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.