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SYSTEMATIC REVIEW

Reproductive outcomes after rescue luteal phase support for women with low serum progesterone in artificial cycles around frozen embryo transfer day: Systematic review and network meta-analysis of over 7500 patients

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Abstract

Background: Low serum progesterone levels around the time of frozen embryo transfer (FET) in artificially prepared cycles have been associated with reduced reproductive success. Rescue luteal phase support (LPS) has been proposed as a strategy to optimize outcomes in these cases.

Objectives: This study assesses the effectiveness of rescue LPS in improving reproductive outcomes among women with suboptimal serum progesterone levels prior to FET.

Method: A comprehensive literature search was conducted to identify randomized and non-randomized (prospective or retrospective) studies evaluating the impact of additional progesterone administration in women with low serum levels around FET in artificial cycles. Twelve observational studies comprising more than 7500 participants were included. Eligible studies assessed clinical outcomes following supplemental progesterone via various routes in patients with below-threshold serum levels. A network meta-analysis was performed to compare the effectiveness of different rescue LPS protocols. Routes of progesterone administration included intramuscular, vaginal, oral, subcutaneous, and rectal. Primary outcomes included clinical pregnancy rate, live birth rate, ongoing pregnancy rate, pregnancy loss rate, and biochemical pregnancy rate.

Results: Rescue LPS in women with low serum progesterone was associated with improved reproductive outcomes, approaching that observed in women with adequate progesterone levels. Intramuscular and vaginal administration were frequently ranked highest, although no protocol demonstrated clear superiority. Significant heterogeneity existed across studies, particularly regarding progesterone cutoff values.

Conclusion: Rescue luteal phase support appears to be a promising approach for managing low serum progesterone before FET. However, randomized controlled trials with standardized thresholds and protocols are needed to confirm these findings and guide clinical practice.

KEYWORDS
clinical pregnancy rate, frozen embryo transfer, infertility, luteal phase support, rescue protocol, serum progesterone

1 | INTRODUCTION

1.1 | Background

Frozen embryo transfer (FET) has become a predominant approach in contemporary assisted reproduction, with national surveillance systems routinely reporting assisted reproductive techniques (ART) activity and outcomes.[1,2] In the United States, the Centers for Disease Control and Prevention (CDC) provides national ART summary figures derived from all reporting clinics, offering an updated picture of ART use and outcomes at the population level.[3] In parallel, the Society for Assisted Reproductive Technology (SART), in collaboration with the American Society for Reproductive Medicine (ASRM), periodically releases national and clinic-specific ART data; the most recent release reported that US IVF activity in 2023 resulted in over 95 000 babies being born, highlighting the sustained and increasing utilization of ART.[4]

Not surprisingly, the strategy of endometrial preparation in FET cycles has gained increasing attention. Today, several endometrial preparation protocols are available, including: (i) hormone replacement therapy (HRT), (ii) natural cycle (NC), (iii) modified spontaneous cycle (mNC), and (iv) ovulation induction by low doses of gonadotropins. The debate concerns not only the efficacy but also the safety of the different endometrial preparation strategies. Specifically, it is known that hormone replacement therapy (HRT)-FET cycles might be less safe compared with NCs for both mother and fetus.[5] In fact, the absence of corpus luteum and, as a consequence, of circulating vasoactive factors such as relaxin, would determine an increased risk of pre-eclampsia in.[6] An aspect that is still unresolved and that is common to all endometrial preparation strategies is the method of supplementing the luteal phase with progesterone (P). Indeed, there is still disagreement on the best treatment method, dosage, and duration for luteal phase support (LPS).[7] As demonstrated by multiple studies, low serum P levels can negatively affect reproductive outcomes, both in HRT[8,9] and in NC FET,[10] and both in homologous[11] and heterologous[12] cycles. Further, reduced serum P levels seem to be associated with a higher risk of early pregnancy loss.[13] Currently, there is still no unified consensus on the optimal level of serum P levels below which it would be unwise to perform embryo transfer (ET) as well on the benefit of rescue LPS support in women with low serum P levels.[10,14–16] Moreover, because each route of administration for P in LPS has its pros and cons,[17–19] as or May 2024, there is no unanimous agreement on the dosage and route of administration of the "rescue" dose as well.

1.2 | Objectives

The purpose of the present systematic review and network meta-analysis was to define the efficacy and usefulness of rescue LPS and to identify which LPS rescue protocol would provide the best reproductive outcomes in HRT-FET cycles.

2 | METHODS

2.1 | Eligibility criteria

Any randomized, prospective, or retrospective study that enrolled infertile women undergoing HRT-FET followed by LPS with at least two cohorts (i.e., one group of patients in which low P serum levels, defined according to each study's threshold, were supplemented by additional P, and another group without rescue LPS) were considered for inclusion.

The exclusion criteria were as follows: studies evaluating non-hormonal LPS, studies including the same route of administration in two different cohorts, studies without a control (no supplementation) group, and women undergoing NC-fresh embryo transfer (ET), NC-FET or a different IVF protocol not involving HRT.

2.2 | Information sources

The methods outlined in the Mbuagbaw et al.[20] methodological specifications and the Cochrane Handbook for Systematic Reviews of Interventions[21] were followed in the execution of this network meta-analysis. The extension statement for network meta-analyses (PRISMA-NMA) of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[22] was followed. On May 7, 2024, the study protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42024540499).

2.3 | Search strategy

Electronic databases including SCOPUS, MEDLINE (accessible through PubMed), LILACS, EMBASE, Scielo.br, and PROSPERO were searched with the following Medical Subject Heading (MeSH) terms and keywords: "rescue" or "individualized" and "luteal phase support" and "frozen embryo transfer" or "frozen-thawed embryo transfer" without any date restriction. The search string was modified according to each database's format. Full database-specific search strings are provided in Supplemenary Table S1. Further searches were performed on CINAHL, PsycINFO, and AMED to find more relevant papers to reduce publication bias. We also examined the Cochrane Central Register of Controlled studies, Clinicaltrials.gov, and the International Clinical Trials Registry Platform of the World Health Organization to locate other randomized controlled trials. Additionally, a search of the gray literature (NTIS and PsycEXTRA) was conducted for abstracts of national and international conferences. We also searched the references and pertinent reviews of the included study to locate additional articles that missed our first search. There were no language or location-based limitations. The analysis did not include any editorials, letters to the editor, comments, or second thoughts publications.

2.4 | Study selection and data extraction

The abstraction forms were developed specifically for this meta-analysis of networks. The study's duration, setting, inclusion and exclusion criteria, ART procedure, features, treatment kinds, serum P levels threshold, outcomes evaluated, mean treatment and follow-up time, outcomes, and quality factors were all recognized as essential components. Each abstract was independently examined and categorized by two reviewers (AE and GR). To reach consensus on eligibility, the same two reviewers (AE and GR) assessed the full texts of selected studies and independently extracted relevant information on study characteristics and key findings. Disagreements were resolved through discussion between AE and GR; if consensus could not be reached, a third reviewer (AV) adjudicated. ADA was consulted when additional methodological input was required. When study protocols indicated additional outcome data collection, unpublished data were obtained by directly contacting the original study authors.

2.5 | Assessment of risk of bias

Each observational study's risk of bias was assessed based on the Newcastle–Ottawa scale criteria.[23] These criteria state that the selection and comparability of study groups, along with the determination of the intended outcome, form the basis for the evaluation of the research. A study is categorized based on a set of criteria that includes evaluating the representativeness of the exposed group, choosing the non-exposed cohort, identifying exposure, and presenting proof that the desired outcome was unlikely to happen on its own at the beginning of the trial. Research comparability is evaluated in cases by looking at cohort equivalency ascertained by design or analysis. Further, the methods used to assess the length, quality, and outcome of interest of the follow-up are also applied to assess the effectiveness of the exposure. A study might receive up to one star on the Newcastle-Ottawa Scale for each numbered item in the selection and outcome categories. For comparison, a maximum of two stars might be used. According to the standards of the Newcastle–Ottawa scale, a maximum score of nine can be awarded. A detailed item-by-item assessment is reported in Table S2. Three authors (VA, AD, CW) separately scored the risk of bias assessment. Once the debate was concealed from CA, AB, and PELS, it was settled. Further, the Confidence in Network Meta-Analysis framework (CINeMA) criteria were used to assess the certainty of the evidence.[24] CINeMA evaluates confidence across six domains (within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence), which are combined to derive an overall certainty rating for each network estimate (high, moderate, low, or very low).

2.6 | Outcomes measures and data synthesis

The primary outcome of this systematic review and network meta-analysis was clinical pregnancy rate (CPR), where clinical pregnancy is defined as a pregnancy diagnosed by ultrasound visualization of one or more gestational sacs or definitive clinical signs of pregnancy. Since the conclusions on the efficacy of treatment based on CPR or LBR as endpoints are comparable,[25] this choice was considered appropriate. Secondary outcomes were:

- LBR, where the live birth was defined as the complete expulsion or extraction from a woman of a product of fertilization, after 22 completed weeks of gestational age
- Ongoing pregnancy rate (OPR), where the ongoing pregnancy was defined as a viable intrauterine pregnancy of at least 12 weeks duration confirmed on an ultrasound scan;
- Pregnancy loss rate (PLR), where the miscarriage was defined as the spontaneous loss of an intra-uterine pregnancy prior to 22 completed weeks of gestational age.
- Biochemical pregnancy rate (BPR), where the biochemical pregnancy was defined as a pregnancy diagnosed only by the detection of beta hCG in serum or urine.

With the exception of OPR, which was defined according to the definition provided by Braakhekke et al.,[26] all the other outcomes were considered according to the definition provided by the International Glossary on Infertility and Fertility Care.[27]

For all data analysis and graphical displays, STATA version 14.1 (StataCorp, College Station, TX) was utilized. For every significant result, the network assumption of general consistency was statistically confirmed using the command <network meta consistency>.

The local test on loop inconsistencies was then carried out using the command <network sidesplit all> and the splitting technique known as Separating Indirect from Direct Evidence (SIDE). When no variation was found in the outcomes of the local or global testing, the consistency assumption was adopted. The consistency model in this case demonstrated that the impact of the intervention and chance mistakes were the only reasons for any changes in the outcomes and that both direct and indirect comparisons within the study would undoubtedly yield meaningful results.

The summary measurements were represented as odds ratios (OR) for categorical variables with 95% confidence intervals (CI) using the Der Simonian and Laird random effects model. A Higgins I^2 score greater than 0 suggested the possibility of heterogeneity. Sensitivity analyses were performed to find relevant sources of heterogeneity in scenarios with significant heterogeneity. We examined the symmetry of the funnel plot to search for signs of publishing bias. However, the Egger test was also used to assess publication bias because different observers could have deduced different conclusions from the same funnel plot. An error alfa (or p value) of 0.05 was considered statistically significant.

To compare the efficacy of individualized and rescue LPS strategies, we produced forest plots and prediction interval plots for each outcome and generated ranking plots based on the Surface Under the Cumulative Ranking curve (SUCRA). SUCRA summarizes the ranking probabilities of each intervention on a 0–100% scale (higher values indicate a higher probability of being among the best options). Local inconsistency was assessed using the separating indirect from direct evidence (SIDE) approach by contrasting direct and indirect estimates.

3 | RESULTS

3.1 | Study selection

A total of 130 studies were initially identified using database searches. Of those, 18 were removed as duplicates. After title and abstract screening, 97 papers were subsequently removed (Figure 1). Fifteen studies underwent full text assessment, of which two were excluded for absence of a control (no rescue LPS) group[28] and one for considering NC-FET cycles[16] (Figure 1). Twelve studies[8,14,15,29–37] were included in the systematic review and network meta-analysis (Figure 1). The following additional supplementations as well as no supplementation for LPS were directly and indirectly compared: intramuscular (IM) P 100 mg,[35] IM P 40 mg,[29] vaginal P 600 mg,[8] vaginal P 100 mg,[37] oral P 30 mg,[31,32,36] subcutaneous (SC) P 25 mg,[14,15,30,31,33] and rectal P 800 mg.[34]

3.2 | Study characteristics

The main characteristics of the included studies are summarized in the Table 1. Among the 12 included studies, five were prospective cohort studies[14,30,33–35] and seven were retrospective cohort studies.[8,15,29,31,32,36,37]

Of these, three studies were from France,[8,31,32] two from Spain,[14,15] two from Belgium,[36,37] two from Turkey,[30,33] one from Denmark,[34] one from Egypt[35] and one from China.[29] A total of 7595 patients were included; of these, 3123 received LPS rescue protocols, in particular: 1295 received IM P 100 mg,[35] 177 received IM P 40 mg,[29] 85 received vaginal P 600 mg,[8] 210 received vaginal P 100 mg,[37] 347 received oral P 30 mg,[31,32,36] 895 received SC P 25 mg,[14,15,30,31,33] and 114 rectal P 800 mg.[34] The other 4472 patients formed the control groups. Rescue protocols were offered to patients for the following serum P levels: <8.75 ng/mL,[30] <8.8 ng/mL,[36] <9.2 ng/mL,[15,35] <10.0 ng/mL,[8,29,33,37] <10.6 ng/mL,[14] and <11.0 ng/mL.[31,32,34]

3.3 | Risk of bias for included studies

The 12 observational studies[8,14,15,29–37] all revealed high scores, ranging from a minimum of seven to a maximum of nine, using the Newcastle–Ottawa scale criteria. The maximum score was achieved for comparability of cohorts based on controls for age, duration of infertility, and serum P levels as the joint most relevant criteria, as well as on controls for estradiol levels and infertility factor as supplementary factors. A comprehensive, point-by-point evaluation is included in Table S2. There were no RCTs eligible for this network meta-analysis (Table 2).

According to funnel plot analysis (Figure S1) and Egger's test ($P=0.115$), no publication bias was retrieved for the primary outcome.

According to CiNeMA criteria, certainty of evidence among the study outcomes varied, ranging from low to very low evidence due to study designs, imprecision, and incoherence of network analysis (Appendix S1).

3.4 | Synthesis of results

The CPR was evaluated in all 12 included studies.[8,14,15,29–37] IM P 100 mg, IM P 40 mg, oral P 30 mg, rectal P 800 mg, SC P 25 mg, vaginal P 10 0 mg and vaginal P 600 mg were directly and indirectly compared. The most accurate direct comparisons and the frequency of examined therapies are displayed in Figure 2a. According to the inconsistency analysis, there was no global inconsistency ($P=0.157$). According to Table S3, the SIDE analysis revealed no distinctions between the direct and indirect estimates, or between the consistency and inconsistency models, in the closed loops that were taken into consideration for the network (local inconsistency). The impact of different approaches on the rise in CPR is demonstrated by the forest plot and interval plot, respectively, in Figure 2b,c. There were no clear differences between the comparison between the treatments and controls as well as among the treatments, based on an examination of the two plots (low certainty of evidence). According to the

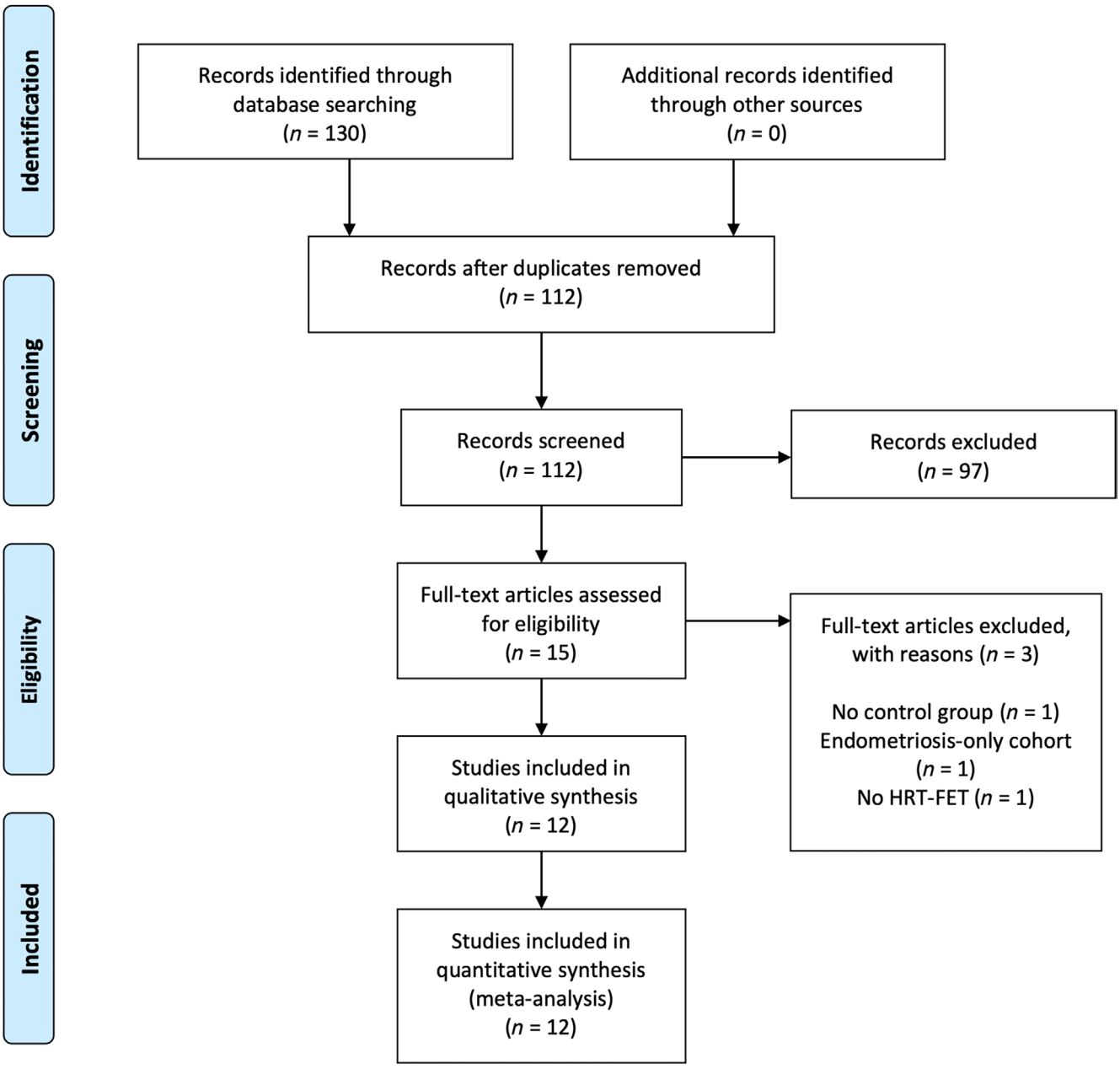

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart of included studies in systematic review and network meta-analysis.

SUCRA ranking (Figure 2d), the different protocols of LPS rescue augmentation had similar chances of being ranked first, with 600 mg of vaginal P (27.3%), 100 mg of vaginal P (22.1%), SC P (18.4%), and IM P 40 mg (17.3%) being the highest. The LBR was evaluated in six out of 12 studies,[8,14,15,29,32,36] including data for direct and indirect comparisons of IM P 40 mg, oral P 30 mg, SC P 25 mg, vaginal P 600 mg and no supplementation (Figure 3a).

The test for inconsistency revealed no sources of inconsistency ($P = 1.000$). Therefore, the SIDE analysis was not performable (Table S3). The network forest plot and prediction interval plot analyses revealed no appreciable variations between the four evaluated approaches and their comparison with no supplementation at all (Figure 3b,c) (very low certainty of evidence).

Accordingly, the SUCRA analysis showed that additional IM P 40 mg (44.3%) and vagina P 600 mg (42.7%) had increased chances of being ranked treatment of choice for being efficacious in raising the LBR (Figure 3d). Eleven studies[8,14,15,30–37] calculated the OPR following LPS in treatment and control groups. The rescue LPS approaches IM P 100 mg, oral P 30 mg, rectal P 800 mg, SC P 25 mg, vaginal P 100 mg, and vaginal P 600 mg were directly and indirectly compared (Figure 4a). The entire analysis found non-significant inconsistencies ($P = 0.055$), while the analysis on the closed loops for this outcome did not show any local inconsistency (Table S3). According to network forest plot and prediction interval plot analysis, no LPS approach showed significant differences among the treatments as well as compared with controls with no rescue LPS

TABLE 1 Characteristics of the included studies.

Author	Year	Type	Standard LPS protocol	Treatment	P measurement day	P levels cutoff	Rescue treatment starting day	Single or Multiple ET	PGT	BMI, kg/m^2, mean ± SD	Trial registration
Cédrin-Durnerin et al.	2019	Retrospective cohort study	Vaginal micronized P 200 mg three times a day	Group 1: Rescue with vaginal P 600 mg Group 2: Control group (vaginal P 600 mg)	ET day—afternoon	10 ng/ml	ET day—afternoon (Day 4 of vaginal P administration)	Both	NA	Group 1: 25 ± 4.5 Group 2: 24 ± 4	None
Alvarez et al.	2021	Prospective observational study	Vaginal micronized P 200 mg three times a day	Group 1: Rescue with SC P 25 mg Group 2: Control group (vaginal P 600 mg)	One day before ET (Day 4 of vaginal P administration)	10.6 ng/ml	Day 4 of vaginal P administration	Single	Yes (all)	NA	NCT03740568
Gao et al.	2021	Retrospective cohort study	Vaginal micronized P capsules 200 mg and oral dydrogesterone 20 mg twice a day	Group 1: Rescue with IM P 40 mg Group 2: Control group (oral P 40 mg + vaginal P 400 mg)	ET day	10 ng/ml	ET day	Both	NA	Group 1: 22.1 ± 3.2 Group 2: 21.8 ± 3.1	None
Labarta et al.	2022	Retrospective cohort study	Vaginal micronized P 400 mg twice a day	Group 1: Rescue with SC P 25 mg Group 2: Control group (vaginal P 800 mg)	ET day (afternoon)	9.2 ng/ml	ET day (between the two vaginal doses)	Both	Yes (Standard 19.9% vs. Rescue 21.5%)	Group 1: 24.1 ± 4.5 Group 2: 23.0 ± 3.9 *	IVI-PRO-2018-01
Du Boulet et al.	2022	Retrospective cohort study	Vaginal micronized Progesterone 400 mg twice a day	Group 1: Rescue with oral P 30 mg Group 2: Rescue with SC P 25 mg Group 3: Control group (vaginal P 800 mg)	Day 3 of vaginal P administration (ET on day 4 or 5)	11 ng/mL	Day 3 of vaginal P administration	Both	Yes (all)	Group 1: 23.1 ± 2.8 Group 2: 23.5 ± 4.2 Group 3: 22.3 ± 3.1	None
Lecourt et al.	2022	Retrospective cohort study	Vaginal micronized P 400 mg twice a day	Group 1: Rescue with Oral P 30 mg Group 2: Control group (vaginal P 800 mg)	Day 1 of vaginal P administration (ET on day 2. 3 or 5)	11 ng/ml	Day 1 of vaginal P administration	Both	NA	Group 1: 24.8 ± 4.8 Group 2: 25.1 ± 4.3	None

TABLE 1 (Continued)

Author	Year	Type	Standard LPS protocol	Treatment	P measurement day	P levels cutoff	Rescue treatment starting day	Single or Multiple ET	PGT	BMI, kg/m^2, mean ± SD	Trial registration
Ozcan et al.	2022	Multicentre prospective cohort study	100 mg vaginal micronized P two times per day with 250 mg IM hydroxyprogesterone caproate depot twice a week	Group 1 Rescue with SC P 25 mg Group 2: Control group (vaginal P 200 mg + IM P 250 mg Depot)	ET day (Day 3 or 5 of vaginal P administration)	10 ng/ml	ET day (Day 3 or 5 of vaginal P administration)	Both	NA	Group 1: 23.4 ± 3.1 Group 2: 23.2 ± 3.5	NCT04769401
Alsbjerg et al.	2023	Prospective interventional study	Vaginal micronized P 400 mg twice a day	Group 1: Rectal P 800 mg Group 2: Control group (vaginal P 800 mg)	ET day—morning (Day 6 of vaginal P administration)	11 ng/ml	ET day—evening (Day 6 of vaginal P administration)	Both	NA	Group 1: 26.0 ± 3.4 Group 2: 24.8 ± 3.5	2019–001539-29
Mackens et al.	2023	Single center retrospective cohort study	Vaginal micronized P 400 mg twice a day	Group 1: Rescue with Oral P 30 mg Group 2: Control group (vaginal P 800 mg)	ET day (Day 6 of vaginal P administration)	8.8 ng/ml	ET day (Day 6 of vaginal P administration)	Single	Yes (all)	Group 1: 24.9 ± 4.7 Group 2: 24.2 ± 4.4	None
Bakry et al.	2023	Prospective cohort study	Vaginal micronized P 400 mg twice a day	Group 1: Rescue with IM P 100 mg Group 2: Control group (vaginal P 400 mg)	ET day—morning (Day 5 of vaginal P administration)	9.2 ng/ml	ET day (Day 5 of vaginal P administration)	Multiple	NA	Group 1: 27.9 ± 4.8 Group 2: 28.0 ± 5.2	NCT04837768
Yarali et al.	2021	Retrospective cohort study	Vaginal P gel 90 mg twice a day or SC P 25 mg twice a day	Group 1: Rescue with SC P 25 mg Group 2: Control group (vaginal gel P 8%)	One day before ET (Day 5 of P administration—morning)	8.75 ng/ml	Day 5 of P administration (afternoon)	Both	NA	Group 1: 25.2 ± 3.8 Group 2: 24.6 ± 3.7 *	None
Lawrenz et al.	2024	Retrospective cohort study	Vaginal micronized P 100 mg three times a day with oral dydrogesterone 30 mg twice a day	Group 1: Rescue with vaginal P 100 mg Group 2: Control group (oral P 30 mg + vaginal P 300 mg)	ET day (Day 3 to 6 of vaginal P administration)	10 ng/ml	ET day (Day 3 to 6 of vaginal P administration)	Single	Yes (all)	Group 1: 27.9(24.5 to 32) Group 2: **26.9** (24.4 to 31.1) *	None

Abbreviations: BMI, body-mass index; ET, embryo transfer; IM, intramuscular; IVM, in vitro maturation; LPS, luteal phase support; P, progesterone; PGT, pre-implantation genetic test; SC, subcutaneous; SD, standard deviation.

*p-value <0.05.

TABLE 2 Inclusion, exclusion criteria and main outcomes of the included studies.

Author	Inclusion criteria	Exclusion criteria	Main outcomes
Cédrin-Durnerin et al.	• Patients undergoing FET with HRT	• Oocyte donation cycles • Cycles with missing information on serum hormones	Live birth rate, biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate at 12 weeks, first trimester pregnancy loss rate
Alvarez et al.	• Patients undergoing FET of an euploid blastocyst	• Patients who underwent FET of a mosaic blastocyst • Patients who did not follow standard LPS	Ongoing pregnancy rate, pregnancy rate, clinical pregnancy rate, miscarriage rate, biochemical pregnancy rate, live birth rate, percentage of rescued cycles, percentage of canceled cycles
Gao et al.	• Women undergoing the first HRT FET cycle	• Older than 42 years of age • History of RPL or RIF • Systemic diseases • Uterine diseases (e.g., fibroids and congenital uterine malformation) or hydrosalpinx • Cycles with missing information on serum hormones	Live birth rate; Secondary outcomes: implantation, biochemical pregnancy, clinical pregnancy, miscarriage and perinatal outcomes
Labarta et al.	• Women aged <50 years • Adequate endometrial pattern (triple layer) and thickness (≥6.5 mm) • LPS with only micronized P administered vaginally • ET ≤2 blastocysts	• Patients with personalized initiation of exogenous P according to the endometrial receptivity assay test • Uterine diseases or hydrosalpinx	Live birth rate, biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, biochemical miscarriage rate, clinical miscarriage rate, ectopic pregnancy rate
Du Boulet et al.	• HRT FET cycles • Age ≥18 ≤43-year-old • Preimplantation genetic testing • Progesterone concentration monitored after starting Vaginal P	• History of RPL (≥3) • Uterine malformations • Hydrosalpinx • Cycles in which the standard LPS protocol was not strictly followed	Ongoing pregnancy rate, serum P concentration on embryo transfer day and pregnancy test day, positive pregnancy test rate, implantation rate, biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate
Lecourt et al.	• Patients undergoing HRT FET with Vaginal P only	• Embryos obtained from oocyte donation or IVM oocytes	Live birth rate, biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, mean delivery term, mean birth weight
Ozcan et al.	• Patients undergoing HRT FET • Age ≥18 ≤42-year-old • BMI ≤25 kg/m^2	• Patients with cycle cancellation due to lack of a viable embryo • Patients who refused to participate • Patients with intrauterine anomalies not corrected by surgery	Ongoing pregnancy rate, clinical pregnancy rate, miscarriage rate
Alsbjerg et al.	• Age ≥18 ≤45-year-old • At least one autologous vitrified blastocyst for transfer • BMI >18.5 <34 kg/m^2	• Endometrial thickness <7 mm after 12–20 days of 6 mg oestradiol treatment • No blastocyst for transfer after thawing • Uterine abnormalities • Oocyte donation • Dysregulated severe chronic medical diseases	Ongoing pregnancy rate
Mackens et al.	• Patients performing a single blastocyst FET in a HRT cycle	• History of RPL • Uterine anatomical distorsion (polyp, fibroid or Mullerian anomaly) • Oocyte donation • FET following IVM oocytes • FET following PGT • incomplete data in the electronic records	Live birth rate, early pregnancy loss rate

TABLE 2 (Continued)

Author	Inclusion criteria	Exclusion criteria	Main outcomes
Bakry et al.	• Infertile women aged 20–40 years • BMI of less than 40 kg/m^2 • Endometrial thickness of more than 7 mm • Double ET (day 5) of grade 1 or 2	• Women with autoimmune diseases, uncontrolled medical conditions, recurrent implantation failure, or anatomical uterine abnormalities (polyps, fibroids, or Müllerian anomalies)	Ongoing pregnancy rate, clinical pregnancy rate, miscarriage rate
Yarali et al.	• Patients with one or more vitrified day 5 or 6 blastocysts for transfer after rewarming	• Preimplantation genetic testing for aneuploidy, monogenic disorders or structural rearrangements • BMI >35 kg/m^2 • More than 4 previous failed IVF attempts	Ongoing pregnancy rate, clinical pregnancy rate, miscarriage rate
Lawrenz et al.	• Patients undergoing single euploid HRT FET cycles • Serum P4 level on the day of the ET and cycle outcome known	• FET following PGT • Previous downregulation	Ongoing pregnancy rate, no-ongoing pregnancy (not pregnant, biochemical pregnancy, early miscarriage)

Abbreviations: BMI, body-mass index; ET, embryo transfer; FET, frozen embryo transfer; HRT, hormone replacement therapy; IVM, in vitro maturation; LPS, luteal phase support; P, progesterone; PGT, pre-implantation genetic test; RIF, repeated implantation failure; RPL, recurrent pregnancy loss.

(Figure 4b,c) (low certainty of evidence). Among all, the SUCRA ranking showed that vaginal P 600 mg (48.5%) and IM P 100 mg (33.3%) had more chances of being the best treatment of choice for increasing the OPR (Figure 4d). The PLR was evaluated in 10 out of 12 studies.[14,15,29–31,33–37] IM P 100 mg, IM P 40 mg, oral P 30 mg, rectal P 800 mg, SC P 25 mg, and vaginal P 100 mg alongside no rescue were directly and indirectly compared (Figure S2).

Inconsistency was not found throughout the investigation ($P=0.069$). There were no local inconsistencies in the closed loops examined for this result (Table S3). There were no discernible differences between the treatments according to the evaluation of the network forest plot and interval plot (Figure S2) (low to very low certainty of evidence). According to SUCRA analysis, the rescue LPS with higher chances of being ranked first were IM P 100 mg (40.6%) and rectal P 800 mg (37.7%) (Figure S2). Ten of 12 investigations investigated the BPR.[8,14,15,29–32,34–36] IM P 100 mg, IM P 40 mg, oral P 30 mg, rectal P 800 mg, SC P 25 mg, vaginal P 100 mg, and the controls in the available research were evaluated (Figure S3). Throughout the consistency analysis, no inconsistencies were found ($P=0.176$). The closed loops tested for this finding showed no local discrepancies (Table S3). The network forest plot and prediction interval plot analyses showed that a no rescue protocol approach was less efficacious than IM P 40 mg (OR 0.80 [95% CI 0.68 to 0.93]; low certainty of evidence). Moreover, IM P 40 mg was more efficacious than oral P 30 mg (OR 1.60 [95% CI 1.17 to 2.19]; low certainty of evidence) and rectal P 800 mg (OR 1.65 [95% CI 1.02 to 2.66]; low certainty of evidence) in increasing the BPR. No other significant differences between the reported LPS approaches and with the comparison with a no rescue approach (Figure S3) were reported (low certainty of evidence). According to the SUCRA ranking analysis, the use of a supplementation of LPS with IM P 100 mg (47.7%) or 40 mg (43.7%) had the highest chance of being the treatment of choice (Figure S3).

4 | CONCLUSION

4.1 | Comparisons with existing literature

Our results suggest that several strategies aimed at increasing serum P levels with a rescue dose during LPS might be effective in restoring the reproductive outcomes of patients with reduced serum P around the day of FET in artificial cycles and equalizing them to those of patients with normal serum P levels. However, our analysis did not establish the absolute superiority of one protocol over all others. Nevertheless, the addition of vaginal P or IM P to the standard LPS used in the included studies seems to ensure better results. LPS is, nowadays, one of the most discussed topics of reproductive medicine and could truly be the core for consolidating the success of ART.[38] In the present systematic review and network meta-analysis, we aimed to investigate whether rescue LPS with additional P supplementation in women presenting with low serum P levels around the FET day in artificial cycles could achieve comparable outcomes to those with adequate serum P levels who receive the standard LPS.

Several LPS protocols among the studies available in the literature to date have been described as able to compare the detection of serum P to reproductive outcomes such as CPR, LBR, and PLR; however, there is currently a lack of established guidelines on P doses, duration, and different routes of administration.[39] In 2010, a Cochrane reviewed four randomized controlled trials comparing the vaginal and IM routes of administration and found no statistically significant differences in CPR, LBR, and PLR.[40] However, other

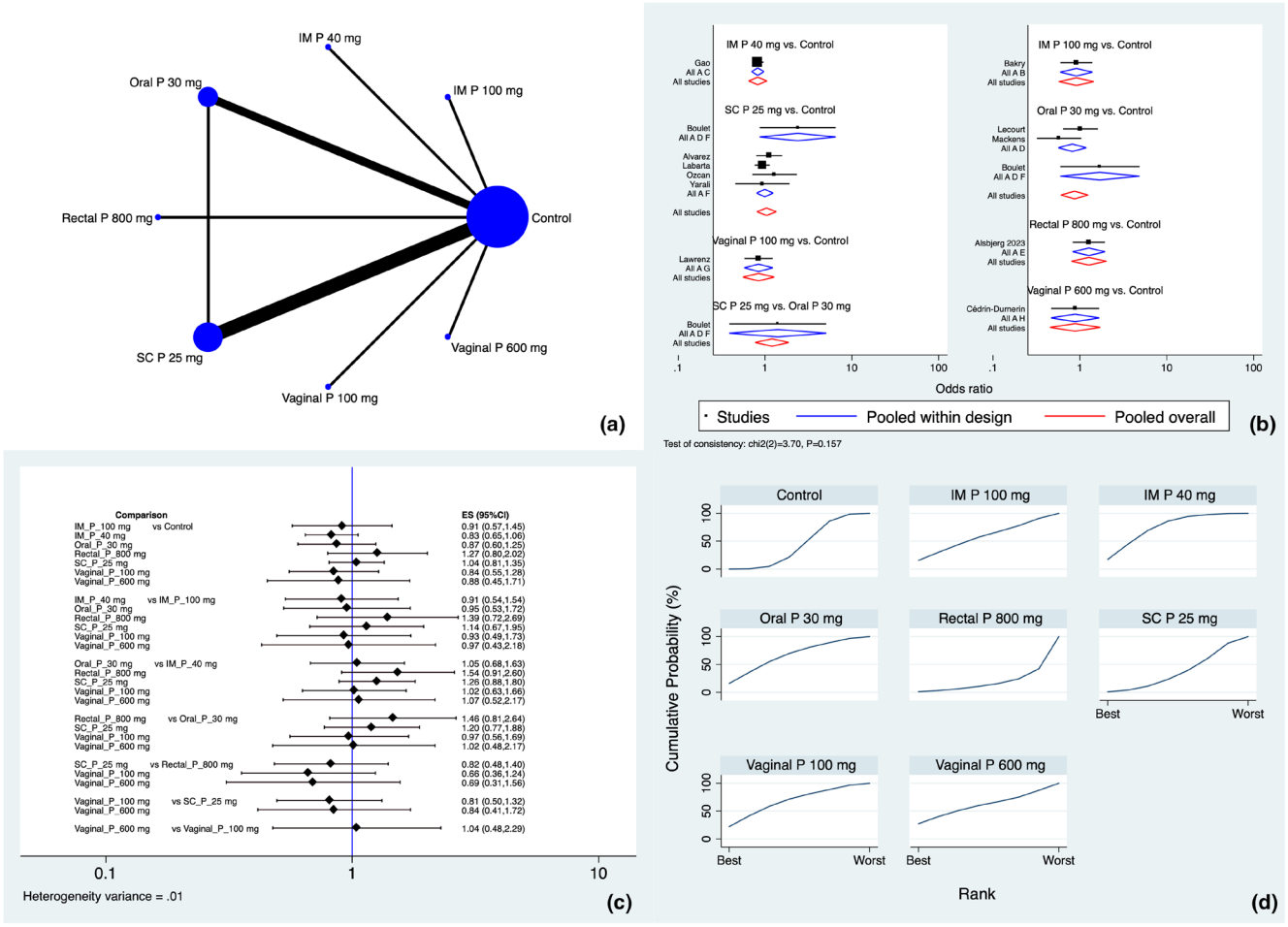

FIGURE 2 Clinical pregnancy rate: (a) network of comparisons of interventions analyzed in included studies, (b) forest plot for the outcome, (c) interval plot, and (d) ranking plot according to Surface Under the Cumulative Ranking curve (SUCRA) analysis.

routes of administration are available today. Despite this, there is still no unanimous consensus on the best LPS for patients undergoing HRT-FET cycles.[41] Although most of the authors of the studies included in this analysis used a vaginal LPS with 800 mg/day of P for their control groups,[15,31,32,34,36] others used the same route of administration at different dosages (vaginal P 600 mg or 400 mg),[8,14,35] or associations of different routes of P administration, such as vaginal P 400 mg + oral P 40 mg,[29] vaginal P 300 mg + oral P 30 mg,[37] and vaginal P 200 mg + IM P 250 mg depot.[33] All these made the control group heterogeneous.

At present, a substantial problem that does not seem surmountable is the definition of normal serum P levels. Serum P might not reliably reflect endometrial P exposure, particularly with vaginal administration, where tissue concentrations can be high despite comparatively lower serum levels. Therefore, "correcting" a low serum value might not equate to a meaningful improvement in endometrial receptivity in all patients and might lead to overtreatment in those who are already adequately supported at tissue level. These pharmacokinetic considerations should temper interpretation of serum-based "rescue" strategies and support the need for standardized, route-specific thresholds. From a patient-centered perspective, rescue supplementation—especially intramuscular regimens—might increase discomfort, cost, and treatment burden. In the absence of consistent high-certainty evidence of benefit, routine escalation based solely on a single serum measurement might represent unnecessary medicalization for a proportion of women. Another concern is reverse causation: low serum P might be a marker of cycle characteristics (e.g., absorption variability, adherence, or endometrial factors) that are not fully modifiable by late supplementation. Moreover, adequate P exposure is required early in the implantation window; thus, rescue initiated only after detecting low serum P might be suboptimal in some cases. Observed benefits in non-randomized studies could, therefore, reflect residual confounding rather than true causal efficacy. Therefore, there is a need to establish how the optimal level of serum P might change in relation to diseases such as endometriosis.[42] Although some authors have proposed 8.75 ng/mL as the serum P threshold below which a rescue dose of P should be administered,[43] only one of the included studies applied this cutoff.[30] Some other authors reported that in cycles with serum $P < 10$ ng/mL, LBR was significantly reduced[8]; while another large retrospective trial showed a slightly lower LBR for a group who received a rescue LPS with IM P 40 mg compared with the routine administration of their LPS protocol (oral P 40 mg + vaginal P 400 mg), considering the same cutoff of serum concentration.[29] A similar threshold for serum P level

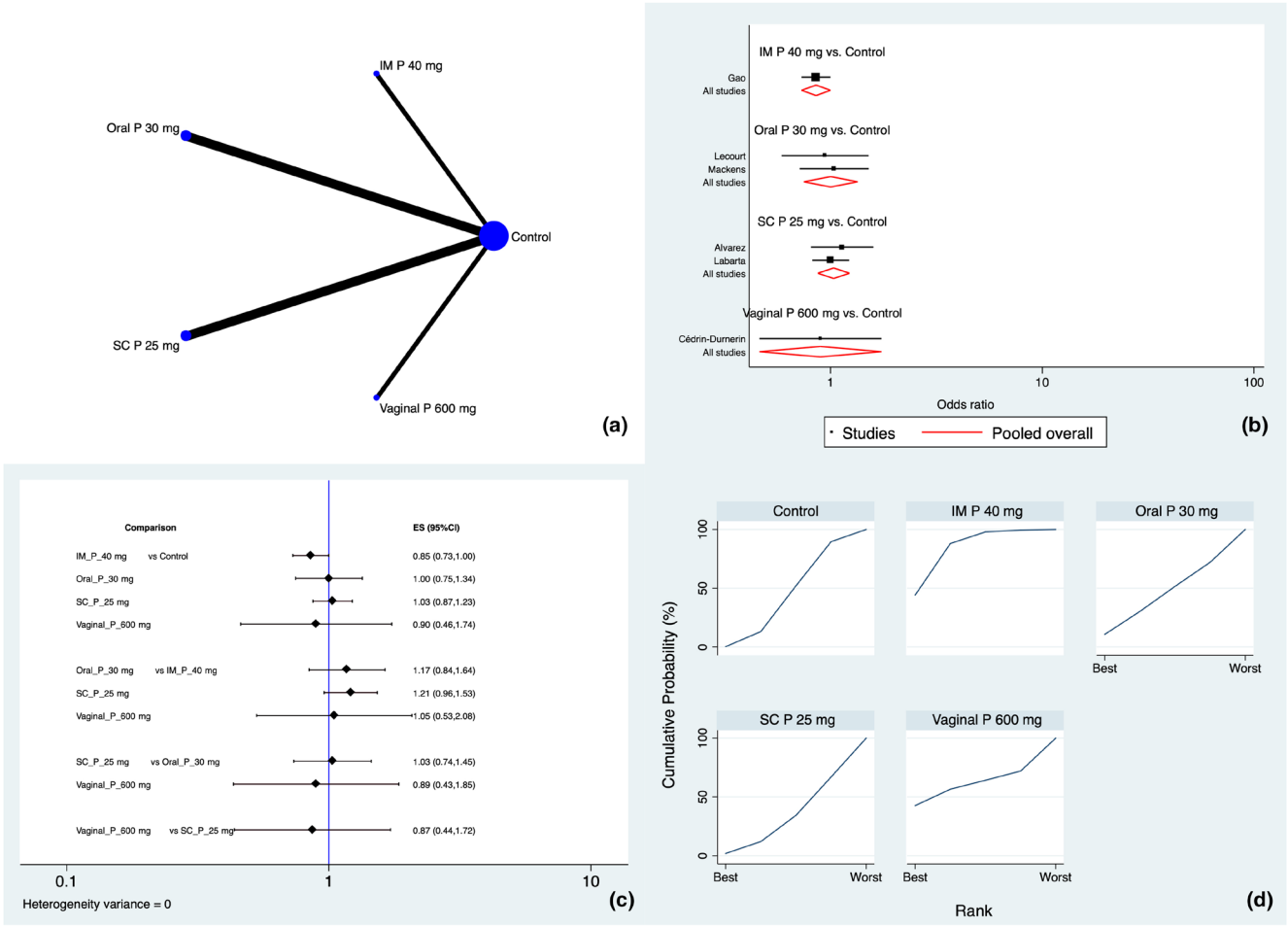

FIGURE 3 Ongoing pregnancy rate. (a) Network of comparisons of interventions analyzed in included studies. (b) Forest plot for the outcome. (c) interval plot. (d) Ranking plot according to Surface Under the Cumulative Ranking curve (SUCRA) analysis.

(10.6 ng/mL) on the day of the ET was adopted by Álvarez et al. to decide whether the supplemental administration of SC P 25 mg was needed. They did not find statistically significant differences regarding the mentioned outcomes between the group with adequate serum P level and the group with low P level who received the rescue dose.[14] Although the rescue IM P formulations considered in this study were not depot formulations,[29,37] one of the authors included in the present systematic review and network meta-analysis used hydroxyprogesterone caproate depot in their protocol of standard LPS (vaginal P 200 mg + IM P 250 mg depot) administered to their patients.[33] It is worth noting that there a review on hydroxyprogesterone caproate medicines was initiated by the European Medicines Agency (EMA) in May 2023, which ended in June 2024 following concerns about the safety and efficacy of these medicines. The EMA considered that the benefits of as hydroxyprogesterone caproate do not outweigh its risks in any authorized use.[44]

Summarizing our findings, we can assess that CPR, OPR, LBR, and PLR between the two groups were comparable, proposing that if a rescue dose is administered in the low serum P group, similar outcomes with those patients having adequate circulating P levels might be achieved. Regarding the routes of P administration, although the addition of vaginal P and IM P seems to be preferred to maximize the chance of success in most of the outcomes, we are not able to highlight a specific dosage (vaginal P 100 mg vs. vaginal P 600 mg and IM P 40 mg vs. IM P 100 mg) due to the significant differences between the analyzed studies in terms of protocols and wide range of the threshold P serum value chosen by the different authors.[8,29,35,37] This field of research, however, remains hampered by the absence of randomized controlled trials, and the reason might also be rooted in ethical issues. Administration of a rescue dose of P is, indeed, considered useful in clinical practice. This belief raises concerns whether would be ethically right to enroll a subgroup of patients with low serum P level as a "no-treat" control for a randomized controlled trials.

4.2 | Strenghts and limitations

Some limitations could be ascertained in this network meta-analysis. First, studies few studies met the inclusion criteria. A key limitation is the substantial clinical and methodological heterogeneity across included studies. "Low progesterone" was defined using different cutoffs (≈8.75–11.0 ng/mL), and measurement timing was not standardized (including variability in relation to timing of exogenous P administration

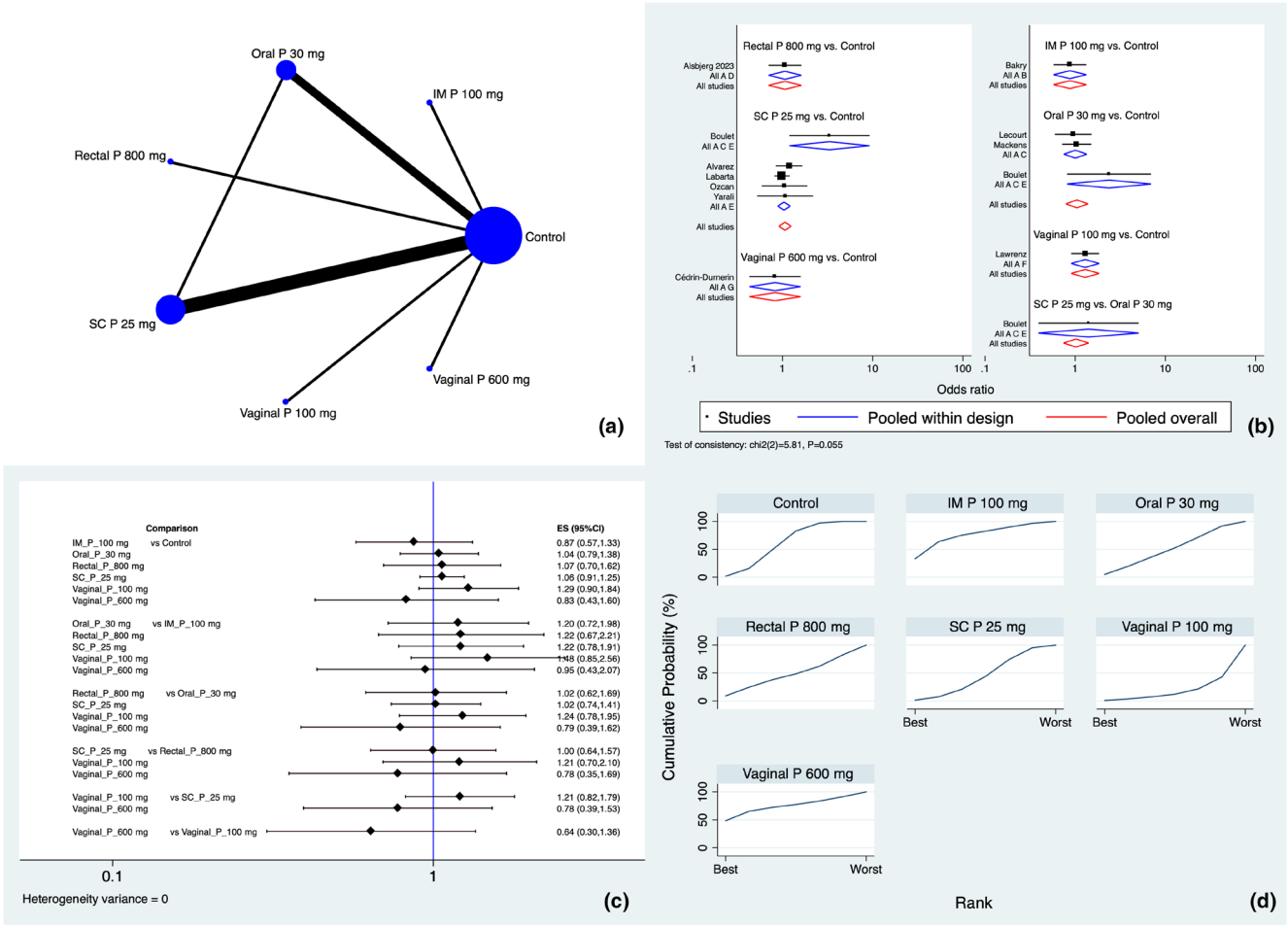

FIGURE 4 Live birth rate. (a) Network of comparisons of interventions analyzed in included studies. (b) Forest plot for the outcome. (c) interval plot. (d) Ranking plot according to SUCRA analysis.

and time-of-day sampling). In addition, rescue strategies differed markedly by route, formulation, and dose, and P assays were not uniform across studies. Collectively, these factors reduce comparability, widen prediction intervals, and limit the transferability of pooled estimates to routine practice. Although most cutoffs clustered within a relatively narrow range, residual misclassification remains possible given differences in assays and sampling timing. For these reasons, it was not possible to conduct meaningful subgroup analyses. Although funnel plot symmetry and Egger's test did not suggest major publication bias for the primary outcome, these approaches have limited power with a small number of studies. Further, network meta-analysis relies partly on indirect comparisons; when heterogeneity is high, treatment ranking metrics (e.g., SUCRA) might convey an unwarranted sense of precision. Accordingly, rankings should be interpreted as hypothesis-generating rather than definitive.

A further limitation of the study is the absence of disaggregated data on reproductive outcomes in relation to embryo stage (cleavage vs. blastocyst)[8,16,29,31–33] and embryo quality.[14,15,30,34] In addition, serum P levels at the time of blastocyst or G2/G3 embryo transfer could be profoundly different because the time the patient was exposed to exogenous P is also different (2 or 3 days vs. 5 days). Therefore, it is necessary to determine whether it is worthwhile to perform progesteronemia assay even if blastocysts are not obtained and cleavage embryo transfer is opted for. For all the evaluated outcomes, all the studies came from single centers. Compared to multiple center studies, there is a higher risk of bias in selection, performance, detection, and reporting, even with the inclusion of independent individuals. Although variability was exacerbated by the unpredictable changes in research lengths, the extended duration should, in theory, increase the sensitivity of pregnancy rate detection, perhaps leading to higher accuracy.

One of the study's several advantages is its capacity to extrapolate its conclusions to a wide range of geographical areas. Further, this quantitative synthesis represents the first study to use data from various groups of women who had FET and various rescue LPS procedures in a network meta-analysis. Moreover, even with a moderate number of studies, the total number of participants should be deemed sufficient to ensure the validity of the results. Additionally, the given findings are rescued by the application of the CiNeMA approach for assessing evidence and certainty. Finally, as all the data used are from separate cohorts from several locations, there is no overlap in the data from studies.

4.3 | Implications

Our analysis suggests that a rescue strategy could be a useful approach to optimize the reproductive outcomes in women with low serum P levels around the day of the FET in HRT cycles and to equal them to patients with normal progesteronemia. Overall, no LPS rescue strategy performed significantly better than others, despite vaginal P and IM P approaches appearing the most promising as being ranked first for the majority of the outcomes. Unfortunately, the retrospective design of included studies as well as the heterogeneity among them significantly hamper the reliability of these findings and prevent the formulation of recommendations for clinical practice.

Our findings lay the rational foundation for future research. Well-conducted randomized trials are urgently needed to definitively clarify the efficacy of such a promising and potentially simple-to-implement intervention.

AUTHOR CONTRIBUTIONS

AE, VA, MDD, and GR were responsible for the acquisition, analysis, and interpretation of the data. AE, AD, and VA were responsible for drafting the work. AC, CA, and AV were responsible for revising the work critically for important intellectual content. AL, AB, PLS, and CW gave final approval of the version to be published. AE and AD agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors met the International Committee of Medical Journal Editors criteria for authorship and have read and agreed to the current version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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