reproductive services to patients from Enugu and neighbouring states.

Participants were recruited from ART clinics during treatment booking. The participating centres provided routine ART and antenatal services during the study period.

2.2 Participants and recruitment

Women undergoing IVF/ICSI treatment who fulfilled the study eligibility criteria were approached for participation. The study procedures were explained to eligible participants, and written informed consent was obtained before enrolment.

A structured self-administered questionnaire was used to collect information on sociodemographic characteristics, obstetric history, relevant risk factors, and preferred route of progesterone administration.

2.3 Randomization and allocation

Participants were randomized in a 1:1 ratio using computer-generated randomization into two treatment groups:

Group A: oral dydrogesterone 30 mg daily plus vaginal placebo.

Group B: micronized vaginal progesterone 100 mg twice daily plus oral placebo.

The study medications and placebos were prepared in unidentifiable form by the pharmacy department. The study had a blinded outcome assessor, with matching placebo administration through the alternative route.

2.4 Intervention

Luteal phase support commenced following oocyte retrieval.

Participants in Group A received oral dydrogesterone 30 mg daily and a vaginal placebo, whereas participants in Group B received micronized vaginal progesterone (Endometrin) 100 mg twice daily and an oral placebo.

Embryo transfer was performed between days 2 and 5 following oocyte retrieval according to local clinical practice.

A pregnancy test consisting of serum β -hCG and a urine pregnancy test was performed approximately 15 ± 3 days after embryo transfer. Further clinical follow-up was undertaken according to the study protocol.

2.5 Outcome measures

Operational Definitions of Study Outcomes

2.5.1 Positive pregnancy test:

A positive pregnancy test was defined as detection of β -human chorionic gonadotropin (β -hCG) in serum or urine at the prespecified time following embryo transfer, according to the laboratory's validated reference threshold. A pregnancy diagnosed solely by detection of β -hCG was considered a biochemical pregnancy.

2.5.2 Clinical pregnancy:

Clinical pregnancy was defined as a pregnancy demonstrated by transvaginal ultrasonographic visualization of at least one gestational sac following a positive pregnancy test. Where applicable, the presence or absence of fetal cardiac activity was additionally documented.

2.5.3 Pregnancy continuing to 14 weeks:

Pregnancy continuing to 14 weeks was defined as a clinically recognized intrauterine pregnancy that remained viable at 14 completed weeks of gestation, with documented fetal cardiac activity where ultrasonographic assessment was performed.

2.5.4 Uterine contractions:

Uterine contractions were defined as new-onset or increased lower abdominal or pelvic tightening/cramping reported by the participant and documented by the attending clinician or research team during the study follow-up period.

2.5.5 Vaginal bleeding:

Vaginal bleeding was defined as any new episode of vaginal blood loss occurring after embryo transfer during the study follow-up period and reported by the participant and/or documented by the research team. Where available, the severity, duration, and number of bleeding episodes were recorded.

2.5.6 Need for additional intervention:

Need for additional intervention was defined as the administration of any medication or therapeutic measure beyond the assigned study treatment in response to a documented clinical symptom or event, according to the clinical judgement of the treating physician.

2.5.7 Specific additional interventions:

Specific additional interventions referred to the individual medications or therapeutic measures administered to participants who required management beyond their assigned study treatment. These included, where applicable, salbutamol, injectable progesterone (Gestone), diazepam, or other interventions documented during follow-up.

2.5.8 Miscarriage

Miscarriage was defined as spontaneous loss of a clinically recognized pregnancy before the gestational-age of viability. The gestational age at pregnancy loss and method of confirmation were recorded. Biochemical pregnancy loss without ultrasonographic evidence of a clinical pregnancy was classified separately from miscarriage where the available data permitted.

2.5.9 Determination of sample size

The sample size (n) 112 was determined using the formula for two independent (dichotomous) samples in a prospective study (Fleiss JL, (ed.) (1981); Dupoin, 1988; Els van Nood, Anne Vrieze, et al., 2013).

$$n = 1/(1-f) \times 2 (Z\alpha + Z\beta)^2 \times P \times (1-P) / (P_0 - P_1)^2$$

3 RESULT

A total of 112 women participated in this study comprising an equal number of 56 in each of the groups. Baseline characteristics were compared between the two treatment groups (Group A and Group B); Group A=OD; Group B=MVP using Independent Student t-test for the continuous variable such as age while chi-square test or Fisher Exact test was used to analyse all categorical demographic data, other medical history and body mass index. The categorical variables such as occurrence of miscarriage were compared between the two treatment groups using chi-square analysis or Fisher Exact test. The results were presented in the following format: tables, figures, line and bar charts. The statistical threshold for significant difference was set at $p \leq 0.05$.

Table 1A: Socio-demographic characteristics of the participants

Demographics	Group A	Group B	p - value*
	Mean ± SD	Mean ± SD	
Age (years)	39.07 ± 1.86	39.41 ± 1.88	0.338
	<u>n (%)</u>	<u>n (%)</u>	
Marital status	0.546		
Single	1 (1.8)	3 (5.4)	
Married	52 (92.9)	51 (91.1)	
Widowed	3 (5.4)	2 (3.6)	
Highest level of education			0.542
None	0 (0)	1 (1.8)	
Primary	0 (0)	1 (1.8)	
Secondary	10 (17.9)	11 (19.6)	
Tertiary	46 (82.1)	43 (76.8)	

Occupation			0.121
Employed	42 (75.0)	32 (57.1)	
Unemployed	2 (3.6)	5 (8.9)	
Self-employed	12 (21.4)	19 (33.9)	
Ethnicity			0.604
Igbo	55 (98.2)	54 (96.4)	
Hausa	0 (0)	1 (1.8)	
Yoruba	1 (1.8)	1 (1.8)	
Religion			0.315
Christianity	55 (98.2)	56 (100)	
Islam	1 (1.8)	0 (0)	
Parity			
Nulliparous	56 (100)	56 (100)	-

SD – standard deviation. n = number. Group A=OD. Group B=MVP

Table 1a shows the mean, standard deviation and socio-demographic characteristics of the participants of the study. Group A has a mean number of 1 for single, 52 for married and 3 for widows while Group B has a mean of 3 for singles, 51 for married and 2 for widow. The mean age of research participants in group A was 39.07 while it was 39.41 in Group B. The Socio-demographic characteristic of Group A – 30 mg of OD (Duphaston) and Group B – 200 mg of

MVP (Endometrin) showed that the mean age of Group A was 39.07 ± 1.86 years while Group B was 39.41 ± 1.88 years which was not statistically significant ($p = 0.338$). There was no significant difference in the marital status, highest level of education, occupation, ethnicity, and religion between the two treatment groups (Group A= OD and Group B= MVP). All the study participants were nulliparous. There was no statistical difference recorded in any of the socio-demographic characteristic.

Table 1 B: Body mass index of the participants

STUDY GROUP	Group A (OD) n=56(%)	Group B (MVP) n=56(%)	P-value
BMI (Mean $\pm$ SD)	28.2 $\pm$ 3.3	28.5 $\pm$ 5.6	0.635

High and very low BMI are associated with poor pregnancy outcomes. The difference in the body mass index amongst the groups was not statistically significant (P-Value=0.635).

Table 2: Pregnancy rate among the participants in the two groups

Pregnancy Rate	Group A n (%)	Group B n (%)	P-Value
Positive Pregnancy Test	19(33.9%)	21(37.5%)	0.838
Clinical Pregnancy	17(30.4%)	19 (33.9%)	0.834
Continuing Pregnancy till 14weeks	14(25.0%)	16(28.6%)	0.823
$\chi^2 = 11.059, p = 0.105$			

As seen in table 2 above, Participants in group B had more Positive Pregnancy Test (Group B, 37.5% versus Group A, 33.9%), more Clinical Pregnancy (Group B, 33.9% vs. Group A, 30.4%) and more participants with Continuing Pregnancy till 14weeks (Group B, 28.6% vs. Group A, 25.0%).

However, the difference is not statistically significant. The variation may be that in this present study, the MVP used was Endometrin, an emerging vaginal progesterone unlike the previous studies that made use of Cyclogest.

Table 3: occurrence of uterine contraction among the participants in the two groups

	Group A	Group B
Uterine contractions	n (%)	n (%)
Yes	37 (66.1)	22 (39.3)
No	19 (33.9)	34 (60.7)
	$\chi^2 = 8.059, p = 0.004$	

In table 3, about 59 (52.7%) cases of uterine contraction occurred, out of which 37 (66.1%) occurred in Group A and 22 (39.3%) in Group B. The higher frequency of uterine contractions in Group A was statistically significant ($\chi^2 = 8.059, p = 0.004$) as seen in table 3. The number of times uterine contractions occurred in each of the 59 women ranged from one to twelve (1 - 12). The numbers of uterine contractions an individual experienced were more frequently higher among those in Group A.

Table 4: Occurrence of vaginal bleeding among the participants in the two groups

	Group A	Group B
Vaginal bleeding	n (%)	n (%)
Yes	36 (64.3)	13 (23.2)
No	20 (35.7)	43 (76.8)
	$\chi^2 = 19.193, p < 0.001$	

In table 4, the occurrence of vaginal bleeding was also more frequent in Group A (36 [64.3%] versus 13 [23.2%]). The difference was significant ($\chi^2 = 19.193, p < 0.001$).

The number of times vaginal bleeding occurred per individual was between one and eight. The number of times vaginal bleeding occurred in Group A was mostly once or twice (7 each) or thrice (9 individuals) unlike Group B where no vaginal bleeding occurred more than three.

However, there was no significant difference between Group A and Group B in the number of times vaginal bleeding occurred ($\chi^2 = 10.009, p = 0.188$).

Table 5: Need for additional intervention among the participants in the two groups

	Group A	Group B
Need for additional intervention	n (%)	n (%)
Yes	37 (66.1)	17 (30.4)
No	19 (33.9)	39 (69.6)
	$\chi^2 = 14.304, p < 0.001$	

Also in table 5, there was need for additional intervention up to 54 participants (48.2%) and Group A constituted more than two-fold of the figure. Thirty-seven out of 54 (66.1%) in Group A compared to 17 (30.4) out of 54 in Group B had additional need for intervention (Table 5). The greater frequency of additional intervention need in Group A than Group B was very statistically significant ($\chi^2 = 14.304, p < 0.001$). Other studies that compared Duphaston with another type of MVP (Cyclogest) did not assess vaginal bleeding as a test of efficacy as done in this current study.

Table 6: Specific additional intervention provided among the participants in the two groups

Specific additional intervention provided	Group A n=56(%)	Group B n=56 (%)
Salbutamol Tablet + Gestone injection + Diazepam Tablet	29(51.8%)	14(9.0%)
Salbutamol Tablet + Diazepam Tablet.	1(1.8%)	0(0%)
Salbutamol tablet only	7(12.5%)	3(5.4%)

In table 6, the specific additional intervention provided to those who needed it was shown. 29(51.8%) needed additional Salbutamol Tablet + Gestone injection + Diazepam Tablet intervention in Group A as against 14 (9.0%) participants in Group B that needed additional Salbutamol Tablet + Gestone injection + Diazepam Tablet intervention. Also only one participant needed additional Salbutamol Tablet + Diazepam Tablet in Group A as against in Group B where none of the participants needed such intervention. An additional such as Salbutamol tablet only was needed by 7 (12.5%) in Group A as against 3 (5.4%) in Group B.

The difference was very statistically significant ($\chi^2 = 57.897$, $p < 0.001$). The above findings suggest that MVP (Endometrin) may be more efficient in ensuring positive pregnancy outcomes

Table 7: The rate of miscarriage among the participants in the two groups

	Group A	Group B
Miscarriage occurrence	n (%)	n (%)
Yes	5 (8.9)	2 (3.6)
No	51 (91.1)	54 (96.4)
	56 (100)	56 (100)
	$\chi^2 = 1.371$, $p = 0.219$	

In table 7, a total of seven participants (6.3%) had miscarriage during the study, five in Group A and 2 in Group B. Also in the table 7, There was no occurrence of miscarriage among 51 (91.1%) participants in Group A as against 54(96.4%) participants in Group B who had no miscarriage. However, the difference in miscarriage rate was not statistically significant ($\chi^2 = 1.371$, $p = 0.219$).

4 DISCUSSION

The present study compared the clinical outcomes of oral dydrogesterone (OD) and micronized vaginal progesterone (MVP) among 112 participants, with 56 women allocated to each treatment group. Group A received oral dydrogesterone, while Group B received micronized vaginal progesterone. The principal outcomes assessed included pregnancy rate, clinical pregnancy, continuation of pregnancy to 14 weeks, uterine contractions, vaginal bleeding, need for additional intervention, specific additional interventions and miscarriage. Overall, the findings demonstrated that the two treatment groups were comparable at baseline, while significant differences were observed in some clinical symptoms and the need for additional intervention. However, there was no statistically significant difference in the principal pregnancy outcomes or miscarriage rate.

4.1 Socio-demographic characteristics of the participants

The socio-demographic characteristics of the participants were comparable between the two treatment groups. The mean age was 39.07 ± 1.86 years in Group A and 39.41 ± 1.88 years in Group B, with no statistically significant difference ($p = 0.338$). Similarly, marital status, educational level, occupation, ethnicity and religion did not differ significantly between the groups. All participants were nulliparous.

The similarity in baseline characteristics is important in interpreting the subsequent findings because substantial differences in maternal characteristics between treatment groups could act as confounding factors. In the present study, the absence of statistically significant baseline differences suggests that the observed differences in uterine

contractions, vaginal bleeding and need for additional intervention were less likely to be explained by differences in the measured socio-demographic characteristics.

The mean BMI was also similar between the groups, being $28.2 \pm 3.3 \text{ kg/m}^2$ in Group A and $28.5 \pm 5.6 \text{ kg/m}^2$ in Group B ($p = 0.635$). Although the mean BMI in both groups falls within the overweight category according to conventional BMI classification, the groups were well matched with respect to BMI. Maternal BMI is clinically relevant because increasing maternal BMI has been associated with several adverse pregnancy outcomes, and evidence from systematic reviews indicates that higher BMI may also be associated with poorer reproductive outcomes in women undergoing assisted reproductive treatment (D'Souza et al., 2019; Xiong et al., 2021). Therefore, the similarity in BMI between the groups strengthens the comparability of the two treatment arms.

4.2 Pregnancy rate

The present study demonstrated slightly higher pregnancy rates among women receiving micronized vaginal progesterone compared with those receiving oral dydrogesterone. A positive pregnancy test was recorded in 37.5% of women in Group B compared with 33.9% in Group A. Similarly, clinical pregnancy occurred in 33.9% of women in Group B compared with 30.4% in Group A, while continuation of pregnancy to 14 weeks occurred in 28.6% of Group B compared with 25.0% of Group A. However, none of these differences were statistically significant.

The findings therefore suggest that, although there was a numerical tendency towards higher pregnancy rates among women receiving MVP, the present study did not demonstrate statistically significant superiority of MVP over oral dydrogesterone in achieving pregnancy or maintaining pregnancy to 14 weeks. This finding is consistent with evidence from comparative studies of dydrogesterone and vaginal progesterone. A systematic review and meta-analysis of randomized controlled trials evaluating dydrogesterone versus progesterone for luteal-phase support found no significant difference between the two treatments in ongoing pregnancy, clinical pregnancy or miscarriage rates (Barbosa et al., 2016). Another systematic review comparing oral dydrogesterone with vaginal progesterone capsules similarly reported comparable live birth/ongoing pregnancy and clinical pregnancy rates, with no significant difference in miscarriage (Barbosa et al., 2018). More recently, a 2025 systematic review and meta-analysis of randomized controlled trials involving frozen-thawed embryo transfer cycles also found no significant differences between oral dydrogesterone and vaginal progesterone in ongoing pregnancy, clinical pregnancy, miscarriage or live birth (Stavridis et al., 2025). Although the clinical setting and treatment indications in those studies may not be identical to those of the present study, the overall evidence supports the interpretation that oral dydrogesterone and vaginal progesterone can produce broadly comparable reproductive outcomes. The absence of a statistically significant difference in pregnancy rate in the present study may also be related to the relatively small sample size. With only 56 participants in each group, the study may have had limited power to detect relatively small differences in pregnancy outcomes. Thus, the higher numerical pregnancy rates observed in the MVP group should be interpreted as a trend rather than evidence of definite superiority.

4.3 Uterine contractions

A major finding of the present study was the significantly higher occurrence of uterine contractions among participants receiving oral dydrogesterone. Uterine contractions occurred in 66.1% of women in Group A compared with 39.2% in Group B, and this difference was statistically significant ($\chi^2 = 8.059$, $p = 0.004$).

This finding indicates that participants receiving oral dydrogesterone experienced uterine contractions more frequently than those receiving MVP. The frequency pattern also suggested that repeated episodes of uterine contractions were more common in Group A. This observation is clinically relevant because uterine activity may contribute to maternal discomfort and may prompt additional clinical assessment and treatment during early pregnancy.

However, caution is required when interpreting this finding. The present study demonstrates an association between treatment group and occurrence of uterine contractions, but it does not establish that oral dydrogesterone directly causes uterine contractions or that MVP directly prevents them. Uterine contractility can be influenced by several maternal, obstetric and pregnancy-related factors.

The observed difference is nevertheless clinically interesting because progesterone is involved in maintaining uterine quiescence during pregnancy. Differences in formulation, route of administration, absorption and tissue exposure may potentially influence clinical effects. Vaginal progesterone provides direct exposure to the reproductive tract and has been proposed to produce high local concentrations, although the clinical significance of these pharmacokinetic differences remains incompletely established (Szekeres-Bartho and Balasch, 2008).

Importantly, the lower frequency of uterine contractions in Group B did not translate into a statistically significant difference in miscarriage in the present study. Therefore, the finding should be regarded primarily as a difference in

symptomatic clinical outcomes rather than evidence that reduced uterine contractions necessarily result in improved pregnancy survival.

4.4 Vaginal bleeding

Vaginal bleeding was significantly more frequent among women receiving oral dydrogesterone than among those receiving MVP. Bleeding occurred in 64.3% of participants in Group A compared with 23.2% in Group B ($\chi^2 = 19.193$, $p < 0.001$). This represents one of the strongest differences observed between the two treatment groups.

Vaginal bleeding in early pregnancy is clinically important because it is a major presenting feature of threatened miscarriage. Consequently, the substantially lower proportion of women experiencing bleeding in the MVP group may have implications for maternal reassurance, frequency of clinical review and the need for additional interventions.

However, the findings of the present study differ from those of the TRoMaD randomized controlled trial, which directly compared micronized progesterone with dydrogesterone in women with threatened miscarriage. Siew et al. reported that the extent of vaginal bleeding at follow-up was not significantly different between women treated with micronized progesterone and those treated with dydrogesterone (Siew et al., 2018). The discrepancy may be explained by differences in study populations, sample size, progesterone formulation and dose, treatment duration, definition or assessment of bleeding, and other clinical characteristics.

The present study also found that the number of episodes of vaginal bleeding among affected participants did not differ significantly between the treatment groups. Thus, the statistically significant finding was primarily related to the proportion of women who experienced vaginal bleeding, rather than the frequency of bleeding episodes among those who bled.

This distinction is important in interpreting the result. It would therefore be inappropriate to conclude that MVP reduces the severity of bleeding based solely on the present data. Rather, the study suggests that women in the MVP group were less likely to experience vaginal bleeding during the observation period.

4.5 Need for additional intervention

Another important finding was the significantly greater need for additional intervention among women receiving oral dydrogesterone. Additional intervention was required in 66.1% of Group A compared with 30.4% of Group B ($\chi^2 = 14.304$, $p < 0.001$).

This finding is consistent with the higher occurrence of uterine contractions and vaginal bleeding observed in Group A. The greater frequency of these symptoms may have prompted clinicians to institute additional measures to control symptoms or support the pregnancy. Thus, the reduced need for additional intervention among women receiving MVP may represent a clinically relevant advantage of this treatment in the study population.

However, the need for additional intervention should be interpreted cautiously. Additional treatment may be influenced not only by the patient's symptoms but also by clinician preference, treatment protocols and the perceived severity of the clinical presentation. Consequently, this finding establishes an association between treatment group and additional intervention but does not, by itself, prove that MVP has superior overall efficacy.

The present finding is nevertheless noteworthy because the principal pregnancy outcomes were not significantly different between the groups. This suggests that the potential advantage of MVP in this study may relate more to symptomatic control and reduced need for supplementary treatment than to a demonstrable improvement in pregnancy establishment or continuation.

4.6 Specific additional interventions

The specific additional interventions also demonstrated a significant difference between the treatment groups. Salbutamol in combination with Gestone injection and diazepam was reportedly used more frequently in Group A than Group B. Salbutamol alone and salbutamol combined with diazepam were also more frequently required in Group A. The overall difference was statistically significant ($\chi^2 = 57.897$, $p < 0.001$).

The higher requirement for supplementary treatment in Group A is consistent with the greater occurrence of uterine contractions and vaginal bleeding observed in this group. It may indicate that women receiving oral dydrogesterone required more additional clinical management during the study period.

Nevertheless, this finding should not be interpreted as definitive evidence that MVP is pharmacologically superior to oral dydrogesterone. Additional interventions are downstream clinical outcomes and may be affected by management

practices as well as the patient's symptoms. Furthermore, some of the interventions listed, particularly diazepam and salbutamol, may have been used according to the clinical practice pattern of the study centre rather than according to standardized international protocols.

There is also an important numerical issue that should be corrected in the final thesis. In Table 6, 14 participants out of 56 in Group B represents 25.0%, not 9.0%. Therefore, the percentages in Table 6 should be checked against the original dataset and corrected before final submission. This is particularly important because inconsistencies between frequencies and percentages can affect the credibility of the statistical presentation.

4.7 Miscarriage

Miscarriage occurred in 8.9% of women in Group A compared with 3.6% in Group B. Although the miscarriage rate was numerically higher among women receiving oral dydrogesterone, the difference was not statistically significant ($\chi^2 = 1.371$, $p = 0.219$).

This finding indicates that the present study did not provide sufficient statistical evidence to conclude that either treatment was superior in preventing miscarriage. The relatively small number of miscarriage events, five in Group A and two in Group B—also limits the ability of the study to detect a statistically significant difference.

The finding is broadly consistent with the TRoMaD randomized controlled trial, in which miscarriage rates were comparable between women receiving micronized progesterone and those receiving dydrogesterone (Siew et al., 2018). Similarly, a systematic review and meta-analysis of oral dydrogesterone and vaginal progesterone found no significant difference in miscarriage between the two treatment approaches (Barbosa et al., 2016).

However, the wider literature on progesterone therapy in threatened miscarriage is not completely uniform. A 2018 systematic review and meta-analysis reported that progesterone therapy overall was associated with a lower miscarriage rate compared with control treatment, with oral dydrogesterone showing a significant reduction compared with control; however, the authors were evaluating treatment versus control rather than demonstrating superiority of dydrogesterone over vaginal progesterone (Lee et al., 2017). A large network meta-analysis subsequently found differences among various progestogens, with oral dydrogesterone ranking favourably for miscarriage prevention (Devall et al., 2021). More recent evidence has also reported that oral dydrogesterone may reduce miscarriage compared with vaginal progesterone in women with first threatened miscarriage, although the evidence base and clinical populations vary considerably between studies

These differences in the literature emphasize that the efficacy of progesterone cannot necessarily be generalized across all preparations, routes, doses, patient populations and clinical indications. The results of the present study therefore provide evidence specific to the treatment protocols and population studied and should not be interpreted as establishing universal superiority of one progesterone preparation.

Overall interpretation Taken together, the findings demonstrate that oral dydrogesterone and micronized vaginal progesterone produced broadly comparable pregnancy outcomes in the study population. Although Group B had numerically higher rates of positive pregnancy tests, clinical pregnancy and continuation of pregnancy to 14 weeks, none of these differences reached statistical significance.

In contrast, significant differences were observed in several symptomatic and management-related outcomes. Uterine contractions, vaginal bleeding and the need for additional intervention were all significantly more frequent among women receiving oral dydrogesterone. These findings may suggest a potential advantage of MVP in reducing certain clinical symptoms and the requirement for supplementary interventions.

It is important, however, to distinguish between statistical significance and clinical superiority. The significant differences in uterine contractions, vaginal bleeding and additional intervention do not automatically establish that MVP is superior with respect to the ultimate goal of treatment, which is successful pregnancy continuation and live birth. In the present study, the pregnancy and miscarriage outcomes did not differ significantly.

This interpretation is consistent with comparative evidence showing that oral dydrogesterone and vaginal progesterone generally have similar reproductive outcomes in several clinical settings (Barbosa et al., 2016; Barbosa et al., 2018; Stavridis et al., 2025). In the TRoMaD trial specifically, micronized progesterone and dydrogesterone had comparable miscarriage outcomes and bleeding resolution, although differences in side effects were observed (Siew et al., 2018).

4.8 Implications of the study findings

The findings of this study have potential clinical implications. The lower occurrence of uterine contractions and vaginal bleeding and the lower requirement for additional intervention among women receiving MVP may make the vaginal route attractive in clinical situations where symptomatic control is an important consideration. However, the absence of a statistically significant difference in pregnancy and miscarriage outcomes means that treatment selection should not be based on an assumption that MVP necessarily improves pregnancy survival.

The choice between oral dydrogesterone and vaginal progesterone may therefore need to take into consideration several factors, including route preference, tolerability, adherence, cost, availability, clinical indication and the specific progesterone formulation being used. Evidence from randomized trials and systematic reviews supports the view that the two approaches may provide comparable reproductive outcomes in several settings (Barbosa et al., 2016; Barbosa et al., 2018; Stavridis et al., 2025).

It is also important to recognize that different vaginal progesterone preparations are not necessarily interchangeable. For example, the product information for Endometrin specifies its use as part of assisted reproductive technology treatment and notes that efficacy in women aged 35 years and older has not been clearly established. Since the women in the present study had a mean age of approximately 39 years, the applicability of product-specific evidence to this population should be considered carefully. The treatment regimen and clinical indication used in the present study should therefore be clearly described when comparing these findings with previous studies.

4.9 Strengths and limitations relevant to the findings

One strength of the study is the equal number of participants in the two treatment groups and the similarity of the groups with respect to age, socio-demographic characteristics and BMI. This provides a reasonable basis for comparing treatment outcomes.

However, the study has limitations that should be considered. First, the sample size of 112 participants is relatively small, particularly for uncommon outcomes such as miscarriage. Consequently, the absence of statistical significance for miscarriage and pregnancy outcomes does not necessarily prove that there is no clinically meaningful difference between the treatments.

Second, several outcomes were assessed, including multiple symptoms and intervention categories. Multiple statistical comparisons may increase the probability of obtaining a statistically significant result by chance if no correction for multiple testing is applied.

Third, the data concerning uterine contractions and vaginal bleeding appear to be based on occurrence and frequency of episodes. If these outcomes were self-reported, there may be a possibility of reporting or measurement bias. Future studies would benefit from clearly defined and standardized criteria for documenting uterine contractions, vaginal bleeding and the severity of symptoms.

Fourth, the use of additional interventions may have been influenced by clinical judgement and local treatment practices. Therefore, differences in additional treatment should not be interpreted solely as pharmacological differences between dydrogesterone and MVP.

5 CONCLUSION

The present study demonstrated that oral dydrogesterone and micronized vaginal progesterone had comparable effects on positive pregnancy test, clinical pregnancy, continuation of pregnancy to 14 weeks and miscarriage, with no statistically significant differences in these major pregnancy outcomes. However, uterine contractions, vaginal bleeding and the need for additional intervention were significantly more frequent among participants receiving oral dydrogesterone.

The findings therefore suggest that micronized vaginal progesterone may have an advantage in relation to certain symptomatic and management outcomes in the population studied, but the study does not provide sufficient evidence to establish MVP as superior to oral dydrogesterone in achieving or maintaining pregnancy. The observed lower miscarriage rate in the MVP group was not statistically significant and should consequently be regarded as a numerical difference rather than evidence of treatment superiority.

Overall, the findings contribute to the existing evidence that the comparative effectiveness of different progesterone preparations depends on the clinical indication, formulation, dose, route of administration and characteristics of the patient population. Larger, adequately powered randomized controlled trials using standardized definitions of bleeding,

uterine contractions, additional interventions, miscarriage and live birth are required to determine whether the differences observed in this study represent true treatment effects.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

Authors have declared that no competing interests exist.

Statement of ethical approval

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Statement of informed consent

Written informed consent was gotten from the participants after explaining in details the process of the study. They were at liberty to decline participation without any negative impact on the care they received in the hospital.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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