ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

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.
Clinical Trial Registration Number: NCT00246506. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
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 stepwise 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) ≤ 38 in the woman, and a sperm concentration of ≥ 15 million total motile sperm or ≥ 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 ≥ 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 ≥ 17 mm or 2–3 follicles ≥ 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 μg 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