ORIGINAL ARTICLE

In Vitro Fertilization or Intrauterine Insemination in Unexplained Infertility

L.R. Prentice,[1,2] L.C. Sadler,[1,3] K.L. Anderson,[1] J.D. Wilkinson,[4] M.A. Vercoe,[1] S.F. Lensen,[5] E.J. Glanville,[6] S.A. Wakeman,[7] L.M. Searle,[8] and C.M. Farquhar[1]

ABSTRACT

BACKGROUND

Although international guidelines recommend intrauterine insemination (IUI) with ovarian stimulation as first-line treatment for unexplained infertility, evidence from comparisons of this method with in vitro fertilization (IVF) is limited.

METHODS

We conducted a sequential, multicenter, randomized, controlled trial involving couples with unexplained infertility. Stage 1 was a noninferiority comparison between IUI with ovarian stimulation (up to four cycles) and IVF (one complete cycle, with transfer of all embryos). After 7 months, couples without live birth or ongoing pregnancy could proceed to stage 2: couples in the IUI group could undergo up to two IVF cycles, and those in the IVF group could undergo one further IVF cycle. The primary outcome was the cumulative live-birth rate resulting from stage 1. Couples who were in stage 1 during lockdowns due to coronavirus disease 2019 were omitted from the analysis of the primary outcome. A secondary outcome was the cumulative live-birth rate resulting from stages 1 and 2. Live births were included in analyses if day 1 of the treatment cycle that led to pregnancy or day 1 of the last menstrual period before conception occurred within 7 months (stage 1) or 20 months (stage 2) after randomization. The noninferiority margin for the primary outcome was a between-group difference of 10 percentage points.

RESULTS

A total of 737 couples underwent randomization: 365 couples were assigned to undergo IUI with ovarian stimulation before IVF, and 372 were assigned to undergo first-line IVF (1 couple in the IVF group withdrew consent for the use of data). The primary-outcome analysis included 585 couples (288 in the IUI group and 297 in the IVF group). The cumulative live-birth rate from stage 1 was 31% (89 births among 288 couples) with IUI with ovarian stimulation and 55% (164 births among 297 couples) with IVF (adjusted risk difference, –24 percentage points; 95% confidence interval [CI], –31 to –16). The cumulative live-birth rate from stages 1 and 2 among all the couples who had undergone randomization and provided consent was 70% (257 births among 365 couples) and 71% (265 births among 371 couples), respectively (adjusted risk difference, 0 percentage points; 99% CI, –9 to 8). Overall, serious adverse events occurred in 6 couples in the IUI group and in 14 couples in the IVF group; most serious adverse events were related to oocyte retrieval or hyperstimulation.

CONCLUSIONS

In couples with unexplained infertility, treatment with four cycles of IUI with ovarian stimulation was not noninferior to treatment with one complete cycle of IVF with respect to the cumulative live-birth rate. (Funded by the Health Research Council of New Zealand and others; FIIX Australian New Zealand Clinical Trials Registry number, ACTRN12619001003167.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Lucy R. Prentice can be contacted at lucy.prentice@auckland.ac.nz or at the Department of Obstetrics, Gynaecology and Reproductive Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.

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Infertility affects one in six couples, with up to one third having unexplained infertility, which is diagnosed when standard investigations find no cause.[1,2] Treatment options for unexplained infertility include intrauterine insemination (IUI) with ovarian stimulation and in vitro fertilization (IVF). In IUI with ovarian stimulation, systemic gonadotrophins or oral ovulation-induction agents are used to stimulate the development of two to three follicles before insemination of prepared sperm into the uterus.[3] IVF involves ovarian stimulation, oocyte retrieval, fertilization, and embryo culture and transfer, with cryopreservation of surplus embryos.[3]

IUI with ovarian stimulation is a low-cost, less-invasive alternative to IVF for couples who have unexplained infertility with a poor prognosis for unassisted conception and is recommended as first-line treatment by major international guidelines.[1,4,5] Among seven trials that compared IUI with IVF in unexplained infertility,[6-12] cumulative live-birth rates were similar in the two groups, but evidence quality was rated as low.[13] Six trials used IUI with gonadotrophins for ovarian stimulation, which is more expensive than IUI with the use of oral ovulation-induction agents and carries a higher risk of multiple pregnancy.[14] Most trials evaluated only the first embryo transfer, rather than the cumulative live-birth rate after the transfer of all embryos, a more patient-centered outcome that better reflects the overall effectiveness of an IVF cycle.[15,16]

Data are lacking with respect to the effects of IUI with ovarian stimulation as pretreatment for IVF, the approach recommended in international guidelines, as compared with first-line treatment with IVF.[1,4,5] We conducted FIIX (Fertility and IVF and IUI Trial for Unexplained Infertility) to assess whether treatment with multiple cycles of IUI with oral agents for ovarian stimulation was noninferior to treatment with a complete IVF cycle with respect to the cumulative live-birth rate and to evaluate longer-term outcomes of the use of IUI with ovarian stimulation before IVF as compared with first-line IVF.

Methods

Trial Design

We conducted this open-label, pragmatic, randomized, controlled trial at six fertility clinics in New Zealand. Feedback on the trial design was sought from the infertility community, Fertility New Zealand, and Indigenous peoples of New Zealand (Māori). Trial conduct was overseen by a data and safety monitoring committee. The trial was approved by the Central Health and Disability Ethics Committee in New Zealand (reference code, 19/CEN/40), and locality approval was obtained for each participating center.

The trial was a comparison of two parallel, sequential care pathways evaluated at prespecified time points (7 months for stage 1 and 20 and 24 months for stage 2). Stage 1 was a noninferiority comparison between treatment with four cycles of IUI with ovarian stimulation and treatment with one complete cycle of IVF (with transfer of all embryos). Couples without live birth or ongoing pregnancy resulting from stage 1 could proceed to stage 2, which consisted of IVF treatment for both groups (up to two IVF cycles for couples in the IUI group and one further IVF cycle for those in the IVF group). As a whole, the trial assessed treatment with four cycles of IUI with ovarian stimulation followed by two cycles of IVF as compared with treatment with two IVF cycles. The trial protocol (available with the full text of this article at NEJM.org) has been published previously.[17]

An updated statistical analysis plan, available with the protocol, was published to incorporate changes associated with the coronavirus disease 2019 (Covid-19) pandemic. Separate analyses of the cost-effectiveness of treatment and of the acceptability of treatment are planned. Details about trial oversight and author responsibilities are provided in the Supplementary Appendix, available at NEJM.org.

Eligibility

Couples were identified from wait lists for public fertility treatment. The following eligibility criteria provided confirmation of a diagnosis of unexplained infertility: regular menstrual cycles, tubal patency (for one or both fallopian tubes) as confirmed by hysterosalpingogram or laparoscopy or by a history of clinical miscarriage within 24 months before randomization, and a total motile sperm count of more than 10 million. Full eligibility criteria are provided in Table S1 in the Supplementary Appendix. Couples were excluded if the female partner had stage III or IV endometriosis, a history of tubal ectopic pregnancy or tubal surgery, or submucous or other clinically

significant fibroids or if gamete donation was warranted. All the couples provided written informed consent.

RANDOMIZATION

An online data collection and randomization system (Research Electronic Data Capture [REDCap]) was used to verify couple eligibility and conceal trial-group assignments. Couples were randomly assigned in a 1:1 ratio with the use of blocks of concealed, variable size (between 2 and 16). Randomization was stratified according to center and maternal age (<36 years vs. ≥36 years). Concealing trial-group assignments from the couples and clinic staff was not feasible given the nature of the interventions.

INTERVENTION

The trial was pragmatic, and clinics were permitted to use their usual treatment protocols. Public funding was used for all trial treatments, including repetition of canceled cycles. For IUI, canceled cycles were defined as those that did not reach the point of insemination. For IVF, canceled cycles included those that did not reach the point of egg collection or, unexpectedly, did not produce an embryo that was suitable for transfer; however, if a poor result was anticipated or if a biopsy after preimplantation genetic testing for aneuploidy showed an embryo unsuitable for transfer, the cycle was counted as complete.

IUI with Ovarian Stimulation

Orally administered clomiphene citrate or letrozole was used for ovarian stimulation for IUI. IUI without ovarian stimulation was considered to be off protocol. All the participating clinics had a policy of canceling a cycle if more than three dominant follicles developed. Couples could undergo up to four cycles of IUI with ovarian stimulation, excluding canceled cycles.

IVF

A complete cycle of IVF included the transfer of all embryos (fresh and frozen) until a live birth occurred or until no further embryos were available. Transfer of single embryos was standard practice. Couples whose IVF cycle was canceled or did not produce a transferable embryo could undergo a repeat cycle if the outcome was unexpected. Preimplantation genetic testing for aneuploidy was an optional, patient-funded add-on procedure.

TRIAL PROGRESS

Stage 1

Stage 1 comprised a 6- or 7-month treatment period. The initially planned period of 6 months was extended to 7 months for couples who underwent randomization after August 19, 2021, to account for Covid-19–related treatment delays. In the IUI group, couples could discontinue cycles in the event of a tubal ectopic pregnancy or two or more cycles with poor sperm wash or if a cycle was canceled three times for medical reasons. Couples could not proceed to stage 2 IVF treatment earlier than 7 months, even if stage 1 treatment was complete, to enable direct comparison between the groups in stage 1.

Stage 2

All trial treatments across stages 1 and 2 were intended to be completed within 20 months (extended from the initially planned 18 months). Couples were followed until 24 months for trial or nontrial treatment and all conceptions and pregnancy outcomes. A couple exited the trial if a live birth occurred.

Live births were included in analyses if day 1 of the treatment cycle that led to pregnancy or day 1 of the last menstrual period before conception occurred within 7 months after randomization for stage 1 or within 20 or 24 months after randomization for stage 2. Prespecified assessments were performed at 20 months and at 24 months after randomization, with outcomes occurring within 20 months designated a priori as the most relevant, because the couples were expected to complete treatment within 20 months.

OUTCOMES

The primary outcome was the cumulative live-birth rate resulting from stage 1 treatment (as defined above). Key secondary outcomes were the cumulative live-birth rate resulting from both stages 1 and 2 (as defined above), the time from randomization to day 1 of the treatment cycle that led to live birth or from randomization to day 1 of the last menstrual period before conception that led to live birth, the number of frozen embryos at the completion of treatment, and pregnancy outcomes. A complete list of outcomes and definitions is provided in the Supplementary Appendix. Data were also collected on serious adverse events. Only one live birth was considered per couple. All other pregnancy out-

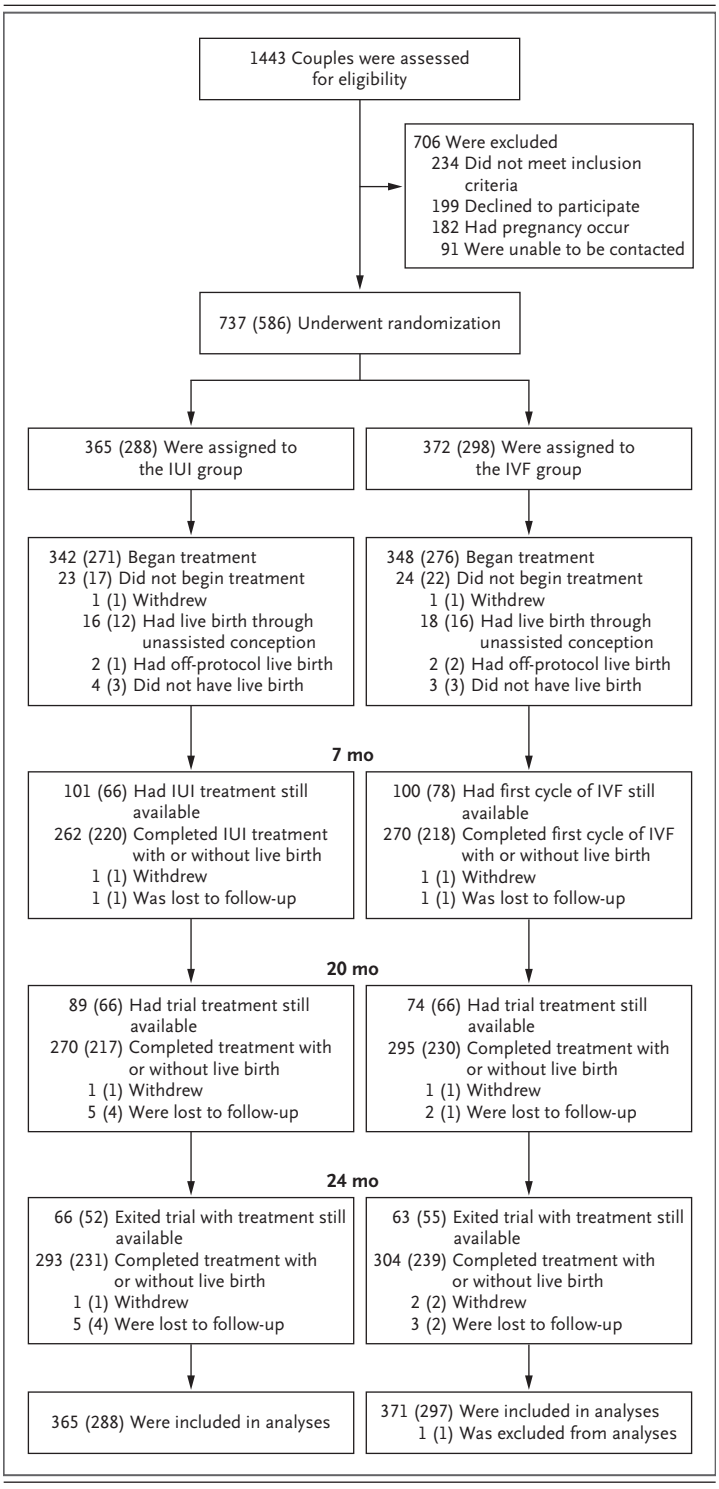


Figure 1. Screening, Randomization, and Follow-up.

Of the 737 couples who underwent randomization, 151 had a treatment period affected by the coronavirus disease 2019 (Covid-19) pandemic and were excluded from the analysis of the primary outcome. Numbers of couples remaining after the omission of treatment periods affected by Covid-19 are indicated in parentheses. Live births were included in analyses at 7, 20, and 24 months after randomization if day 1 of the treatment cycle that led to pregnancy or day 1 of the last menstrual period before conception occurred within these time periods. Among 365 couples assigned to undergo intrauterine insemination (IUI) with ovarian stimulation in stage 1 (the IUI group), 338 began treatment in stage 1, and 4 began in stage 2. Among 371 couples assigned to undergo in vitro fertilization (IVF) in stage 1 (the IVF group), 343 began treatment in stage 1, and 5 began in stage 2. At 20 and 24 months, the number of couples who had completed treatment included 1 couple in the IUI group who withdrew from the trial after a live birth, which was included in the total number of live births; neonatal data for the infant were missing. At 24 months, the number of couples who had completed treatment included 1 couple in the IVF group who was lost to follow-up after treatment was complete.

comes could be counted multiple times per couple. Live-birth and pregnancy outcomes included all events arising from trial and nontrial treatments, as well as unassisted conceptions.

STATISTICAL ANALYSIS

The sample size was calculated on the basis of the hypothesis of noninferiority of IUI to IVF, with an estimated cumulative live-birth rate of 30% in both groups.[18,19] We calculated that an overall sample size of 580 couples (290 in each group) would provide the trial with 80% power to reject the null hypothesis that the groups would differ by more than 10 percentage points in favor of IVF at the one-sided 5% significance level, with allowance for the withdrawal of 10% of the couples. This noninferiority margin was considered to be clinically meaningful and is consistent with margins in previous trials.[20-23] The sample size was increased to 730 to account for the omission of 151 couples from the primary-outcome analysis owing to the effects of Covid-19 lockdowns.

The primary analysis was conducted with logistic regression with regression standardization to obtain a risk difference that was adjusted for the stratification factors of maternal age and center. A bootstrap procedure (with 10,000 replicates) was used to calculate the 90% confidence interval (which was prespecified) and the 95% confidence interval, which corresponded to noninferiority testing at the 5% and 2.5% significance levels. A per-protocol analysis was performed post

Table 1. Demographic and Clinical Characteristics of the Couples at Baseline.*

Characteristic	IUI (N=365)	IVF (N=371)
Maternal age		
Mean — yr	35±3.1	34±3.4
Distribution — no. (%)		
<36 years	228 (62)	236 (64)
≥36 years	137 (38)	135 (36)
Median duration of infertility (IQR) — mo	63 (54–73)	63 (52–75)
Maternal BMI†	24±3.8	25±3.8
Maternal race or ethnic group — no. (%)‡		
Māori	16 (4)	19 (5)
Pacific Islander	18 (5)	14 (4)
Asian	168 (46)	180 (49)
Middle Eastern, Latin American, or African	13 (4)	20 (5)
European	150 (41)	138 (37)
Maternal history — no. (%)§		
Previous live birth	55 (15)	83 (22)
Previous IVF	18 (5)	33 (9)
Previous IUI with ovarian stimulation	68 (19)	68 (18)
Endometriosis, minimal or mild	52 (14)	49 (13)
Laparoscopy within 5 years before randomization	75 (21)	74 (20)
Median total sperm count in male partner (IQR) — million	86 (42–159)	84 (46–154)
Median sperm concentration (IQR) — million/ml	59 (32–113)	58 (33–101)
Sperm motility — %	57±13.2	58±13.3
Median Hunault prediction score (IQR) — %¶	17.9 (12.6–23.6)	18.1 (13.2–24.3)
Anti-Müllerian hormone level — ng/ml‖	3.2±2.3	2.7±1.9

* Plus–minus values are means ±SD. Data are shown for all the couples who underwent randomization and provided consent. To compare intrauterine insemination (IUI) with in vitro fertilization (IVF) as first-line treatment for unexplained infertility, couples were assigned to undergo IUI with ovarian stimulation before IVF (the IUI group) or to undergo first-line treatment with IVF (the IVF group). IQR denotes interquartile range.
† Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ Race and ethnic group were reported by the participant.
§ Shown are numbers of couples in which the female partner had a history of the indicated event or treatment.
¶ The Hunault prediction score is a measure of the probability of unassisted conception within 12 months. A score of less than 30% indicates a poor prognosis for unassisted conception.
‖ The level of anti-Müllerian hormone (a marker of ovarian reserve) was missing for six women (five in the IUI group and one in the IVF group).

hoc for the primary outcome, given the noninferiority hypothesis. Linear regression was used for continuous secondary outcomes and logistic regression for binary secondary outcomes, with the calculation of 99% confidence intervals and adjustment for the stratification factors; the confidence intervals for these outcomes were not fully adjusted for multiplicity and should not be used in place of hypothesis testing. For time from randomization to day 1 of the treatment cycle that led to live birth or day 1 of the last menstrual period before conception that led to live birth, the cumulative incidence of live birth was plotted. A comparison of restricted mean survival time in the two groups was performed owing to nonproportional hazards. Deviations from the statistical analysis plan are noted in the Supplementary Appendix.

Prespecified subgroup analyses were performed according to maternal age and previous treatment

Table 2. Primary and Secondary Outcomes.*

Outcome	Stage 1 (7 Mo)†			Stage 2 (20 Mo)†		
	IUI (N=365)	IVF (N=371)	Adjusted Risk Difference (95% or 99% CI)‡§	IUI (N=365)	IVF (N=371)	Adjusted Risk Difference (99% CI)‡
			percentage points			*percentage points*
Primary outcome						
Cumulative live-birth rate from stage 1 — no. of births/no. of couples (%)¶‖	89/288 (31)	164/297 (55)	−24 (−31 to −16)	—	—	—
Secondary outcomes						
Cumulative live-birth rate from stages 1 and 2 — no. of births/no. of couples (%)¶						
Primary-analysis population‖**	—	—	—	208/288 (72)	207/297 (70)	4 (−6 to 13)
All couples	113/365 (31)	203/371 (55)	−23 (−30 to −16)	257/365 (70)	265/371 (71)	0 (−9 to 8)
Pregnancy outcomes — no. of couples (%)						
Miscarriage††						
Any	12 (3)	21 (6)	−2 (−6 to 1)	25 (7)	25 (7)	0 (−5 to 5)
1	11 (3)	20 (5)		23 (6)	20 (5)	
2	1 (<1)	1 (<1)		2 (1)	5 (1)	
Early pregnancy loss‡‡						
Any	8 (2)	22 (6)	−4 (−8 to 0)	27 (7)	33 (9)	−2 (−7 to 3)
1	8 (2)	22 (6)		27 (7)	31 (8)	
2	0	0		0	2 (1)	
Biochemical pregnancy§§	28 (8)	46 (12)	−5 (−10 to 1)	60 (16)	62 (17)	0 (−7 to 7)
Multiple pregnancy						
Any	7 (2)	4 (1)	—	10 (3)	5 (1)	1 (−1 to 4)
Twins	7 (2)	3 (1)	—	10 (3)	4 (1)	—
Triplets	0	1 (<1)	—	0	1 (<1)	—
Multiple birth	4 (1)	3 (1)	—	5 (1)	3 (1)	—
Ectopic pregnancy	8 (2)	2 (1)	—	10 (3)	3 (1)	—
Termination of pregnancy	2 (1)	2 (1)	—	2 (1)	2 (1)	—
Stillbirth¶¶	0	2 (1)	—	0	2 (1)	—

attempts. The primary analyses were performed with R software, version 4.5.3 (R Foundation for Statistical Computing), and outcome data were assumed to be missing at random given the stratification factors. A sensitivity analysis was conducted under the assumption that couples did not have a live birth unless there was an ongoing pregnancy of more than 12 weeks of gestation at the time of loss to follow-up. Couples were assessed according to their assigned groups. No interim analysis was planned or performed.

Recruitment started before the Covid-19 pandemic. Lockdown measures in New Zealand resulted in pauses in treatment, with differential effects among centers. This situation prompted modifications to the statistical analysis plan (with the outcome data blinded) to ensure that the trial yielded results that were relevant outside a pandemic context.[24] All the couples in stage 1 during lockdown periods (September 22, 2019, to March 25, 2020, and February 14, 2021, to August 18, 2021) were omitted from the primary-outcome analysis, and time points used for stages 1 and 2 were extended. Analyses of all outcomes were performed in the overall trial population (all the couples who underwent randomization and provided consent) and in the primary-analysis population (which excluded couples who had been omitted because of Covid-19 lockdowns) (see the Supplementary Appendix).

RESULTS

COUPLES

Recruitment occurred from August 2019 through March 2024 (Fig. S1 and Table S2). A total of 1443 couples were assessed for eligibility, and 737 underwent randomization: 365 were assigned to the IUI group, and 372 to the IVF group. A total of 4 couples withdrew, including 1 couple assigned to the IVF group who withdrew consent for the use of all data and was removed from the analyses. Screening, randomization, and follow-up are summarized in Figure 1. Of the 736 couples who underwent randomization and provided consent, 46 (6%) did not start treatment, mostly owing to unassisted conceptions (in the case of 34 couples).

The characteristics of the couples at baseline were similar in the two groups, except for a history of previous live birth, which appeared to be more common in the IVF group than in the IUI

* Data are shown for all the couples who underwent randomization and provided consent. A total of 9 couples were lost to follow-up and were assumed to have no further pregnancy or live birth; 1 couple withdrew in stage 1 with missing outcome data and was assumed to have no live birth (a second couple who withdrew in stage 1 also withdrew consent for use of data and was excluded from all analyses); 2 couples withdrew in stage 2 (at 20 months), 1 after an ongoing pregnancy (for whom no live birth was assumed) and 1 after a live birth that was counted toward the total number of live births, but with access to neonatal data withdrawn. Dashes indicate not applicable.

† Outcome data are included if day 1 of the treatment cycle that led to pregnancy or day 1 of the last menstrual period before conception occurred within 7 months after randomization for stage 1 and within 20 months after randomization for stage 2 (or within 6 and 18 months, respectively, for the 327 couples who underwent randomization before August 19, 2021).

‡ Adjusted risk differences were calculated under the assumption that data were missing at random. Differences for all secondary outcomes were calculated by the delta method. For all secondary outcomes, 99% confidence intervals were not fully adjusted for multiplicity and should not be used in place of hypothesis testing.

§ Values in parentheses are 99% confidence intervals, except those for cumulative live-birth rate, which are 95% confidence intervals.

¶ Live birth was defined as birth after 20 completed weeks of gestation of a baby that breathes or shows any other evidence of life.

‖ This outcome was assessed in the primary-analysis population, which included all the couples who underwent randomization and provided consent, with the exception of those who underwent stage 1 treatment during a period affected by lockdowns due to the coronavirus disease 2019 (Covid-19) pandemic.

** Data for stage 1 were primary-outcome data and are reported above.

†† Miscarriage was defined as spontaneous loss of a pregnancy with a fetal heartbeat before 20 completed weeks of gestation.

‡‡ Early pregnancy loss was defined as the absence of a fetal heartbeat at the time of ultrasonography at 6 to 8 weeks of gestation.

§§ Biochemical pregnancy was defined by the detection of beta–human chorionic gonadotropin in serum or urine without progression to confirmation of pregnancy by ultrasonography.

¶¶ Stillbirth was defined as the death of a fetus before delivery at or after 20 completed weeks of gestation.

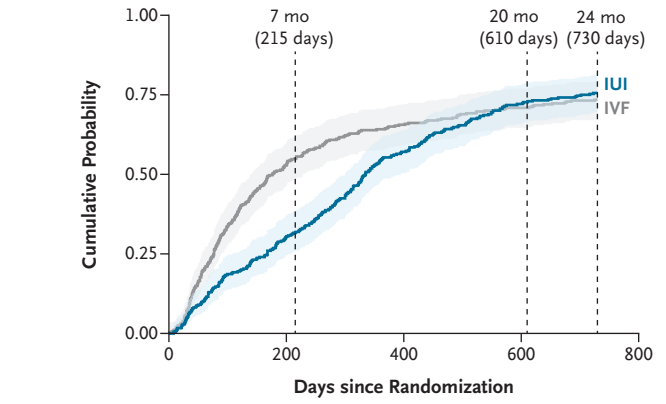


Figure 2. Time from Randomization to Treatment Cycle Leading to Live Birth, According to Trial Group.

Shown is the cumulative probability of a live birth over time among all the couples who underwent randomization (excluding 10 couples in the IUI group and 9 in the IVF group for whom day 1 of the last menstrual period before live birth occurred before randomization, with pregnancy undetected at the time of randomization owing to the early stage after conception). In the time-to-event analysis, time was measured from randomization to day 1 of the treatment cycle that led to pregnancy or from randomization to day 1 of the last menstrual period before conception. Vertical dashed lines indicate follow-up periods at 7 months, 20 months, and 24 months. Shading indicates 99% confidence intervals. Numbers in parentheses below the x axis are numbers of live births that occurred between the indicated time point and the following time point. Data for individual couples were censored at the time of withdrawal or loss to follow-up or at 24 months. Figure S2 shows results according to trial group and maternal age.

group (Table 1). The mean maternal age was 34.3 years, the median duration of infertility was 63 months, and the median Hunault prediction score (a measure of the chance of unassisted conception within 12 months) was 18%.[25] The trial population was representative of a general population of couples with unexplained infertility with a poor prognosis (Table S3).

STAGE 1

In the IUI group, 338 couples began treatment with IUI with ovarian stimulation, with a total of 1154 cycles started; cancellation occurred in 15% of cycles (169 of 1154) (Table S4A). Another 4 couples in the IUI group did not begin treatment until stage 2. Among 365 couples assigned to the IUI group, 101 (28%) did not complete IUI with ovarian stimulation within 7 months (Table S5). Clomiphene citrate was used in 67% of cycles (658 of 985 completed cycles), and letrozole was used in 32% (319 of 985); 1% of cycles (8 of 985) were carried out without ovarian stimulation.

In the IVF group, 343 couples started IVF, with 372 cycles initiated; cancellation occurred in 11% of cycles (40 of 372) (Table S4B). Another 5 couples in the IVF group did not begin treatment until stage 2. Among 371 couples assigned to the IVF group, 100 (27%) did not complete IVF treatment within 7 months. Antagonist protocols were used in 96% of cycles (356 of 372), intracytoplasmic sperm injection in 25% (94 of 372), and preimplantation genetic testing for aneuploidy in 1% (5 of 372).

A total of 49 protocol violations occurred in the IUI group, and 18 occurred in the IVF group (Table S6). Among 736 couples in the overall trial population, 409 (56%) had an extended stage 1 treatment period of 7 months.

With the periods affected by Covid-19 omitted, the cumulative live-birth rate was 31% (89 births among 288 couples) in the IUI group and 55% (164 births among 297 couples) in the IVF group (adjusted risk difference, –24 percentage points; 95% confidence interval [CI], –31 to –16), results that excluded the noninferiority of IUI. The results were unchanged in the missing-data sensitivity analysis (adjusted risk difference, –24 percentage points; 95% CI –31 to –16). In a per-protocol analysis, the cumulative live-birth rate was 34% (85 births among 252 couples) in the IUI group and 56% (158 births among 284 couples) in the IVF group (adjusted risk difference, –21 percentage points; 95% CI, –29 to –13) (Table S7). Results appeared to be generally similar across prespecified subgroups and in a post hoc subgroup analysis with subgroups defined according to a history of previous live birth (Table S8); the results also appeared to be consistent after a post hoc adjustment for previous live birth (Table S9).

When all the couples who had undergone randomization were included, the results were materially unchanged (Table 2). The restricted mean survival time to live birth was 174 days (99% CI, 165 to 183) in the IUI group and 143 days (99% CI, 133 to 154) in the IVF group (difference, 31 days; 99% CI, 17 to 45) (Fig. 2). Table S10 summarizes all births according to the type of treatment that led to conception.

Results for other pregnancy outcomes are shown in Table 2. Ectopic pregnancy occurred in 2% of couples (8 of 365) in the IUI group and in 1% (2 of 371) in the IVF group. In both groups,

Table 3. Serious Adverse Events.*

Event	Stage 1 (7 Mo)		Stage 2 (20 Mo)	
	IUI (N=365)	IVF (N=371)	IUI (N=365)	IVF (N=371)
	number of events			
Hospital admission for treatment-related causes				
Ovarian hyperstimulation syndrome	1†	4	2†	4
Hemorrhage after oocyte retrieval	0	3	0	3
Infection after oocyte retrieval	0	1	1	1
Pain after oocyte retrieval	0	0	1	0
Pain during frozen-embryo transfer cycle (ovarian cyst)	0	1	0	1
Major congenital anomaly identified within first 6 wk after birth	0	3	1	4
Neonatal death within first 6 wk after birth	0	0	1	1
All events	1	12	6	14

* Data are shown for all the couples who underwent randomization and provided consent. Serious adverse events were included in the numbers for a given stage if day 1 of the treatment cycle associated with the event or day 1 of the last menstrual period before conception occurred within 7 months after randomization for stage 1 and within 20 months after randomization for stage 2 (or within 6 and 18 months, respectively, for couples who underwent randomization before August 19, 2021). Couples could have more than one event. Numbers for stage 2 are cumulative. The cumulative numbers of serious adverse events at 24 months were the same as those at 20 months. No participants were hospitalized for ovarian hyperstimulation syndrome that warranted drainage of ascites or pleural effusions, and no deaths or serious drug reactions occurred.

† Ovarian hyperstimulation syndrome was associated with off-protocol IVF treatment.

multiple births occurred in 1% of the couples, and 9% of infants were born preterm; Table S11 summarizes all neonatal outcomes.

STAGE 2

At 20 months, 24% of couples (89 of 365) in the IUI group and 20% (74 of 371) in the IVF group had trial treatment remaining. The percentages dropped to 18% (66 of 365) and 17% (63 of 371), respectively, at 24 months. In the IUI group, 42% of couples (152 of 365) completed their first IVF cycle and 9% (33 of 365) completed their second; in the IVF group, 68% (253 of 371) completed their first IVF cycle, and 16% (58 of 371) completed an additional cycle. Across stages 1 and 2 (from randomization through 24 months), 85 protocol violations occurred in the IUI group, and 67 occurred in the IVF group. No couple was lost to follow-up during pregnancy (Table S12).

Overall, the cumulative live-birth rate was 70% (257 births among 365 couples) in the IUI group and 71% (265 births among 371 couples) in the IVF group (adjusted risk difference, 0 percentage points; 99% CI, –9 to 8). When periods affected by Covid-19 were omitted, the results were materially unchanged (Table 2). The restricted mean survival time to live birth was 373 days (99% CI, 339 to 408) in the IUI group and 309 days (99% CI, 271 to 347) in the IVF group (difference, 64 days; 99% CI, 13 to 116) (Fig. 2). In the IUI group, 40% of the couples (147 of 365) had one or more cryopreserved embryos remaining at trial completion, as compared with 68% (253 of 371) in the IVF group (risk difference, –28 percentage points; 99% CI, –37 to –19) (Table S13). The results for other pregnancy outcomes through 20 months are shown in Table 2; Table S14 shows outcomes at 24 months.

SERIOUS ADVERSE EVENTS

During stage 1 of the trial, 1 serious adverse event occurred in the IUI group and 12 occurred in the IVF group; across stages 1 and 2 (from randomization through 24 months), 6 serious adverse events occurred in the IUI group and 14 in the IVF group (Table 3). These events were mostly related to hyperstimulation or complications of oocyte retrieval. Major congenital anomalies were identified by 6 weeks of age in three infants in the IVF group in stage 1 and in one infant in the IUI group and four infants in the IVF group across both stages.

DISCUSSION

In this pragmatic, multicenter, randomized trial involving couples with unexplained infertility, treatment with four cycles of IUI with ovarian stimulation was not noninferior to treatment with one complete cycle of IVF with respect to the cumulative live-birth rate. Stage 2 of the trial showed a similar cumulative live-birth rate among the couples assigned to undergo IUI with ovarian stimulation before IVF and those who underwent first-line IVF. The time to day 1 of the treatment cycle that led to live birth or to day 1 of the last menstrual period before conception that led to live birth appeared to be shorter with the use of IVF as first-line treatment in stage 1 than with IUI, although the results for the two groups appeared to converge in stage 2. Serious adverse events, which occurred mainly in the IVF group during stage 1, largely comprised complications of oocyte retrieval and hyperstimulation.

This trial expands on previous trials that directly compared treatment with IUI with ovarian stimulation and treatment with IVF, and unlike previous trials, it assessed IUI with ovarian stimulation as pretreatment for IVF, as compared with first-line IVF. The cumulative live-birth rate of 31% with IUI with ovarian stimulation in stage 1 was consistent with the rate we anticipated and with the rates reported in other trials involving couples with unexplained infertility and a poor prognosis for unassisted conception.[18,26] The cumulative live-birth rate with IVF in this trial (55%) was higher than those in previous trials, a result that could be explained by several factors: our inclusion of live births that resulted from a complete IVF cycle, the contribution of unassisted conceptions that resulted in live birth (which comprised 14% of live births in the IVF group), and improvements in the probability of success with IVF in the years since the results of many of the previous trials were published (9 to 26 years ago).[27]

International guidelines recommend IUI with ovarian stimulation as first-line treatment before IVF for couples with unexplained infertility.[1,4,5] Evidence supporting these recommendations is limited, and the guidelines are based largely on trials that showed a benefit of IUI with ovarian stimulation over expectant management.[18,26] Only one small trial (involving 154 couples) compared the use of IUI with oral agents for ovarian stimulation with the use of IVF; that trial recruited women of advanced reproductive age (38 to 42 years) rather than those with unexplained infertility.[9] Our finding that IUI with ovarian stimulation was not noninferior to IVF in stage 1 calls into question current international guideline recommendations. The cumulative live-birth rate in stage 2 appeared to be similar in the two groups, although the number of embryos that were cryopreserved (which provides potential opportunities for future conception) and the time to live birth appeared to favor IVF. However, the choice of first-line treatment should be guided not only by effectiveness but also by cost-effectiveness at stage 1, access to care, patient preferences, treatment burden, and safety.

The limitations of our trial should be considered. Couples had a long duration of infertility and represented a population with a poor prognosis for unassisted conception. The observed treatment effect may not be generalizable to couples with unexplained infertility of shorter duration. Our definition of unexplained infertility was broader than the most widely used definition (infertility in couples with apparently normal ovarian and testicular function, apparently normal anatomy [including fallopian tubes, uterus, cervix, pelvis, and genitourinary anatomy], a normal ejaculate, and adequate coital frequency).[28] We allowed for minor abnormalities in semen characteristics and only one patent fallopian tube and included women with minimal or mild endometriosis, an approach that was consistent with the eligibility criteria used in previous trials.[6-12] Women with undiagnosed endometriosis may have been included, because only 20% of the women had undergone laparoscopy in the 5 years preceding randomization. In addition, blinding was not feasible given the nature of the interventions, which may have contributed to protocol violations, particularly in the IUI group. The Covid-19 pandemic posed several challenges; however, changes to the protocol and analyses ensured an adequate sample size.[24]

In this trial, treatment with four cycles of IUI with ovarian stimulation was not noninferior to treatment with one complete cycle of IVF. At 20 months, pretreatment with IUI with ovarian stimulation followed by treatment with IVF was associated with a cumulative live-birth rate similar to that with first-line IVF.

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AUTHOR INFORMATION

Lucy R. Prentice, F.R.A.N.Z.C.O.G., C.R.E.I.,[1,2] Lynn C. Sadler, M.P.H.,[1,3] Karyn L. Anderson, M.P.H.,[1] Jack D. Wilkinson, Ph.D.,[4] Melissa A. Vercoe, P.G.Dip.,[1] Sarah F. Lensen, Ph.D.,[5] Elizabeth J. Glanville, F.R.A.N.Z.C.O.G., C.R.E.I.,[6] Sarah A. Wakeman, F.R.A.N.Z.C.O.G., C.R.E.I.,[7] Leigh M. Searle, F.R.A.N.Z.C.O.G., C.R.E.I.,[8] and Cynthia M. Farquhar, M.D.Res.[1]

[1] Department of Obstetrics, Gynaecology and Reproductive Sciences, University of Auckland, Auckland, New Zealand; [2] Fertility Plus, National Women's, Auckland, New Zealand; [3] Auckland City Hospital, National Women's, Auckland, New Zealand; [4] Centre for Biostatistics, University of Manchester, Manchester, United Kingdom; [5] Department of Obstetrics, Gynaecology and Newborn Health, University of Melbourne, Melbourne, VIC, Australia; [6] Repromed, Auckland, New Zealand; [7] Fertility Associates, Christchurch, New Zealand; [8] Fertility Associates, Wellington, New Zealand.

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