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SYSTEMATIC REVIEW

Optimizing intrauterine insemination: A systematic review and meta-analysis of the effectiveness and safety of clinical treatment add-ons

Elpiniki Chronopoulou[1] | Andrea Gaetano-Gil[2] | Sadaf Shaikh[3] | Claudia Raperport[4,5] | Bassel H. Al Wattar[6,7] | Gabriel Ruiz-Calvo[2] | Javier Zamora[2,5,8,9] | Priya Bhide[5]

[1]The Centre for Reproductive and Genetic Health (CRGH), London, UK

[2]Clinical Biostatistics Unit, Hospital Universitario Ramon y Cajal (IRYCIS), Madrid, Spain

[3]CREATE Fertility, London, UK

[4]London North West University Healthcare NHS Trust, London, UK

[5]Women's Health Research Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, UK

[6]Institute for Women's Health, University College London, London, UK

[7]Women's Health Department, University College London Hospital, London, UK

[8]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiology and Public Health CIBERESP), Clinical Biostatistics, Madrid, Spain

[9]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

Correspondence
Priya Bhide, Women's Health Research Unit, Wolfson Institute of Population Health, Queen Mary University of London, Yvonne Carter Building, Ground Floor, 58 Turner Street, E1 2ABLondon UK.
Email: priya.bhide@nhs.net

Abstract

Introduction: Intrauterine insemination (IUI) is one of the most widespread fertility treatments. However, IUI protocols vary significantly amongst fertility clinics. Various add-on interventions have been proposed to boost success rates. These are mostly chosen arbitrarily or empirically. The aim of this systematic review and meta-analysis is to assess the effectiveness and safety of add-on interventions to the standard IUI protocol and to provide evidence-based recommendations on techniques used to optimize the clinical outcomes of IUI treatment.

Material and Methods: Systematic review and meta-analyses were performed in accordance with PRISMA guidelines. A computerized literature search was performed from database inception to May 2023. Randomized controlled trials (RCTs) were included reporting on couples/single women undergoing IUI with any protocol for any indication using partner's or donor sperm. A meta-analysis based on random effects was performed for each outcome and add-on. Three authors independently assessed the trials for quality and risk of bias and overall certainty of evidence. Uncertainties were resolved through consensus. Primary outcomes were ongoing pregnancy rate (OPR) or live birth rate (LBR) per cycle/per woman randomized. Registration number PROSPERO: CRD42022300857.

Results: Sixty-six RCTs were included in the analysis (16 305 participants across 20 countries). Vaginal progesterone as luteal phase support in stimulated cycles was found to significantly increase LBR/OPR (RR 1.37, 95% CI 1.09–1.72, $I^2 = 4.9\%$) (moderate/low certainty of the evidence). Endometrial scratch prior/during stimulated IUI cycles may increase LBR/OPR (RR 1.44, 95% CI 1.03–2.01, $I^2 = 1.8\%$), but evidence is very uncertain. Results from two studies suggest that follicular phase ovarian stimulation increases LBR/OPR (RR 1.39, 95% CI 1.00–1.94, $I^2 = 0\%$) (low certainty of

Abbreviations: CI, confidence interval; CPR, clinical pregnancy rate; IUI, intrauterine insemination; IVF, in vitro fertilization; LBR, live birth rate; MPR, multiple pregnancy rate; MR, miscarriage rate; OPR, ongoing pregnancy rate; RCT, randomized controlled trial.

evidence). No significant difference was seen for the primary outcome for the other studied interventions.

Conclusions: The findings of this systematic review and meta-analysis suggest that vaginal luteal phase progesterone support probably improves LBR/OPR in stimulated IUI treatments. In view of moderate/low certainty of the evidence more research is needed for solid conclusions. Further research is also recommended for the use of endometrial scratch and ovarian stimulation. Future studies should report on results according to subfertility background as it is possible that different add-ons could benefit specific patient groups.

KEYWORDS
add-ons, bed rest, insemination, IUI, progesterone, scratch

1 | INTRODUCTION

Intrauterine insemination (IUI) is one of the oldest and most widespread forms of fertility treatment worldwide.[1] Artificial insemination follows the simple principle of increasing the sperm number close to the site of fertilization bypassing any vaginal/cervical barriers.

IUI has evolved since its inception but not at the pace of IVF (in vitro fertilization), despite being a simple, safe and cost-effective treatment option for various indications. It is considered first-line treatment for people who are unable to have vaginal intercourse, for patients using partner or donor sperm; for single women and same-sex couples. Common indications include unexplained infertility, mild male factor, and anovulatory infertility in conjunction with ovulation induction. In clinical practice, it is also offered in low ovarian reserve, endometriosis, unilateral tubal blockage, longstanding subfertility.[2] The main safety concern is multiple pregnancy rate and the quoted success rates (which are dependent on cycle characteristics and patients' background) vary significantly and remain on average less than 15% with most pregnancies occurring in the first four cycles.[2,3] While there has been intense discussion in the literature around optimizing IVF, IUI add-ons (ovarian stimulation, use of trigger, bed rest, luteal phase support, etc.) have not received the same attention. Results are often derived from a heterogenous, unselected patient population, using a wide variety of protocols. As a result, it is challenging to find trials on IUI with sufficient homogeneity.[4] Most IUI add-ons and variations are chosen arbitrarily or empirically and there is little or no variation in clinical practice to adjust for the indication of IUI.

The aim of this systematic review and meta-analysis is to assess the effectiveness and safety of add-on interventions to the standard IUI protocol performed for any indication and to provide evidence-based recommendations on techniques used to optimize the clinical outcomes of IUI treatment.

Key message

There are multiple add-ons offered in intrauterine insemination cycles, but further research is needed to establish their effectiveness and safety. Among the proposed interventions, current evidence suggests that vaginal luteal phase support may improve success rates in stimulated intrauterine insemination treatment.

2 | MATERIAL AND METHODS

This review has been conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Appendix S1)[5] and has been registered in PROSPERO (International Prospective Register of Systematic Reviews) (CRD42022300857).

2.1 | Literature search

A computerized literature search was performed using EMBASE, MEDLINE, and CINAHL as well as the Cochrane Central register of trials from database inception to May 2023. References of relevant studies were cross-checked. Meeting proceedings of ESHRE and ASRM were also hand-searched. MeSH terms and text words were used as relevant to the research question (Appendix S2).

Two authors (EC, SS) independently performed the literature search and screened all relevant titles and abstracts. Papers eligible for inclusion were accessed as full texts and independently screened by the two authors. Disagreements between individual judgments were resolved with consensus or with the help of a third author (PB).

2.2 | Types of studies

Prospective randomized controlled trials (RCTs) were included (Appendix S3). Studies which randomized per woman and per cycle were included (Appendix S4 and S5); in case of the latter, outcomes for the first treatment cycle only included where possible. We

extracted data on the number of events and the number of women randomized for all trials, including those trials in which women have had more than one IUI cycles.

2.3 | Excluded studies

- Quasi-randomized and cross-over trials.
- Literature not available in English.
- Abstracts.
- Studies not relating to human subjects.
- Studies on intracervical or intrafallopian sperm perfusion.
- Studies which do not report on the outcomes of interest.
- Studies which do not give raw numbers in results.
- Studies assessing interventions aiming to improve the baseline condition and not the IUI protocol (such as supplements for male subfertility, GnRH analogues for endometriosis, metformin, myoinositol for polycystic ovary syndrome, treatments for thin endometrium, supplements for decreased ovarian reserve, etc.).
- Studies comparing dosages or brand names.
- Studies comparing ovarian stimulation protocols.
- Studies assessing protocol variations and not add-ons. We have defined protocol variations as alterations to the standard reference protocol. These include differences in sperm production (in clinic or at home, days of abstinence, single vs consecutive ejaculates), sperm preparation techniques (variations in sperm washing and storage medium, storage temperature/pH, sperm volume), IUI devices including laboratory and clinical disposables (semen containers, IUI catheters), time intervals for IUI (timing from LH kit detected ovulation or trigger to IUI), ultrasound follicular tracking methods and variations in IUI technique (full bladder vs. empty bladder, tenaculum vs. no tenaculum, bolus vs. slow insemination).

2.4 | Participants

Couples/single women undergoing one or more cycles of IUI with any treatment protocol for any indication using partner's or donor sperm.

2.5 | Controls

Patients undergoing standard IUI treatment or IUI using a different add-on.

2.6 | Intervention

As "standard IUI protocol" was defined a natural cycle IUI with single, blind insemination, LH kits to detect ovulation, immediate mobilization post-IUI and no other intervention or luteal phase support. Any additions to the standard protocol, as described above, was considered as an add-on. The value and safety of each add-on was assessed versus no add-on/control and comparisons amongst different add-ons were included. Some add-ons may relate to specific patient groups/protocols based on biological plausibility and where possible we have considered these factors.

Add-ons were assessed in three different stages.

Before IUI: endometrial scratch, hydrotubation, ovarian stimulation, use of ovulation trigger, type of trigger.
IUI: double insemination, ultrasound guidance, use of oxytocin, misoprostol and tocolytic agents.
After IUI: bed rest, luteal phase support.

2.7 | Outcome measures

The outcomes of interest were indicative of the effectiveness and the safety of every studied add-on.

2.8 | Primary outcomes

Ongoing pregnancy rate (OPR) or live birth rate (LBR) per cycle/per woman randomized. LBR was primarily used and in case this was not reported, and OPR was used.

2.9 | Secondary outcomes

Pregnancy (positive urine pregnancy test or positive blood beta hCG), clinical pregnancy (ultrasound confirmation of gestational sac and/or heart beat), ongoing pregnancy (viable pregnancy beyond 12 weeks of gestation), miscarriage, and multiple pregnancy.

2.10 | Data extraction and analysis

2.10.1 | Data extraction

Two authors (EC, SS) independently extracted data from the included trials. Data were entered on a bespoke data collection excel spreadsheet. Each trial included in this study was given a unique identification number. Discrepancies in data abstraction were resolved through discussion amongst the authors.

2.10.2 | Risk of bias and quality of evidence

Three authors (EC, SS, CR) independently assessed the trials for quality and risk of bias (ROB) using the domain-based evaluation tool described in the Cochrane Handbook for Systematic Reviews

of Interventions[6] (ROB of all RCTs, Appendix S6). Study characteristics were assessed including methods of randomization, treatment allocation, and blinding methods. Tools for the assessment of RCTs were based on the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions as updated in March 2011. The likely magnitude and direction of the bias has been reported and whether it is likely to impact on the findings. Any uncertainties were resolved through consensus.

The overall certainty of evidence across RCTs were assessed for each intervention (when at least two studies were included) by two authors (PB, BHA) by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[7] This was done by assessing the type of evidence (in this case, high quality as all included studies are RCTs) and then interrogating the risk of bias, indirectness, and publication bias risk for individual trials and the imprecision and inconsistency of the groups of trials for each outcome. The number of trials included for each outcome, width of individual confidence intervals and similarity of results between trials, similarities and appropriateness of populations studied and funding sources were all assessed and an overall certainty rating applied to each outcome. Publication bias was assessed graphically using a funnel plot and the asymmetry of this plot was checked by Egger's test. This analysis was restricted to comparisons including at least 10 studies.

2.10.3 | Data synthesis

A DerSimonian and Laird random effects meta-analysis was performed for each outcome and add-on.[8] The primary and secondary outcomes were analyzed whenever data were available for every add-on. The effect sizes of the outcomes were reported using risk ratio (RR) with 95% confidence interval (CI). To account for the heterogeneity found among trials, we calculated I^2, and its significance tested by Cochrane-Q test.

For endometrial scratch, we explored different sources of heterogeneity by fitting meta-regression models with the log (RR) as the dependent variable and the age of the mother in the add-on scratch as corresponding covariates as independent terms, weighted by the standard error of the log (RR). We applied subgroup analysis to explore the following characteristics: timing of scratch and risk of bias of the trials included. Stata 15 was used in all analysis.[9]

3 | RESULTS

3.1 | Results of the search

The literature search retrieved 6685 studies. From these studies, 66 RCTs were included in the final analysis as depicted in the PRISMA flowchart (Figure 1). The included RCTs were conducted across

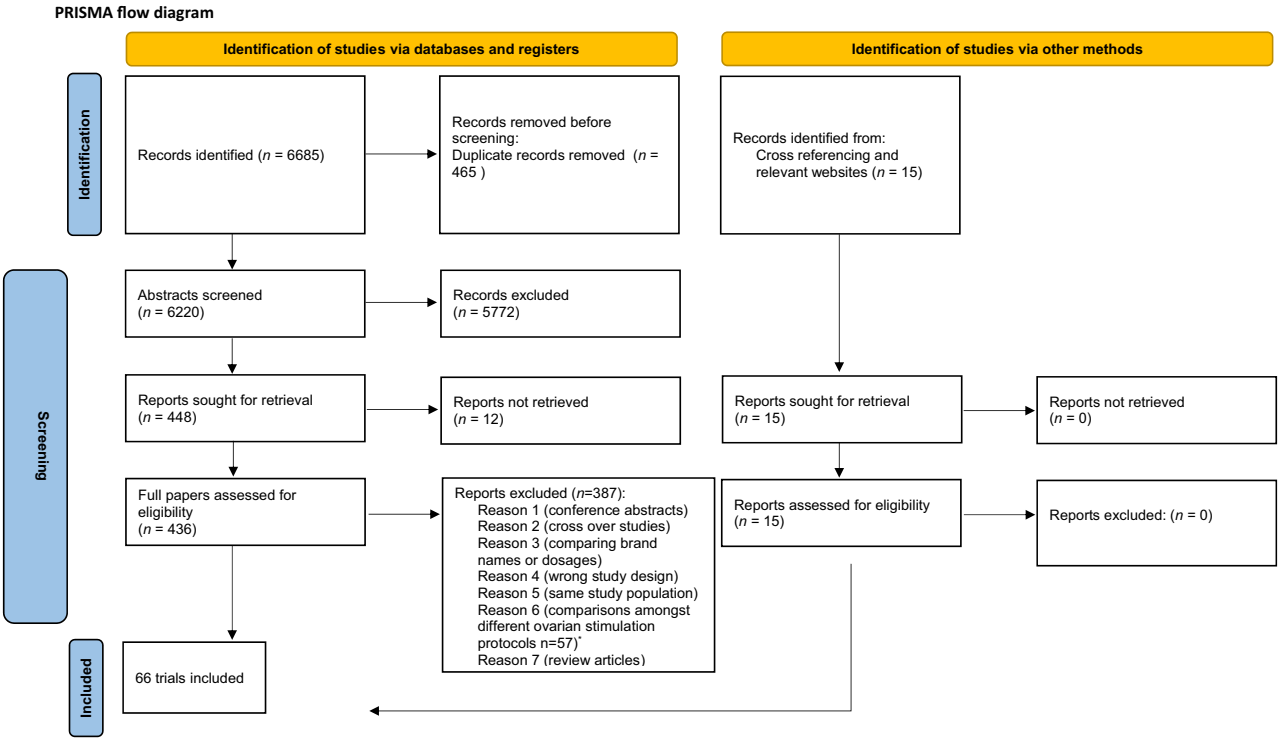

FIGURE 1 Selection and inclusion process for randomized controlled trials evaluating add-on interventions in women undergoing intrauterine insemination cycles. From Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi: 10.1136/bmj.n71.

20 countries between 1992 and 2021. Nine were multicenter, 57 (86%) were single center. The largest RCT was from Spain with 893 participants.[10]

Eleven add-on interventions were assessed. The number of studies and participants included for each intervention is detailed in Table 1. Study characteristics are presented in Supplementary material (Appendix S4).

3.2 | Participants

This review included 16 305 participants of reproductive age (range 18–44 years) undergoing IUI treatment for a variety of indications. Across all the add-ons assessed, the indications for IUI treatment included unexplained infertility, male factor infertility, endometriosis, same-sex couples, single women, tubal factor, anovulation, more than one factors, and patients with repeated failed IUI cycles. The vast majority of included trials recruited participants for more than a single indication and did not report results per subfertility diagnosis. There was heterogeneity in the inclusion criteria for trials based on age, BMI, and duration of subfertility (Figure 2).

Details and demographics of participants for all included trials are detailed in supplementary material (Appendix S5).

TABLE 1 Number of randomized controlled trials and participants for each intervention.

Add-on	Number of RCTs	Number of participants randomized
Endometrial scratch	16	2979
Hydrotubation	3	523
Follicular phase stimulation	2	737
Ovulation trigger	4	942
hCG trigger vs. agonist trigger	6	1297
Double insemination	11	3388
Bed rest after IUI	3	984
Ultrasound guided IUI	6	1225
Use of oxytocin	1	86
Use of misoprostol	3	550
Luteal phase support	11	3594

Abbreviations: IUI, intrauterine insemination; RCT, randomized controlled trials.

3.3 | Synthesis of results

Evidence of moderate/low certainty indicates that vaginal progesterone as luteal phase support in stimulated cycles probably increases LBR/OPR without increasing the chance of miscarriage or multiple pregnancy. Endometrial scratch may increase the chance of clinical pregnancy and the chances of ongoing pregnancy or live birth without increasing chances of miscarriage or multiple pregnancy but evidence is very uncertain. Stimulated cycles seem to be more effective than natural cycles but there are only two multicenter RCTs on this comparison and this intervention has the potential to increase MPR therefore results should be interpreted with caution. No significant difference was found for LBR/OPR for hydrotubation, use of trigger and type of trigger, use of misoprostol, oxytocin, double insemination, ultrasound guidance, and bed rest according to the results of this meta-analysis. The certainty of the evidence for these interventions was overall low/very low. We have detected no publication bias in the three comparisons assessed (double insemination, endometrial scratch, and luteal phase support) (funnel plots in Figure S11).

Summary of recommendations is presented in Table 2.

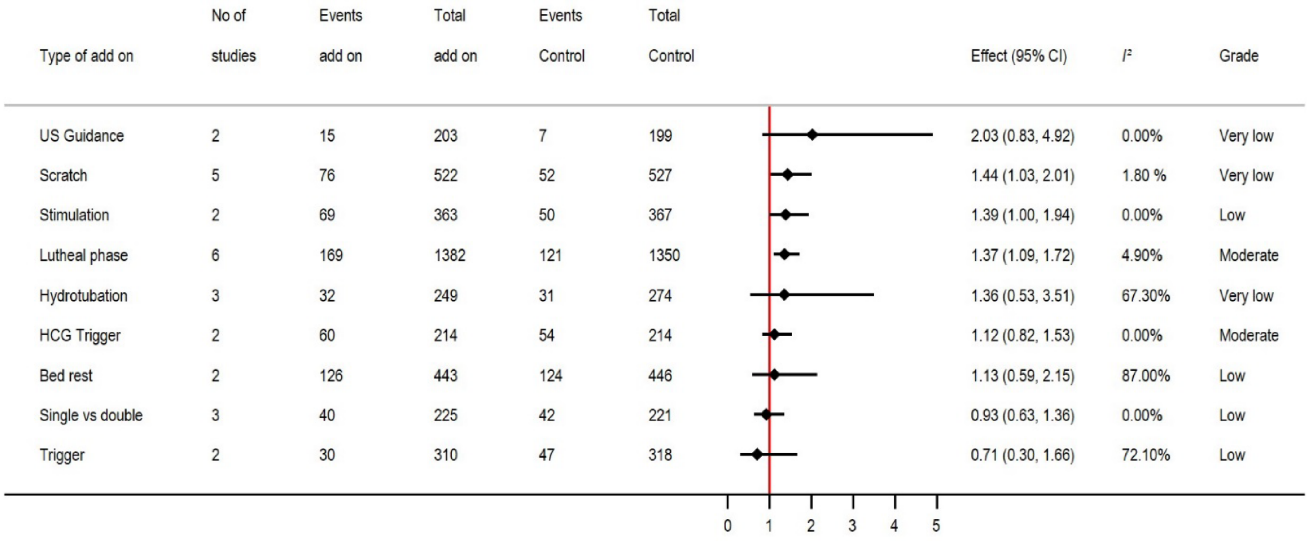

FIGURE 2 Summary forest plot of effect estimates of evaluated interventions before during or after intrauterine insemination on live birth rate/ongoing pregnancy rate.

TABLE 2 Summary of recommendations.

Intervention	Number of RCTs	Certainty l of evidence	Narrative statements based on evidence
Hydrotubation	3	Very low	Hydrotubation is not recommended as an add-on to improve IUI success rates for couples with unexplained infertility.
Endometrial scratch	16	Very low/low	Evidence of very low certainty suggests benefit in success rates. Well-designed studies needed (as evidence very uncertain) with clear description of methods and of timing.
Stimulation	2	Low	Results from two studies (low certainty) suggest benefit of stimulation compared with natural cycles. Further research needed. Any stimulation strategy aiming to increase success rates should be safe in terms of multiple pregnancy.
Trigger	4	Low/very low	The use of trigger does not seem to affect the clinical outcomes of IUI.
Type of trigger	6	Moderate/low	The type of trigger used (hCG vs. agonist) does not seem to affect the clinical outcomes of IUI.
Double insemination	11	Low/very low	Current evidence does not suggest benefit from double insemination to clinical outcomes. Further studies could assess the value of double insemination according to subfertility background (male factor). Timing and cost-effectiveness should also be assessed.
Bed rest	3	Low/very low	The findings of this review do not support the use of bed rest after IUI.
USS guidance	6	Very low	Routine use of transabdominal ultrasound guidance is not recommended (could still prove necessary in individual cases).
Misoprostol	3	Very low	Current evidence does not support its use.
Luteal phase support	11	Moderate/low	Vaginal progesterone post-stimulated IUI probably improves clinical outcomes (moderate/low certainty). More well-designed RCTs needed. Subfertility diagnosis and stimulation strategy should be taken under consideration when presenting results.

Abbreviations: IUI, intrauterine insemination; RCT, randomized controlled trials.

3.4 | Before IUI

3.4.1 | Hydrotubation

Three RCTs (523 participants) were included assessing the value of hydrotubation/perturbation on IUI cycles for patients with unexplained infertility. Meta-analysis including all three RCTs did not demonstrate benefit from the use of hydrotubation before IUI for LBR/OPR (RR 1.36, 95% CI 0.53–3.51, $I^2=67.3\%$) or clinical pregnancy rate (CPR) (RR 1.57, 95% CI 0.24–10.51, $I^2=82.3\%$) (Figure S1). No significant difference was found among the groups for miscarriage rate (MR) (RR 1.13, 95% CI 0.23–5.53, $I^2=0\%$). Only one trial reported on multiple pregnancies without showing any significant difference.[11] The certainty of the evidence was assessed as very low (Table S1).

3.4.2 | Endometrial scratch

Sixteen trials (2979 participants)[12–27] were included for the use of endometrial scratch.

Endometrial scratch was found to increase the chance of clinical pregnancy (RR 2.05, 95% CI 1.56–2.71, $I^2=51.2\%$) (number needed to treat 6) and the chance of ongoing pregnancy or live birth (RR 1.44, 95% CI 1.03–2.01, $I^2=1.80\%$) (number needed to treat 17) without increasing chances of miscarriage (RR 1.18, 95% CI 0.66–2.09, $I^2=0\%$) or multiple pregnancy (OR 1.02, 95% CI 0.35–-2.99, $I^2=0\%$) (Figure 3; Figure S11b). No difference was found when accounting for maternal age (Figure S2) and of the ROB of trials (Figure S3). The certainty of evidence was assessed as very low for live birth/ongoing pregnancy, miscarriage, and multiple pregnancy and low for clinical and biochemical pregnancy (Table S2); therefore, the evidence is very uncertain.

In five trials, the scratch was performed during the month preceding the IUI cycle and in eight trials it was performed during the follicular phase of the same month as the IUI treatment. Three RCTs randomized participants in three groups (endometrial injury during the previous cycle vs. same cycle vs. no scratch). All RCTs reported in stimulated IUI cycles with hCG trigger and single insemination. Five trials used pipelle catheter for the scratch. Other methods of scratch included outpatient hysteroscopy (1 trial), Tao brush (2), embryo mucus aspiration catheter (Rocket medical) after cutting the tip of the catheter sheath obliquely (1), Novak curette (2), neonatal feeding tube (2), vaginal cannula No. 4 (Vitaimed Instrument Company, LTD, Iran) (1), Karman's cannula no. 4 (1), and one trial did not report which method was used.

Three studies only included participants with unexplained infertility,[14,22,24] and one study did not specify the indication for IUI.[20] The rest of the studies included participants with different backgrounds of subfertility but did not report results per indication.

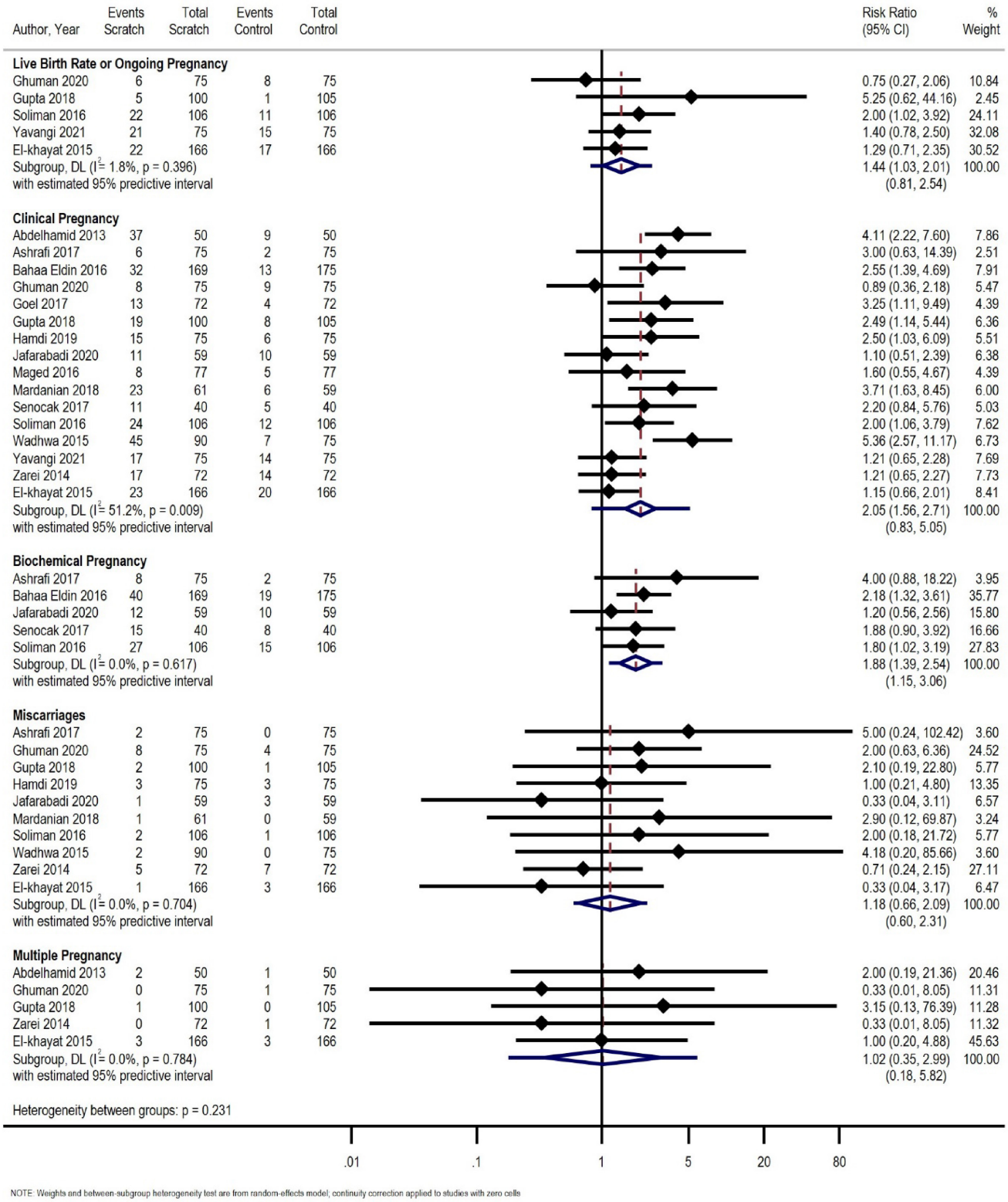

FIGURE 3 Study estimates of the comparison of the add-on endometrial scratch on the outcome live birth or ongoing pregnancy, clinical pregnancy, biochemical pregnancy, miscarriages, and multiple pregnancies. Predicted intervals are only calculated when more than two studies were included in the analysis.

3.4.3 | Follicular phase ovarian stimulation

Two multicenter RCTs (737 participants) were included comparing stimulated IUI using gonadotrophins versus natural cycle.[28,29] Based on these two trials, follicular phase ovarian stimulation in IUI cycles increases the chance of live birth/ongoing pregnancy (RR 1.39, 95% CI 1.00–1.94, $I^2 = 0\%$) (number needed to treat 17) without increasing MR (RR 2.15, 95% CI 0.61–7.6, $I^2 = 59.6\%$) (Figure S4). Steures

et al. (2007)[28] found no significant difference in multiple pregnancy rates (RR 2.02, 95% CI 0.18–21.96, $I^2=0\%$). Low certainty evidence for LBR/OPR and very low for miscarriage and multiple pregnancy (Table S3).

In the trial by Guzick et al. (1999)[29] the cycle was canceled after Day 3 if the serum estradiol concentration exceeded 3000 pg/mL (11 010 pmol/L), trigger was administered when at least two follicles reached more than 18 mm and the serum estradiol concentration ranged from 500 to 3000 pg/mL (1835 to 11 010 pmol/L). The authors do not provide results in relation to number of dominant follicles. In the trial by Steures et al. (2007) the aim of ovarian stimulation was to achieve multifollicular growth. Trial protocol dictated ovarian stimulation with FSH but in 7.1% of IUI cycles, clomiphene was used. Stimulation continued until at least one 16 mm follicle was seen. The authors report that no clear differences in the pregnancy rates were seen between the cycles with monofollicular and multifollicular growth. Cycle was canceled if there were more than three follicles with a diameter of 16 mm or more, or five follicles with a diameter of 12 mm or more.

3.4.4 | Ovulation trigger

Four RCTs[30–33] (942 participants) were identified comparing the IUI outcomes following use of hCG trigger vs spontaneous ovulation. No statistically significant difference was found for LBR/OPR (results from two trials) (RR 0.71, 95% CI 0.30–1.66, $I^2=72.1\%$) or CPR (RR 1.18, 95% CI 0.79–1.78, $I^2=0\%$) (Figure S5). Only two trials reported on multiple pregnancies (RR 1.99, 95% CI 0.50–7.96, $I^2=0\%$) and one on miscarriages (RR 0.35, 95% CI 0.01–8.53, $I^2=0\%$) without significant difference amongst the two groups. One trial was in natural cycle IUI,[30] and three were on stimulated cycles using gonadotrophins[32,33] or clomiphene.[31]

The certainty of the evidence was assessed as low for live birth/ongoing pregnancy and clinical pregnancy and very low for miscarriage/multiple pregnancy (Table S4).

3.4.5 | hCG trigger versus agonist trigger

Six RCTs[34–39] (1597 participants) were included comparing IUI outcomes following the use of hCG trigger versus agonist trigger. All participants had stimulated cycles for various indications. Two trials[34,36] reported on OPR/LBR (RR 1.12, 95% CI 0.82–1.53, $I^2=0\%$) and six reported on CPR (RR 1.03, 95% CI 0.79–1.35, $I^2=33.3\%$) (moderate certainty of the evidence, Table S5). The dose for triggers were 5000 or 10 000 IU of hCG intramuscularly versus 0.1 or 0.2 mg of subcutaneous triptorelin. In the Shalev et al. (1995a, 1995b) trials, patients had double insemination, in the rest of the trials the IUI procedure was performed at 36 h post trigger. No difference was noted for any of the studied outcomes (Figure S6).

3.5 | During IUI

3.5.1 | Ultrasound guidance

Six trials[40–45] (1225 participants with mixed fertility backgrounds) were identified assessing the value of ultrasound guidance during the IUI procedure. Two RCTs reported OPR/LBR[41,45] (RR 2.03, 95% CI 0.83–4.92, $I^2=0\%$). Six trials reported on clinical pregnancy (OR 1.34, 95% CI 0.96–1.88, $I^2=0\%$). No significant difference was found in any of the clinical outcomes for ultrasound-guided procedures versus blind insemination as suggested by evidence of very low certainty (Figure S7; Table S6).

3.5.2 | Double insemination

Eleven trials (3388 participants) assessed double insemination.[46–56] Nine trials reported on CPR but only three reported on LBR/OPR (Figures S8 and S11a). There was no significant difference in CPR (RR 1.29, 95% CI 0.96–1.73, $I^2=49.2\%$) or LBR/OPR (RR 0.93, 95% CI 0.63–1.36, $I^2=0\%$). There was no significant difference in MR (RR 1.65, 95% CI 0.93–2.95, $I^2=0\%$) and MPR (RR 1.09, 95% CI 0.46–2.60, $I^2=0\%$). The certainty of the evidence was low/very low (Table S7).

The timing of single insemination after trigger was between 34 and 38 h, and the timing of double insemination had greater variation (18 + 40 – 42 h, 12 + 34 – 36 h, 34 + 60 h, 24 + 48 h, 18 – 24 h, 36 – 48 h). All trials reported on stimulated cycles with the use of trigger. The authors included various indications. Two studies gave results per indication of subfertility.[49,50] Three studies had in their inclusion criteria longstanding subfertility of more than 2 or 3 years.

3.6 | After IUI

3.6.1 | Bed rest

Four RCTs were identified on bed rest following IUI. Three were included in the analysis (984 participants) (Figure S9; Table S8). There was no statistically significant difference between 15 min bed rest and immediate mobilization following IUI for OPR/LBR (RR 1.13, 95% CI 0.59–2.15, $I^2=87.0\%$) based on the two trials which reported on these outcomes[57,58] (low certainty of the evidence). The RCT by Saleh et al. (2000)[59] was the only trial reporting on CPR and showed significantly increased CPR for the group of patients who had 10 min bed rest following IUI (16 vs. 4 pregnancies, RR 2.91, 95% CI 1.05–8.04, $I^2=0\%$) (evidence of very low certainty). There was no significant difference among the groups for MPR (RR 1.84, 95% CI 0.65–5.18, $I^2=0\%$) (data from three trials) and MR (RR 0.79, 95% CI 0.40–1.57) (data from one trial).

The RCT by Orief et al. (2015)[60] was excluded as it compares different durations for bed rest, and there is no control group with

immediate mobilization. For all three trials, the randomization was per woman. Participants were randomized for a maximum of three cycles[58,59] and for six cycles.[57]

3.6.2 | Use of oxytocin

One RCT assessed the use of 8 IU nasal oxytocin vs placebo immediately following IUI.[61] No significant difference was found in pregnancy rates between the two groups (pregnancy rate per cycle 13.4% vs. 12.3%, not significant). This was a pilot study, not adequately powered, with 132 IUI cycles (86 participants) randomized (67 cycles in the placebo group and 65 in the treatment group). Subgroup analysis on natural vs stimulated IUI and based on duration of subfertility did not demonstrate any significant difference either. No adverse effects were documented (Table 3).

3.6.3 | Use of misoprostol

There were three RCTs (550 participants), exploring the effect of vaginal misoprostol following IUI on clinical pregnancy rates (Figure S10). The trials were double blinded, placebo controlled. There was not statistically significant difference in CPR with the use of misoprostol vs placebo (RR 1.20, 95% CI 0.66–2.20, I^2=64.5%) based on evidence of very low certainty (Table S9). The authors did not report results for any of the other outcomes of interest. Two trials used 200 μg[62,63] and one 400 μg[64] misoprostol as a single dose administered vaginally.

3.6.4 | Luteal phase support

Eleven RCTs (3594 participants)[10,65–74] assessed the effect of luteal phase support (Figure 4; Figure S11c; Table 4). The use of luteal phase support in stimulated cycles was shown to statistically significant increase LBR/OPR (RR 1.37, 95% CI 1.09–1.72, I^2=4.9%) (certainty of the evidence moderate/low) (number needed to treat 21, results from six trials) as well as CPR (RR 1.37, 95% CI 1.15–1.62, I^2=0%) (certainty of the evidence low) without affecting the chance of miscarriage (RR 1.13, 95% CI 0.69–1.86, I^2=0%) or multiple pregnancy (RR 1.05, 95% CI 0.49–2.27, I^2=0%) (certainty of the evidence very low). Four trials[71–74] only included couples with unexplained subfertility and the rest included patients with mixed indications.

All RCTs used follicular phase stimulation and hCG trigger for ovulation. In 9 out of 11 trials participants were advised bed rest following the insemination.

Participants had vaginal progesterone as luteal phase support (pessaries/vaginal gel). One pilot multicenter RCT used vaginal ring.[71] The dose of progesterone varied between 200 and 800 mg per day for pessaries, and the gel preparation (90 mg of progesterone) was used once daily. The progesterone was started 1 or 2 days

TABLE 3 Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of evidence from randomized trials evaluating endometrial scratch prior to intrauterine insemination (IUI).

Patient or population: Women undergoing IUI					
Setting: Fertility clinics					
Intervention: Endometrial scratch					
Comparison: No endometrial scratch					
	Anticipated absolute effects (95% CI)				
Outcomes	**Risk with no endometrial scratch**	**Risk with endometrial scratch**	**RR (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**
Live birth/ongoing pregnancy	99 per 1000	146 per 1000	1.44 (1.03–2.01)	1049 (5)	Very low
Clinical pregnancy	106 per 1000	227 per 1000	2.05 (1.56–2.71)	2718 (16)	Low
Biochemical pregnancy	119 per 1000	227 per 1000	1.88 (1.39–2.54)	904 (5)	Low
Miscarriage	25 per 1000	31 per 1000	1.18 (0.66–2.09)	1746 (10)	Very low
Multiple pregnancy	13 per 1000	13 per 1000	1.02 (0.35–2.99)	931 (5)	Very low

Note: We downgraded our assessment of the quality of the evidence for live birth/ongoing pregnancy once for risk of bias, twice for imprecision due to suboptimal information size and wide confidence intervals and once for inconsistency due to wide variation in the point estimate between studies. We downgraded our assessment of the quality of the evidence for clinical pregnancy once for imprecision due to suboptimal information size and once for inconsistency due to wide variation in the point estimate between studies, minimal overlap between confidence intervals, test for heterogeneity <0.05 and high I^2. We downgraded our assessment of the quality of the evidence for biochemical pregnancy once for risk of bias, once for imprecision due to suboptimal information size. We downgraded our assessment of the quality of the evidence for miscarriage twice for imprecision due to low event rate/suboptimal information size and wide confidence intervals and once for inconsistency due to wide variation in the point estimate and confidence intervals between studies. We downgraded our assessment of the quality of the evidence for multiple pregnancy twice for imprecision due to low event rate/suboptimal information size and wide confidence intervals and once for inconsistency due to wide variation in the point estimate and confidence intervals between studies.

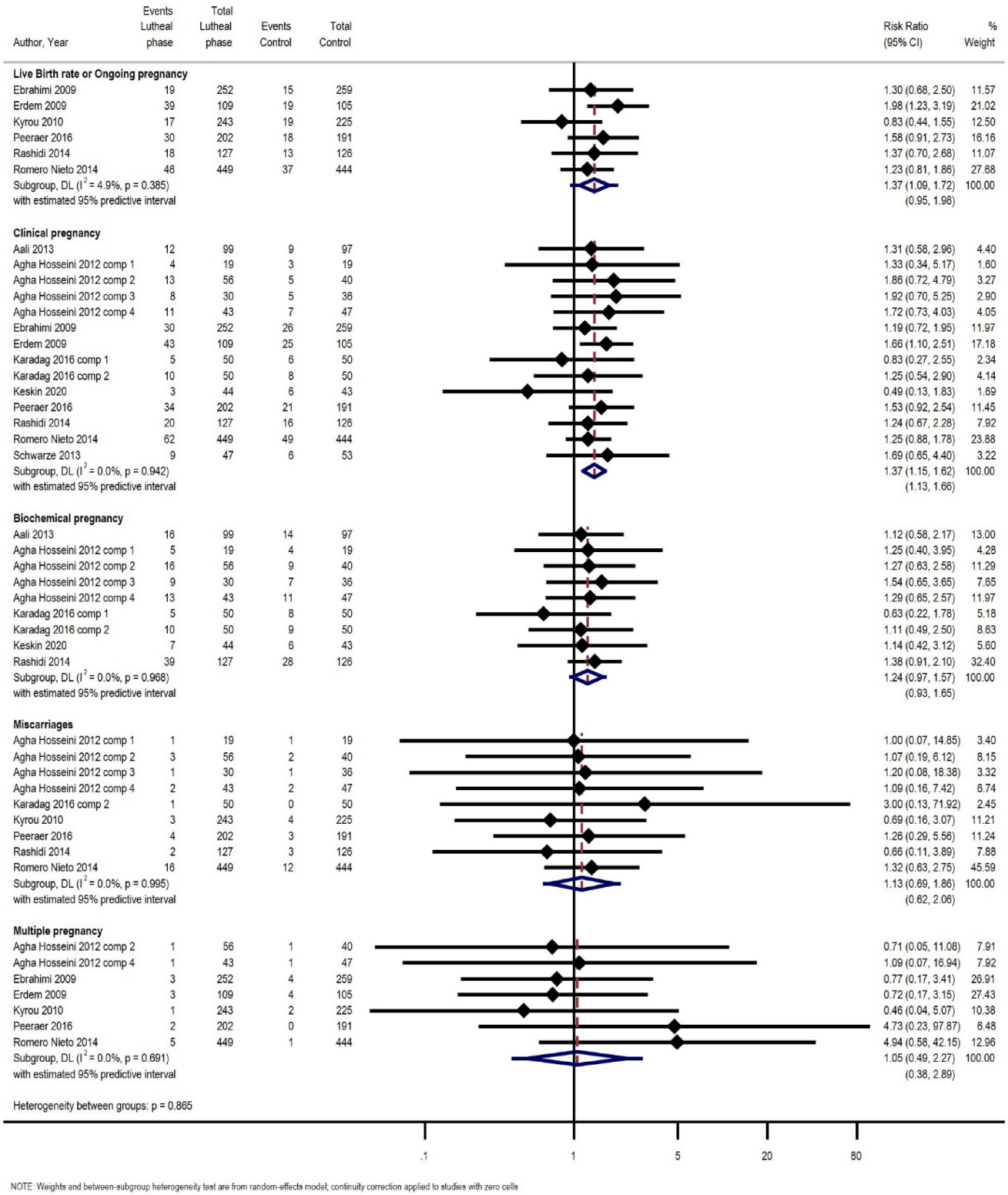

FIGURE 4 Study estimates of the comparison of the add-on luteal phase on the outcome live birth or ongoing pregnancy, clinical pregnancy, biochemical pregnancy, miscarriages, and multiple pregnancies.

following insemination. Keskin et al. (2020) started luteal phase support on the day of the insemination. The duration of progesterone administration ranged among different trials between 10 days post IUI up to 12 weeks of pregnancy.

4 | DISCUSSION

Although small pair-wise comparisons have been published in the past for individual add-ons, this is, to our knowledge, the first systematic

TABLE 4 Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of evidence from randomized trials evaluating luteal phase support following intrauterine insemination (IUI).

Patient or population: Women undergoing IUI					
Setting: Fertility clinics					
Intervention: Luteal phase support					
Comparison: No luteal phase support					
	Anticipated absolute effects (95% CI)				
Outcomes	**Risk with no luteal phase support**	**Risk with luteal phase support**	**RR (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**
Live birth/ongoing pregnancy	89 per 1000	123 per 1000	1.37 (1.09–1.72)	2732 (6)	Moderate/low
Clinical pregnancy	122 per 1000	169 per 1000	1.37 (1.15–1.62)	3137 (14)	Low
Biochemical pregnancy	188 per 1000	232 per 1000	1.24 (0.97–1.57)	1028 (9)	Low
Miscarriage	24 per 1000	27 per 1000	1.13 (0.69–1.86)	2397 (9)	Very low
Multiple pregnancy	10 per 1000	12 per 1000	1.05 (0.49–2.27)	2665 (7)	Very low

Note: We downgraded our assessment of the quality of the evidence for live birth/ongoing pregnancy once for imprecision due to suboptimal information size. We downgraded our assessment of the quality of the evidence for clinical pregnancy once for risk of bias, once for imprecision due to suboptimal information size. We downgraded our assessment of the quality of the evidence for biochemical pregnancy once for high risk of bias, once for imprecision due to suboptimal information size. We downgraded our assessment of the quality of the evidence for miscarriage once for risk of bias, twice for imprecision due to low event rate/suboptimal information size and wide confidence intervals. We downgraded our assessment of the quality of the evidence for multiple pregnancy once for risk of bias, twice for imprecision due to low event rate/suboptimal information size and wide confidence intervals.

review and meta-analysis providing a holistic update assessing the value of all possible add-ons to the standard IUI protocol in relation to clinical outcomes both in terms of success rates and safety. While some previous reviews have looked in to both timed sexual intercourse and IUI cycles (different patient populations), this review has only focused on IUI cycles. Our results are clinically relevant aiming to provide evidence-based recommendations for clinical practice. This comprehensive review and meta-analysis has robust methodology, in terms of an extensive literature review with detailed search strategy and strict inclusion and exclusion criteria, statistical analysis, data synthesis, and quality assessment. The large number of the included RCTs and randomized participants strengthen the results.

The limitations of this review are derived from the limitations of the existing literature. The certainty of the evidence was overall low/very low in view of limitations in study design (high risk of bias, heterogenous patient population). Most trials were underpowered for the primary outcomes and the meta-analysis for a pooled estimate also demonstrated suboptimal information size. Not all trials reported results for the primary outcomes (LBR/OPR) or safety outcomes (MPR/MR). Communication was not attempted with authors for missing data. Limiting our review to English literature could have introduce some bias. However, we think that this bias should be small because our publication bias analysis did not detect any bias.

The vast majority of the existing RCTs have not taken into consideration the indication for IUI when presenting results to allow conclusions for specific patient groups (such as unexplained infertility). Similarly, there was no standardized approach regarding the semen analysis results and cases with severe male factor were often randomized along with mild male factor (variable definitions) or normal/donor sperm. This heterogeneity in studied population can affect outcomes.[2] Whilst it would be clinically useful to be able to provide recommendations for IUI in unexplained subfertility, the term "unexplained" is, at the moment, a big umbrella term including multiple and sometimes significantly variable definitions. Almost every study used different diagnostic criteria for unexplained subfertility which could also include tubal factor (unilateral patency), endometriosis, and male factor (Table S10). Different add-ons could benefit specific patient groups but based on the available data, safe recommendations cannot be proposed according to subfertility diagnosis. Furthermore, since currently there are no uniform IUI protocols, most trials have used different stimulation regimes, multiple add-ons as well as variations rendering it impossible to adjust for all possible confounders. We included both stimulated and natural IUI cycles but for the add-ons which showed significant difference in outcomes (luteal phase support and endometrial scratch), all comparisons were in stimulated cycles. Sperm preparation techniques, ejaculatory abstinence, semen processing, timing of insemination, and the equipment used could all affect outcomes. Recent reviews on these variations identified low-quality evidence; limited number of trials, not reporting on LBR with significant heterogeneity.[75,76]

Lastly, some trials randomized the same woman/couple for multiple cycles and did not provide results per cycle. In these cases, we included results for all cycles.

Our review reports a consistent positive direction of effect among studies assessing progesterone support post-IUI; however, the certainty of the evidence is moderate/low. There remains uncertainty for its use in specific patient groups and the dose and duration of treatment. These may be resolved with well-designed RCTs and with the use of individual participant data meta-analysis. Exogenous progesterone has an excellent safety profile reiterated by this review and is a low cost easily administered medication. The results of this review and meta-analysis suggest that there may be benefit from the use of progesterone as an add-on for stimulated IUI treatments and highlights the need for more research. Compared to a recent Cochrane review,[77] we only included studies on IUI, we excluded abstracts and studies with no available raw data and included more RCTs. Three previous meta-analyses concluded that there is benefit from progesterone supplementation for luteal phase support in IUI cycles when gonadotrophins were used for ovarian stimulation but not for clomiphene-stimulated cycles.[78–80]

5 | CONCLUSION

The findings of this systematic review and meta-analysis suggest that vaginal luteal phase progesterone support probably improves LBR/OPR in stimulated IUI treatments. The safety profile of exogenous progesterone is reassuring and it is an easily administered, low cost medication. In view of moderate/low certainty of the evidence, more research is needed before routinely recommending its use in clinical practice. Further research is also recommended for the use of endometrial scratch and ovarian follicular phase stimulation for sound conclusions. Trigger may be used based on the availability of fertility services and staffing, similarly ultrasound guidance for difficult IUI procedures. Current evidence does not support the use of hydrotubation, agonist trigger as opposed to HCG, double insemination misoprostol, oxytocin, and bed rest after the IUI.

This review highlights the need for well-designed RCTs reporting on IUI treatment which is one of the most commonly used fertility treatments worldwide. Future studies should explore the value of IUI add-ons for specific patient groups. The diagnostic criteria for unexplained subfertility, and the IUI protocols used should be uniform in order to facilitate the scientific dialogue and allow homogeneous comparisons. Every intervention proposed to increase success rates should also be assessed for its safety, in terms of MR/MPR, therefore these results should be reported. Cost-effectiveness and couple's preferences should also be taken into consideration. In order to optimize IUI treatment, we need to create evidence-based guidelines and to standardize current practice.

AUTHOR CONTRIBUTIONS

Elpiniki Chronopoulou: Study design; data collection; data extraction; manuscript drafting and revision. Andrea Gaetano-Gil: Data synthesis; statistical analysis; interpretation of data; manuscript drafting. Sadaf Shaikh: Data extraction; quality assessment and interpretation of data. Claudia Raperport: Data collection; quality assessment of evidence; manuscript editing. Bassel H. Al Wattar: Quality assessment of evidence; data synthesis; manuscript revision. Gabriel Ruiz-Calvo: Manuscript revision; data analysis and synthesis. Javier Zamora: Study design; data synthesis and analysis; critical input to the final manuscript. Priya Bhide: Conception of this study; study design; quality assessment of data and interpretation; edited draft; critical input to final manuscript. All authors approved the final revised manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare that are relevant to the content of this article.

ORCID

Elpiniki Chronopoulou https://orcid.org/0000-0002-5714-1395
Priya Bhide https://orcid.org/0000-0003-0871-6508

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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