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IVF versus IUI with ovarian stimulation for unexplained infertility: a collaborative individual participant data meta-analysis

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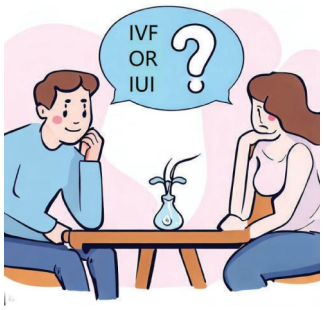
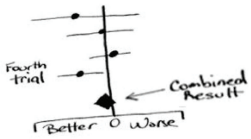
GRAPHICAL ABSTRACT



Couples with unexplained infertility often wonder whether they should try IUI-OS first or go for IVF directly.

We pooled individual-level data of 4 RCTs in a **meta-analysis** to compare IVF and IUI-OS regarding chances of cumulative live birth and multiple pregnancy.



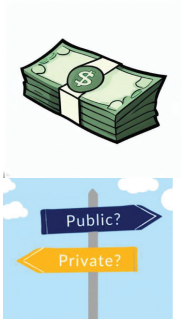
We found **NO** significant difference in cumulative live birth rates and multiple pregnancy rates between IVF and IUI-OS.

Cumulative live birth:
Hazard ratio 1.19, 95% CI 0.81 to 1.74

Multiple pregnancy:
Odds ratio 0.78, 95% CI 0.41 to 1.50

Important considerations in decision-making:

- ✓ Costs
- ✓ Public or private funding
- ✓ Couple's preference



IVF and IUI with ovarian stimulation are both viable options regarding effectiveness and safety for managing unexplained infertility.

ABSTRACT

BACKGROUND: IVF and IUI with ovarian stimulation (IUI-OS) are widely used in managing unexplained infertility. IUI-OS is generally considered first-line therapy, followed by IVF only if IUI-OS is unsuccessful after several attempts. However, there is a growing interest in using IVF for immediate treatment because it is believed to lead to higher live birth rates and shorter time to pregnancy.

OBJECTIVE AND RATIONALE: Randomized controlled trials (RCTs) comparing IVF versus IUI-OS had varied study designs and findings. Some RCTs used complex algorithms to combine IVF and IUI-OS, while others had unequal follow-up time between arms or compared treatments on a per-cycle basis, which introduced biases. Comparing cumulative live birth rates of IVF and IUI-OS within a consistent time frame is necessary for a fair head-to-head comparison. Previous meta-analyses of RCTs did not consider the time it takes to achieve pregnancy, which is not possible using aggregate data. Individual participant data meta-analysis (IPD-MA) allows standardization of follow-up time in different trials and time-to-event analysis methods. We performed this IPD-MA to investigate if IVF increases cumulative live birth rate considering the time leading to pregnancy and reduces multiple pregnancy rate compared to IUI-OS in couples with unexplained infertility.

SEARCH METHODS: We searched MEDLINE, EMBASE, CENTRAL, PsycINFO, CINAHL, and the Cochrane Gynaecology and Fertility Group Specialised Register to identify RCTs that completed data collection before June 2021. A search update was carried out in January 2023. RCTs that compared IVF/ICSI to IUI-OS in couples with unexplained infertility were eligible. We invited author groups of eligible studies to join the IPD-MA and share the deidentified IPD of their RCTs. IPD were checked and standardized before synthesis. The quality of evidence was assessed using the Risk of Bias 2 tool.

OUTCOMES: Of eight potentially eligible RCTs, two were considered awaiting classification. In the other six trials, four shared IPD of 934 women, of which 550 were allocated to IVF and 383 to IUI-OS. Because the interventions were unable to blind, two RCTs had a high risk of bias, one had some concerns, and one had a low risk of bias. Considering the time to pregnancy leading to live birth, the cumulative live birth rate was not significantly higher in IVF compared to that in IUI-OS (4 RCTs, 908 women, 50.3% versus 43.2%, hazard ratio 1.19, 95% CI 0.81–1.74, $I^2 = 42.4\%$). For the safety primary outcome, the rate of multiple pregnancy was not significantly lower in IVF than IUI-OS (3 RCTs, 890 women, 3.8% versus 5.2% of all couples randomized, odds ratio 0.78, 95% CI 0.41–1.50, $I^2 = 0.0\%$).

WIDER IMPLICATIONS: There is no robust evidence that in couples with unexplained infertility IVF achieves pregnancy leading to live birth faster than IUI-OS. IVF and IUI-OS are both viable options in terms of effectiveness and safety for managing unexplained infertility. The associated costs of interventions and the preference of couples need to be weighed in clinical decision-making.

Keywords: IVF / ovarian stimulation / IUI / / infertility / meta-analysis / individual participant data / unexplained infertility / time to pregnancy / cumulative live birth rate

Introduction

Unexplained infertility is a diagnosis made following unsuccessful attempts to conceive after 12 months of regular unprotected sexual intercourse, with subsequent routine fertility investigations unable to reveal a clear cause (Carson and Kallen, 2021). This type of infertility has been shown to affect up to 30% of couples who are unable to conceive (Practice Committee of the American Society for Reproductive Medicine, 2006). There is a wide range of approaches to managing unexplained infertility in clinical practice, but not all recommendations regarding their use are evidence-based (Practice Committee of the American Society for Reproductive Medicine, 2006; Carson and Kallen,

2021). These approaches range from expectant management to interventions including ovarian stimulation (OS), IUI (with or without OS), and IVF/ICSI (Kamath et al., n.d.; Practice Committee of the American Society for Reproductive Medicine, 2006).

Both IVF (including ICSI) and IUI-OS have been important treatment options for couples with a poor prognosis of natural conception. Although IVF was first used as a treatment option for tubal infertility, its indication has been expanded to manage a wider range of couples with infertility in the last three decades, including those with unexplained infertility. For IUI in unexplained infertility, most procedures are now performed in combination with OS rather than natural cycles to improve pregnancy rates through multiple follicle growth (Huang et al., 2018). In practice, IUI-OS is commonly considered first-line therapy for unexplained infertility, followed by IVF only if IUI-OS is unsuccessful after several attempts. However, some centres offer immediate IVF given the argument that IVF could reduce the emotional and physical burden on couples by shortening the time required to achieve pregnancy.

Several randomized controlled trials (RCTs) have been conducted to establish which approach is more effective but the findings are inconclusive (Goverde et al., 2000; Custers et al., 2011; Bensdorp et al., 2015; Nandi et al., 2017). A 2019 Cochrane review identified eight RCTs comparing IVF to IUI-OS in couples with unexplained infertility, of which only three RCTs were included for the analysis of live birth, as the others did not define time limits for follow-up or used complex algorithms to combine treatments. Based on three trials, the review concluded that there is insufficient evidence to demonstrate a benefit of IVF over IUI-OS for live birth (odds ratio (OR): 1.17, 95% CI 0.64–2.12, low-certainty evidence) (Wang et al., 2019). In contrast, based on the same collection of RCTs as the Cochrane review and ignoring variations in study design, another meta-analysis pooled all eight RCTs and found that IVF was associated with a higher live birth rate (risk ratio 1.53, 95% CI 1.01–2.32), noting high heterogeneity among studies (Nandi et al., 2022).

Both IVF and IUI-OS take place over months, such that the time horizon becomes a crucial part of the design of RCTs that compare them. However, some RCTs on this topic did not establish a follow-up time limit, while others compared treatments on a per-cycle basis, which skews results in favour of IVF. To ensure fairness, it is important to perform head-to-head comparisons and make sure that the follow-up time is the same between IVF and IUI-OS and both interventions are ongoing during follow-up. Also, it is best to use 'time to pregnancy leading to live birth' as the outcome for effectiveness, because this time-to-event outcome incorporates not only whether pregnancy occurred, but also when it occurred (Aalberts and van Wely, 2023). Unfortunately, these are not possible in previous meta-analyses using aggregate data given the limitations in trial design and reporting.

Unlike aggregate data meta-analysis (AD-MA), which is confined by the reporting of included trials, individual participant data meta-analysis (IPD-MA) allows standardization of follow-up time and time-to-event analysis to address the issues of absent time limits or comparison on a per cycle basis in some trials. An IPD-MA also allows for the exploration of a differential treatment effect in subgroups (i.e. treatment covariate interactions) (Clarke, 2005; Riley et al., 2010). This function of IPD-MA may overcome another issue with the AD-MA, where many included trials did not consider the prognosis of the couples with unexplained infertility.

Therefore, we performed an IPD-MA that systematically pooled the available individual-level data regarding the comparison of IVF and IUI-OS for unexplained infertility.

Methods

Registration and literature search

We performed this IPD-MA according to a pre-registered protocol (PROSPERO CRD42021224077). The study obtained ethics approval from the Monash University Human Research Ethics Committee (project ID 26430) before data enquiry. The reporting of this study followed the Preferred Reporting Items for Systematic Review and Meta-analyses of individual participant data (PRISMA-IPD) statement.

RCTs before 6 September 2018 were identified from the 2019 Cochrane review on interventions for unexplained infertility (Wang et al., 2019) We updated the Cochrane literature search on 8 December 2020 to identify any new RCTs (published or unpublished) after the Cochrane review. The following electronic databases were searched: The Cochrane Gynaecology and Fertility Group (CGF) Specialised Register of Controlled Trials, The Cochrane Central Register of Studies Online, MEDLINE, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL). In brief, the search strategy contained both index terms and free words on unexplained infertility and idiopathic male infertility (Supplementary Materials and Methods). We did not apply language restrictions. All studies identified during the updated literature search were uploaded into Covidence (covidence.org), where duplicates were removed. On 15 January 2023, we conducted another update for our literature search in MEDLINE and Embase to find any new RCTs that have been published since the last search.

Eligibility criteria

We included RCTs that compared IVF/ICSI to IUI-OS in couples with unexplained infertility, with data collection completed before the search. We excluded pseudo-randomized trials and other study designs. RCTs that used complex algorithms involving a combination of IVF and IUI-OS were only eligible if the IPD of the trial could empower a head-to-head comparison between IVF and IUI-OS at the time of randomization. The study population of included studies consisted of all randomized participants for whom IPD were available. We did not specify any additional participant inclusion or exclusion criteria. For interventions, only IUI with OS was eligible for this study and natural IUI was excluded. There was no restriction on the number of cycles of IVF or IUI-OS.

Outcome measures

The primary effectiveness outcome was cumulative live birth, defined as the time to conception leading to live birth, starting from randomization. Date of conception was calculated from the moment of insemination, the moment of embryo transfer, or from early pregnancy ultrasounds. The primary safety outcome was multiple pregnancies per randomized patient. The secondary outcomes were live birth as a binary event, clinical pregnancy, ovarian hyperstimulation syndrome (OHSS), pregnancy loss (including ectopic pregnancy, miscarriage, stillbirth, and termination of pregnancy), gestational age at delivery, birthweight, neonatal mortality, and major congenital anomaly.

Study selection and data collection

Two members of the research team (S.L. and W.L.) independently assessed the titles and abstracts to exclude ineligible studies and

subsequently reviewed the full-text articles to evaluate their relevance. Disagreements were resolved by discussion with a third author (B.W.M. or R.W.).

Initially, we reached out to the primary and last/corresponding authors of potentially eligible studies to participate in the IPD collaboration and provide the deidentified IPD of their RCTs if the study was confirmed eligible. In case of no response, we sent reminders three times. If there was still no response, we contacted the co-authors and the institutions where the RCT was conducted. We made efforts to schedule video conferences with the author teams to encourage them to join. Where applicable, data transfer agreements were arranged between participating trialists and our research group to ensure clarity of data-sharing parameters. We developed coding sheets and a database structure that were shared with participating trialists. After receiving the datasets, we examined them for missing data, errors, internal consistency, consistency with the publication, and pattern of treatment allocation and data presentation, where possible. Identified issues were communicated with trial investigators for a solution before being included in the analysis.

The de-identified IPD obtained included treatment allocation and baseline characteristics, such as maternal age, BMI, infertility duration and type of infertility, gravidity and parity, total motile sperm count (TMSC), and percentage of motile sperm as well as the reproductive outcomes and neonatal outcomes, as described above.

Risk of bias assessment and GRADE approach

Two members of the research team (S.L. and W.L.) independently evaluated the risk of bias in each eligible study regardless of whether IPD was shared or not, using the Risk of Bias 2 (RoB2) tool (Sterne *et al.*, 2019). Inconsistencies between the two investigators were resolved by a discussion. According to the Cochrane Handbook (Higgins *et al.*, 2019), each item of bias was scored as low, high, or some concerns. In cases where study quality was not clear from trial protocols/publications, or when any questions were raised, the principal investigators were contacted for clarification. We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to assess the overall certainty of the evidence for outcomes (Higgins *et al.*, 2019).

Data synthesis

Baseline tables were constructed separately for each trial and displayed only the baseline characteristics of those participants included in the analysis. We reported a mean (±SD) if a continuous variable was normally distributed or a median with interquartile ranges if the variable was non-normally distributed. Binary and categorical variables were presented as the number of total and percentage.

All participants were included in the analysis and evaluated according to the treatment to which they were randomized—intention to treat principle. All analyses were presented as IVF versus IUI-OS (i.e. reference group). We used the 'two-stage' meta-analysis method to synthesize the IPD. In the first stage, the outcomes were compared between the IVF and IUI-OS groups for each included study. For the primary effectiveness outcome (cumulative live birth), hazard ratios with 95% CIs were calculated with the Cox proportional hazard regression model. We standardized the follow-up time between groups for each trial if possible. To ensure consistency between groups with differing intervention and follow-up durations, we truncated follow-up time with the shorter duration and dropouts were censored at the last time point during the follow-up period. For one trial with missing time values, we imputed time using the median cycle length of IVF or IUI-OS in those with time information. For the primary safety outcome and other binary outcomes, OR with 95% CIs were calculated for each trial. For continuous outcomes, mean difference with 95% CIs was computed. In the second stage, the generated estimates for each trial were combined using a random-effects model (DerSimonian-Laird method), as we assume differences in treatment effect caused by between-study heterogeneity. The I^2 statistic was calculated to provide a measure of between-study heterogeneity. We performed treatment-covariate interaction analyses for the primary outcome. Within-trial level interaction terms of each study were estimated and then pooled in a meta-analysis of interactions. We studied the following hypothesized patient-level modifiers of treatment for the primary effectiveness outcome: female age, duration of infertility, primary or secondary infertility, TMSC, and prognosis of natural conception, which was calculated based on the Hunault model (Hunault *et al.*, 2004). We performed a *post hoc* sensitivity analysis on the primary outcome by including one potentially eligible study that did not provide IPD (Goldman *et al.*, 2014). We reconstructed IPD from the published Kaplan–Meire curve using the R package named 'IPDfromKM' and its Shiny web application (Liu *et al.*, 2021) for the study phase where IVF was directly compared with IUI-OS since randomization.

We performed all the analyses in Stata software version 17.0 (Stata Corp, College Station, TX, USA).

Results

Study inclusion

All eight studies identified in the 2019 Cochrane review were considered potentially eligible. The updated literature search returned 559 non-duplicated studies. Screening of titles and abstracts led to the exclusion of 544 irrelevant studies. The remaining 15 articles underwent a full text review and only one new study was considered potentially eligible.

Out of nine potentially eligible studies, IPD was not sought from one study (444 couples) owing to insufficient contact information and the fact that this study was published >30 years ago (Crosignani *et al.*, 1991). For the remaining eight studies (1886 couples), the investigators were contacted to share more information on the primary studies. Principal investigators of two RCTs declined to be involved in this IPD-MA (n = 2) (Reindollar *et al.*, 2010; Goldman *et al.*, 2014). Because these two trials used algorithms that combined IVF and IUI-OS in arms, we were unable to verify if their data could enable head-to-head comparison of IVF and IUI-OS without further information from the trialists and, therefore, these two trials were classified as awaiting clarification. IPD from two studies were not available owing to failure to respond to requests (n = 1) (Parinaud, n.d.) and non-response of the first author with co-authors unaware of where the data were stored (n = 1) (Nandi *et al.*, 2017). The trial in which authors failed to respond was terminated before completion and unpublished. From four remaining studies (934 couples), IPD were available for at least one outcome (Goverde *et al.*, 2000; Custers *et al.*, 2011; Elzeiny *et al.*, 2014; Bensdorp *et al.*, 2015) (Fig. 1).

Study characteristics

Three included trials were from the Netherlands (Goverde *et al.*, 2000; Custers *et al.*, 2011; Bensdorp *et al.*, 2015), and one from Australia (Elzeiny *et al.*, 2014). All four RCTs were published in English between 2000 and 2015. Two trials set unexplained or mild male infertility with an unfavourable prognosis of natural conception as the inclusion criteria (Custers *et al.*, 2011; Bensdorp

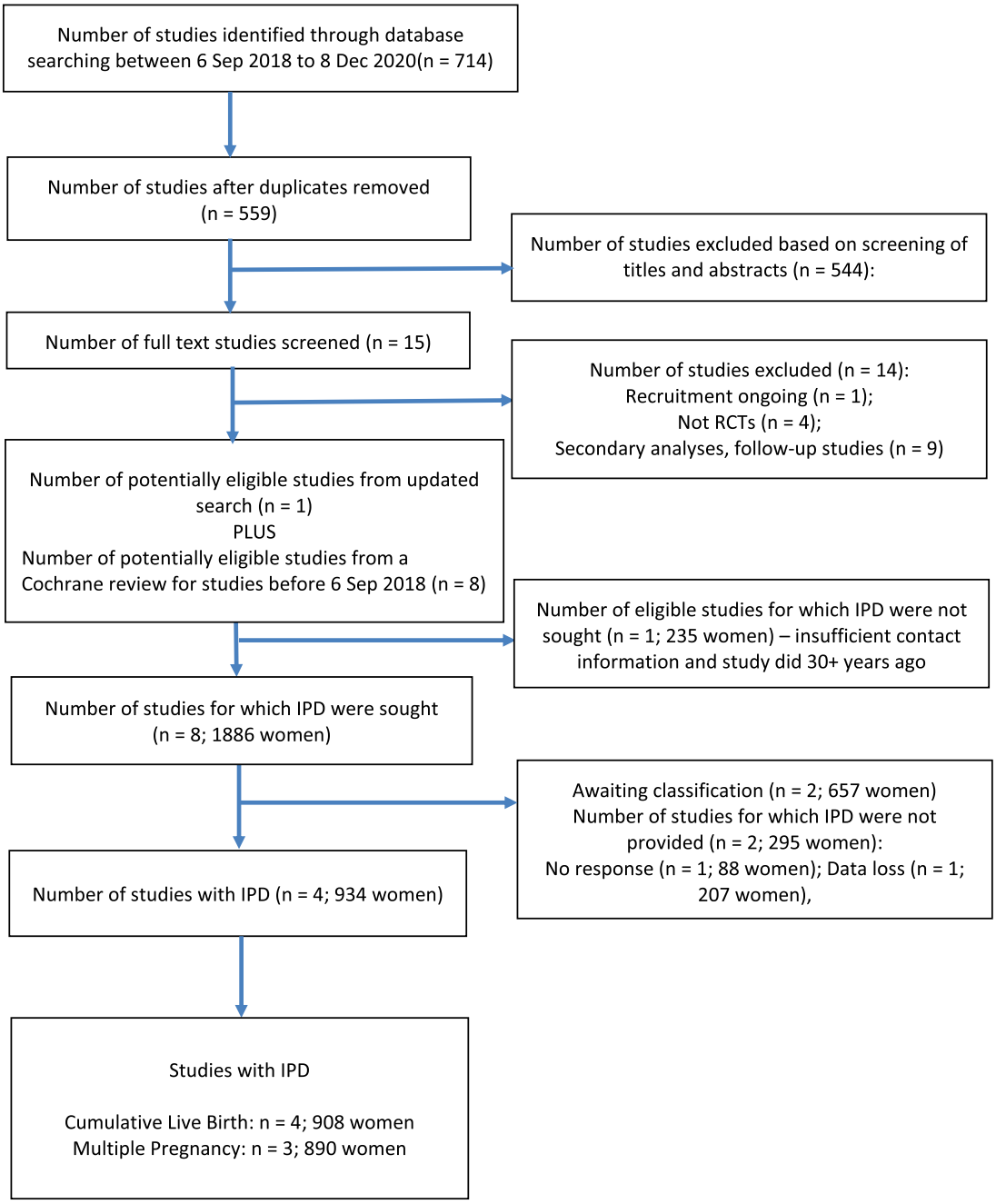


Figure 1. Flowchart of this IPD-MA of data on IVF versus IUI with ovarian stimulation for unexplained infertility. IPD-MA, individual participant data meta-analysis.

et al., 2015). One trial (Goverde *et al.*, 2000) only included couples with an unfavourable prognosis defined by the Hunault model (Hunault *et al.*, 2004) although this could not be specified in the inclusion criteria because the trial was carried out before the development of the Hunault model. Another trial did not include the prognosis in the inclusion criteria and only randomized those who had two to three preovulatory follicles at triggering using the same OS protocol for IVF and IUI-OS (Elzeiny *et al.*, 2014). The ratio of IVF: IUI-OS cycles was 1:1 (Elzeiny *et al.*, 2014), 3:6 (Bensdorp *et al.*, 2015), 1:3 (Custers *et al.*, 2011), and 6:6 (Goverde *et al.*, 2000), respectively. For IVF, three trials allowed double embryo transfer and in one trial (Goverde *et al.*, 2000) three embryos could be transferred in women >35 years. For IUI-OS, all trials used gonadotrophin for stimulation and one trial (Bensdorp *et al.*, 2015) also used clomiphene citrate. Three trials specified cancellation criteria in IUI-OS with variations in the number and size of follicles (Table 1). Characteristics of couples in each trial are summarized in Supplementary Table S1.

Quality of studies

Upon the assessment according to the ROB2 tool, one RCT had a low risk of bias, one had some concerns, and two had a high risk of bias. Most concerns were in the domain of deviations from the intended interventions because blinding was not possible for this comparison (Fig. 2). There were no concerns regarding data integrity for trials that shared IPD.

Primary outcomes

Considering the time to conception resulting in live births, cumulative live birth rates were not significantly different between IVF

Table 1. Characteristics and design of studies included in an individual participant data meta-analysis of IVF versus IUI with ovarian stimulation for unexplained infertility.

Author (year)	Country	Sample size	Population			IVF		IUI-OS	
			Overall criteria	Criteria for female age	Criteria for semen analysis	Cycles	Embryo transfer	Cycles	Cancellation criteria
Elzeiny (2014)	Australia	44	Unexplained infertility; 2–3 preovulatory follicles at triggering	18–42 years	Normal semen*	1 stimulated cycle	S/DET; cleavage	1 cycle (gonadotrophin)	None
Bensdorp (2015)	The Netherlands	602	Unexplained/mild male infertility with an unfavorable prognosis.	18–38 years	Pre-wash total motile sperm count: >3 million	3 stimulated cycles or 6 modified natural cycles	SET; cleavage	6 cycles (Clomiphene citrate or gonadotrophin)	>3 follicles with a diameter of 16 mm or >5 follicles with a diameter of 12 mm
Custers (2011)	The Netherlands	116	Unexplained/mild male infertility with an unfavorable prognosis.	18–38 years	Pre-wash total motile sperm count: >3 million	1 stimulated cycle	SET**; cleavage	3 cycles (gonadotrophin)	>3 dominant follicles
Goverde (2000)	The Netherlands	172	Unexplained/male infertility	None	Post-wash progressively motile sperm: >1 million	6 stimulated cycles	S/D/TET***; cleavage	6 cycles of IUI-OS (gonadotrophin)	>3 follicles with a diameter of at least 18 mm or >6 follicles with a diameter of at least 14 mm

OS, ovarian stimulation; SET, single embryo transfer; DET, double embryo transfer; TET, triple embryo transfer.
* Normal semen: concentration ≥20 million/ml, progressive motility ≥25%, abnormal morphology ≤5%, and negative sperm antibodies.
** Two embryos were transferred when there were no good-quality embryos available.
*** Up to two embryos in women ≤35 years, and three in women >35 years.

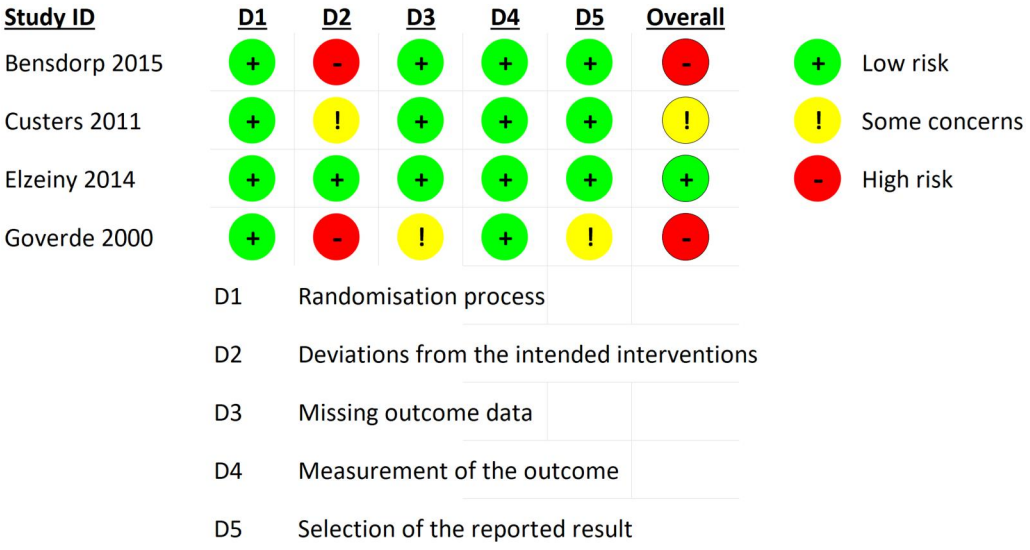


Figure 2. Risk of bias summary of the included RCTs according to the Risk of Bias 2 tool. RCT, randomized controlled trials.

and IUI-OS (4 RCTs, 908 couples, 50.3% versus 43.2%, HR 1.19, 95% CI 0.81–1.74, $I^2 = 42.4\%$; moderate certainty) (Fig. 3A). The time for 25% of the women to become pregnant which leads to live birth in the IVF and IUI-OS groups was 3.3 (95% CI 2.8–4.4) months and 4.0 (95% CI 3.2–5.3) months, respectively. For the safety primary outcome, the rates of multiple pregnancy were not significantly different between the two interventions (3 RCTs, 890 couples, 3.8% versus 5.2% of all couples randomized, OR 0.78, 95% CI 0.41–1.50, $I^2 = 0.0\%$; low certainty) (Fig. 3B, Table 2).

Secondary outcomes

We did not find significant differences between IVF and IUI-OS for live birth as a binary outcome (4 RCTs, 927 couples, OR 1.23, 95% CI 0.75–2.02, $I^2 = 49.0\%$) and clinical pregnancy (4 RCTs, 933 couples, OR 1.09, 95% CI 0.78–1.53, $I^2 = 14.3\%$). There was no indication that pregnancy loss was more common in IVF or IUI-OS (3 RCTs, 760 couples, OR 0.97, 95% CI 0.55–1.72, $I^2 = 0.0\%$). In terms of neonatal outcomes, there were no significant differences between the two interventions on gestational age (2 RCTs, 344 couples, weighted mean difference 0.08 weeks, 95% CI −0.58 to 0.75 weeks, $I^2 = 0.0\%$) and birthweight (2 RCTs, 342 couples, weighted mean difference 342.65 g, 95% CI −532.27 to 1217.57 g, $I^2 = 56.1\%$), although only two RCTs recorded these two outcomes. There were insufficient data or events for assessing OHSS, neonatal death, and congenital anomalies (Table 2).

Treatment–covariate interaction

Meta-analyses of interactions did not demonstrate significant effect modifications on cumulative live birth rate for female age, infertility duration, type of infertility, or TSMC. There were insufficient data to analyse interactions between the prognosis of couples and the treatment options because three RCTs only, or almost only, included poor prognosis couples (Table 3).

Sensitivity analysis and data unavailability bias

We performed a *post hoc* sensitivity analysis for primary outcomes that excluded participants who were allocated to IVF in a modified natural cycle in one trial. Cumulative live birth rates (4 trials, 718 couples, HR 1.22, 95% CI 0.85–1.75, $I^2 = 35.2\%$) and multiple pregnancy rates (3 trials, 696 couples, OR 0.84, 95% CI 0.42–1.66, $I^2 = 0.0\%$) were still not significantly different between IVF and IUI-OS.

We performed another *post hoc* sensitivity analysis by including reconstructed IPD for the first 3 months in one study that was classified as awaiting clarification (Goldman *et al.*, 2014). Censoring at the third month was to ensure that the follow-up time was consistent between IVF and IUI-OS and both interventions were ongoing during follow-up. The overall finding was consistent with the main finding (cumulative live birth rate: 5 trials, 1062 couples, HR 1.17, 95% CI 0.85–1.61, $I^2 = 27.7\%$) (Supplementary Fig. S1).

In comparing ORs for available outcomes in this IPD-MA to those generated in the 2019 Cochrane review using aggregate data (Wang *et al.*, 2019), the estimates were comparable for live birth, multiple pregnancy, and OHSS, suggesting the scale of data unavailability is likely small (Supplementary Table S2).

Discussion

This IPD-MA found no significant difference between IVF and IUI-OS in couples with unexplained infertility regarding cumulative live birth, multiple pregnancy, clinical pregnancy, pregnancy loss, gestational age at delivery, and birthweight at delivery. Subgroup analysis showed no significant difference in cumulative live birth in couples of differing female ages, duration of infertility, type of infertility, or sperm analysis results.

Strengths and limitations

An important utility of an IPD-MA, especially when compared to AD-MA, is the ability to analyse and compare time-to-event measurements and treatment effect modification. Traditional design that compares IVF and IUI-OS with a 1:1 ratio in terms of cycle number would provide biased results in favour of IVF because one cycle of IVF takes a longer time to complete and therefore more time to achieve pregnancy than one cycle of IUI-OS. In this IPD-MA, we were able to make fair comparisons in terms of time by standardizing follow-up time and analysing time-to-pregnancy leading to live birth. This approach addressed the issue of absent time limits or data compared on a per-cycle basis in some trials that introduced biases. The use of IPD provides greater analytical flexibility, allowing us to test the interaction between treatment and some baseline characteristics. Also, our study used the preferable outcome of cumulative live birth as the primary outcome in this analysis (Gadalla *et al.*, 2018). Lastly, a

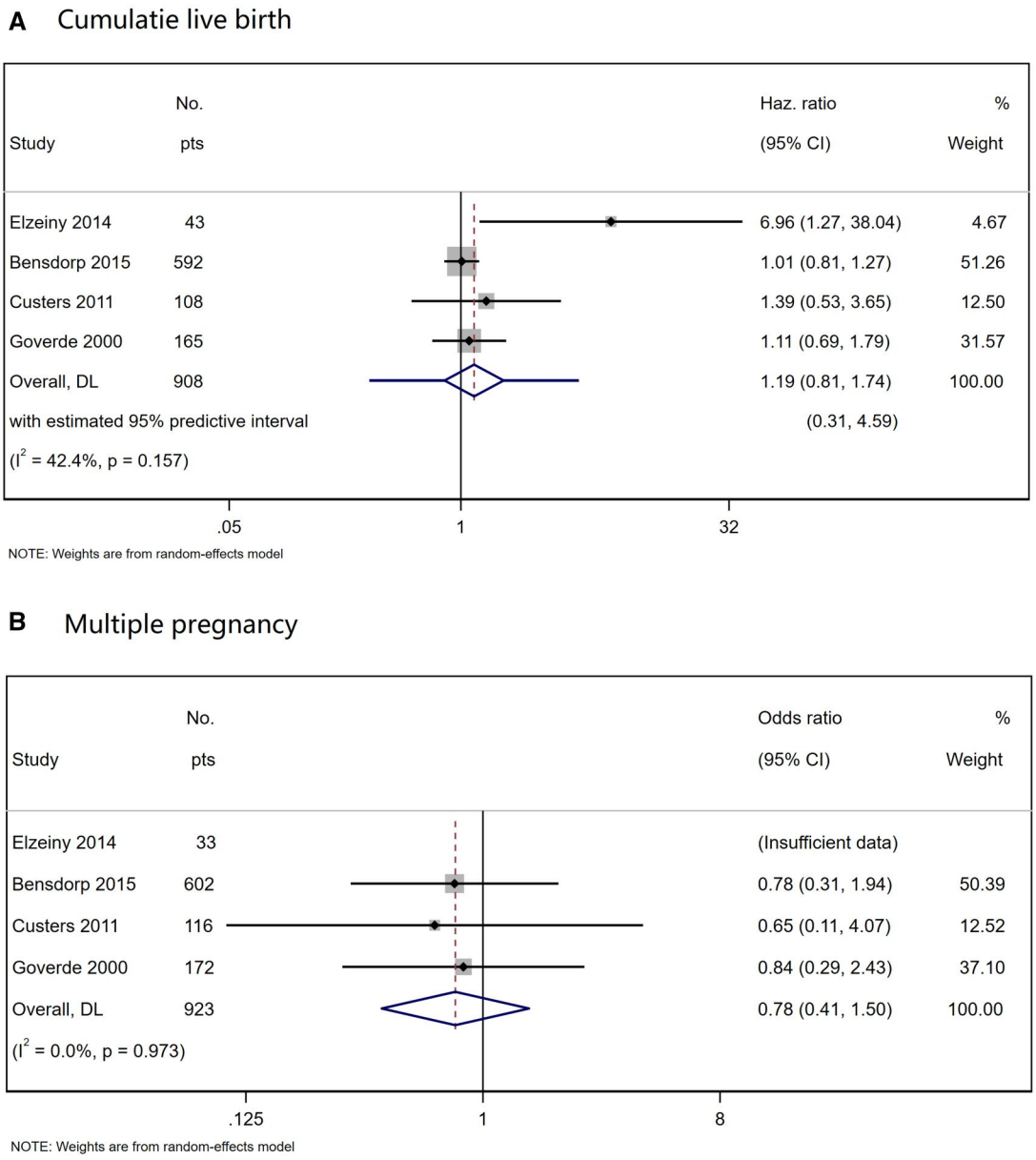


Figure 3. Forest plots for primary outcomes. (**A**) cumulative live birth; (**B**) multiple pregnancy. Comparisons were IVF versus IUI with ovarian stimulation (reference group). In each forest plot, the study level estimate was based on individual patient data (IPD) of each individual study and the summary estimate was based on a two-stage IPD meta-analysis. In (B), the study level estimate was not shown for Elzeiny (2014) because of the presence of 0 events in one group.

thorough and robust search strategy was implemented to ensure all eligible RCTs were included in our IPD requests to comprehensively include the existing literature.

This IPD-MA is limited by a few factors. Importantly, we were unable to obtain the IPD for all potentially eligible studies identified, although we did not observe differences, owing to the unavailability of the data. IPD were available for 66.7% (4/6) of the eligible studies, one trial that could not contribute data was unpublished and no results have been reported (Parinaud, n.d.). Difficulties in obtaining IPD from all studies from which it is sought is a known issue in performing IPD-MA and can result in a less comprehensive analysis of the study question (Ventresca *et al.*, 2020). IPD unavailability for this meta-analysis was to the result of data loss, no response to requests and investigators declining to participate. Our meta-analysis was also limited by insufficient data for some planned outcomes and subgroup analyses, in particular in couples with a good or moderate prognosis of natural conception. Similarly, some analysed outcomes were based on fewer included studies and therefore the subsequent results should be interpreted with caution.

Additionally, three out of four RCTs included in this study were conducted in the Netherlands (Goverde *et al.*, 2000; Custers *et al.*, 2011; Bensdorp *et al.*, 2015), which may limit the generalizability of the findings. Lastly, one included trial (Goverde *et al.*, 2000) dates to the late 1990s and the protocols used back then may not fully represent the effectiveness and safety of IVF and IUI-OS as they are nowadays, owing to improvements in OS and laboratory procedures, the increasing use of single embryo transfer in IVF, and the implementation of strict cancellation criteria in IUI-OS. However, the relative estimates for effectiveness and safety in this trial did not deviate much from those in more recent trials.

Table 2. Meta-analyses and GRADE assessments of primary and secondary outcomes.

Outcome	No. of trials	No. of women	OR/HR (95% CI)	I^2 (%)	Certainty of evidence
Multiple pregnancy	3	890	OR 0.78 (0.41–1.50)	0	Low[#]
Time to conception leading to live birth	4	908	HR 1.19 (0.81–1.74)	42.4	Moderate[†]
Live birth	4	927	OR 1.23 (0.75–2.02)	49.0	Moderate[†]
Clinical pregnancy	4	933	OR 1.09 (0.78–1.53)	14.3	High
OHSS	Insufficient data				
Pregnancy loss	3	760	OR 0.97 (0.55–1.72)	0	Low[#]
Neonatal death	Insufficient data				
Congenital anomaly	Insufficient data				
	No. of trials	**No. of women**	**MD (95% CI)**	**I^2 (%)**	**Certainty of evidence**
Gestational age (weeks)	2	344	0.08 (−0.58 to 0.75)	0	Low[*‡]
Birthweight (g)	2	342	342.65 (−532.27 to 1217.57)	56.1	Very low[*†‡]

OR, odds ratio; HR, hazard ratio; MD, mean difference; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; OHSS, ovarian hyperstimulation syndrome.
[#] Downgraded two levels for high imprecision.
[†] Downgraded one level for inconsistency.
[*] Downgraded one level for imprecision.
[‡] Downgraded one level for concerns about data completeness.

Table 3. Meta-analyses of treatment–covariate interaction on cumulative live birth.

Factor	No. of trials	No. of couples	Interaction HR (95% CI)	I^2 (%)
Age (years)	4	908	1.00 (0.95–1.05)	0
Infertility duration (months)	4	904	1.00 (0.99–1.01)	0
Type of infertility	3	865	1.32 (0.80–2.18)	0
Total motile sperm count (millions)	3	701	1.00 (0.99–1.01)	78.3
Prognosis for natural conception*	Insufficient data for interaction analysis because most couples had poor prognosis			

HR, hazard ratio.
[*] Probability of natural conception within 12 months resulting in live birth calculated with the Hunault model. Good prognosis: probability >40%. Moderate prognosis: probability between 30% and 40% inclusively; Poor prognosis: probability <30%.

Clinical interpretation

From our study, IVF and IUI-OS are shown to be both acceptable and successful methods of first choice for couples with unexplained infertility to achieve live birth and avoid multiple pregnancy. This conclusion does not deviate from findings from several previous systematic reviews, including a Cochrane review (Gunn and Bates, 2016; Wang *et al.*, 2019), although their findings were less precise and subject to a higher level of uncertainty. In addition, our evaluation of the effectiveness incorporated the time required to achieve pregnancy.

Our study contradicts another previous meta-analysis that found higher live birth rates with IVF compared to IUI-OS (Nandi *et al.*, 2022). This previous meta-analysis pooled data from all RCTs without considering differences in trial design and time frames in follow-up. The favourable effect of IVF in the binary outcome of live birth was driven by three RCTs that studied algorithms combining IVF and IUI-OS or compared the two interventions on a per-cycle basis (Reindollar *et al.*, 2010; Elzeiny *et al.*, 2014; Goldman *et al.*, 2014). This 'all in' approach resulted in a high heterogeneity between RCTs ($I^2 = 86\%$). Importantly, this previous meta-analysis was the only reference cited for the recommendation regarding the comparative effectiveness of IVF versus IUI in the 2023 unexplained infertility *Guideline of European Society of Human Reproduction and Embryology* (The Unexplained Infertility Guideline Group, 2023).

Reindollar *et al.* (2010) compared an accelerated strategy (three cycles of IUI–clomiphene citrate, followed by IVF) and a conventional strategy (three cycles of IUI–clomiphene citrate, followed by three cycles of IUI-gonadotrophins and then IVF). However, this study is sometimes misinterpreted as a head-to-head comparison of IVF with IUI-OS. In fact, this trial showed a shorter time to pregnancy leading to live birth (HR 1.25, 95% CI 1.00–1.56) because of the use of the accelerated strategy. This difference is not necessarily equivalent to a difference between IVF and IUI-OS if they were randomized from the start. It is worth noting that both arms received the same intervention in the first three cycles (IUI–clomiphene citrate) and therefore should expect similar outcomes within the first 3 months. However, in this timeframe, the Kaplan–Meier curve already showed faster pregnancy leading to live birth in the accelerated arm. In particular, the accelerated arm had an 8% higher pregnancy rate than the conventional arm at the moment of randomization. This may have occurred by chance or because of performance bias. Given that the chance of pregnancy after three cycles of IUI–clomiphene citrate became different in the two arms, we could not reconstruct useful data from the Kaplan–Meier curve of this trial to compare IUI–gonadotrophins with IVF for sensitivity analysis.

Goldman *et al.* (2014) compared two cycles of one of the following regimens: IUI–clomiphene citrate, IUI–gonadotrophin, or immediate IVF. This trial found, after two cycles of treatment, the immediate IVF group had a significantly shorter time to pregnancy than the IUI-OS group (HR 2.86; 95% CI 1.22–6.68). However, comparing these interventions on a per-cycle basis creates a time-led bias because one cycle of IUI takes less time than one cycle of IVF. As a result, two cycles of IUI were completed in about 3 months, while it took 6 months to complete two cycles of IVF. This introduces a bias in favour of IVF because counting the additional 3 months when only IVF was active during follow-up

skews the results. Using reconstructed data from the Kaplan–Meier curve of this trial, the chance of pregnancy leading to live birth was similar between IVF and IUI-OS within the first 3 months (HR 1.46; 95% CI 0.51–4.20).

One RCT included in our IPD-MA (Elzeiny *et al.*, 2014) showed a large treatment effect of IVF compared to IUI-OS even though we harmonized the follow-up time and used time-to-event analysis. This may partly be explained by the small study effects because it had a notably smaller sample size than the three other included RCTs (44 women versus 116, 172, 602 women). Also, in this RCT all women received the same OS protocol (recombinant FSH) for both IVF and IUI-OS and randomization was only carried out in those who had two or three preovulatory follicles at hCG injection, while the other three RCTs randomized couples at baseline and used treatment-specific OS protocols. Finally, the live birth rate in the IUI-OS group in this trial was lower than that in other trials.

Although the majority of the included studies were conducted in the Netherlands, the findings may still be considered generalizable to other countries, as the cycle-based live birth rates for IUI-OS and IVF were overall comparable to the corresponding live birth rates reported in the European and the US registries during the study period (Ferraretti *et al.*, 2013; Kupka *et al.*, 2014; de Geyter *et al.*, 2020). A more recent study using causal inference methods to emulate a target trial based on a large observational database of US administrative claims of >29 000 women found that one cycle of IVF and three cycles of IUI were comparable in terms of live birth rates (Chiu *et al.*, 2022). This is consistent with the findings from this IPD-MA. As our sensitivity analysis showed, a similar estimate was also seen in the first 3 months of the Goldman 2014 trial which was performed in the USA (Goldman *et al.*, 2014).

There have been concerns about the unpopularity of the use of IUI in clinical practice, but a survey among the UK clinics showed 96% of clinics continued to offer IUI despite the recommendation of the NICE guideline against the use of IUI for unexplained infertility (Kim *et al.*, 2015). Moreover, a recent analysis of the European registry data showed a relatively consistent use of IUI in Europe over the past decade, with ~150 000 cycles per year (Wessel *et al.*, 2023).

The population in the included studies was mostly restricted to couples with a poor prognosis of natural conception based on the Hunault prediction model (Hunault *et al.*, 2004). As a result, the median duration of infertility was over 2 years, which might be longer than general couples in some settings. This should also be considered when extrapolating the findings. Also, it is important to note that the studies we looked at only involved IUI cycles with OS. This means that the results may not apply to IUI in natural cycles. Most of the included studies used gonadotrophin as the drug for OS, except for the largest one where either gonadotrophin or clomiphene citrate was used (Bensdorp *et al.*, 2015). The latest IPD-MA of OS strategies in IUI cycles has shown that the use of gonadotrophins generally leads to higher live birth rates than clomiphene citrate, at the cost of a higher multiple pregnancy rate. However, if strict cancellation criteria and lower starting doses are used, comparable live birth rates and multiple pregnancy rates can be achieved for different agents (Wessel *et al.*, 2022). Therefore, our findings may be relevant to other OS strategies besides gonadotrophins, but caution is needed when interpreting the results.

When choosing between IVF and IUI-OS, couples may take into account not only effectiveness and safety but also financial considerations. The cost of ART can often be a barrier to couples seeking treatment, and the amount can quickly accrue depending on the nature and number of procedures undertaken (Chambers *et al.*, 2013; Mosalanejad *et al.*, 2013). Therefore, cost-effectiveness is an important decision-making factor, especially in countries where IVF or IUI-OS is not publicly funded (Connolly *et al.*, 2010). To this effect, given there is a negligible difference in clinical outcomes between IVF and IUI-OS, the cost may be the deciding factor. Economic evaluations between these two treatments have been conducted in different countries. Data from Australia, the Netherlands, and UK showed a significantly higher cost associated with IVF compared to IUI-OS (Chambers *et al.*, 2010; Van Rumste *et al.*, 2014; Tjon-Kon-Fat *et al.*, 2015). Therefore, the overall cost-effectiveness would depend on the willingness to pay for an additional healthy live birth from the society's perspective and it would be helpful to establish the country-specific cost-effectiveness of both interventions to form policy. This would play an even more important role in developing countries owing to limited resources and financial constraints (Darvishi *et al.*, 2020). The data on the preferences of the couples are relatively limited. Earlier studies showed that although the dropout rates between IVF and IUI-OS were comparable, most of the couples would prefer continuing IUI over IVF within the first three cycles of IUI-OS, with a clear shift in favour of IVF after six cycles (van Weert *et al.*, 2007; Bensdorp *et al.*, 2016). Interestingly, such a difference in preference was not affected by the risk of multiple pregnancies (van Weert *et al.*, 2007). It should be noted that these preference studies were both carried out in the Netherlands, which may limit its generalizability.

Research implications

The relative lack of eligible studies from our literature search and the subsequent lack of IPD received from requests highlight the need for more large and well-designed trials to contribute to the overall data pool. Given our insufficient sub-analysis on different prognosis groups, these subgroup results are not definite. We encourage more research that randomizes couples of differing prognostic groups—on their chances of natural conception, in particular those who have a moderate prognosis.

It is important to recognize that reporting cumulative rates is a significantly more objective method to evaluate clinical success, especially in situations that involve time-varying interventions such as ART (Gadalla *et al.*, 2018). The design and analysis of interventions regarding infertility usually need to consider the cumulative effect in multiple cycles rather than the first cycle. Also, it is important to compare interventions on a fair time basis, which is not necessarily equivalent to the same number of cycles because different interventions could take up different times in one cycle. A fair comparison can be set up by following up all cycles of interventions within a reasonable period, usually 12 or 18 months since randomization. Given the lack of data on long-term outcomes, including obstetrics, perinatal, and childhood outcomes, future research assessing IVF compared to IUI-OS may choose to include these measures that are also relevant to couples of unexplained infertility.

IPD-MAs are well regarded and recognized for their utility in informing study design and interpreting intervention effects (Tierney *et al.*, 2015). Given the increasing use of IPD-MA to guide evidence-based medicine, it is important to recognize the obstacles faced when attempting to complete them. For this study in particular, the lack of access to eligible data may increase uncertainty in our overall results and highlight a need for better data-sharing practices, culture, processes, and policies in the research landscape (Polanin and Williams, 2016; Ventresca *et al.*, 2020).

Conclusion

In conclusion, this IPD-MA demonstrates that for women with unexplained infertility, there is no significant difference in effectiveness or safety outcomes when undergoing IVF compared to IUI-OS. There is no evidence that IVF reduces the time to pregnancy leading to live birth compared to IUI-OS. Both interventions are viable options for managing unexplained infertility. Their costs and the preference of couples need to be weighed in clinical decision-making.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

The data underlying this article were provided by author groups of included studies under separate data transfer agreements. Data will be shared on reasonable request to the corresponding author with permission of all author groups and institutions where data are owned.

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Authors' roles

W.L. and B.W.M. designed the meta-analysis and were responsible for overseeing all aspects of conduct. R.W., M.v.W., C.F., and M.C. contributed to the design of the study. S.L. and W.L. contributed to various stages of the project including literature search, eligibility screening, data extraction, risk of bias assessment, IPD checking and trial analysis. S.L. managed the project and collaborative process, W.L. carried out data synthesis. M.v.W., A.J.G., I. M.C., A.J.B., and H.E. provided data of trials. S.L. and R.W. wrote the manuscript revised by W.L. with input from all authors. All authors had opportunities to comment on the interpretation of results and were involved in the decision to submit the manuscript. Trial investigators also prepared and supplied data and answered questions about their trials.

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Conflict of interest

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