

A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T)

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Objective: To determine the optimal infertility therapy for women at the end of their reproductive potential.

Design: Randomized clinical trial.

Setting: Academic medical centers and private infertility center in a state with mandated insurance coverage.

Patient(s): Couples with ≥ 6 months of unexplained infertility; female partner aged 38–42 years.

Intervention(s): Randomized to treatment with two cycles of clomiphene citrate (CC) and intrauterine insemination (IUI), follicle stimulating hormone (FSH)/IUI, or immediate IVF, followed by IVF if not pregnant.

Main Outcome Measure(s): Proportion with a clinically recognized pregnancy, number of treatment cycles, and time to conception after two treatment cycles and at the end of treatment.

Result(s): We randomized 154 couples to receive CC/IUI (N = 51), FSH/IUI (N = 52), or immediate IVF (N = 51); 140 (90.9%) couples initiated treatment. The cumulative clinical pregnancy rates per couple after the first two cycles of CC/IUI, FSH/IUI, or immediate IVF were 21.6%, 17.3%, and 49.0%, respectively. After all treatments, 110 (71.4%) of 154 couples had conceived a clinically recognized pregnancy, and 46.1% had delivered at least one live-born baby; 84.2% of all live-born infants resulting from treatment were achieved via IVF. There were 36% fewer treatment cycles in the IVF arm compared with either COH/IUI arm, and the couples conceived a pregnancy leading to a live birth after fewer treatment cycles.

Conclusion(s): A randomized controlled trial in older women with unexplained infertility to compare treatment initiated with two cycles of controlled ovarian hyperstimulation/IUI versus immediate IVF demonstrated superior pregnancy rates with fewer treatment cycles in the immediate IVF group.

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Key Words: Advanced reproductive age, clomiphene citrate, controlled ovarian hyperstimulation, follicle-stimulating hormone, FORT-T Trial, intrauterine insemination (IUI), in vitro fertilization, unexplained infertility

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During the early years of assisted reproduction, treatment for unexplained infertility usually began with controlled ovarian hyperstimulation (COH) using clomiphene citrate (CC) and intrauterine insemination (IUI) (1). If pregnancy was not achieved, couples proceeded in a step-wise fashion to gonadotropin (FSH)/IUI treatment and then, if not pregnant,

on to in vitro fertilization (IVF) (1). In 1999, a randomized clinical trial to compare FSH/IUI with IUI alone, FSH alone, and intracervical insemination alone, reported that the most successful treatment arm was FSH/IUI (2). One-third of the participating couples conceived after four treatment cycles. However, the success rate per cycle was only 9%, and approximately one-third of the pregnancies were multiple births, including triplets and quadruplets. At that time, the results supported the use of FSH/IUI over the other treatments studied. However, its high cost for a low success rate and high risk of multiple births, especially high-order multiples, suggested that it might be more effective to move directly to IVF (3–5).

Recently, we reported in the Fast Track and Standard Treatment (FASTT) trial that FSH/IUI was of no added value in the treatment of younger couples with unexplained infertility (5). Results of the FASTT trial raised questions about optimal treatment strategies for couples with unexplained infertility who are at the end of the woman's reproductive potential when there is a shortened time frame for conceiving. There has been the belief that, if using COH/IUI, it is best to bypass CC/IUI and begin with FSH/IUI. Supporting this approach is the decrease in the incidence of adverse events such as ovarian hyperstimulation syndrome (OHSS) and multiple births in this age group. On the other hand, gonadotropin costs increase as the dose of medication needed for COH in older women rises. Because both CC/IUI and FSH/IUI were commonly used in this population of women at the time the study was designed and because the per-cycle pregnancy rates for CC/IUI and FSH/IUI were similar in the FASTT trial data, we felt that equipoise existed and that it was important to compare all three treatments in this trial.

We report the results of a randomized clinical trial (RCT) to identify an effective treatment strategy for couples with unexplained infertility who present for care at the end of their reproductive years. The trial was designed to compare efficacy after the first two treatment cycles of CC/IUI, FSH/IUI, or IVF, and at the end of all treatment. The hypothesis tested was that immediate IVF is a more effective treatment strategy for reproductively older women who demonstrate a reasonable chance for success than treatments that begin with two cycles of COH/IUI.

MATERIALS AND METHODS

We conducted a three-arm RCT to evaluate treatment strategies for older infertile couples. Treatment began with two cycles of one of the following regimens: CC/IUI, FSH/IUI, or immediate IVF. Couples who did not become pregnant were treated with IVF, up to a study maximum of six IVF cycles. The protocol was approved by the participating institutions' institutional review boards. An independent data and safety monitoring board (DSMB) met annually.

Study Population

Couples in which the woman was 38–42 years of age who sought care for unexplained infertility from August 2004 to November 2009 at Boston IVF and November 2008 to November 2009 at Brigham and Women's Hospital were screened. Eligibility criteria included 6 months of attempted

conception; at least one ovary and ipsilateral patent fallopian tube confirmed by hysterosalpingogram or laparoscopy; regular menstrual cycles of 21–45 days; and no pelvic pathology, ectopic pregnancy, or previous infertility treatment (except up to three cycles of clomiphene without IUI). Acceptable ovarian reserve was demonstrated by a clomiphene challenge test (100 mg clomiphene on cycle days 5–9; FSH values of <15 mIU/mL on cycle days 3 and 10; and estradiol value of <100 pg/mL on cycle day 3). Normal prolactin and thyroid-stimulating hormone levels and a body mass index (BMI) \leq 38 in the woman, and a sperm concentration of \geq 15 million total motile sperm or \geq 5 million total motile sperm at reflex IUI preparation in her partner were required. Randomization was performed using permuted blocks of varying sizes, stratified by the woman's age (38th–41st vs. 42nd–43rd birthday). The allocation sequence was generated by an independent biostatistician and was implemented by an epidemiologist. Randomization was never conducted by clinical staff, and all clinical investigators were blinded to the outcome determinations.

Treatment Protocol

Couples were treated with a standardized protocol agreed upon by all participating physicians. Treatment with CC was 100 mg orally daily for 5 days starting between cycle days 3–5, with serial ultrasound monitoring beginning between cycle days 10–12 and luteinizing hormone (LH) home monitoring beginning on cycle day 11. One IUI was performed either the day after the LH surge was detected or 36–40 hours after subcutaneous/intramuscular (SC/IM) administration of 10,000 IU of human chorionic gonadotropin (hCG) when the lead follicle was \geq 18 mm, whichever came first. If pregnancy was not achieved after two treatment cycles, patients proceeded to IVF.

Gonadotropin therapy was initiated on cycle day 3 with 300 IU of recombinant FSH SC for 3 days; the dose was adjusted as indicated by age (38–40 year olds could be given 150–300 IU FSH), pelvic ultrasound, and serum estradiol assessment until a lead follicle \geq 17 mm or 2–3 follicles \geq 15 mm in size were detected. A single IUI was performed the second morning after SC/IM administration of 10,000 IU of hCG. The protocol was repeated for a second FSH cycle unless the cycle was cancelled due to poor ovarian response or there were more than six follicles $>$ 14 mm. Patients who demonstrated poor ovarian response in one cycle were treated with a low-responder protocol consisting of an oral contraceptive followed by microdose leuprolide acetate. Patients with two cycles hindered by poor ovarian response were withdrawn unless they conceived and miscarried, in which case they were offered a third FSH cycle. Patients with an adequate response who completed two cycles of FSH/IUI proceeded to IVF if not pregnant.

Patients randomized to the immediate IVF arm initiated therapy with an IVF protocol consisting of 21 days of an oral contraceptive followed by a microdose leuprolide acetate protocol (40 μ g SC twice/day until the hCG injection) with a starting dose of twice daily gonadotropins (300 IU FSH in the morning and 150 IU human menopausal gonadotropin

[hMG] in the afternoon) for 3 days beginning on day 3 or 4 of leuprolide acetate. Adjustments to the gonadotropin dosage were determined by estradiol monitoring and ultrasound; 10,000 IU hCG was given SC or IM when the lead follicle was ≥ 17 mm and at least three follicles were ≥ 15 mm in size. Oocyte retrieval was performed 36 hours after hCG administration, and embryos were routinely transferred on day 3. The number of embryos transferred was based on American Society for Reproductive Medicine (ASRM) guidelines for day-3 embryo transfers (6). Standardized cancellation criteria and low response protocols were used. Intracytoplasmic sperm injection (ICSI) was used only after failed fertilization or when < 10 million total motile sperm were available at IVF. Preimplantation genetic diagnosis (3.6% of cycles) and assisted embryo hatching (one-third of cycles) were performed when considered necessary.

Patients in all arms who did not become clinically pregnant after two treatment cycles continued with the IVF protocol up to a maximum of six IVF cycles, usually four fresh and two thaw cycles, if available.

Study Outcomes

Patients were enrolled until they completed the treatment protocol, discontinued treatment due to poor response, took a hiatus from treatment of ≥ 1 year, or conceived an ongoing pregnancy of ≥ 20 weeks' gestation. Couples were observed until discharge from the hospital of both mother and infant(s), if pregnant, or until 1 year after completing the treatment protocol. Hiatus from treatment occurred for various medical and personal reasons. The closing date of the study for end point events was September 15, 2011.

The primary end point was clinical pregnancy rate after two cycles of treatment. The primary comparisons were of clomiphene/IUI versus immediate IVF and FSH/IUI versus immediate IVF, compared using Fisher's exact test with a two-sided $\alpha = 0.025$. Although the goal was a live-born baby, we used the clinical pregnancy rate as the primary outcome because we believe it best reflects implantation and thus treatment efficacy. Additional analyses evaluated live-birth rates after two cycles of treatment and clinical pregnancy and live-birth rates after all treatments, as well as time to conception. Clinical pregnancy was defined as a fetal sac visible on ultrasound. Time to conception (TTP) was defined as the length of time from the date of randomization to the date a pregnancy that resulted in a live birth was established. For those who did not conceive, time was censored either at the last menstrual period plus 28 days for those who completed the protocol, dropped out of the study after initiation of treatment, or were disenrolled for poor ovarian response; or date of disenrollment for those who went on hiatus for > 1 year (1 year + 1 day) or those who dropped out of the study (date of dropping out) before initiation of treatment.

Statistical Analysis

Analyses were by intention to treat and included all couples who were randomized. Per-protocol analyses are also presented to evaluate outcomes for those couples who initiated

at least one cycle of treatment. Exact binomial 97.5% confidence intervals were calculated. The TTP was analyzed using a Cox proportional hazards model; hazard ratios and their 95% confidence limits are presented. Cumulative incidence of time to conception was plotted as one minus Kaplan-Meier estimates. $P < .025$ was considered statistically significant for the primary comparison; $P < .05$ was considered statistically significant elsewhere (all two-sided). Data analyses were performed with SAS 9.2 statistical software (SAS Institute).

Original power estimates indicated that we would have 85% power to detect a difference in clinical pregnancy rates between each IUI arm and the immediate IVF arm with a sample size of 150 couples per arm. After several years of recruitment, it was apparent that a smaller sample size would achieve sufficient power due to the rising success rates of IVF. At an unplanned interim analysis, the DSMB determined that clinical pregnancy rates for each arm were sufficiently different from the assumptions used in the original power calculations to show that we would have adequate power to achieve a statistically significant result for the primary outcome with approximately 60 patients per arm. Given these estimates along with evolving clinical practice that threatened equipoise and a slower than anticipated rate of recruitment, we were advised by the DSMB to conclude recruitment at 150 couples.

RESULTS

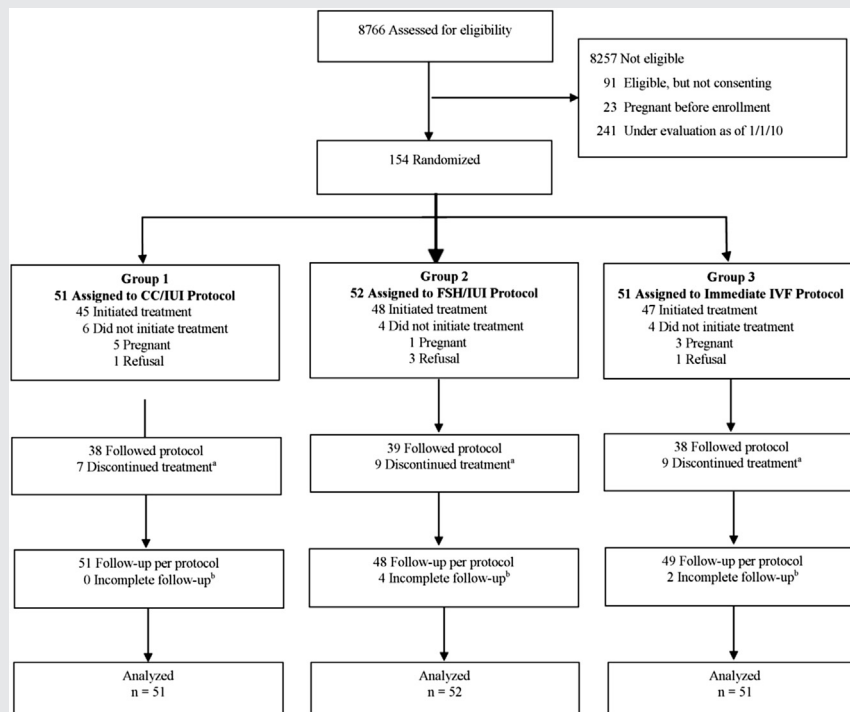
The study population comprised 154 couples with unexplained infertility who were randomized to the CC/IUI arm ($n = 51$), FSH/IUI arm ($n = 52$), or immediate IVF arm ($n = 51$) (Fig. 1). The most common reasons for ineligibility were age outside the range, prior infertility treatment or not a candidate for study treatments, or not covered by a participating insurer. Fourteen couples (9.1%) did not initiate treatment; of these, nine conceived before starting, and five deferred treatment. Of the 140 who initiated treatment, 115 (82.1%) completed the treatment protocol, and 25 discontinued treatment after an average of 3.9 (interquartile range [IQR] 3.0–5.0) treatment cycles over 12.8 months (IQR 8.8–17.4). There were six couples for whom follow-up after treatment was incomplete; their median follow-up time was 18.3 (IQR 12.0–21.4) months compared with 17.5 months (IQR 12.3–21.9) for the 148 couples who completed the follow-up period.

Baseline demographic and reproductive characteristics of the couples in the three arms were similar (Table 1). No statistically significant differences were noted for age at randomization, race, smoking history, female BMI, parity, or semen analysis. Statistically significant differences were observed for gravidity (a higher percent of those in the immediate IVF arm had never conceived) and cycle day 3 FSH values (slightly higher mean value for the FSH arm).

Pregnancy Rates

Statistically significant differences in the clinical pregnancy rates per couple were observed after the first two cycles of treatment: 21.6%, 17.3%, and 49.0%, for CC/IUI, FSH/IUI,

FIGURE 1



Screening, randomization, and enrollment of study couples. When we considered only the first two cycles of treatment, the results were identical except for two couples in the IVF arm who discontinued treatment after the first IVF cycle. ^a25 couples chose to discontinue treatment after a median of 4.0 cycles (interquartile range: 3–5 cycles) over a median duration of 12.2 months (interquartile range: 8.8–17.4 months). ^bThe median duration of follow-up for the couples we were unable to contact was 18.3 months (interquartile range: 12.0–21.4 months); the median duration was 17.5 months (interquartile range: 12.3–21.9 months) for couples who completed the follow-up period.

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and immediate IVF, respectively ($P=.0067/P=.0007$) (Table 2). The number of initiated cycles was 263, and 11 of the 45 clinical pregnancies were treatment independent. The live-birth rates per couple were 15.7%, 13.5%, and 31.4%, respectively ($P=.101/P=.035$). When comparing couples who initiated treatment in the COH groups (CC/IUI and FSH/IUI) combined to the immediate IVF group after two treatment cycles, there were also statistically significant differences in clinical pregnancy rates per cycle—7.3% (95% confidence interval [CI], 3.9–13.2) versus 24.7 (95% CI, 16.6–35.1) ($P=.0003$), and per couple: 14.0 (95% CI, 7.7–22.7) versus 44.7 (95% CI, 30.2–60.0) ($P=.0001$)—and live-birth rates per cycle: 5.1% (95% CI 2.2–11.0) versus 15.3% (95% CI, 8.3–26.4) ($P=.008$), and per couple: 9.7% (95% CI, 4.5–17.6) versus 27.7% (95% CI, 15.6–42.6) ($P=.01$).

The 140 couples who initiated treatment underwent a total of 487 treatment cycles (Table 3). Couples in the immediate IVF arm completed 36% fewer cycles than those in either one of the COH/IUI arms. Also, 39 (86.7%) of 45 couples in the CC/IUI arm and 37 (77.1%) of 48 couples in the FSH/IUI arm did not conceive after two cycles of treatment compared with 23 (48.9%) of 47 couples in the IVF arm ($P=.0004$). All unsuccessful couples moved on to IVF, where 35 (35.4%) of 99 couples conceived a pregnancy leading to a live birth. For all randomized couples at the end of treatment, 110 (71.4%) of

154 conceived a clinically recognized pregnancy, and 71 (46.1%) of 154 delivered at least one live-born baby (see Table 2). Twenty-three (14.9%) of the clinical pregnancies and 14 (9.1%) of the live births were treatment cycle independent, occurring either before initiation or between study treatment cycles. Excluding these independent pregnancies, 48 (84.2%) of the 57 live births were conceived through IVF. Of all couples who delivered a live birth, pregnancy resulted from IVF for 15 (83.3%) of 18 starting treatment with CC/IUI and 15 (71.4%) of 21 starting with FSH/IUI.

Among those who had a live birth, the average number of treatment cycles needed to establish the pregnancy was 3.4 (± 1.5) in the CC/IUI arm, 3.3 (± 1.9) in the FSH/IUI arm, and 1.9 (± 0.8) in the immediate IVF arm ($P=.004$).

Time to Conception

After two cycles of treatment, the comparison of the TTP between the COH and immediate IVF groups was statistically significantly different both when excluding (hazard ratio [HR] 2.86; 95% CI, 1.22–6.68; $P=.02$) (Supplemental Fig. 1A, available online) or including (HR 2.24; 95% CI, 1.17–4.32; $P=.02$) the treatment cycle-independent pregnancies (see Supplemental Fig. 1B). The mean TTP after two treatment cycles of CC/IUI was 2.1 ± 0.1 months, for FSH/IUI was

TABLE 1

Demographic and reproductive characteristics of couples (N = 154), by treatment group.

Characteristic	Mean ± SD or N (%)					
	Clomiphene/IUI (n = 51)		Gonadotropin/IUI (n = 52)		Immediate IVF (n = 51)	
	Female	Male	Female	Male	Female	Male
Age at randomization (y)	40.3 ± 1.3	39.6 ± 4.4	40.6 ± 1.2	40.0 ± 4.6	39.9 ± 1.4	40.1 ± 5.3
Caucasian	40 (78.4)	42 (82.4)	43 (84.3)	47 (90.4)	44 (88.0)	42 (87.5)
Hispanic	1 (2.1)	1 (2.0)	3 (6.0)	1 (2.0)	0 (0)	0 (0)
Current or past cigarette smoking	14 (27.5)	17 (33.3)	13 (25.0)	13 (25.0)	15 (30.6)	21 (45.7)
Household income						
<\$60,000	3 (5.9)		3 (5.8)		3 (5.9)	
\$60,000–99,000	11 (21.5)		10 (19.2)		3 (5.9)	
\$100,000–139,000	13 (25.5)		10 (19.2)		12 (23.5)	
≥\$140,000	23 (45.1)		29 (55.8)		32 (62.7)	
Unknown	1 (2.0)		0 (0)		1 (2.0)	
Female body mass index (kg/m ²)	24.9 ± 4.8		24.9 ± 4.2		23.7 ± 4.5	
Female reproductive history						
Prior use of oral contraceptives	43 (84.3)		43 (82.7)		40 (80.0)	
Prior laparoscopy (<1 y)	0 (0)		0 (0)		0 (0)	
Absence of prior pregnancies	29 (58.0) ^a		21 (40.4) ^a		35 (68.6) ^a	
Absence of prior live births	15 (30.0)		11 (21.2)		16 (31.4)	
Cycle day-3 FSH (mIU/mL)	7.3 ± 2.2 ^b		8.8 ± 2.7 ^b		7.8 ± 2.4 ^b	
Cycle day-3 estradiol (pg/mL)	46.7 ± 17.7		39.8 ± 14.3		44.7 ± 17.8	
Male semen analysis:						
Sperm concentration (M/mL)						
Mean ± SD	72.5 ± 81.5		72.4 ± 57.0		78.4 ± 57.2	
25th–50th–75th percentiles	36.0–55.5–87.0		33.0–54.0–101.0		41.0–76.0–104.0	
Sperm motility (%)						
Mean ± SD	64.1 ± 14.5		62.3 ± 12.0		64.5 ± 14.5	
25th–50th–75th percentiles	57.0–63.5–74.0		54.0–64.0–71.0		55.0–67.0–76.0	
Study site						
Boston IVF	48 (94.1)		47 (90.4)		46 (90.2)	
Brigham and Women's Hospital	3 (5.9)		5 (9.6)		5 (9.8)	
Insurance company at randomization						
Blue Cross/Blue Shield of MA	28 (54.9)		39 (75.0)		32 (62.8)	
Harvard Pilgrim Health Care	13 (25.5)		9 (17.3)		8 (15.7)	
Tufts Health Plan	10 (19.6)		4 (7.7)		11 (21.6)	

Note: CC = clomiphene citrate; FSH = follicle-stimulating hormone; IUI = Intrauterine insemination; IVF = In vitro fertilization; SD = standard deviation.

^a P = .01.

^b P = .009.

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3.0 ± 0.1 months and for immediate IVF was 5.7 ± 0.2 months, reflecting the longer time it takes to prepare for and complete one IVF cycle. After completion of all treatment, however, the average times were 9.1 ± 0.6, 12.4 ± 1.0, and 8.7 ± 0.5 months for CC/IUI, FSH/IUI, and immediate IVF, respectively. For both COH arms combined versus immediate IVF, the average times to conception were 12.2 ± 0.7 and 8.7 ± 0.5 months, indicating that those who conceived in the IVF arm did so on average 3.5 months faster.

Adverse Events

There were no statistically significant differences in the number of adverse outcomes or multiple births between the groups (Supplemental Table 1, available online). There were 12 sets of twins (16.9% of all live births) during the treatment cycles, one each from CC/IUI and FSH/IUI treatment and a treatment independent pregnancy and nine from IVF cycles. Higher-order multiple births were limited to one set of triplets in the immediate IVF arm (IVF cycle 1). The most common protocol deviation was cancelled IVF cycles, which occurred

in approximately 20% of all IVF cycles and did not differ significantly by treatment assignment.

DISCUSSION

In this RCT of reproductively older couples with unexplained infertility, the clinical pregnancy rates in the immediate IVF arm were statistically significantly higher after two cycles of treatment than in the treatment arms that initiated therapy with either CC/IUI or FSH/IUI. In addition, when comparing the number of treatment cycles per live birth for each of the arms, a statistically significant difference existed with fewer treatment cycles per live birth in the immediate IVF arm. At the conclusion of the trial, 46% of couples delivered a baby, the majority of whom were conceived using IVF.

We hypothesized that for older women treatment beginning with immediate IVF would be the most successful strategy so long as there was evidence of a reasonable chance for success before and during treatment. For this, we used a baseline clomiphene challenge test that required an acceptable ovarian response and established criteria to assess predicted

TABLE 2

Clinical pregnancy and live birth rates per couple, by randomization assignment for the first two treatment cycles and at the end of all treatment.

Randomized treatment arm	No. of couples (%)	First two treatment cycles		Duration of study	
		No. of clinical pregnancies ^{a,b} (%; 97.5% CI)	No. of live births ^c (%; 97.5% CI)	No. of clinical pregnancies ^d (%; 97.5% CI)	No. of live births ^d (%; 97.5% CI)
CC/IUI	51 (33.1)	11 (21.6, 10.2–37.3)	8 (15.7, 6.2–30.5)	38 (74.5, 58.4–86.9)	25 (49.0, 32.9–65.2)
Gonadotropin (FSH)/IUI	52 (33.8)	9 (17.3, 7.3–32.2)	7 (13.5, 4.9–27.6)	34 (65.4, 49.0–79.5)	22 (42.3, 27.1–58.7)
Immediate IVF	51 (33.1)	25 (49.0, 32.9–65.2)	16 (31.4, 17.7–47.9)	38 (74.5, 58.4–86.9)	24 (47.1, 31.2–63.4)
Total ^e	154	45 (29.2, 21.3–38.2)	31 (20.1, 13.4–28.4)	110 (71.4, 62.5–79.3)	71 (46.1, 37.0–55.4)

Note: Includes treatment-independent pregnancies; CC = clomiphene citrate; CI = confidence interval; FSH = follicle-stimulating hormone; IUI = Intrauterine insemination; IVF = In vitro fertilization.

^a Number of clinical pregnancies; includes all ultrasound confirmed pregnancies, including pregnancy losses.

^b For clinical pregnancy rate after first two treatment cycles: $P = .0067$ for comparison between CC/IUI and immediate IVF; $P = .0007$ for comparison between FSH/IUI and immediate IVF.

^c For live-birth rate after first two treatment cycles: $P = .101$ for comparison between CC/IUI and immediate IVF; $P = .035$ for comparison between FSH/IUI and immediate IVF.

^d For clinical pregnancy and live-birth rates after all treatment, there are no statistically significant differences, reflecting subsequent IVF treatment in all arms.

^e Of these, there were 5, 2, and 4 clinical pregnancies and 5, 1, and 3 live births in the CC/IUI, FSH/IUI and immediate IVF arms, respectively, that occurred before treatment was initiated or between treatment cycles one and two. Over the duration of the study there were 11, 3, and 9 clinical pregnancies and 7, 1, and 6 live births in the CC/IUI, FSH/IUI, and immediate IVF arms, respectively, that occurred outside of treatment cycles.

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success during the trial. Evidence has shown that the use of FSH/IUI does not increase pregnancy rates sufficiently over those of CC/IUI for younger women (5, 7, 8). Studies for these younger couples have demonstrated an increased risk of multiple births, especially high-order multiples from gonadotropin therapy (9). Costs for gonadotropins used in IUI protocols are estimated to be two to five times higher than costs for clomiphene (1, 10).

There are few randomized trials comparing treatment strategies for women at the end of their reproductive years. The lack of data for women 40 years or older has hampered clinical care. Historically, there has been the practice of beginning therapy with FSH/IUI, avoiding CC/IUI in reproductively older women, based on limited data. It is known, however, that older women require larger doses of gonadotropins with resulting higher economic cost. Given that success rates for COH/IUI reported from RCTs in younger women are mostly <10% per cycle and similar when either CC or FSH is used, we predicted that these success rates would drop further as the female partner approached the end of reproduction. Success rates for CC/IUI and FSH/IUI in our trial were similar and minimally lower than the reported rates for younger women (2, 5, 8, 9). When combined, COH/IUI live birth rates in our trial were only 5.1% per cycle, and COH/IUI was responsible for only 15.8% of all treatment-related live births.

We had a number of couples in this older group who were eligible but declined participation because of the concern of being randomized to immediate IVF. Thus, there are couples who may want to begin treatment with COH/IUI. The trial data support the use of CC/IUI for such treatment; it is similar in efficacy to FSH/IUI and easier and less costly for the patients.

A strength of FORT-T is the Massachusetts Infertility Mandate that requires insurers to pay for treatment. Generous insurance coverage allowed trial couples to complete therapy per protocol. The lack of comprehensive insurance coverage for infertility treatment is the reason why other infertility RCTs are only able to compare treatments over a limited number of cycles rather than compare entire treatment strategies. Comparison of treatment strategies makes it possible to determine the maximum success of tested treatment paradigms. Another strength was the fact that the trial was conducted at two large IVF centers, allowing for standardization of protocols and a large volume of patients for recruitment.

Limitations, as with many RCTs, include the relatively small number of participants on which to base generalizations, but this does not impact the internal validity of the results. Second, by necessity, neither the patients nor their providers were blind to their treatment assignment. To prevent this knowledge from influencing treatment assignment, choice, or outcome determinations, standardized eligibility criteria at baseline and for continuing treatment, including formal continuation and stopping rules, were applied by the study investigators. Randomization was conducted off-site by the epidemiologist and transmitted to the couple after consent was obtained. Acceptable ovarian reserve was demonstrated by clomiphene challenge test, the standard practice during the time of the study. Although there may be a shift toward the use of antimüllerian hormone (AMH) levels and

TABLE 3

Number (%) of couples initiating treatment cycles, total number of cycles initiated, and pregnancy rates by treatment group per initiated cycle and per couple who initiated treatment, separately for the first two cycles of treatment and subsequent IVF treatments.

Randomized treatment arm and treatment type	No. of couples initiating treatment (%)	No. of cycles initiated	Clinical pregnancy rates ^a			Live-birth rates		
			No.	Per cycle % (97.5% CI)	Per couple %, (97.5% CI)	No.	Per cycle % (97.5% CI)	Per couple % (97.5% CI)
CC/IUI (n = 51)								
CC/IUI	45 (88.2)	87	6	6.9 (2.5–17.7) ^b	13.3 (4.3–28.8) ^b	3	3.4 (0.7–16.1) ^b	6.7 (1.1–20.1) ^b
IVF	39 (86.7)	95	21	22.1 (13.0–35.0)	53.8 (38.5–68.5)	15	15.8 (7.9–29.1)	38.5 (21.6–57.6)
Total		182	27	14.8 (9.7–22.1)	60.0 (42.3–76.0)	18	9.9 (5.5–17.0)	40.0 (24.0–57.7)
FSH/IUI (n = 52)								
FSH/IUI	48 (92.3)	91	7	7.7 (2.8–19.6) ^c	14.6 (5.3–29.7) ^c	6	6.6 (2.1–18.9) ^c	12.5 (4.0–27.1) ^c
IVF	37 (77.1)	96	24	25.0 (14.7–39.1)	64.9 (45.2–81.5)	15	15.6 (7.5–29.6)	40.5 (24.8–57.9)
Total		187	31	16.6 (11.0–24.3)	64.6 (47.4–79.4)	21	11.2 (6.3–19.1)	43.8 (27.7–60.8)
Immediate IVF (n = 51)								
First 2 IVF	47 (92.2)	85	21	24.7 (16.1–35.7)	44.7 (28.4–61.9)	13	15.3 (7.6–28.3)	27.7 (14.3–44.7)
≥3rd IVF	23 (48.9)	33	8	24.2 (10.5–46.6)	34.8 (14.5–60.1)	5	15.2 (4.5–40.4)	21.7 (6.3–46.7)
Total		118	29	24.6 (16.1–35.7)	61.7 (44.4–77.1)	18	15.3 (8.2–26.7)	38.3 (22.9–55.7)
All treatment initiated	140 (90.9)	487	87	17.9 (14.3–22.1)	62.1 (52.4–71.3)	57	11.7 (8.8–15.4)	40.7 (31.8–50.2)

Note: For IVF treatment cycles, two of the cycles in the CC/IUI arm, two of the cycles in the FSH/IUI arm, and three of the cycles in the immediate IVF arm used cryopreserved embryos that had been collected in an earlier cycle and frozen for use in subsequent cycles. CC = clomiphene citrate; FSH = follicle-stimulating hormone (gonadotropin); IUI = intrauterine insemination; IVF = in vitro fertilization.

^a Number of clinical pregnancies includes all ultrasound confirmed pregnancies, including pregnancy losses.

^b P values for comparison between CC/IUI vs. first two immediate IVF cycles: P = .0015 for clinical pregnancy rate per cycle; P = .0012 for clinical pregnancy rate per couple; P = .0085 for live-birth rate per cycle; P = .0119 for live-birth rate per couple.

^c P values for comparison between FSH/IUI vs. first two immediate IVF cycles: P = .0033 for clinical pregnancy rate per cycle; P = .0016 for clinical pregnancy rate per couple; P = .09 for live-birth rate per cycle; P = .08 for live-birth rate per couple.

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antral follicle count today, these results remain generalizable to current practice given that the best assessment of ovarian reserve is response during treatment. Finally, costs are not considered. We made the decision to focus on treatment efficacy after two cycles of treatment rather than cost effectiveness, noting that the high cost of adverse outcomes would be limited in this age group due to the relative infrequency of OHSS and high-order multiple births and the need to understand the best treatment in the shortened time frame for success in these reproductively older women.

In conclusion, in one of the only RCTs to compare treatment strategies for older couples with unexplained infertility, the data show that for couples who present at the end of their reproductive years and who demonstrate a reasonable chance for continued success, the most successful treatment is immediate IVF. About half will have a live birth (more than 80% of these will be singletons). For couples who do not want immediate IVF, our data support the use of CC/IUI rather than FSH/IUI, given the comparable success rates. However, for couples initiating treatment with CC/IUI who then move on to IVF, the majority of their infants will be conceived by IVF and, on average, they will undergo more treatment cycles than patients who elect immediate IVF.

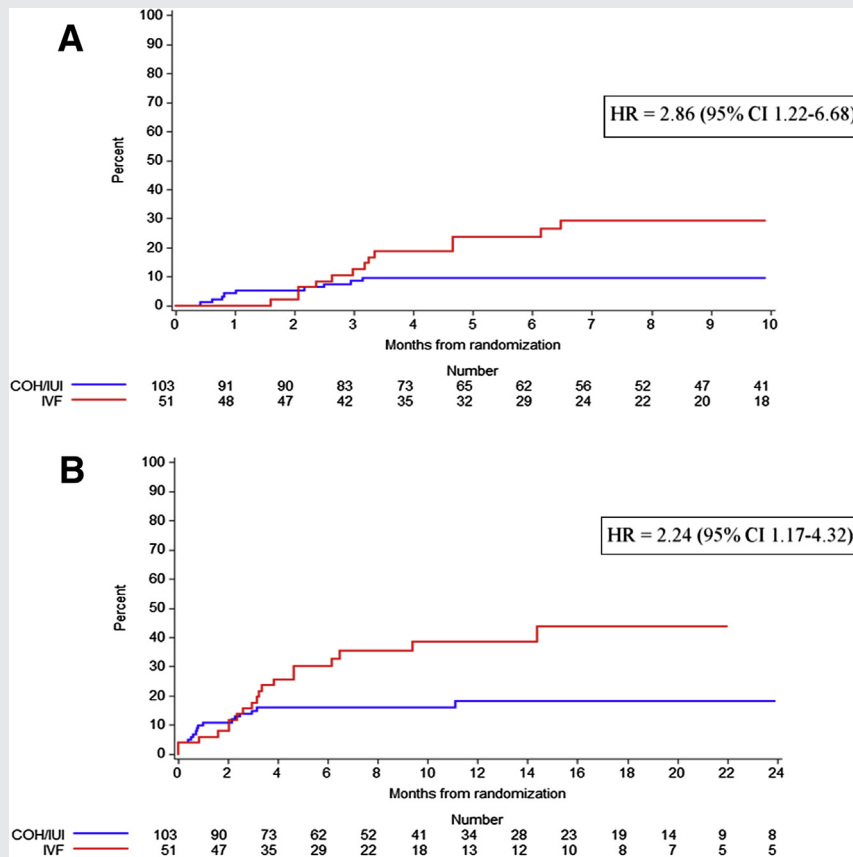
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SUPPLEMENTAL FIGURE 1



(A) Kaplan-Meier estimates of cumulative incidence of pregnancy leading to delivery of a live born for the controlled ovarian hyperstimulation arms combined versus the immediate IVF group. Analysis used a Cox proportional hazards model, $P=.02$. (B) Estimates with treatment cycle-independent pregnancies included, $P=.02$. HR = hazard ratio.

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SUPPLEMENTAL TABLE 1

Number (%) of women with adverse outcomes and multiple births from treatment and independent pregnancies combined.

Outcome	Randomization arm			Total
	Clomiphene/UII	Gonadotropin/UII	Immediate IVF	
No. women randomized	51	52	51	154
Adverse cycle outcomes				
Hyperstimulation ^a	2 (3.9)	3 (5.8)	3 (5.9)	8 (5.2)
Ectopic or heterotopic pregnancy	1 (2.0)	3 (5.8)	0 (0)	4 (2.6)
Spontaneous abortion (<20 wk) ^b	8 (15.7)	10 (19.2)	11 (21.6)	29 (18.8)
Therapeutic abortion (<20 wk)	0 (0)	0 (0)	1 (2.0) ^c	1 (0.6)
Selective reduction	0 (0)	1 (1.9) ^d	0 (0)	1 (0.6)
Fetal demise (≥20 wk)	1 (2.0)	0 (0)	0 (0)	1 (0.6)
No. of women with live birth(s)	25	22	24	71
Multiple births				
Twins ^e	6 (24.0)	3 (13.6)	3 (12.5)	12 (16.9)
Triplets	0 (0)	0 (0)	1 (4.2)	1 (1.4)
Neonatal death	0 (0)	0 (0)	0 (0)	0 (0)
Preterm delivery (<37 wk)	4 (16.0)	6 (27.3)	2 (8.3)	12 (16.9)
Birth weight (of ≥ 1 babies) ^f				
Low (1,500–2,500 g)	2 (8.0)	2 (9.1)	2 (8.3)	6 (8.5)
Very low (<1,500 g)	2 (8.0)	1 (4.5)	0 (0)	3 (4.2)

^a In the FSH/UII arm one woman had two episodes of hyperstimulation.

^b There were four, two, and two women with a treatment-cycle independent pregnancy resulting in spontaneous abortion in the CC/UII, FSH/UII, and immediate IVF arms, respectively. There were multiple occurrences of SABs: two women had two SABs and one had three SABs in the CC/UII arm, two women had two SABs in the FSH/UII arm, and two women had two SABs in the immediate IVF arm.

^c Therapeutic abortion in a treatment-cycle independent pregnancy.

^d Pregnancy with two fetal sacs of which one was selectively reduced and one was subsequently spontaneously aborted.

^e One set from CC/UII, four sets from IVF, and one set from a treatment-cycle independent pregnancy in the CC/UII arm; one set from FSH/UII, and two from IVF in the FSH/UII arm; and three from IVF in the IVF arm.

^f There were two twin gestations (one CC/UII and one FSH/UII) with one low birth weight and one very low birth weight twin.

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