A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial

Richard H. Reindollar, M.D.,[a] *Meredith M. Regan, Sc.D.,*[b] *Peter J. Neumann, Sc.D.,*[c] *Bat-Sheva Levine, M.D.,*[c] *Kim L. Thornton, M.D.,*[d] *Michael M. Alper, M.D.,*[d] *and Marlene B. Goldman, Sc.D.*[e]

[a] Department of Obstetrics and Gynecology, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; [b] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts; [c] Center for the Evaluation of Value and Risk in Health, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts; [d] Department of Obstetrics, Gynecology and Reproductive Biology, Division of Reproductive Endocrinology and Infertility, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Boston IVF, Waltham, Massachusetts; and [e] Departments of Obstetrics and Gynecology and Community and Family Medicine, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Objective: To determine the value of gonadotropin/intrauterine insemination (FSH/IUI) therapy for infertile women aged 21–39 years.
Design: Randomized controlled trial.
Setting: Academic medical center associated with a private infertility center.
Patient(s): Couples with unexplained infertility.
Intervention(s): Couples were randomized to receive either conventional treatment (n = 247) with three cycles of clomiphene citrate (CC)/IUI, three cycles of FSH/IUI, and up to six cycles of IVF or an accelerated treatment (n = 256) that omitted the three cycles of FSH/IUI.
Main Outcome Measure(s): The time it took to establish a pregnancy that led to a live birth and cost-effectiveness, defined as the ratio of the sum of all health insurance charges between randomization and delivery divided by the number of couples delivering at least one live-born baby.
Result(s): An increased rate of pregnancy was observed in the accelerated arm (hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.00–1.56) compared with the conventional arm. Median time to pregnancy was 8 and 11 months in the accelerated and conventional arms, respectively. Per cycle pregnancy rates for CC/IUI, FSH/IUI, and IVF were 7.6%, 9.8%, and 30.7%, respectively. Average charges per delivery were $9,800 lower (95% CI, $25,100 lower to $3,900 higher) in the accelerated arm compared to conventional treatment. The observed incremental difference was a savings of $2,624 per couple for accelerated treatment and 0.06 more deliveries.
Conclusion(s): A randomized clinical trial demonstrated that FSH/IUI treatment was of no added value. (Fertil Steril® 2010;94:888–99. ©2010 by American Society for Reproductive Medicine.)

Key Words: Unexplained infertility, FASTT Trial, intrauterine insemination, in vitro fertilization

Since the delivery of Louise Brown in 1978, infertility management has become increasingly successful, largely because of advances in IVF. For couples with unexplained infertility and mild male factor, superovulation with clomiphene citrate or gonadotropins combined with intrauterine insemination (IUI) have provided less invasive options before proceeding

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Reprint requests: Richard Reindollar, M.D., Department of Obstetrics and Gynecology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756 (FAX: 603-650-0906; E-mail: Richard.H.Reindollar@Hitchcock.org).

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to IVF. Before the late 1980s, the success of gonadotropin/IUI was similar to that of IVF. Over the last two decades as IVF stimulation protocols, laboratory procedures, and transfer catheters and techniques have improved, IVF success rates for couples in which the woman is younger than 40 years have nearly doubled. Neither the treatments nor the success rates of gonadotropin/IUI therapy, however, have changed (1–5). Furthermore, unlike IVF, gonadotropin/IUI is associated with an increased risk of unpreventable high-order multiple births (4, 5). At the same time, the health care costs of all infertility treatments and of twin and higher order multiple births have soared (6–8). One unanswered question is the cost-effectiveness of gonadotropin/IUI in contemporary infertility treatment.

In 1999, a multicenter clinical trial to evaluate gonadotropin/IUI found that 33% (77/231) of couples who were randomized to the gonadotropin/IUI arm became pregnant over four treatment cycles, a rate that was 3.2-fold greater than that for couples randomized to the group that had intracervical insemination without gonadotropins (9). The pregnancy rate per gonadotropin/IUI treatment cycle was only 9%, far lower than retrospective reports of 15–20% per cycle and similar to reports of pregnancy rates after treatment with clomiphene/IUI (4, 5, 10–14). Nearly 30% of all pregnancies resulting from treatment with gonadotropins were multiple; seven (8.1%) were high-order multiple gestations. For gonadotropin/IUI treatment, the high-order multiple births included two sets of quadruplets and three sets of triplets, thus raising questions about its continued use.

We designed the current study to compare the time to pregnancy and health care costs (i.e., costs related to treatment, pregnancy, and newborn care), as well as the efficacy and adverse events, of two infertility treatment strategies for couples who were candidates for ovulation induction with IUI as their initial treatment. We hypothesized that an accelerated track to IVF would result in a shorter time to pregnancy, fewer treatment- and pregnancy-related complications, and at an estimated cost savings compared with conventional care. Given the probabilistic nature of conception in any one cycle, the time it takes to establish a pregnancy that leads to a live birth is a sensitive measure of treatment efficacy across all types of treatment cycles. Achieving success after the minimum number of cycles needed to establish a sustained pregnancy reduces patient burden, exposure to ovulation induction, and the need to cryopreserve unused embryos, and it lessens the impact of the known decline in fertility with increasing age—all important considerations when counseling patients about their family building options (15, 16).

MATERIALS AND METHODS

A randomized clinical trial was conducted to evaluate an accelerated treatment strategy for couples with unexplained infertility that consisted of three cycles of clomiphene/IUI and up to six cycles of IVF, compared with a step-wise treatment course of three cycles of clomiphene/IUI, three cycles of gonadotropin/IUI, and up to six cycles of IVF. The study protocol was approved by institutional review boards at the participating institutions. Study participants gave written informed consent. An independent Data and Safety Monitoring Board met annually.

Study Population

All couples in which the woman was 21–39 years old and who sought care for unexplained infertility at Boston IVF or Harvard Vanguard Medical Associates were screened. Eligibility criteria included 12 months of attempted conception; at least one ovary and ipsilateral patent fallopian tube confirmed by hysterosalpingogram or laparoscopy; and no pelvic pathology, ectopic pregnancy, or previous infertility treatment (with the exception of up to three cycles of clomiphene without IUI). Sufficient ovarian reserve, demonstrated by cycle day 3 FSH and estradiol values of <15 mIU/mL and <100 pg/mL, respectively, and a sperm concentration of ≥ 15 million total motile sperm or ≥ 5 million total motile sperm at reflex IUI preparation were required. Exclusion criteria included the presence of hydrosalpinges, stage III or IV endometriosis, donor sperm, or the need for assisted reproductive technique procedures other than IVF. Randomization was performed using permuted blocks of varying sizes, stratified by the woman's age (<35 vs. ≥ 35 years), laparoscopy within the past year (yes or no), and study site (Boston IVF or Harvard Vanguard Medical Associates). The allocation sequence was produced by use of random numbers generated by a congruence method. The sequence was developed by the biostatistician and implemented by the epidemiologist. Although it was not feasible to blind the physicians or patients to the treatment regimen, the investigators were blinded to all outcome determinations.

Treatment Protocols

Standardized treatment protocols were agreed upon by all participating physicians. All couples initiated treatment with up to three cycles of clomiphene citrate (CC) and IUI. A CC dose of 100 mg orally on cycle days 3–7 was followed by one IUI the day after a positive ovulation predictor kit result. Ultrasound monitoring was used in the absence of an LH surge by cycle day 15. When the lead follicle was ≥ 18 mm, hCG (10,000 IU) was given subcutaneously (SC).

Couples in the conventional arm who were not pregnant after three cycles of CC/IUI treatment received up to three cycles of gonadotropin/IUI. Recombinant FSH (150 IU) was given SC; the dose of FSH was adjusted as indicated by ultrasound and serum estradiol assessment until a lead follicle measured ≥ 17 mm and 2–3 follicles ≥ 15 mm in size were detected. A single IUI followed approximately 36 hours after the hCG was administered. If a pregnancy was not achieved, couples received up to six cycles of IVF therapy, two of which could be thaw cycles with cryopreserved embryos. Couples in the accelerated arm who had not become pregnant after three cycles of clomiphene/IUI omitted the gonadotropin/IUI treatment and moved directly to IVF.

The same standardized IVF protocol was used for both study arms as follows: leuprolide acetate, 10 units SC beginning on cycle day 21, decreasing to 5 units on cycle day 1 until hCG administration. Follicle-stimulating hormone (225 IU SC) was given with dosage adjustments determined by standard monitoring; SC hCG followed when a lead follicle measured $\geq$17 mm and there were at least three follicles $\geq$15 mm in size. Oocyte retrieval was performed 36 hours later. Intracytoplasmic sperm injection was allowed only for men who had repeated sperm counts <5 million total motile sperm identified at IUI and then directed to IVF, or for couples after an unexpected failed fertilization, or when <10 million total motile sperm were available at IVF. Embryos were transferred routinely on day 3 (occasionally on day 5); the number transferred was based on American Society for Reproductive Medicine guidelines. Standardized cancellation criteria were used.

Low response protocols were used for patients not responding well (fewer follicles and lower estrogen levels than considered optimal by predetermined criteria) to standard gonadotropin stimulation for either FSH/IUI or IVF.

Patients (n = 18) with hypoestrogenic, hypothalamic anovulation, or polycystic ovary syndrome, who had not become pregnant after three ovulatory treatment cycles, were included because they were also candidates for subsequent treatment with IUI and IVF. They received gonadotropin/IUI as an initial treatment if randomized to the conventional arm or immediate IVF if randomized to the accelerated arm.

Study Outcomes

The primary endpoints were the length of time from the date of randomization to the date a pregnancy resulting in a live birth was established and cost-effectiveness, defined for each randomized treatment arm as the ratio of the sum of health insurance charges for all couples divided by the number of couples delivering at least one live-born baby. Secondary endpoints were per cycle pregnancy rates, per couple pregnancy rates, and adverse events for each treatment.

Time to pregnancy was the length of time from the date of randomization to the date a pregnancy resulting in a live birth was established (i.e., events in the denominator of the cost-effectiveness ratio) as follows: the date of the IUI, the oocyte retrieval, or the embryo thaw; or, for pregnancies that occurred outside a treatment cycle, the date of coitus, last menstrual period plus 14 days, or 38 weeks before the expected delivery date. Randomization could occur after the IUI in the first CC/IUI cycle, as long as the outcome of the cycle was not yet known. If a pregnancy was achieved in that first treatment cycle, then the date of randomization was used as the date the pregnancy was established.

Charge data were obtained from participating health insurers, Blue Cross Blue Shield of Massachusetts, Harvard Pilgrim Health Care, and Tufts Health Plan. Charges reflected all health care items and services for women covered by insurance during the time of the trial, from randomization through delivery hospital discharge of both mother and baby, or until 1 year after completing the trial treatment protocol without pregnancy. The charges included: physician or health professional time, medications, medical equipment, diagnostic tests, infertility treatments, care of complications, hospitalizations, and delivery/post-delivery care. In addition, we collected data on the out-of-pocket costs for a subsample of subjects in the trial. Cost diaries were provided to subjects after the first cycle for each stage of the process (i.e., for the conventional arm, diaries were provided after clomiphene cycle 1, after FSH cycle 1, and after IVF cycle 1). Respondents were asked to keep track of certain medical expenses that occurred during the treatment phase of this study, such as copayments for prescription drugs and nonprescription items and any mental health services, such as visits to a therapist or psychiatrist. They were also asked to record transportation costs and the amount of time that they and their partner missed from work to receive treatment. The 2007 average hourly nonfarm wage of $17.43 was used to estimate the value of time lost from work (17).

The closing date of the study for costs and delivery of at least one live-born baby was April 30, 2006. All couples were followed until discharge from the hospital of both mother and baby or until 1 year after completing the treatment protocol. For couples who had not delivered at the closing date, time was censored at the date of the ultrasound confirming the pregnancy or at the date of last contact if not pregnant. Hiatus from treatment occurred for medical reasons and personal choice; when couples did not return to treatment within 1 year they were considered to have completed treatment by patient choice prior to the break. Any pregnancy that occurred during the trial period was documented under the intention-to-treat paradigm, including those that did not directly result from a protocol treatment cycle and those that occurred within 1 year of completing the treatment protocol.

Statistical Analysis

Computer simulations preceding the trial estimated that a sample size of 800 couples provided >99% power to detect a reduction in time-to-pregnancy with the accelerated regimen using the log-rank test. In addition, a sample size of 800 provided 98% power to detect a difference in cost-effectiveness ratios between the arms that favored the accelerated regimen and 74% power to observe a one-sided and 64% power to observe a two-sided 95% bootstrap confidence interval that excluded zero for the cost-effectiveness ratios. The trial was designed with the understanding that we would have excellent power to detect a difference in both time to pregnancy and cost. Given the variable nature of cost data, however, we realized that the study might not have sufficient power to observe confidence intervals around the cost difference that excluded zero, a common strategy in health economic analyses. According to the results of a blinded review conducted by the Data and Safety Monitoring Board

at their April 2005 meeting, the protocol was amended to stop recruitment when 500 couples were enrolled. The board's decision included power considerations with 500 couples, an unplanned interim analysis of the time to pregnancy data, and the additional time that would be required to enroll the planned 800 couples. With 500 couples, it was estimated that the study would have >99% power to demonstrate a shorter time to pregnancy and 95% power to detect a difference in cost-effectiveness ratios that would favor the accelerated regimen. Given the relatively little loss in the power estimates, it was decided that stopping enrollment at 500 couples would not alter the ability of the trial to achieve its aims.

Analyses were by intention to treat and included all couples who were randomized. Time to pregnancy was analyzed using a log rank analysis and Cox proportional hazards model with interactions of treatment arm with three time intervals, because of nonproportional hazards over time (18). Nonproportionality was investigated by checking for an interaction of treatment assignment and time and by graphical methods (18). Hazard ratios and their 95% confidence limits were calculated for three time segments: 0 to 3 months, an a priori assumption confirmed by the observed data; >3 to 11 months, a data-driven decision because the hazard functions crossed at approximately11 months; and >11 months. Cumulative incidence of time to pregnancy was plotted as one minus Kaplan-Meier estimates.

In our base cost–effectiveness analysis, we calculated total insurance charges for infertility-related care from randomization through either discharge of a live-born baby or end of follow-up. In sensitivity analyses, we analyzed the difference in the infertility treatment-related charges per delivery between the two arms. We also examined results with and without those outlier cases whose total charges were >3 SD above the mean. Missing charge data were imputed for 55 couples based on mean per cycle treatment charges and pregnancy outcomes for the couples for whom we had insurance charge data. For example, in the accelerated arm, for a subject with missing charge data who received three CC cycles and 2 IVF cycles before delivering a singleton, we used the mean charge for similar subjects for whom we had insurance data. Bootstrapped 95% confidence intervals (CIs) were calculated for each cost-effectiveness ratio and their difference (19–22).

To test the generalizability of the cost data, a simulation was performed using clinical data from the trial, but using different assumptions about the average cycle costs to show a "break-even" analysis (i.e., how different a typical facility's IVF treatment costs would have to be to change the conclusions from the trial-based insurance charge data about cost-effectiveness).

Among randomized couples, proportions were compared using Fisher's exact tests and exact binomial 95% confidence intervals; continuous variables were compared using Wilcoxon rank sum tests. Cycle-specific outcomes with multiple observations per couple were analyzed using over-dispersed logistic regression. Statistical significance was defined as $P < 0.05$ (two-sided). Data analyses used SAS 9.1 statistical software (SAS Institute Inc., Cary, NC) and S-Plus 6.2 (Insightful Corp., Seattle, WA).

RESULTS

Between September 14, 2001 and August 31, 2005, we enrolled 503 couples with unexplained infertility; 247 couples were randomized to a conventional and 256 to an accelerated treatment course (Fig. 1); 493 (98%) couples initiated and 417 (83%) followed the treatment protocol. Nineteen couples were in active treatment as of the closing date of the study. Seventy-nine couples took a break from treatment as follows: 22 couples (11 in each arm) stopped for longer than 6 months but returned to continue treatment; six couples (three in each arm) conceived within 1 year of starting their break; eight couples were on a break as of the closing date of the study (five in the conventional and three in the accelerated arm); and 43 couples (20 in the conventional arm and 23 in the accelerated arm) did not return to treatment after a 1-year break. The demographic and reproductive characteristics of the couples in the two treatment groups were similar (Table 1). The 493 couples initiating treatment cycles underwent a total of 2,355 cycles, 1,346 and 1,009 in the conventional and accelerated arms, respectively (Table 2).

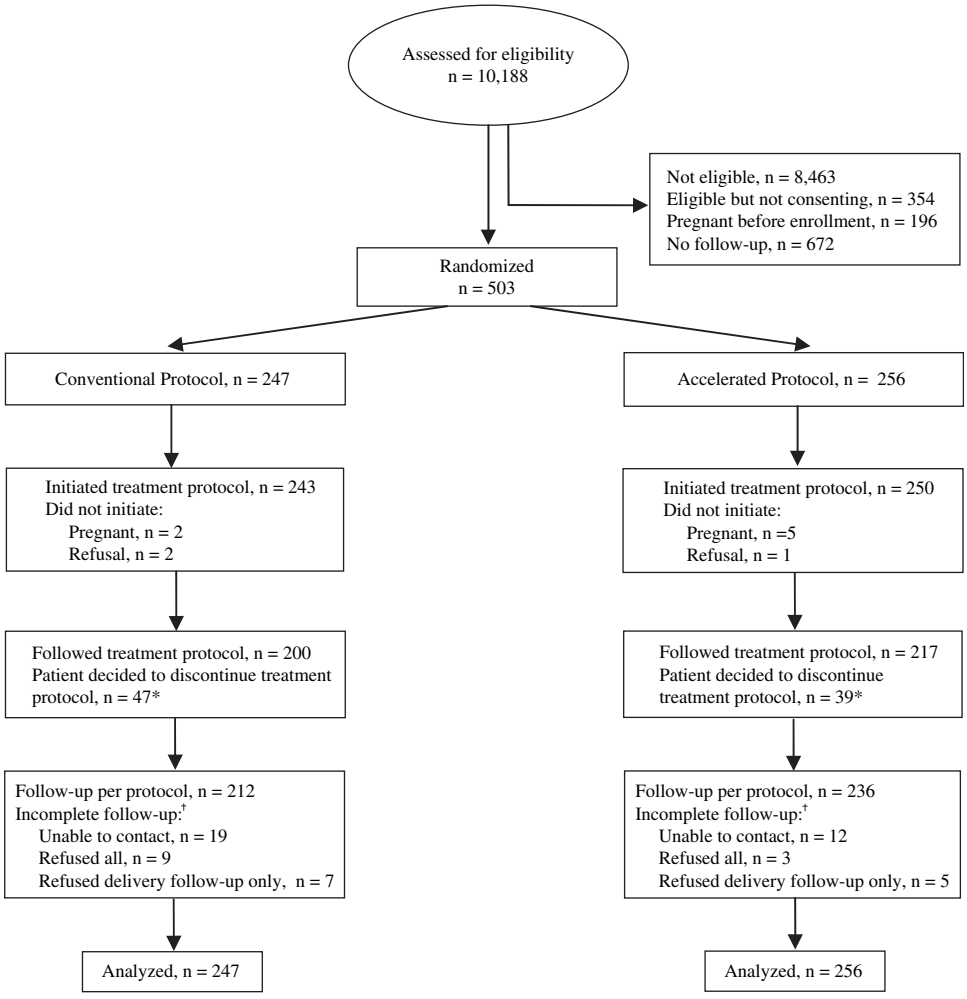
Efficacy

Sixty-four percent (321/503) of couples delivered at least one live-born baby as of April 30, 2006 (150 conventional and 171 accelerated). Time to pregnancy was statistically significantly shorter in the accelerated arm compared with the conventional arm (hazard ratio [HR], 1.25; 95% CI, 1.00–1.56; log-rank P=0.045). The estimated median time to pregnancy was 8 months in the accelerated arm and 11 months in the conventional arm. When analyzed using a Cox proportional hazards model, a 40% increased rate of pregnancy (HR, 1.40; 95% CI, 1.03-1.90; P=0.03; Fig. 2) was noted during the period 3–11 months after randomization. During the initial 3-month period couples in the accelerated arm also experienced an increased rate of pregnancy (HR, 1.52; 95% CI, 1.02–2.28; P=0.04), reflecting an increase during the first month of treatment with CC/IUI, but this difference disappeared by three months. The cumulative percentage of pregnancies for conventional and accelerated treatment arms were 31.9% and 43.2%, 43.8% and 54.7%, and 55.4% and 65.4% at 6, 9, and 12 months, respectively.

Per cycle pregnancy rates for CC/IUI, FSH/IUI, and IVF were 7.6%, 9.8%, and 30.7%, respectively (Table 2). These pregnancy rates include live births as well as the 63 couples (35 conventional and 28 accelerated) who had an ongoing viable pregnancy at ≥20 weeks' gestation at the closing date. Fifty-two (14%) pregnancies occurred in menstrual cycles for

FIGURE 1

Screening and Enrollment of Infertile Couples. * 86 couples chose to discontinue treatment after a median of 4.5 cycles (interquartile range, 3 to 6 cycles) over a median duration of 8 months (interquartile range, 3 to 15 months). † The median duration of follow-up for these couples was 6 months (interquartile range, 3 to 14 months) and was 14 months (interquartile range, 11 to 18 months) among couples who completed follow-up.



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which study treatments were not given and were called *treatment cycle-independent* (Table 2).

The average number of oocytes retrieved (10.9 ± 6.1 vs. 10.5 ± 6.1), embryos transferred (2.2 ± 1.0 vs. 2.3 ± 0.9), and embryos frozen (1.3 ± 2.1 vs. 1.4 ± 2.3) per IVF cycle were similar between the conventional and accelerated arms, respectively. Adverse outcomes are presented in Table 3. Multiple birth rates did not differ significantly between the two arms, 38/185 (21%) vs. 45/199 (23%) of sustained pregnancies (P=0.72). High-order multiple births were limited to five sets of triplets: two sets in the conventional arm (one of which was reduced and delivered as twins) resulted from gonadotropin/IUI treatment, and three sets in the accelerated arm (one from CC/IUI treatment and two from IVF; Table 3).

Cost Effectiveness

Insurance charge data were obtained for 448 (89%) of 503 couples (Table 4). Total insurance charges for infertility-related care from randomization through either discharge of live-born babies or end of follow-up were $9.4 million for 215 conventionally-treated couples, of whom 132 delivered, and $9.6 million for 223 fast track couples, of whom 156 delivered. Observed charges per delivery were $9,846 lower (95% CI, $25,099 lower to $3,869 higher; P=0.084) for the accelerated ($61,553 per delivery; 95% CI, $54,075–69,489) than the conventional arm ($71,399 per delivery; 95% CI, $60,168–84,490). The difference in the infertility treatment-related charges per delivery was $5,802 (95% CI, –$14,388 to +$2,299; P=0.08). When charges for the 55 couples with missing insurance data

TABLE 1

Demographic and reproductive characteristics of couples (n = 503), by treatment group.

Characteristic	Mean ± SD or n (%)			
	Conventional (n = 247)		Fast Track (n = 256)	
	Female	Male	Female	Male
Age at randomization	33 ± 3	34 ± 5	33 ± 3	35 ± 5
Female age ≥35 y	88 (36)	—	92 (36)	—
Caucasian	209 (85)	212 (86)	227 (89)	227 (89)
Hispanic	9 (4)	6 (2)	9 (4)	12 (5)
Current or past cigarette smoking	68 (27)	67 (27)	73 (29)	75 (29)
Years married or living as married	4 ± 3		4 ± 3	
Household income				
<$60,000	24 (10)		22 (9)	
$60,000–99,000	77 (31)		78 (30)	
$100,000–139,000	70 (28)		71 (28)	
≥$140,000	68 (28)		82 (32)	
Unknown	8 (3)		3 (1)	
Female body mass index (kg/m^2)	24 ± 5		24 ± 4	
Female reproductive history				
Prior oral contraceptives	203 (82)		224 (88)	
Prior laparoscopy (within past year)	14 (6)		22 (9)	
No. of prior pregnancies	152 (62)		145 (57)	
No. of prior live births	199 (81)		210 (82)	
Cycle day 3 FSH (mIU/mL)	6.6 ± 2.2		6.7 ± 2.2	
Cycle day 3 Estradiol (pg/mL)	42.2 ± 17.3		42.6 ± 32.5	
Male semen analysis				
Sperm concentration (M/mL)				
Mean ± SD	89 ± 72		85 ± 83	
25th—50th—75th percentiles	45—65—112		40—62—103	
Sperm motility (%)				
Mean ± SD	63 ± 15		62 ± 15	
25th—50th—75th percentiles	54–64–75		52–61–73	
Study site				
Boston IVF	237 (96)		241 (94)	
Harvard Vanguard Medical Associates	10 (4)		15 (6)	
Insurance company at randomization				
Blue Cross/Blue Shield of Massachusetts	121 (49)		136 (53)	
Harvard Pilgrim Health Care	63 (26)		67 (26)	
Tufts Health Plan	60 (24)		51 (20)	
Other	3 (1)		2 (1)	

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were imputed, the values changed only slightly. Charges per delivery were approximately $9,700 lower (95% CI, $23,300 lower to $3,600 higher; P=0.079) for the fast track ($61,700 per delivery; 95% CI, $54,800–69,600) than the conventional arm ($71,400 per delivery; 95% CI, $60,900–83,500). The observed incremental difference in charges per couple was a savings of $2,624 ($41,211–43,835) for accelerated treatment, and an increase in the proportion of couples with deliveries of 0.06 (0.67–0.61). For these reasons, in the parlance of cost-effectiveness analysis, accelerated treatment dominates conventional therapy.

Of 334 subjects who completed diaries (180 in the fast track and 154 in the conventional), mean costs per couple were $485 for the fast track and $495 for the conventional. The main items included time involved in treatment and co-payments for drugs and physician visits. The value of time

TABLE 2

Number of couples initiating treatment cycles, total number of cycles initiated, and pregnancy rates by treatment group as of April 30, 2006.

	Treatment type and randomization strategy								
	CC/IUI			FSH/ IUI	IVF			Total	
	Conventional	Fast track	All	Conventional	Conventional	Fast track	All	Conventional	Fast track
No. couples initiating	233	242	475	169	111	172	283	247	256
No. of cycles initiated	646	648	1294	439	261[a]	361[a]	622	1346	1009
No. of pregnancies									
Total[b]	55	68	123	50	95	145	240	200	213
Losses	10	15	25	7	22	27	49	39	42
Ongoing ($\geq$ 20 wks)	4	2	6	6	15	18	33	35[c]	28[c]
Live birth	41	51	92	37	58	100	158	150[c]	171[c]
Pregnancy rates (live birth + ongoing)									
Per initiated cycle	7.0 (4.8-10.0)	8.2 (5.8-11.4)	7.6 (6.2-9.2)	9.8 (6.8-14.0)	28.0 (21.8-35.2)	32.7 (27.0-38.9)	30.7 (27.1-34.5)		
Per couple	19.3 (14.5-25.0)	21.9 (16.9-27.7)	20.6 (17.1-24.6)	25.4 (19.1-32.7)	65.8 (56.2-74.5)	68.6 (61.1-75.5)	67.5 (61.7-72.9)	74.9 (69.0-80.2)	77.7 (72.1-82.7)

Note: CC = clomiphene citrate; IUI = intrauterine insemination; FSH = gonadotropin.

[a] For IVF, 32 of the conventional and nine of the fast track cycles used cryopreserved embryos that had been collected in an earlier IVF cycle and frozen for later use. These cycles, called thaw cycles, are included in the calculation of the pregnancy rates per initiated cycle.

[b] Total pregnancies include all ultrasound confirmed pregnancies, including spontaneous abortions.

[c] Of these, there were 18 ongoing pregnancies (10 in conventional and 8 in fast track) and 34 live births (14 in conventional and 20 in fast track) that occurred outside of treatment cycles.

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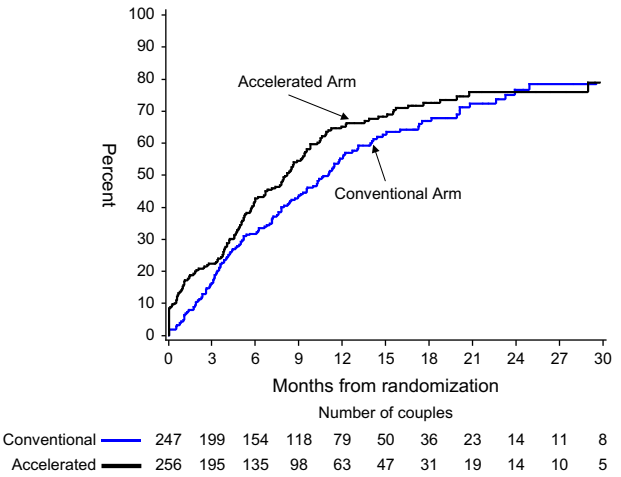
FIGURE 2

Kaplan-Meier Estimates of Cumulative Incidence of Pregnancy Leading to Delivery of a Live Born, According to Treatment Arm. HR = 1.251 (95% CI, 1.00 to 1.56; log rank P = 0.0452). Analysis also used a piecewise Cox proportional hazards model, overall P = 0.0067. Out of 106 couples who had their IUI prior to the date of randomization (but before pregnancy could be determined), 15 (3/50 conventional and 12/56 accelerated) became pregnant. Additionally, 4 couples in the accelerated arm became pregnant before initiating their first treatment cycle. These couples are shown as achieving pregnancy on day of randomization.



Time Period (m)	Hazard Ratio	95% CI		P-value
≤ 3	1.52	1.02	2.28	0.04
> 3 to 11	1.40	1.03	1.90	0.03
> 11	0.60	0.34	1.06	0.08

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lost was slightly higher for conventional ($211) than accelerated ($178) treatment. The identified diary costs reflect only approximately 1% of the total charges of couples in the study. Moreover, there were virtually no differences in the two arms of the study. A sensitivity analysis of the costs per delivery, which included these costs, had virtually no affect on results.

A simulation using the clinical data from the trial but varying the average cycle costs demonstrated that, if average costs for CC/IUI and gonadotropin/IUI were $500 and $2,500, the cost per delivery with accelerated IVF is lower under varying assumptions about the cost of an IVF cycle. The cost of an IVF cycle would have to exceed $17,749 for the conventional arm to have a lower cost per delivery (Table 5) (13).

DISCUSSION

The fast track and standard treatment (FASTT) trial provided the rare opportunity to follow 503 treatment-naïve couples through their entire treatment course, including voluntary hiatuses from care, and to compare two different standardized treatment strategies. In this large randomized controlled trial that compared a conventional treatment paradigm to an accelerated strategy to IVF for infertile couples, it was found that gonadotropin/IUI use was of no added value. Couples in the accelerated arm became pregnant at a faster rate, with fewer treatment cycles. The results suggest that compared with conventional treatment, accelerated treatment saves money and results in a greater proportion of couples with delivery of a live-born baby. For all analyses performed regarding charges (i.e., treatment charges per couple and per delivery, total charges per couple and per delivery), the charges were less for couples in the accelerated compared with the conventional arm. The CIs for the differences in infertility treatment charges and total charges per delivery overlap zero, indicating that observed charge differences are not significant at the 0.05 alpha level. However, the asymmetry of the 95% bootstrapped CIs indicates that the accelerated arm is not more costly and suggests cost savings for accelerated compared with conventional care. Furthermore, a simulation demonstrates that the accelerated arm is favored, even under extreme assumptions about the cost of IVF. The cost of an IVF cycle would have to exceed $17,749 for the conventional arm to have a lower cost per delivery if the average costs for CC/IUI and FSH/IUI were $500 and $2,500, respectively. The simulation helps address questions about the generalizability of the results: it suggests that as long as a facility's IVF costs per cycle are <$17,749, the accelerated strategy is likely the less costly one, given plausible assumptions about other infertility costs.

Gonadotropin/IUI has historically been the mainstay of infertility treatment before IVF. Its cost and unavoidable multiple births, especially high-order multiples, and the risk of hyperstimulation syndrome have brought this treatment under closer scrutiny. The ability to achieve higher pregnancy rates with fewer embryos transferred through IVF has evoked further questions regarding the role for gonadotropin/IUI. The multicenter randomized trial reported by Guzick et al. examined its success (8). Whereas one third of patients became pregnant over four treatment cycles, the per cycle pregnancy rate when gonadotropin/IUI was used to initiate therapy was 9% per cycle, much lower than prior reports (9, 10). The FASTT trial supports this low success rate when gonadotropin/IUI follows three cycles of CC/IUI (9.7% per cycle). In addition, our CC/IUI success rate was similar to prior reports (7.6% per cycle) and, interestingly, not much different from the success rates of gonadotropin/IUI reported by this trial and the multicenter randomized trial (8).

One strength of this trial was the Massachusetts Infertility Mandate that requires insurers to cover the cost of treatment. Such a large trial would not have been possible in a self-pay or partial coverage environment in which the

TABLE 3

Number (%) of adverse outcomes, protocol deviations, and multiple births.

	Conventional	Fast Track	Total
No. women randomized	247	256	503
Adverse cycle outcomes			
Hyperstimulation	18 (7.3)	18 (7.0)[a]	36 (7.2)
Ectopic or heterotopic pregnancy	8 (3.2)	10 (3.9)	18 (3.6)
Spontaneous abortion (<20 wk)	32 (13.0)	38 (14.8)	70 (13.9)
Therapeutic abortion (<20 wk)	0 (0)	1 (0.4)	1 (0.2)
Selective reduction	2 (0.8)	0 (0)	2 (0.4)
Fetal demise (≥20 weeks)	2 (0.8)	5 (2.0)	7 (1.4)
No. of women with protocol deviations			
>3 Clomiphene cycles	11	12	23
>3 FSH cycles	9		9
FSH/IUI cycles cancelled	14		14
FSH/IUI cycles converted to IVF	16		16
IVF cycles converted to IUI	6	8	14
No. women with a sustained pregnancy	185	199	384
Multiple births			
Twins			
Delivered	30 / 150 (20.0)[b]	34 / 171 (19.9)	64 / 321 (19.9)
Expected as of April 30, 2006	7 / 35 (20.0)	8 / 28 (28.6)	15 / 63 (23.8)
Triplets			
Delivered	1 / 150 (0.7)[c]	2 / 171 (1.2)[d]	3 / 321 (0.9)
Expected as of April 30, 2006	0 / 35 (0)	1 / 28 (3.6)[e]	1 / 63 (1.6)
No. women delivered	150	171	321
Neonatal death	1 (0.7)[f]	1 (0.6)[g]	2 (0.6)
Pre-term delivery (<37 wk)	34 (22.7)	40 (23.4)	74 (23.0)
Birth weight (of one or more babies)			
Low (1500-2500 g)	23 (15.3)	30 (17.5)	53 (16.5)
Very low (<1500 g)	4 (2.7)	3 (1.8)	7 (2.2)

[a] Only one severe case of hyperstimulation required hospitalization (in the accelerated arm).
[b] Includes a set of triplets, resulting from gonadotropin/IUI therapy, that was reduced and delivered as twins.
[c] This set of triplets resulted from gonadotropin IUI.
[d] One set resulted from CC/IUI and the other from IVF.
[e] This set of triplets resulted from IVF and included a singleton and a set of identical twins.
[f] The remaining neonate of a twin gestation that was reduced because of trisomy 13 died three days after delivery at 34 weeks' gestation because of severe neonatal hypoxia.
[g] One twin died after delivery at 20 weeks' 3 days' gestation following an earlier intrauterine fetal demise. The discharge diagnosis was incompetent cervix, pneumonia, and hematoperitoneum.

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cost of care is a much larger factor in couples' choice of therapy. This coverage is likely the reason for the low drop-out rate. A second strength was the large volume of patients available at a single IVF center, allowing for standardized protocols and procedures. Lastly, prior studies have used estimated costs of treatment only, and none have received comprehensive charge data from insurers through discharge from birthing hospitalization for mothers and babies or for one year following completion of the trial treatment protocol. In a trial of 96 subjects who were randomized to conventional treatment or to IVF, only costs of treatment were determined, and 34% of couples dropped out of the study (23).

Limitations include the fact that insurance data involved charges, which are not the same as costs, because charges are set by the insurers and may not reflect the economic cost of providing a service or payments made. Whereas the charges for services in the trial may not represent actual costs, and may differ to varying degrees from charges or costs in

TABLE 4

Summary of charge data.

Arm	No. of couples with charge data[a]	No. of deliveries, N (proportion)	Infertility charges during treatment[b]			Total charges throughout trial[c]		
			Total	Per couple ± SE	Per delivery	Total	Per couple ± SE	Per delivery
Conventional	215	132 (0.61)	$4,594,361	$21,368 ± 1,548	$34,806	$9,424,646	$43,835 ± 3,255	$71,399
Fast Track	233	156 (0.67)	$4,524,522	$19,418 ± 1,229	$29,003	$9,602,269	$41,211 ± 2,104	$61,553
Δ		+24 (0.06)			–5,802 (95% CI, –14,388, 2,299)		–$2,624	–9,846 (95% CI, –25,099–3,869)

[a] Charge data were available for 448/503 (89%) of couples. Data were missing for 12 couples who refused to allow insurance data to be provided, 5 couples insured by nonparticipating carriers, and 38 couples whose insurance data were unavailable because of contractual arrangements with the participants' employer.

[b] Infertility charges include charges associated with treatment cycles.

[c] Total charges include infertility treatment charges as well as charges incurred for all hospitalizations including those associated with pregnancy, delivery, and neonatal care until discharge. There were nine couples whose total charges were >3 SD above the mean, six in the conventional and three in the fast track arm. With those couples removed we observed a $4,175 (95% CI, $16,500 lower to $7,800 higher) cost per delivery saving for the fast track arm.

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other regions of the country, the strength of our analysis is the focus on the difference in charges per delivery after randomization, not the absolute value of service costs.

With time, other treatment changes will occur that will further influence the cost effectiveness of a more rapid approach to IVF. The practice of single embryo transfer for selected cases has only recently emerged and was not a part of our study protocol. The Belgian experience suggests that even if the pregnancy rate per IVF cycle is lower in single embryo transfer cycles, the cost saving from the elimination of multiple births is remarkable (24, 25).

In the current study, the rate of multiple births after gonadotropin/IUI, although double the rate after CC/IUI, was lower than the rate reported in the multicenter randomized trial and other studies, despite similar stimulation protocols (8, 9, 10). Several factors may explain the lower than expected multiple birth rate. First, guidelines were present for canceling hyperstimulated cycles (n = 14) and, as practice changed over time, couples were allowed to convert to IVF (n = 16; Table 3). Second, FASTT, performed almost entirely at one treatment center, may have allowed for greater standardization of cycle management than was possible for the multicenter trial. Finally, we preceded gonadotropin/IUI treatment with three cycles of CC/IUI. In the multicenter trial the most fertile couples, who have the highest risk for multiple births, had their first exposure to superovulation with gonadotropin/IUI. The FASTT results indicate that initiating treatment with CC/IUI allows a reasonable percentage of couples to become pregnant with minimal risk of multiple births before embarking on IVF. If our multiple birthrate after gonadotropin/IUI had been higher, the difference in cost per delivery between the two arms would have been even greater.

In summary, the trial results demonstrate that contemporary infertility treatments are highly successful. For couples with unexplained infertility who reside in states such as Massachusetts that require comprehensive insurance coverage, the majority will succeed. The overall success of treatment and low dropout rates observed for couples, largely because of comprehensive coverage, make a case for similar coverage nationwide. For couples without insurance coverage, the results provide guidance for a cost-effective and safe approach to treatment. Beginning treatment with CC/IUI will result in pregnancy in nearly one fourth of the couples, with minimal risk of multiple births and at a low cost. As clinical practice moves to limiting the number of embryos transferred during IVF procedures in young women to one or two embryos, eliminating gonadotropin/IUI from the step-wise infertility paradigm will result in pregnancies with the lowest possible risk for multiple births (24–27). Compared with conventional infertility treatment and when the woman is younger than 40 years, an accelerated approach to IVF that starts with CC/IUI, but eliminates gonadotropin/IUI, results in a shorter time to pregnancy, with fewer treatment cycles, and at a suggested cost savings.

TABLE 5

Break-even analysis.

Costs	Conventional	Fast track	Reference
CC/IUI (per cycle)	$500	$500	Assumption
FSH/IUI (per cycle)	$2,500	$2,500	Assumption
IVF (per cycle)			
Base case	$10,000	$10,000	Assumption
Expensive scenario	$15,000	$15,000	Assumption
Less expensive scenario	$6,000	$6,000	Assumption
Delivery cost (per delivery)			
Singleton	$14,842	$14,842	Assumption based on TL Callahan et al., NEJM 1994, adjusted for inflation[a]
Twins	$59,370	$59,370	Same as above
Triplets	$163,266	$163,266	Same as above
Clinical Outcomes			
Total number of cycles initiated			
CC/IUI	646	648	FASTT trial
FSH/IUI	439	–	FASTT trial
IVF	261	361	FASTT trial
Number of babies			
Singleton	119	134	FASTT trial
Twins	30	34	FASTT trial
Triplets	1	2	FASTT trial
Total number of deliveries	150	170	FASTT trial

Event analysis of all randomized patients: cost per delivery

Scenario	Conventional	Fast track	Difference
Base case (IVF $10,000/cycle)			
Total cost	$7,741,064	$8,267,940	526,876
Cost per delivery	$51,607	$48,635	–$2,972
Expensive IVF (IVF $15,000/cycle)			
Total cost	$9,046,064	$10,072,940	$1,026,876
Cost per delivery	$60,307	$59,253	–$1,055
Less expensive IVF (IVF $6,000/cycle)			
Total cost	$6,697,064	$6,823,940	$126,876
Cost per delivery	$44,647	$40,141	–$4,506

Note: Break-even analysis: if IVF cycle cost = $17,749 per cycle, cost per delivery is equal assuming other base case assumptions.

[a] Inflation adjustment based on the consumer price index (http://www.bls.gov/data/#calculators). Details on the calculation: the costs per treatment cycle (CC, FSH, and IVF) and per delivery (singleton, twins and triplets) were assumed based on the literature. The calculation of total cost is as follows: Total cost = [(number of total CC cycles × CC cost) + (number of total FSH cycles × FSH cost) + (number of total IVF cycles × IVF cost)] + [(number of singleton × delivery cost of singleton) + (number of twins × delivery cost of twins) + (number of triplets × delivery cost of triplets)]. Cost per delivery = total cost ÷ total number of deliveries. In a break-even analysis, given $500 per CC cycle and $2,500 per FSH cycle, we calculated the cost per IVF cycle in a break-even of cost per delivery between Conventional and FASTT arms. [(646 × 500) + (439 × 2,500) + (261 × IVF cost) + (119 × 14,842) + (30 × 59,370) + (1 × 163,266)] ÷ (119 + 30 + 1) = [(648 × 500) + (361 × IVF cost) + (134 × 14,842) + (34 × 59,370) + (2 × 163,266)] ÷ (134 + 34 + 2). The cost of IVF = $17,749 per cycle.

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