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Comparing the outcomes of in-vitro fertilization in patients receiving vaginal, subcutaneous, and intramuscular progesterone for luteal phase support: a three-armed randomized controlled trial

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Abstract

Background The optimal approach to luteal-phase support in infertility treatment remains a subject of debate. This study was conducted to investigate the clinical outcomes, side effects, and patient satisfaction associated with vaginal, subcutaneous, and intramuscular progesterone administration in infertile women undergoing Frozen Embryo Transfer (FET).

Methods This three-armed randomized clinical trial assigned infertile patients eligible for FET to three progesterone treatment groups: vaginal suppositories (400 mg twice daily; $n=100$), subcutaneous injections (25 mg daily; $n=102$), and intramuscular injections (50 mg daily; $n=108$). The primary outcomes were chemical and clinical pregnancy rates per embryo transfer cycle, with chemical pregnancy defined as beta-human chorionic gonadotropin levels > 50 IU/mL two weeks post-transfer and clinical pregnancy confirmed by ultrasound four weeks later. Exploratory outcomes included progesterone-related adverse effects and participant satisfaction, assessed via a Likert-scale survey 12 weeks post-transfer. Statistical analyses included Chi-square tests for categorical data, one-way analysis of variances, and Kruskal–Wallis tests for continuous data.

Results The intramuscular progesterone group had significantly higher chemical pregnancy rates compared to the vaginal and subcutaneous groups (41.7% vs. 26.0% and 27.5%, respectively; $p=0.026$). Although the clinical pregnancy rate was also higher in the intramuscular group (32.4%) compared to the vaginal (23.0%) and subcutaneous groups (21.6%), this difference was not statistically significant ($p=0.148$). Additionally, patient satisfaction was greater with vaginal and subcutaneous applications than with intramuscular injections ($p<0.001$), likely due to a significantly higher incidence of side effects, such as pain and edema at the injection site, in the intramuscular group ($p<0.001$).

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Conclusions We found that intramuscular progesterone resulted in higher chemical pregnancy rates than vaginal or subcutaneous routes, but this did not translate into higher clinical pregnancy rates. Despite its effectiveness, intramuscular administration was associated with more adverse effects and lower patient satisfaction. Future research should explore optimizing progesterone regimens to balance efficacy and patient comfort.

Trial registration The trial protocol was registered on December 6, 2020, in the Iranian Registry of Clinical Trials (IRCT), a primary registry in the World Health Organization (WHO) Registry Network, under the registration number IRCT20141217020351N12.

Keywords Embryo Transfer, Infertility, In Vitro Fertilization, Luteal-phase Support, Progesterone

Background

Pregnancy rates after Frozen Embryo Transfer (FET) can be affected by numerous factors, including the patient's age, endometrial thickness and pattern, the quality and growth stage of the embryo, and the method of freezing [1–4]. An additional factor that can strongly support pregnancy is the administration of progesterone as luteal phase support, which is a routine part of In-vitro Fertilization (IVF) treatment more broadly [5]. The use of progesterone has been associated with higher rates of pregnancy during fertility treatments, as well as with higher rates of live birth, as compared to placebo treatments [6]. However, progesterone can be administered by oral, vaginal, subcutaneous, and intramuscular methods, various studies have shown varying results concerning the efficacy of these different prescription approaches, which have been published by various researchers [7–11].

The effectiveness of oral progesterone is often limited by poor bioavailability due to first-pass hepatic metabolism [12]. On the other hand, progesterone injections are generally considered more effective for pregnancy support, but they are associated with complications such as injection site pain, abscess formation, and inflammatory reactions [13]. Moreover, vaginal progesterone suppositories provide similar pregnancy benefits with fewer side effects and greater ease of use, making them a preferred option for many patients [14–16]. Although studies comparing injectable and vaginal progesterone have produced mixed results regarding their effectiveness in inducing secretory endometrial transformation, increasing evidence supports the use of vaginal progesterone [13]. Despite lower serum progesterone levels compared to injectable forms, vaginal administration effectively induces endometrial transformation, likely due to the first uterine pass effect, which enhances uterine bioavailability and minimizes systemic side effects [13]. However, the pharmacokinetics of vaginal progesterone can vary significantly depending on the formulation used [13].

While progesterone administration has demonstrated potential in optimizing luteal-phase support during FET, significant uncertainty persists regarding the optimal route of administration. Existing studies are heterogeneous, and a consensus has yet to be reached [17]. Furthermore, no study to date has directly compared the outcomes of three distinct methods of progesterone administration for luteal-phase support in FET patients. To address this gap, the present study aimed to provide a comprehensive evaluation of clinical outcomes, adverse events, and patient satisfaction associated with three progesterone delivery routes—vaginal, subcutaneous, and intramuscular. The goal is to offer valuable insights into the advantages and disadvantages of each method to better inform clinical practice and guide individualized treatment decisions.

Methods

Study design and ethical considerations

In this three-armed randomized controlled trial, all consecutive eligible patients with infertility who were candidates for IVF were recruited and followed between December 2020 and March 2022. This study was conducted at the Vali-e-Asr infertility clinic at Imam Khomeini Hospital complex, affiliated with the Tehran University of Medical Sciences, Tehran, Iran. The trial protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences, with the ethical code of IR.TUMS.VCR.REC.1398.1024, and all stages of the study were conducted strictly adhering to the principles of the Declaration of Helsinki [18]. Following a comprehensive presentation of the trial and its specifics informed verbal and written consent was secured from all patients. Participants were apprised of their prerogative to withdraw from the trial at any point without detriment to their therapy or their rapport with healthcare providers.

The trial was registered on December 6, 2020, in the Iranian Registry of Clinical Trials (IRCT), a primary registry in the World Health Organization (WHO) Registry Network, under the registration number IRCT20141217020351N12, accessible at https://irct.behdasht.gov.ir/trial/45786. We present this paper in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [19].

Participants

This trial included Iranian infertile women aged 18–42 years who were eligible for IVF with the potential for FET. Inclusion criteria required participants to have fewer than three previous embryo transfers, baseline follicle-stimulating hormone levels below 15 mIU/mL, a Body Mass Index (BMI) under 30 kg/m^2, and no reported uterine abnormalities or azoospermia in their male partners. Participants were excluded if they declined to participate, lacked proficiency in the Persian language, or had a history of severe endometriosis, submucosal fibroids, uncontrolled adrenal or thyroid disorders, thromboembolic conditions, hydrosalpinx, recurrent miscarriage, or recurrent implantation failure in previous IVF cycles. Additionally, patients who had undergone preimplantation genetic diagnosis to assess embryo quality were excluded from the study. Lastly, patients were excluded if they failed to participate in follow-up assessments after receiving the prescribed treatments.

Randomization and blinding

Patients were randomly assigned to one of the three treatment groups using block randomization (3 alleles, block size of 9), ensuring balanced allocation. This study employed a single-blind design, where the individual responsible for assigning patients to the study groups was blinded to the patients' clinical conditions and preferences. Opaque, sealed envelopes containing the treatment assignments—vaginal suppository, subcutaneous, or intramuscular progesterone—were prepared by a biostatistician at the center. To assign patients, a nurse unaffiliated with the study selected an envelope for each participant. Once opened, the patient's allocation to one of the three progesterone administration routes was confirmed.

Intervention

On the second day of each participant's menstrual cycle, all three groups of participants received 6 mg of oral estradiol valerate daily (2 mg tablets, Abu Reihan Company, Iran). After six days, if the endometrium was not appropriate, an additional 2 mg of estradiol valerate was given to the dosage and monitoring continued. Progesterone was administered to estradiol valerate therapy after the endometrial thickness reached 8 mm, as assessed by vaginal ultrasound. Following this cycle, FET was canceled if the endometrium did not meet the required thickness of 8 mm or lacked acceptable transparency. Embryo transfer was conducted four days after the first dose of progesterone for all participants. According to the executive procedure, a total of two embryos were transferred for each participant. This was done in the embryo cleavage stage under vaginal sonography guidance using two good quality embryos (grades A, AB, or B), transferred via Cook catheter (Cook®, Bloomington, IN, USA). Embryo transfer was followed by 8 weeks of progesterone medication in the absence of an ectopic pregnancy. The progesterone therapy protocols encompassed vaginal suppository (400 mg twice daily; Cyclogest, Barnstaple UK), subcutaneous (25 mg daily; Prolutex, IBSA Switzerland), or intramuscular (50 mg daily; Abu Reihan Company, Iran).

Study measures and outcomes

At the baseline, data regarding the following characteristics were collected from each patient using a predefined checklist: age, height, body weight, infertility duration, infertility type, and cause, history of receiving IVF treatment, and history of previous abortions.

The primary outcomes of this study were chemical and clinical pregnancy rates per embryo transfer cycle. Chemical pregnancy was considered positive when beta-human Chorionic Gonadotropin (beta-hCG) levels exceeded 50 IU/mL two weeks after the embryo transfer. The clinical pregnancy was confirmed if one or more gestational sacs were identified by ultrasound four weeks post-transfer in participants with a positive chemical pregnancy.

Secondary outcomes included multiple pregnancy rates (implantation of more than one embryo), ectopic pregnancy (implantation outside the uterus), and spontaneous abortion (pregnancy loss after ultrasound confirmation) per embryo transfer cycle.

Moreover, adverse effects associated with progesterone administration were documented as exploratory outcomes in our study. These adverse effects included local reactions at the injection site and side effects from vaginal suppositories, such as irritation, inflammation, itching, discharge, and bleeding. Additionally, participant satisfaction with progesterone therapy was assessed 12 weeks post-embryo transfer using a brief Likert-scale survey, which categorized satisfaction into three levels: dissatisfied, partially satisfied, and completely satisfied.

Sample size calculation

The sample size calculation was performed using G*Power 3.1.9.2 software. Reported rates of chemical pregnancy (primary outcome) following luteal-phase support with vaginal, subcutaneous, and intramuscular progesterone during FET were collected at 0.4, 0.6, and 0.8, respectively [20, 21]. Fisher's exact test was used for pairwise comparisons between the study groups, with a two-tailed significance level (alpha) set at 0.05 and a statistical power of 80%, using an allocation ratio of 1:1. The required sample sizes per arm were estimated to be

102 for the vaginal vs. subcutaneous comparison, 40 for the vaginal vs. intramuscular comparison, and 90 for the subcutaneous vs. intramuscular comparison. To ensure a conservative estimate, the largest sample size (102 per arm) was selected. By maintaining a 1:1:1 allocation ratio, the final calculated total sample size was 306 participants.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science (SPSS, version 25.0, IBM Corp., Armonk, NY, USA). Categorical data were reported as frequencies and percentages, while continuous data were expressed as means with standard deviations. To compare the prevalence of categorical variables across the three study groups, the Chi-square test was employed. Prior to comparing the means of continuous variables, the Kolmogorov–Smirnov test was conducted to assess normality. When the data followed a normal distribution, a one-way Analysis of Variance (ANOVA) was used to compare group means. If the data did not follow a normal distribution, the Kruskal–Wallis test was applied. A significance level of $p < 0.05$ was set for all analyses.

Additionally, univariate binary logistic regression was used to assess the predictive ability of various variables, including treatment groups, for achieving chemical and clinical pregnancy, with the calculation of odds ratios (ORs) and 95% confidence intervals (CIs), along with sensitivity, specificity, and overall accuracy measures. Multivariate logistic regression analyses were subsequently performed to determine the independent predictive value of each variable for chemical and clinical pregnancy attainment. A $p < 0.05$ was considered statistically significant in all regression analyses.

Results

Baseline characteristics of the participants

Three hundred and seventy-six patients were screened for eligibility from December 2020 to March 2022, 310 of whom were eligible to be included in this trial. Subsequently, participants were randomly allocated to the vaginal suppository ($n = 100$), subcutaneous ($n = 102$), and intramuscular ($n = 108$) groups. None of the study participants dropped out of the study during the follow-up periods (Fig. 1).

There were no statistically significant differences between the three study groups in terms of their age, infertility duration, history of IVF, or history of previous abortions ($p > 0.05$). However, there were significant differences between them in terms of their mean BMI ($p < 0.001$), infertility types ($p = 0.005$), cause of infertility ($p = 0.002$), number of previous abortions ($p = 0.042$), and received IVF protocol ($p = 0.014$) (Table 1).

Clinical outcomes

Our results indicated a significantly higher rate of chemical pregnancy per cycle in patients receiving intramuscular progesterone for luteal-phase support (41.7%) compared to those receiving vaginal (26.0%) and subcutaneous (27.5%) progesterone ($p = 0.026$). However, although the intramuscular group exhibited a higher rate of clinical pregnancies (32.4%) compared to the vaginal and subcutaneous groups (23.0% and 21.6%, respectively), this difference did not reach statistical significance ($p = 0.148$). Furthermore, no significant differences were observed between the groups regarding spontaneous abortions ($p = 0.111$), multiple pregnancies ($p = 0.555$), or ectopic pregnancies (no cases of ectopic pregnancy were reported in any of the three treatment groups) (Table 2).

Univariate logistic regression analyses were performed to assess the predictive ability of various factors for chemical and clinical pregnancy achievement following FET. The variables analyzed included age, BMI, infertility duration, infertility type, cause of infertility, history of IVF, previous abortion, received treatment protocol (agonist vs, antagonist), and progesterone administration methods (vaginal suppository, subcutaneous, and intramuscular). Our results indicated that only the method of progesterone administration significantly predicted chemical pregnancy attainment (OR = 1.447 [95% CI: 1.074–1.950]; $p = 0.015$). This association remained significant after adjusting for the effects of the other variables in the multivariate analysis (OR = 1.468 [95% CI: 1.078–1.999]; $p = 0.015$). This suggests that intramuscular progesterone administration is linked to higher rates of chemical pregnancy following FET compared to vaginal and subcutaneous routes. However, none of the examined variables, including the progesterone administration method, were significant predictors of clinical pregnancy achievement in either univariate or multivariate logistic regression analyses ($p > 0.05$) (Table 3).

Side effects

Patients in the intramuscular group reported a significantly higher rate of complications ($p < 0.001$), which primarily consisted of pain and swelling at the injection site (75.0% of the participants in this group reported pain and swelling). Other reported side effects encompassed vaginal discharge (5.6%), vaginal bleeding (3.7%), in the intramuscular group, skin irritation (8.8%), vaginal bleeding (4.9%), and perineal irritation (1.0%) in the subcutaneous group, and vaginal discharge (6.0%), vaginal bleeding (4.0%), rectum itching (4.0%), and perineal irritation (3.0%) in the vaginal suppository group (Table 2).

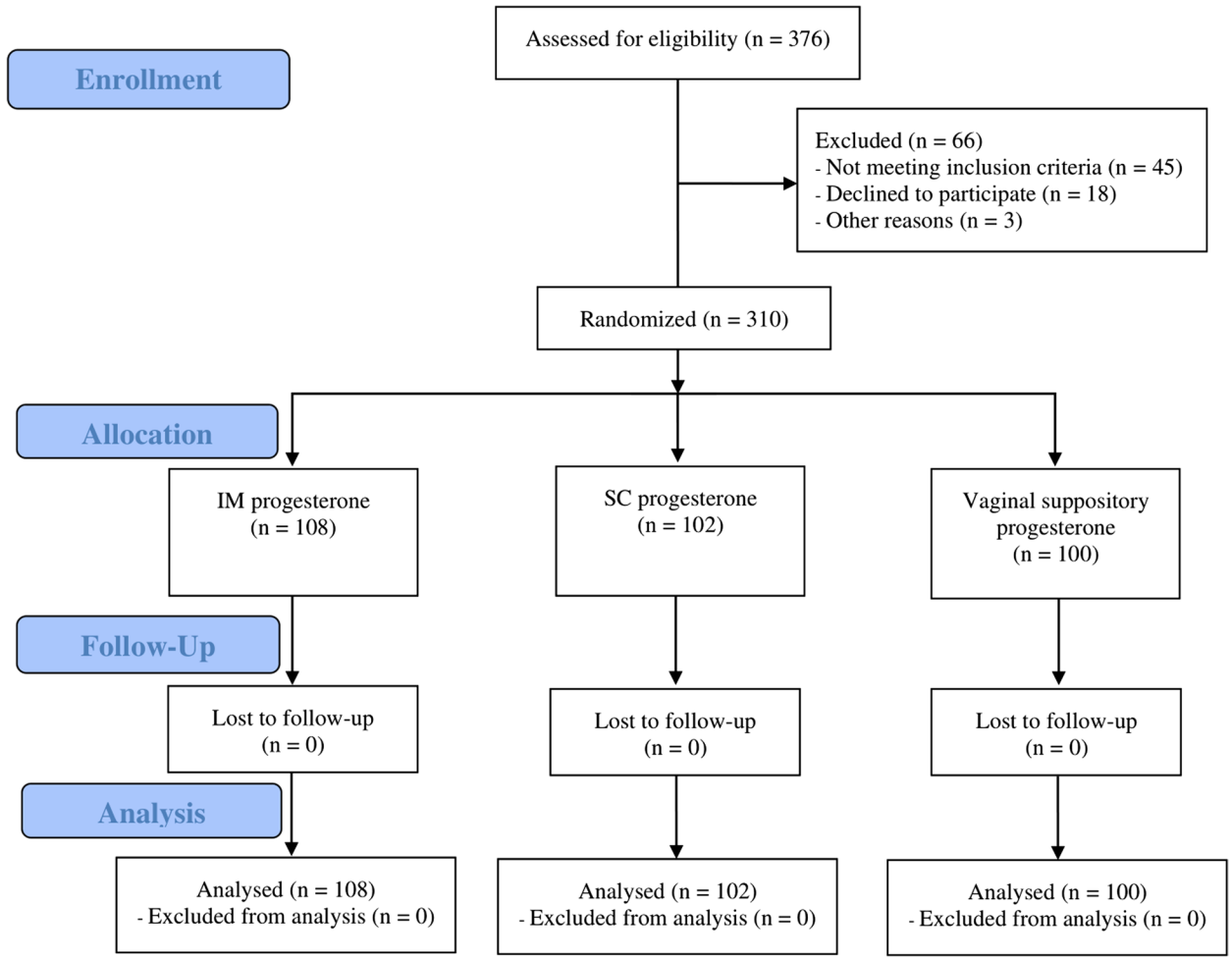

Fig. 1 The process of screening and recruitment of the study participants, based on the CONSORT 2010 flow diagram

Satisfaction of treatment

Based on our survey, there was a significant difference in the patient-reported satisfaction level with the received treatment ($p < 0.001$), with the intramuscular group demonstrating a substantially lower complete satisfaction compared to the vaginal and subcutaneous groups (0.0%, 73.0%, and 71.6%, respectively). These findings highlight that while the intramuscular method of progesterone administration is associated with higher chemical pregnancy rates, given the significantly higher complication rates (specifically the pain and swelling in the injection site) these patients are less satisfied with their treatment than those receiving the vaginal or subcutaneous progesterone for the least-phase support.

Discussion

Key findings

This study demonstrated that intramuscular administration of progesterone for luteal-phase support is associated with higher chemical pregnancy rates two weeks post-embryo transfer compared to vaginal or subcutaneous routes. Although the clinical pregnancy rate was also higher in the intramuscular group, this difference did not reach statistical significance. These findings suggest that the route of progesterone administration may have a greater impact on the implantation process than on the maintenance of pregnancy. Notably, patient-perceived satisfaction with treatment was significantly lower in the intramuscular group than in the vaginal and subcutaneous groups, likely due to the higher incidence of adverse effects and discomfort associated with intramuscular administration.

Comparison of three methods of progesterone administration for luteal-phase support

Previous research has extensively compared the clinical outcomes of vaginal, subcutaneous, and intramuscular routes of progesterone administration for luteal-phase

Table 1 Characteristics of the included patients[a]

Variable	VS	SC	IM	p
Number	100	102	108	
Age, y	35.5 ± 5.7	35.7 ± 6.1	36.2 ± 6.4	0.665[b]
BMI, kg/m^2	21.6 ± 2.8	23.4 ± 3.3	22.5 ± 3.2	< 0.001[c]
Infertility duration, y	4.2 ± 2.9	3.9 ± 2.9	4.3 ± 3.6	0.617[b]
Infertility type:				
Primary	49 (49.0)	73 (71.6)	66 (61.1)	0.005[d]
Secondary	51 (51.0)	29 (28.4)	42 (38.9)	
Cause of infertility:				
Male factor	34 (34.0)	21 (20.6)	30 (27.0)	
Ovarian factor	14 (14.0)	30 (29.4)	34 (31.5)	0.002[d]
Tubal factor	20 (20.0)	7 (6.9)	11 (10.2)	
Male and ovarian factor	32 (32.0)	44 (43.1)	33 (30.6)	
History of IVF	47 (47.0)	57 (55.9)	53 (49.1)	0.466[d]
Previous abortion	33 (33.0)	20 (19.6)	23 (21.3)	0.054[d]
Number of abortions	0.5 ± 0.8	0.2 ± 0.5	0.3 ± 0.7	0.042[c]
Treatment protocol:				
Agonist	3 (3.0)	0 (0.0)	8 (7.4)	0.014[d]
Antagonist	97 (97.0)	102 (100.0)	100 (92.6)	

Abbreviations: *IM* intramuscular, *IVF* in-vitro fertilization, *SC* subcutaneous, *VS* vaginal suppository

[a] Categorical data are presented as numbers (percentage) and continuous data as mean ± standard deviation

[b] One-way ANOVA

[c] Kruskal-Wallis test

[d] Chi-Square test

Table 2 Clinical outcomes and side effects of the three studied groups of the trial[a]

Variable	VS	SC	IM	p
Chemical pregnancy	26 (26.0)	28 (27.5)	45 (41.7)	0.026[b]
Clinical pregnancy	23 (23.0)	22 (21.6)	35 (32.4)	0.148[b]
Spontaneous abortion	1 (1.0)	7 (6.9)	5 (4.6)	0.111[b]
Multiple pregnancies	3 (3.0)	2 (2.0)	1 (0.9)	0.555[b]
Complication:				
Perineal irritation	3 (3.0)	1 (1.0)	0 (0.0)	
Rectum itching	4 (4.0)	0 (0.0)	0 (0.0)	
Vaginal bleeding	4 (4.0)	5 (4.9)	4 (3.7)	< 0.001[b]
Vaginal discharge	6 (6.0)	0 (0.0)	6 (5.6)	
Skin irritation	0 (0.0)	9 (8.8)	0 (0.0)	
Pain and swelling at the injection site	0 (0.0)	0 (0.0)	81 (75.0)	
Total complication	17 (17.0)	15 (14.7)	88 (81.5)	< 0.001[b]
Satisfaction:				
Dissatisfied	0 (0.0)	0 (0.0)	72 (66.7)	
Partially satisfied	27 (27.0)	29 (28.4)	36 (33.3)	< 0.001[b]
Completely satisfied	73 (73.0)	73 (71.6)	0 (0.0)	

Abbreviations: *IM* intramuscular, *SC* subcutaneous, *VS* vaginal suppository

[a] Categorical data are presented as numbers (percentages)

[b] Chi-Square test

support in patients undergoing IVF, typically through pairwise analyses [21–23]. However, to the best of our knowledge, our study is the first to conduct a direct and comprehensive comparison of clinical outcomes and adverse events across all three methods simultaneously. Our findings indicate that, ultimately, the clinical pregnancy rates are comparable among these methods. However, the incidence of adverse events is significantly higher with the intramuscular route, leading to notably lower patient satisfaction compared to the vaginal and subcutaneous routes.

Intramuscular administration of progesterone results in significantly higher serum progesterone levels compared to other methods, but this does not necessarily improve outcomes for embryo transfers [24]. Both intramuscular and vaginal progesterone methods show similar patterns of sub-endometrial contractions and comparable rates of maintaining clinical pregnancies after embryo transfers [24]. Despite lower serum progesterone levels with vaginal administration, it effectively induces endometrial transformation, likely due to the first uterine pass effect that increases local bioavailability while reducing systemic side effects [13]. A systematic review of randomized controlled trials on this topic highlighted comparable live birth rates following both vaginal and intramuscular progesterone administration during luteal-phase support [25]. Additionally, most recent studies have suggested that vaginal and intramuscular progesterone administration methods yield similar results in terms of implantation rates, chemical pregnancy rates, clinical pregnancy rates, ongoing pregnancy rates, live birth rates, and spontaneous abortion rates [25–28]. Moreover, prior research has consistently pointed to a significantly higher level of patient satisfaction among those receiving vaginal suppositories of progesterone compared to those enduring daily intramuscular injections of painful oily progesterone ampules [25, 29].

Currently, vaginal progesterone is the most common approach in IVF practice, largely due to its ease of administration and relatively low incidence of complications [30, 31]. This perspective was strongly supported in the current study, where participants reported a much lower rate of complications and higher satisfaction with vaginal application compared to intramuscular injection. However, it is important to note that some studies have reported higher implantation, chemical pregnancy, clinical pregnancy, ongoing pregnancy, and live birth rates in patients receiving intramuscular progesterone compared to those using vaginal gel [32, 33]. Therefore, while the lower side effects and higher patient satisfaction associated with vaginal treatment are well-established, there still remains controversy regarding its advantages in achieving different pregnancy outcomes. This underscores the need for further research in this area.

Table 3 Findings of the univariate and multivariate logistic regression analysis on the potential predictive abilities of variables for the chemical and clinical pregnancy attainments

Variable	Univariate analysis					Multivariate analysis	
	Accuracy	Sensitivity	Specificity	p	OR [95% CI]	p	OR [95% CI]
1. Chemical pregnancy							
Age	68.1%	0.0%	100.0%	0.554	0.988 [950–1.028]	0.283	0.977 [0.937–1.019]
BMI	68.1%	0.0%	100.0%	0.190	1.052 [0.975–1.134]	0.359	1.037 [0.959–1.121]
Infertility duration	68.4%	1.0%	100.0%	0.200	1.049 [0.975–1.128]	0.195	1.051 [0.975–1.134]
Infertility type	68.1%	0.0%	100.0%	0.449	1.207 [0.742–1.962]	0.644	1.170 [0.601–2.278]
Cause of infertility	68.1%	0.0%	100.0%	0.720	0.965 [0.794–1.173]	0.684	0.958 [0.780–1.177[
History of IVF	68.4%	1.0%	100.0%	0.103	1.414 [0.932–2.146]	0.162	1.360 [0.884–2.092]
Previous abortion	68.1%	0.0%	100.0%	0.292	1.339 [0.778–2.3015]	0.380	1.396 [0.663–2.940]
Treatment protocol	68.1%	0.0%	100.0%	0.749	0.815 [0.233–2.851]	0.823	1.180 [0.276–5.042]
Progesterone administration method	68.1%	0.0%	100.0%	0.015	1.447 [1.074–1.950]	0.015	1.468 [1.078–1.999]
2. Clinical pregnancy							
Age	74.2%	0.0%	100.0%	0.295	0.978 [0.938–1.020]	0.184	0.970 [0.928–1.014]
BMI	74.2%	0.0%	100.0%	0.313	1.042 [0.962–1.129]	0.520	1.027 [0.946–1.115]
Infertility duration	74.2%	0.0%	100.0%	0.300	1.041 [0.965–1.124]	0.379	1.036 [0.957–1.121]
Infertility type	74.2%	0.0%	100.0%	0.891	1.037 [0.617–1.744]	0.436	1.313 [0.662–2.603]
Cause of infertility	74.2%	0.0%	100.0%	0.740	0.965 [0.784–1.189]	0.686	0.956 [0.769–1.188]
History of IVF	74.5%	1.3%	100.0%	0.168	1.285 [0.900–1.835]	0.246	1.275 [0.846–1.922]
Previous abortion	74.2%	0.0%	100.0%	0.627	0.861 [0.471–1.574]	0.593	0.806 [0.366–1.776]
Treatment protocol	74.2%	0.0%	100.0%	0.420	0.596 [0.170–2.094]	0.735	0.783 [0.190–3.235]
Progesterone administration method	74.2%	0.0%	100.0%	0.116	1.287 [0.939–1.762]	0.163	1.259 [0.911–1.739]

Abbreviations: *BMI* body mass index, *CI* confidence interval, *IVF* in-vitro fertilization, *OR* odds ratio

A newer method for progesterone delivery during luteal-phase support is subcutaneous injection [34]. Our study highlighted that subcutaneous progesterone results in comparable chemical and clinical pregnancy rates, as well as a similar rate of adverse events, compared to the vaginal route. Previous research has demonstrated comparable bioavailability for both subcutaneous and intramuscular progesterone methods, with both being significantly greater than that of the vaginal route [35]. Most prior studies examining subcutaneous progesterone have used the vaginal route as the control group, and like our study, reported comparable pregnancy rates for both methods [23, 36]. Additionally, prior research generally indicates favorable acceptance of the subcutaneous route of progesterone administration among the patients [34]. Collectively, these results suggest that subcutaneous progesterone offers bioavailability similar to intramuscular methods and pregnancy rates comparable to the vaginal route while causing fewer adverse events than intramuscular injections. Thus, subcutaneous administration could be considered an effective option for progesterone delivery in luteal-phase support. However, its cost-effectiveness has not yet been well-established yet [34].

Oral progesterone: a new potential route for luteal-phase support

An emerging avenue for progesterone administration in luteal phase support during FET is oral administration. Recent studies have indicated comparable pregnancy rates following oral progesterone administration, demonstrating non-inferiority when compared to vaginal suppositories [37–39]. This suggests that despite the potential impact of primary hepatic metabolism on reducing progesterone bioavailability, oral progesterone could serve as an alternative treatment for patients who are unwilling or unable to use other routes. Consequently, further randomized controlled trials are essential in this domain to ascertain the precise efficacy of oral progesterone administration for luteal phase support.

Strengths and limitations

Despite the strengths of our study, including its relatively large sample size, comprehensive data collection on clinical outcomes, complications, and patient satisfaction following luteal-phase support, as well as the use of well-established statistical methods that allow for adjustments across multiple variables, certain limitations necessitate cautious interpretation of our findings.

First, our examination focused solely on the short-term effects of progesterone applications concerning chemical and clinical pregnancy outcomes and we did not manage to assess its impact on ongoing pregnancy outcomes, live birth rates, or neonatal outcomes, which are crucial factors that warrant examination in future FET studies before definitive practice recommendations can be established. Second, we did not investigate the influence of patients' serum progesterone levels on the clinical outcomes of progesterone therapy in luteal phase support. Third, the lack of an opportunity to conduct preimplantation genetic diagnosis tests on embryonic cells across a large sample necessitated the reliance on qualitative assessments of embryo quality for selection in our study, rather than on the transfer of confirmed euploid blastocysts. Lastly, the embryos were transferred to the uterus during the cleavage stage, a practice for which evidence suggests relatively lower success rates compared to transfer at the blastocyst stage [40]. This approach may also serve as a potential confounding factor in our findings. These circumstances underscore the need for future studies in this field to provide a better understanding of the precise effects of each progesterone administration method on the pregnancy outcomes of patients undergoing IVF.

Conclusions

The present study demonstrated that intramuscular progesterone for luteal-phase support resulted in superior chemical pregnancy rates compared to vaginal suppositories and subcutaneous administration. However, this advantage did not extend to clinical pregnancy rates, highlighting the need for further investigation into why the increase in chemical pregnancies did not translate into more clinical pregnancies and maintaining the pregnancy. Moreover, despite its effectiveness, the intramuscular route was associated with significantly higher adverse effects, including pain and swelling at the injection site, leading to lower patient satisfaction compared to vaginal and subcutaneous routes. This suggests that although intramuscular progesterone may offer better clinical outcomes, it is often not necessarily the patients' preferred option due to discomfort. Consequently, optimizing the dosage and administration of progesterone via vaginal or subcutaneous routes could potentially enhance their efficacy while improving patient experience. Future research is essential to establish standardized guidelines for the optimal route and dosage of progesterone, tailored to patients' medical needs and preferences.

Abbreviations

ANOVA	Analysis of Variance
beta-hCG	beta-human Chorionic Gonadotropin
BMI	Body Mass Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
FET	Frozen Embryo Transfer
IRB	Institutional Review Board
IRCT	Iranian Registry of Clinical Trials
IVF	In-vitro Fertilization
OR	Odds Ratio
SPSS	Statistical Package of Social Science Software
WHO	World Health Organization

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Authors' contributions

EST participated in conceptualization, supervision, providing the study resources, and reviewing and editing the draft of the paper. SA participated in designing the study, data collection, data curation, reviewing, and editing the draft of the paper. EAN participated in data validation and writing the original draft of the paper. NZ participated in the data curation and statistical analysis and participated in writing the original draft of the paper. MS participated in designing the study, supervising, reviewing, and editing the draft of the paper. FH participated in data collection and writing the original draft of the paper. AT participated in conceptualization, designing the study, data collection, supervising, reviewing, and editing the draft of the paper. MP participated in data curation, data validation, statistical analysis, visualization, and writing the original draft of the paper. All of the authors have read and approved the final version of the manuscript for submission.

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Availability of data and materials

Tehran University of Medical Sciences strictly adheres to policies that prohibit the sharing of data to safeguard patient confidentiality and comply with legal and ethical regulations. Requests for data may be directed to the respective ethics committees for consideration.

Declarations

Ethics approval and consent to participate

The study was conducted at the Vali-e-Asr infertility clinic at Imam Khomeini Hospital complex, affiliated with the Tehran University of Medical Sciences, Tehran, Iran. The trial protocol was approved by the Institutional Review Board (IRB) of Tehran University of Medical Sciences, with the ethical code of IR.TUMS.VCR.REC.1398.1024. All procedures adhered strictly to the guidelines of the Declaration of Helsinki. Before enrollment, a detailed verbal and written explanation of the study's aims was provided to the participants. Informed verbal and written consent were obtained from all participants, who were also assured that they could withdraw from the study at any time without affecting their infertility treatments.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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