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Review Article

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Combined Progesterone Administration Versus Single-Route Administration for Luteal Phase Support in IVF: A Narrative Review of Current Evidence

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Abstract

Background: Luteal phase support (LPS) with progesterone is essential for successful implantation and early pregnancy maintenance in IVF cycles. Although various administration routes exist (oral, vaginal, intramuscular, subcutaneous), the comparative effectiveness of combined (dual or triple) versus single-route progesterone regimens remains uncertain due to limited high-quality randomized controlled trials.
Methods: A narrative review was conducted to evaluate studies comparing pregnancy outcomes in IVF cycles using combined versus single-route progesterone administration for LPS. A comprehensive literature search was performed to identify retrospective, prospective, and randomized controlled studies published in peer-reviewed journals. Data regarding clinical pregnancy, live birth, miscarriage, and implantation rates were collected and synthesized narratively due to heterogeneity among included studies.
Results: Most studies did not demonstrate statistically significant differences in outcomes between single-route and combined progesterone regimens, particularly when dydrogesterone was included. However, certain combinations, especially those involving oral dydrogesterone alongside vaginal or intramuscular progesterone, were associated with improved live birth and clinical pregnancy rates. Despite these encouraging findings, the lack of adequately powered RCTs and the methodological variability among studies limit the generalizability of the results.
Conclusion: While single-route progesterone administration remains effective for luteal phase support in IVF cycles, emerging evidence suggests that individualized combined regimens may enhance pregnancy outcomes. The physiological rationale for combined administration, offering both systemic and local endometrial support, is compelling. Further well-designed randomized controlled trials with standardized protocols are necessary to establish evidence-based guidelines for optimal LPS.

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Introduction

Infertility affects approximately 15% of reproductive-age couples worldwide and remains a major public health concern (1, 2). Advances in assisted reproductive technologies (ARTs), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have

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substantially improved the management of infertility. Nevertheless, implantation failure and unsuccessful pregnancy outcomes continue to represent significant challenges in reproductive medicine (3-5).

Progesterone plays a pivotal role in establishing and maintaining early pregnancy. During the luteal phase, progesterone promotes endometrial transformation, facilitates embryo implantation, modulates maternal immune responses, and suppresses uterine contractility (6-10). In stimulated IVF cycles, luteal phase deficiency (LPD) is frequently observed due to altered corpus luteum function and hormonal disruption associated with ovarian stimulation protocols. Consequently, luteal phase support (LPS) with exogenous progesterone has become a standard component of IVF treatment (11-13).

Several progesterone administration routes are currently used in clinical practice, including vaginal, intramuscular, subcutaneous, and oral formulations. Each route offers distinct pharmacokinetic characteristics, advantages, and limitations. Vaginal progesterone provides direct uterine exposure, whereas intramuscular administration achieves stable systemic serum concentrations. Oral dydrogesterone has also gained increasing acceptance because of its ease of administration and favorable patient tolerability (13-15).

More recently, combined progesterone regimens involving two or more administration routes have been introduced with the aim of optimizing both local endometrial exposure and systemic hormonal support. However, available evidence regarding the superiority of combined approaches over single-route administration remains inconsistent.

Although several systematic reviews have evaluated the efficacy of different progesterone formulations or routes of administration for luteal phase support, none has specifically focused on the clinical question of combined progesterone administration versus single-route regimens across IVF cycles. Consequently, the available evidence remains fragmented, and clinicians lack a dedicated synthesis addressing the rationale, efficacy, and potential indications for combination luteal phase support. This gap in the literature provided the rationale for the present narrative review aiming to critically synthesize and discuss the current evidence comparing combined versus single-route progesterone administration for luteal phase support in IVF, ICSI, and frozen embryo transfer (FET) cycles, with particular emphasis on reproductive outcomes and their implications for individualized clinical practice.

Methods

Study design: This paper constitutes a narrative review of the published literature evaluating combined versus single-route progesterone administration for LPS in women undergoing IVF, ICSI, and FET cycles.

Literature search: A comprehensive literature search was conducted in PubMed, Embase, Scopus, and the Cochrane Library to identify studies evaluating combined versus single-route progesterone administration for luteal phase support in assisted reproductive technology.

The search combined controlled vocabulary (where applicable) and free-text terms "(luteal phase support, progesterone, dydrogesterone, vaginal progesterone, intramuscular progesterone, subcutaneous progesterone, in vitro fertilization, intracytoplasmic sperm injection, and frozen embryo transfer)" using Boolean operators (AND/OR). The complete electronic search strategies for each database are provided in supplementary table 1. No restrictions were applied regarding study design during the initial search. Only studies published in English were considered for inclusion. The final search was conducted on December 15, 2024. Reference lists of eligible articles and relevant reviews were also manually screened to identify additional studies. Studies were selected based on their relevance to the topic of combined versus single-route progesterone administration in ART. Eligible studies included randomized controlled trials and observational studies. Reviews, editorials, case reports, conference abstracts, and animal studies were excluded. A total of 13 studies were included in the final analysis.

Methodological approach: A qualitative narrative synthesis of the included studies was performed. Findings were summarized and discussed descriptively according to progesterone administration route, study design, and reported clinical outcomes. Since this study was designed as a narrative review, no formal protocol registration was performed, and no formal risk-of-bias assessment tool (*e.g.*, Cochrane RoB 2 or Newcastle–Ottawa Scale) was applied. Therefore, no study-level risk-of-bias classification was performed.

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Table 1. Characteristics and main findings of studies evaluating combined versus single-route progesterone administration for luteal phase support in IVF

Study	Design and sample size	Single-route regimen	Combined regimen	Main findings
Vidal et al. (2023)	Retrospective cohort study, 391 FET cycles	Oral dydrogesterone (30 *mg/day*); vaginal micronized progesterone gel (90 *mg/day*); micronized progesterone capsules (600 *mg/day*); subcutaneous progesterone (25 *mg/day*)	Dydrogesterone (20 *mg/day*) plus micronized progesterone gel (90 *mg/day*)	Higher live birth rates were observed in the oral dydrogesterone group. No significant differences were observed between the combined regimen and vaginal progesterone gel alone
Gawron et al. (2023)	Prospective randomized study, 250 women	-	Dydrogesterone (10 *mg* three times daily) plus vaginal progesterone gel (90 *mg/day*) versus subcutaneous progesterone (25 *mg/day*) plus vaginal progesterone gel (90 *mg/day*)	No significant differences in live birth rates between the two combined regimens. Outcomes were comparable across treatment groups
Toriumi et al. (2023)	Retrospective study, 206 women	Vaginal micronized progesterone (600 *mg/day*)	Vaginal progesterone plus oral dydrogesterone (45 *mg/day*); vaginal progesterone plus oral dydrogesterone (45 *mg/day*) and intramuscular progesterone (125 *mg/week*)	Addition of dydrogesterone improved clinical and ongoing pregnancy rates compared with vaginal progesterone alone, particularly in women with low serum progesterone levels
Simon et al. (2022)	Retrospective study, 171 women	Oral dydrogesterone (30 *mg/day*)	Oral dydrogesterone (30 *mg/day*) plus long-acting intramuscular progesterone (100 *mg/week*)	Pregnancy and ongoing pregnancy rates were numerically higher in the combined-treatment group; however, differences were not statistically significant
Jalaliani et al. (2022)	Cross-sectional study, 355 women	Vaginal progesterone 400 *mg* twice daily	Vaginal progesterone 400 *mg* twice daily plus intramuscular progesterone 50 *mg/day*	Combined administration was associated with higher chemical and clinical pregnancy rates compared with vaginal progesterone alone
Pabuccu et al. (2016)	Retrospective study, 301 women	Vaginal micronized progesterone 600 *mg/day*	Vaginal progesterone 600 *mg/day* plus intramuscular progesterone 50 *mg/day* for 5 days	Implantation rates were higher in the combined-treatment group, while ongoing pregnancy rates were similar between groups
Vuong et al. (2021)	Prospective cohort study, 1,364 women	Vaginal micronized progesterone 400 *mg* twice daily	Vaginal micronized progesterone 400 *mg* twice daily plus oral dydrogesterone 10 *mg* twice daily	Combined administration resulted in higher live birth rates and lower miscarriage rates compared with vaginal progesterone alone
Polat et al. (2020)	Cohort study, 475 women	Vaginal progesterone gel twice daily	Vaginal progesterone gel plus intramuscular progesterone 50 *mg* every third day	Clinical and ongoing pregnancy rates were similar between groups
Asoglu et al. (2019)	Retrospective cohort study, 767 FET cycles	Intramuscular progesterone 100 *mg/day*	Vaginal progesterone gel (90 *mg* twice daily) plus intramuscular hydroxyprogesterone caproate (250 *mg/week*)	Live birth, implantation, and clinical pregnancy rates were comparable between groups
Gari and Al-Jaroudi (2022)	Retrospective cohort study, 1,162 IVF/ICSI cycles	Vaginal progesterone 400 *mg* twice daily	Weekly intramuscular progesterone 250 *mg* plus vaginal progesterone 400 *mg* twice daily	No significant differences in live birth rates were observed between treatment groups
Devine et al. (2018)	Randomized controlled trial, 590 women	Daily intramuscular progesterone (50 *mg/day*) or vaginal progesterone (200 *mg* twice daily)	Vaginal progesterone (200 *mg* twice daily) plus intramuscular progesterone (50 *mg* every third day)	Vaginal progesterone alone associated with lower ongoing pregnancy rates compared with regimens including intramuscular progesterone; combination therapy showed no clear advantage over daily intramuscular progesterone

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Contd. Table 1. Characteristics and main findings of studies evaluating combined versus single-route progesterone administration for luteal phase support in IVF

Study	Design and sample size	Single-route regimen	Combined regimen	Main findings
Wang et al. (2015)	Prospective randomized trial, 1,500 FET cycles	-	Vaginal progesterone gel (90 *mg/day*) plus oral dydrogesterone (20 *mg/day*) versus intramuscular progesterone (40 *mg/day*) plus oral dydrogesterone (20 *mg/day*)	Live birth, clinical pregnancy, implantation, miscarriage, and ectopic pregnancy rates were similar between groups
Xu et al. (2021)	Retrospective study, 832 FET cycles	Intramuscular progesterone 40 *mg/day*	Vaginal progesterone gel (90 *mg/day*) plus oral dydrogesterone (20 *mg/day*)	Clinical pregnancy, implantation, miscarriage, and live birth rates were comparable between groups

Results

Clinical pregnancy and ongoing pregnancy outcomes: Several studies evaluated the effect of combined progesterone regimens on clinical and ongoing pregnancy outcomes. Evidence generally suggested that combined luteal phase support may improve pregnancy outcomes in certain patient populations (16-19). Studies incorporating oral dydrogesterone in addition to vaginal progesterone reported higher clinical and ongoing pregnancy rates compared with vaginal progesterone alone (16, 19, 20). Similar findings were observed in studies evaluating the addition of intramuscular progesterone to vaginal progesterone, where higher clinical pregnancy and implantation rates were reported (17, 18). However, findings from randomized and observational studies were not entirely consistent. While Gawron et al. (21) reported no significant differences between two combined progesterone regimens, Devine et al. (22) demonstrated that intermittent combined vaginal and intramuscular progesterone did not improve ongoing pregnancy rates compared with daily intramuscular progesterone. Likewise, several cohort studies found no significant differences between combined and single-route regimens (24-26, 28), indicating substantial inconsistency across the available literature.

Live birth outcomes: Evidence regarding live birth rates was conflicting. Some studies reported higher live birth rates with regimens combining oral dydrogesterone and vaginal progesterone (19), while others observed improved outcomes with oral dydrogesterone alone (20). In contrast, multiple retrospective cohorts and randomized studies found comparable live birth rates between combined and single-route progesterone administration (21, 23-27). Overall, the current evidence does not consistently support a clear live birth advantage for combination therapy.

Miscarriage outcomes: A number of studies suggested that combined progesterone administration may reduce miscarriage rates (16, 19). The addition of oral dydrogesterone to vaginal progesterone was associated with lower miscarriage rates in some cohorts, particularly among women with low serum progesterone concentrations (16, 19). Nevertheless, this finding was not consistently observed across all studies, and several investigations reported similar pregnancy loss rates between treatment strategies (23, 26).

Implantation and neonatal outcomes: Implantation outcomes were inconsistently reported. Some studies demonstrated improved implantation rates following the addition of intramuscular progesterone to vaginal progesterone (17, 18), whereas others found no significant differences between treatment protocols (23, 25, 26). Similarly, neonatal outcomes, including gestational age at delivery, birth weight, preterm birth rates, and congenital anomalies, appeared comparable across progesterone regimens (23).

Overall synthesis of evidence: Taken together, the available evidence suggests that combined progesterone regimens may offer potential benefits for clinical pregnancy, ongoing pregnancy, and miscarriage outcomes in selected patient populations, particularly when oral dydrogesterone is incorporated into luteal phase support protocols. However, the majority of studies reported comparable outcomes between combined and single-route administration, especially with regard to live birth rates. Interpretation of these findings is limited by substantial heterogeneity in study design, progesterone formulations, dosing schedules, embryo

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transfer protocols, patient characteristics, and outcome definitions. Furthermore, most included studies were observational or retrospective in nature, limiting the strength of causal inference.

Discussion

The present narrative review explored the available literature comparing combined progesterone administration with single-route progesterone administration for LPS in IVF cycles. Across the included studies, both approaches were generally associated with favorable reproductive outcomes; however, the evidence was heterogeneous, and no consistent superiority of any regimen was demonstrated.

Progesterone remains a fundamental component of LPS in assisted reproductive technology, regardless of the route of administration. Considerable variability was observed across studies in terms of treatment protocols, patient populations, embryo transfer stages, and outcome definitions, which may partly explain inconsistencies in reported results.

Several studies reported no significant differences between single-route and combined progesterone administration. Vidal et al. (20), Xu et al. (23), Polat et al. (12), Asoglu et al. (25), and Wang et al. (26) all demonstrated comparable implantation, clinical pregnancy, and live birth outcomes across different progesterone regimens, suggesting no clear advantage of combination therapy over monotherapy.

In contrast, a subset of studies reported potentially improved reproductive outcomes with combined regimens. Vuong et al. (19) observed higher live birth rates and lower miscarriage rates with the addition of oral dydrogesterone to vaginal progesterone. Jalaliani et al. (17) reported higher pregnancy rates with combined vaginal and intramuscular progesterone compared with single-route administration. Similarly, Toriumi et al. (16) found improved ongoing pregnancy rates following the addition of dydrogesterone. However, these findings were not consistently replicated across studies and should therefore be interpreted with caution.

More recent evidence continues to support this inconsistency. Gawron et al. (21) and Simon et al. (27) reported no significant differences between combined and single-route protocols, whereas Devine et al. (22) found that intermittent combined vaginal and intramuscular progesterone did not improve ongoing pregnancy rates compared with daily intramuscular progesterone. In contrast, Pabuccu et al. (18) and Gari and Al-Jaroudi (24) suggested potential benefits of adding intramuscular progesterone to vaginal regimens in specific clinical contexts. Overall, the current literature does not allow firm conclusions regarding the superiority of combined therapy.

From a physiological perspective, combined progesterone administration has a plausible biological rationale. Oral dydrogesterone provides systemic progestogenic effects, while vaginal and intramuscular routes achieve higher local endometrial concentrations, potentially enhancing endometrial receptivity. Despite this theoretical advantage, clinical evidence does not consistently demonstrate improved reproductive outcomes with combination therapy.

The interpretation of these findings is limited by substantial heterogeneity across studies, including differences in study design, patient characteristics, progesterone formulations, dosing regimens, embryo transfer protocols, and outcome definitions. Furthermore, the majority of studies were observational or retrospective in nature, limiting the strength of causal inference. These limitations highlight the need for well-designed randomized controlled trials to clarify the potential role of combined progesterone regimens in luteal phase support.

Conclusion

The available literature suggests that both single-route and combined progesterone regimens can provide effective luteal phase support in IVF cycles. Although some studies report improved reproductive outcomes with combined approaches, particularly those involving oral dydrogesterone or additional intramuscular progesterone, the evidence remains inconsistent.

Current data do not conclusively support the superiority of combined over single-route progesterone administration for all patients undergoing IVF. The heterogeneity of study designs, patient populations, and treatment protocols, together with the predominance of observational studies, limits the strength of the available evidence.

Nevertheless, combined regimens may represent a reasonable option in selected clinical scenarios and should be considered within an individualized approach to luteal phase support. Further well-designed randomized controlled trials with standardized protocols and uniform outcome definitions are required to clarify the optimal strategy

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for progesterone administration and to identify patients who may benefit most from combination therapy.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this review.

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