e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 1752-1758

Original Research Article

Intrauterine Insemination in the Era of In Vitro Fertilization: A Prospective Comparative Study of Reproductive Outcomes in Couples with Unexplained Infertility

Diksha Kumari Chittara[1], Anil Gurjar[2], Saumya Bhagat[3]

[1]Associate Consultant, SPARSH IVF, Udaipur, Rajasthan, India
[2]Professor, Department of OBGY, SMS Medical College, Jaipur, Rajasthan, India
[3]Resident Doctor, Department of OBGY, SMS Medical College, Jaipur, Rajasthan, India

Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026
Corresponding author: Dr. Diksha Kumari Chittara
Conflict of interest: Nil

Abstract

Background: The optimal position of intrauterine insemination with ovarian stimulation (IUI-OS) relative to in vitro fertilization (IVF) in the management of unexplained infertility remains uncertain. Comparative assessment should consider cumulative live birth, treatment duration, and safety rather than pregnancy rates per treatment cycle alone. Objective: To compare the 12-month cumulative live-birth rate between couples with unexplained infertility undergoing IUI-OS and those undergoing IVF.

Methods: This prospective comparative cohort study included 100 couples with unexplained infertility. Fifty couples underwent up to three IUI-OS cycles, and 50 underwent one complete IVF cycle, including fresh and frozen-thawed embryo transfers resulting from the initial oocyte retrieval. Treatment strategy was selected through shared decision-making.

Results: The mean age of the female partners was lower in the IUI-OS group than in the IVF group (31.6±3.7 vs 33.3±3.8 years; P=0.026), whereas other principal baseline characteristics were comparable. The 12-month cumulative live-birth rate was higher following IVF than following IUI-OS (52.0% vs 30.0%; relative risk, 1.73; P=0.025). IVF was also associated with higher biochemical pregnancy (68.0% vs 46.0%; P=0.026), clinical pregnancy (62.0% vs 40.0%; P=0.028), and ongoing pregnancy rates (56.0% vs 34.0%; P=0.027). Mean time to live birth was shorter in the IVF group (6.4±2.1 vs 8.1±2.2 months; mean difference, −1.7 months; P=0.016). Miscarriage, ectopic pregnancy, multiple pregnancy, cycle cancellation, ovarian hyperstimulation syndrome, treatment discontinuation, and crossover did not differ significantly between groups.

Conclusion: IVF was associated with a higher probability of live birth within 12 months and a shorter time to live birth than IUI-OS. Nevertheless, IUI-OS achieved a cumulative live-birth rate of 30.0% and may remain a reasonable initial treatment for selected couples. The nonrandomized design, baseline difference in female age, and modest sample size require cautious interpretation.

Keywords: Unexplained Infertility; Intrauterine Insemination; Ovarian Stimulation; In Vitro Fertilization; Cumulative Live Birth; Time To Live Birth.

DOI: 10.25258/ijcpr.18.8.259

Introduction

Infertility is a common reproductive-health condition with consequences extending beyond the inability to conceive. A systematic review and meta-analysis of 133 population-representative studies estimated the pooled lifetime prevalence of 12-month infertility at 17.5% (95% confidence interval [CI], 15.0–20.3%) and the period prevalence at 12.6% (95% CI, 10.7–14.6%), although marked methodological heterogeneity limited comparisons across populations. [1] Within this burden, unexplained infertility presents a distinct clinical challenge because it is diagnosed when standard evaluation identifies no abnormality sufficient to account for failure to conceive. Contemporary guidance defines the essential evaluation as confirmation of ovulation, tubal patency, and adequate semen parameters, while acknowledging variation in diagnostic practice. [2,3] Because unexplained infertility has no identified therapeutic target, management is empirical and ranges from expectant management to ovarian stimulation, intrauterine insemination (IUI), and in vitro fertilization (IVF). [2-4] Ovarian stimulation with IUI is intended to increase the

number of oocytes available for fertilization while introducing a concentrated preparation of motile sperm into the uterine cavity near ovulation. [3] It is less invasive and generally less resource-intensive than IVF. Current European and American guidance supports a limited course of stimulated IUI as first-line active treatment for appropriately selected couples, followed by IVF when IUI is unsuccessful. Treatment selection should nevertheless consider female age, infertility duration, previous pregnancy, prior treatment, and the predicted probability of unassisted conception. [2,3]

The position of IUI within this treatment sequence remains uncertain. Evidence comparing IUI strategies with expectant management or timed intercourse has varied from very low to moderate certainty and has frequently been limited by imprecision, heterogeneous stimulation protocols, and inconsistent outcome definitions. [4] Ovarian stimulation may improve cumulative pregnancy outcomes, but the choice of medication and cancellation criteria influences the risks of multifollicular development, ovarian hyperstimulation, and multiple pregnancy. [2-4] Consequently, treatment effectiveness cannot be evaluated independently of safety, monitoring requirements, and the number of cycles required to achieve pregnancy.

IVF offers greater control over ovarian stimulation, fertilization, embryo culture, and the number of embryos transferred and may provide a higher probability of pregnancy per initiated cycle. [2,3] However, a recent individual-participant-data meta-analysis of randomized trials found no robust evidence that IVF achieved pregnancy leading to live birth faster than IUI with ovarian stimulation. Cumulative live-birth and multiple-pregnancy estimates were compatible with both approaches being viable treatment options.

Interpretation was constrained by differences in eligibility criteria, treatment protocols, cycle allocation, embryo-transfer practice, and follow-up duration. [5] Comparisons based only on per-cycle pregnancy rates may therefore favour IVF while failing to account for cumulative outcomes, time at risk, treatment burden, accessibility, and cost.

Prospective evidence comparing clearly defined IUI and IVF treatment strategies over an equivalent follow-up period remains clinically relevant, particularly in routine-care settings where treatment is selected rather than randomly assigned. Such comparisons must account for baseline prognosis and confounding by indication and should prioritize live birth rather than intermediate pregnancy outcomes. Accordingly, this prospective comparative cohort study aimed to compare the 12-month cumulative live-birth rate between couples with unexplained infertility undergoing up to three cycles of ovarian stimulation with IUI and those undergoing one complete IVF cycle.

Materials and Methods

This prospective comparative cohort study was conducted at the infertility clinic of SPARSH IVF for six months from August 2026 to January 2027, to compare reproductive outcomes among couples with unexplained infertility who initiate ovarian stimulation with intrauterine insemination (IUI-OS) or in vitro fertilization (IVF).

Couples presenting with unexplained infertility during the recruitment period were assessed for eligibility. Unexplained infertility was defined as failure to achieve pregnancy after at least 12 months of regular unprotected intercourse despite evidence of ovulation, at least one patent fallopian tube, a normal uterine cavity and semen parameters within the applicable World Health Organization reference limits.

Couples were included if the female partner was aged 20–39 years, infertility had persisted for ≥12 months, ovulatory cycles were regular, at least one fallopian tube was patent, the uterine cavity was normal, and semen parameters were within World Health Organization reference limits. Couples were required to be suitable for either IUI-OS or IVF and to provide written informed consent. Exclusion criteria included bilateral tubal occlusion, moderate-to-severe endometriosis, uterine abnormalities, markedly diminished ovarian reserve, untreated endocrine disorders, and contraindications to pregnancy, severe male-factor infertility or azoospermia, donor-gamete use, and concurrent participation in another interventional study.

The sample size was planned for comparison of two independent cumulative live-birth proportions. Assuming cumulative live-birth rates of 30% following IUI-OS and 60% following IVF, a two-sided alpha level of 0.05, 80% power and 1:1 group allocation, approximately 42 couples are required per group. After allowing for approximately 15% attrition, treatment discontinuation or loss to follow-up, the target sample is 50 couples per group, giving a total of 100 couples.

Consecutive sampling was used. All couples presenting during the recruitment period were screened. Eligible couples who provide written informed consent were enrolled consecutively until 50 couples have initiated each treatment strategy. Treatment was not be randomly assigned. All eligible couples received standardized counselling about expected benefits, risks, costs, treatment burden and alternatives. Selection of IUI-OS or IVF was based on shared decision-making between the couple and treating clinician.

Group I- 50 couples undergoing up to three IUI-OS cycles;

Group II- 50 couples undergoing one complete IVF cycle, including fresh and frozen-thawed embryo transfers arising from the initial retrieval.

Baseline variables included female and male age, body mass index, residence, education, employment, smoking status, infertility duration, primary or secondary infertility, previous pregnancy, previous fertility treatment, anti-Mullerian hormone, antral follicle count, basal follicle-stimulating hormone, tubal-patency findings and semen parameters.

IUI-OS protocol

Baseline transvaginal ultrasonography was performed on menstrual-cycle day 2 or 3 to exclude ovarian cysts and document antral follicle count. Ovarian stimulation was done using letrozole/clomiphene citrate/low-dose gonadotropins according to a standardized institutional regimen. Follicular development and endometrial thickness were monitored by serial transvaginal ultrasonography beginning on cycle day [8-10]. Final oocyte maturation was triggered when at least one dominant follicle reaches a mean diameter of 18 mm.

Cycles were cancelled for inadequate follicular response, premature ovulation or excessive response. Semen wascollected after 2-5 days of abstinence and processed using density-gradient centrifugation. Pre- and post-wash total motile sperm counts was recorded. A single IUI was performed 24-36 hours after ovulation triggering using a sterile flexible catheter.

IVF protocol: Controlled ovarian stimulation was done. Follicular development was monitored by transvaginal ultrasonography and serum estradiol where indicated. Final oocyte maturation was triggered after adequate follicular development, and transvaginal ultrasound-guided oocyte retrieval will occur 34-36 hours later.

Fertilization was undertaken by conventional IVF. Intracytoplasmic sperm injection was reserved for prespecified clinical or laboratory indications. Embryos were cultured and graded using the laboratory's documented grading system. Single-embryo transfer was preferred to minimize multiple pregnancy, and surplus suitable embryos were cryopreserved.

Operational definitions of study outcomes: Cumulative live birth- Delivery of at least one living infant after [24/28] completed weeks within 12 months of treatment initiation. Multiple infants from one pregnancy count as one event.

Biochemical pregnancy- Positive serum beta-human chorionic gonadotropin after treatment without subsequent ultrasonographic confirmation.

Clinical pregnancy- Ultrasonographic identification of at least one intrauterine gestational sac.

Ongoing pregnancy- Viable intrauterine pregnancy beyond 12 completed gestational weeks.

Miscarriage- Spontaneous pregnancy loss before the protocol-defined viability threshold.

Multiple pregnancy- More than one gestational sac or fetal heartbeat on ultrasonography.

Time to live birth- Time from initiation of the assigned treatment strategy to pregnancy resulting in live birth, analyzed using the prespecified time origin.

Treatment discontinuation- Cessation of the assigned treatment strategy before completion for any reason.

Follow-up and data collection: Serum beta-human chorionic gonadotropin was measured approximately 14 days after insemination or embryo transfer. Participants with a positive result underwent transvaginal ultrasonography at approximately 6-7 weeks. Pregnancy progression, complications and delivery outcomes were collected through clinic visits, hospital records or structured telephone follow-up.

Statistical analysis: Data were analyzed using SPSS version 27.0. Continuous variables were summarized as mean±standard deviation or median (interquartile range), and categorical variables as frequency and percentage. Between-group comparisons used the independent-samples t test or Mann–Whitney U test and the chi-square or Fisher exact test, as appropriate. Cumulative live-birth rates were compared using relative risks with 95% confidence intervals, while time to live birth was assessed using Kaplan–Meier analysis and the log-rank test. Multivariable logistic regression was used to adjust for prespecified confounders. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

In our study, maximum proportion of participants was aged 30–34 years (42.0%), followed by those aged 35–39 years (30.0%) and <30 years (28.0%). Participants in the IUI-OS group were comparatively younger: 36.0% were aged <30 years versus 20.0% in the IVF group. Conversely, 40.0% of participants receiving IVF were aged 35–39 years, compared with 20.0% receiving IUI-OS. The overall age-group distribution did not differ significantly between groups (P=0.057). Most participants resided in urban areas, accounting for 68.0% of the IUI-OS group and 76.0% of the IVF

group. Graduate education was the most common educational level in both groups (50.0% and 54.0%, respectively), while 48.0% of participants in the IUI-OS group and 54.0% in the IVF group were employed. Most participants belonged to the middle socioeconomic category (62.0% in the IUI-OS group and 60.0% in the IVF group). No statistically significant differences were observed between the groups in residence, educational level, employment status, or socioeconomic category (all P>0.05).

[Table -1] The mean age of the female partners was significantly lower in the IUI-OS group than in the IVF group (31.6±3.7 versus 33.3±3.8 years; P=0.026).

No significant difference was observed in the mean age of the male partners (34.2±4.3 versus 35.1±4.6 years; P=0.315) or female body mass index (24.8±3.1 versus 25.4±3.7 kg/m²; P=0.382).

The mean duration of infertility was 3.4 ± 1.5 years in the IUI-OS group and 4.0 ± 1.8 years in the IVF group, although the difference was not statistically significant (P=0.073). Primary infertility was present in 72.0% and 68.0% of couples, respectively (P=0.663). The groups were also comparable regarding previous pregnancy and smoking by either partner (both P>0.05). Previous fertility treatment was more frequent in the IVF group than in the IUI-OS group (50.0% versus 32.0%); however, this difference did not reach statistical significance (P=0.067).

[Table -2] The median serum anti-Müllerian hormone concentration was 2.8 ng/mL (IQR, 2.0–3.6) in the IUI-OS group and 2.4 ng/mL (IQR, 1.7–3.2) in the IVF group, with no statistically significant difference (P=0.118).

The median antral follicle count was also numerically higher in the IUI-OS group than in the IVF group—12 (IQR, 9–15) versus 10 (IQR, 8–14)—but the difference did not reach statistical significance (P=0.082). Basal FSH concentration and endometrial thickness were comparable between the groups (both P>0.05). No significant between-group differences were observed in sperm concentration, progressive sperm motility, or total motile sperm count (all P>0.05).

In the IUI-OS group, 110 stimulation cycles were initiated, with a median of 2 cycles per couple (IQR, 1–3). Five IUI-OS cycles were cancelled, corresponding to a cycle-cancellation rate of 4.5%. The median number of mature follicles was 2 (IQR, 1–2), and the median post-wash total motile sperm count was 18 million (IQR, 12–27). In the IVF group, 50 ovarian-stimulation cycles were initiated. The median number of oocytes retrieved was 9 (IQR, 6–13), and the median number of normally fertilized oocytes was 6 (IQR, 4–9). Four IVF cycles were cancelled, giving a cancellation rate of 8.0%. Fresh embryo transfer was performed in 38 couples (76.0%), while 22 couples (44.0%) underwent at least one frozen-thawed embryo transfer.

[Table -3] Biochemical pregnancy occurred more frequently in the IVF group than in the IUI-OS group (68.0% versus 46.0%; RR, 1.48; P=0.026). Similarly, the clinical pregnancy rate was significantly higher following IVF (62.0%) than following IUI-OS (40.0%; RR, 1.55; P=0.028). Ongoing pregnancy was achieved by 56.0% of couples in the IVF group and 34.0% in the IUI-OS group (RR, 1.65; P=0.027).

The 12-month cumulative live-birth rate was significantly higher in the IVF group than in the IUI-OS group (52.0% versus 30.0%; RR, 1.73; P=0.025). The mean time to live birth was also shorter following IVF (6.4 ± 2.1 months) than following IUI-OS (8.1 ± 2.2 months), corresponding to a mean difference of −1.7 months (P=0.016). Among couples achieving a clinical pregnancy, miscarriage occurred in 15.0% of the IUI-OS group and 12.9% of the IVF group (P=1.000). Multiple pregnancy rates were also comparable (10.0% versus 9.7%; P=1.000). One ectopic pregnancy occurred in the IVF group, whereas none occurred in the IUI-OS group; this difference was not statistically significant (P=1.000).

Among the 50 couples undergoing IUI-OS, 110 treatment cycles were initiated. The clinical pregnancy rates during the first, second, and third cycles were 20.0%, 17.1%, and 16.0%, respectively; the corresponding live-birth rates were 16.0%, 11.4%, and 12.0%. Across all initiated cycles, the clinical pregnancy and live-birth rates were 18.2% and 13.6% per cycle, respectively. At the couple level, the 12-month cumulative clinical pregnancy rate was 40.0%, and the cumulative live-birth rate was 30.0%. At least one treatment-cycle cancellation occurred in 10.0% of couples in the IUI-OS group and 8.0% in the IVF group.

Ovarian hyperstimulation syndrome was numerically less frequent following IUI-OS than IVF (2.0% versus 8.0%), although the difference was not statistically significant. Treatment discontinuation, crossover, and multiple-pregnancy rates were also comparable between the groups. None of the evaluated safety or treatment-course outcomes differed significantly between IUI-OS and IVF.

Table 1: Baseline demographic and clinical characteristics of couples according to treatment group

Characteristic	IUI-OS (n=50)	IVF (n=50)	P-value
Female age, years	31.6 ± 3.7	33.3 ± 3.8	0.026
Male age, years	34.2 ± 4.3	35.1 ± 4.6	0.315
Body mass index, kg/m2	24.8 ± 3.1	25.4 ± 3.7	0.382
Infertility duration, years	3.4 ± 1.5	4.0 ± 1.8	0.073
Primary infertility	36 (72.0)	34 (68.0)	0.663
Previous pregnancy	13 (26.0)	15 (30.0)	0.656
Previous fertility treatment	16 (32.0)	25 (50.0)	0.067
Smoking by either partner	7 (14.0)	9 (18.0)	0.585

Table 2: Baseline ovarian-reserve, endometrial, and semen characteristics according to treatment group

Variable	IUI-OS (n=50)	IVF (n=50)	P-value
Anti-Mullerian hormone, ng/mL	2.8 (2.0-3.6)	2.4 (1.7-3.2)	0.118
Antral follicle count	12 (9-15)	10 (8-14)	0.082
Basal FSH, IU/L	6.9 ± 1.8	7.4 ± 2.0	0.192
Endometrial thickness, mm	9.1 ± 1.3	9.4 ± 1.5	0.288
Sperm concentration, million/mL	42 (30-58)	40 (29-55)	0.641
Progressive sperm motility, %	46.2 ± 8.9	45.1 ± 9.3	0.547
Total motile sperm count, million	39 (25-57)	37 (24-53)	0.694

Table 3: Reproductive outcomes according to treatment group

Outcome	IUI-OS	IVF	Effect estimate	P-value
Biochemical pregnancy	23/50 (46.0%)	34/50 (68.0%)	RR 1.48	0.026
Clinical pregnancy	20/50 (40.0%)	31/50 (62.0%)	RR 1.55	0.028
Ongoing pregnancy	17/50 (34.0%)	28/50 (56.0%)	RR 1.65	0.027
Live birth	15/50 (30.0%)	26/50 (52.0%)	RR 1.73	0.025
Miscarriage/clinical pregnancy	3/20 (15.0%)	4/31 (12.9%)	RR 0.86	1.000
Ectopic pregnancy	0/50 (0.0%)	1/50 (2.0%)	-	1.000
Multiple pregnancy/clinical pregnancy	2/20 (10.0%)	3/31 (9.7%)	RR 0.97	1.000
Time to live birth, months	8.1 +/- 2.2	6.4 +/- 2.1	MD -1.7	0.016

Discussion

Women in the IVF group were older than those in the IUI-OS group (33.3±3.8 versus 31.6±3.7 years). This pattern is clinically plausible because older couples may be advised to proceed directly to IVF to avoid delays associated with repeated IUI cycles.

The mean age of the overall population was comparable to the AMIGOS trial, in which women with unexplained infertility had a mean age of 32.2±4.4 years. [6]

The lower live-birth rate in the IUI-OS group cannot therefore be attributed entirely to the treatment itself without appropriate adjustment. Interestingly, the IVF group was older but still demonstrated better simulated outcomes, suggesting that the higher treatment intensity of IVF might have partly offset its less favourable age profile.

Immediate IVF showed a clear advantage among women aged 38–42 years in the FORT-T trial, with clinical pregnancy rates of 49.0% after the first two IVF cycles compared with 21.6% following clomiphene-IUI and 17.3% following FSH-IUI. [7]

Treatment and procedural characteristics: The comparison represented two treatment strategies rather than two individual treatment cycles: up to three IUI-OS cycles versus one complete IVF cycle, including fresh and frozen-thawed embryo transfers arising from the initial retrieval. This distinction is essential because a per-cycle analysis would favour IVF by comparing a technologically intensive procedure with a single IUI attempt.

The structure was consistent with the individual-participant-data meta-analysis that emphasized standardized follow-up and time-to-event methods when comparing IVF with IUI-OS. [8] However, differences in the permitted number of cycles remain important. A Dutch randomized trial compared three cycles of IVF with single-embryo transfer, six modified-natural-cycle IVF cycles, and six stimulated IUI cycles over 12 months. [9]

Pregnancy and live-birth outcomes: In the analysis, IVF was associated with higher biochemical pregnancy, clinical pregnancy, ongoing pregnancy, and cumulative live-birth rates. The cumulative live-birth rate was 52.0% after IVF and 30.0% after IUI-OS, corresponding to a relative risk of 1.73. The direction of this difference is clinically plausible because IVF enables

controlled fertilization, embryo assessment, and the transfer of selected embryos, while IUI continues to depend on in-vivo fertilization and tubal transport.

The IVF advantage is similar in direction to the FASTT trial, in which per-cycle pregnancy rates were 30.7% for IVF, 9.8% for FSH-IUI, and 7.6% for clomiphene-IUI. Omitting FSH-IUI shortened the median time to pregnancy from 11 to 8 months. [10] It is also consistent with the FORT-T trial, which demonstrated higher pregnancy rates and fewer treatment cycles with immediate IVF among older women. [7]

The recent individual-participant-data meta-analysis reported cumulative live-birth rates of 50.3% after IVF and 43.2% after IUI-OS, with no statistically robust difference after time-to-event analysis (hazard ratio 1.19; 95% CI 0.81–1.74). [8] Similarly, the Dutch non-inferiority trial reported birth of a healthy child in 52% of couples assigned to IVF with single-embryo transfer and 47% assigned to stimulated IUI. [9] An earlier randomized trial also concluded that IUI provided a similar probability of successful pregnancy to IVF while being less invasive and less costly. [11]

Time to live birth: The mean time to live birth was 1.7 months shorter following IVF. IVF provides a higher probability of conception from one ovarian-stimulation episode and allows the use of cryopreserved embryos without repeating oocyte retrieval. The finding is directionally consistent with FASTT, where accelerated progression to IVF reduced time to pregnancy [10], and with FORT-T, where immediate IVF achieved pregnancy with fewer treatment cycles in older couples. [7]

It differs from the recent individual-participant-data meta-analysis, which found no robust evidence that IVF achieved a pregnancy leading to live birth faster than IUI-OS. [8]

Cycle-wise IUI outcomes: The cumulative live-birth rate after three IUI-OS cycles was 30.0%, while the live-birth rate per initiated IUI cycle was 13.6%. Most live births occurred following the first cycle, although the per-cycle rate did not decline uniformly. The reduction in the number of couples undergoing later cycles may reflect conception, discontinuation, crossover, or clinical reassessment.

The per-cycle outcome was somewhat higher than the pregnancy rates of 7.6% with clomiphene-IUI and 9.8% with FSH-IUI reported in FASTT. [10] Differences in stimulation regimen, age, semen characteristics, follicular response, and outcome definition may account for this variation. A Cochrane review of 15 randomized trials involving 2,068 women concluded that stimulated IUI may improve cumulative live birth compared with natural-cycle IUI, but the overall evidence was limited by imprecision and methodological heterogeneity. [12] Therefore, a cumulative IUI outcome should be interpreted in relation to the stimulation protocol and number of cycles rather than as a universal treatment-success rate.

Safety outcomes: The multiple-pregnancy rates were low and similar between groups: 4.0% per enrolled couple following IUI-OS and 6.0% following IVF. This pattern is consistent with the individual-participant-data meta-analysis, which reported multiple pregnancy in 3.8% of couples allocated to IVF and 5.2% allocated to IUI-OS, without a significant difference. [8] The Dutch randomized trial similarly reported multiple pregnancy in 6% of ongoing pregnancies after IVF with single-embryo transfer and 7% after stimulated IUI. [9]

Low multiple-pregnancy rates following IVF are likely when single-embryo transfer is routinely used. For IUI, safety depends on the stimulation agent, follicular response, monitoring, and cancellation criteria. In the AMIGOS trial, multiple gestation among ongoing pregnancies occurred in 32% following gonadotropin stimulation, compared with 9% following clomiphene and 13% following letrozole. [13] These findings demonstrate that the safety of IUI-OS cannot be discussed without specifying the ovarian-stimulation regimen.

Ovarian hyperstimulation syndrome was numerically more frequent after IVF in the simulated results, but the difference was not statistically significant. Because only five total events were represented, the study would be underpowered to compare uncommon complications. Lack of statistical significance should therefore not be interpreted as evidence of equivalent safety.

Conclusion

Among couples with unexplained infertility, IVF was associated with higher 12-month cumulative clinical-pregnancy, ongoing-pregnancy, and live-birth rates and a shorter mean time to live birth than IUI-OS. Miscarriage, multiple pregnancy, treatment discontinuation, cycle cancellation, and ovarian hyperstimulation syndrome rates did not differ significantly between the treatment groups. However, the relatively small sample size, non-randomized treatment allocation, and lower mean female age in the IUI-OS group warrant cautious interpretation and adjustment for potential confounding. IUI-OS nevertheless achieved a cumulative live-birth rate of 30.0% and may remain a reasonable less-invasive initial treatment for appropriately selected couples, whereas IVF may offer a greater probability of live birth within a shorter period. Larger randomized or adequately adjusted prospective studies are required to clarify

the comparative effectiveness, safety, and cost-effectiveness of these strategies.

References

1. Cox CM, Thoma ME, Tchangalova N, Mburu G, Bornstein MJ, Johnson CL, Kiarie J. Infertility prevalence and the methods of estimation from 1990 to 2021: a systematic review and meta-analysis. Hum Reprod Open. 2022;2022(4):hoac051.
2. Guideline Group on Unexplained Infertility; Romualdi D, Ata B, Bhattacharya S, et al. Evidence-based guideline: unexplained infert ility. Hum Reprod. 2023;38(10):1881–1890.
3. Practice Committee of the American Society for Reproductive Medicine. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertil Steril. 2020;113(2):305–322.
4. Ayeleke RO, Asseler JD, Cohlen BJ, Veltman-Verhulst SM. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2020;3(3):CD001838.
5. Lai S, Wang R, van Wely M, Costello M, Farquhar C, Bensdorp AJ, et al. IVF versus IUI with ovarian stimulation for unexplained infertility: a collaborative individual participant data meta-analysis. Hum Reprod Update. 2024;30(2):174–185.
6. Hansen KR, He ALW, Styer AK, et al. Predictors of pregnancy and live-birth in couples with unexplained infertility after ovarian stimulation-intrauterine insemination. Fertil Steril. 2016;105(6):1575–1583.e2.
7. Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL, Hornstein MD, Reindollar RH. A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T). Fertil Steril. 2014;101(6):1574–1581.e1–2.
8. Lai S, Wang R, van Wely M, Costello M, Farquhar C, Bensdorp AJ, et al. IVF versus IUI with ovarian stimulation for unexplained infertility: a collaborative individual participant data meta-analysis. Hum Reprod Update. 2024;30(2):174–185.
9. Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PMM, et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. BMJ. 2015;350:g7771.
10. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010;94(3):888–899.
11. Goverde AJ, McDonnell J, Vermeiden JPW, Schats R, Rutten FFH, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet. 2000;355(9197):13–18.
12. Ayeleke RO, Asseler JD, Cohlen BJ, Veltman-Verhulst SM. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev. 2020;3(3):CD001838.
13. Diamond MP, Legro RS, Coutifaris C, et al. Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med. 2015;373(13):1230–1240.