

# Effectiveness and treatment for unexplained infertility

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Up to 30% of couples who are unable to conceive are determined to have unexplained infertility (1). Traditionally, this diagnosis is made only after the basic infertility evaluation fails to reveal an obvious abnormality. The basic evaluation should provide evidence of ovulation, adequate sperm production and patency of the fallopian tubes. However, even the most sophisticated diagnostic assessment cannot reveal all possible abnormalities. Therefore, unexplained infertility appears to represent either the lower extreme of the normal distribution of fertility, or it arises from a defect in fecundity that cannot be detected by the routine infertility evaluation (2). Couples with unexplained infertility suffer from both diminished and delayed fecundity. In a review of studies of unexplained infertility, the average cycle fecundity in the untreated control groups was 1.8% in 11 nonrandomized studies and 3.8% in 6 randomized studies (3). Pregnancy rates are lower with increasing age of the female partner and duration of infertility (4).

In the absence of a correctable abnormality, the therapy for unexplained infertility is, by default, empiric. Proposed treatment regimens include intrauterine insemination (IUI), ovulation induction with oral or injectable medications, combination of IUI with ovulation induction, and assisted reproductive technologies (ART). There is a need for randomized controlled trials to evaluate empiric therapies because conception may occur even without treatment. This summary of treatment for unexplained infertility relies mainly on level I evidence from randomized clinical trials.

## INTRAUTERINE INSEMINATION

The use of IUI appears to improve cycle fecundity when combined with either clomiphene citrate (CC) or gonadotropins (see later), but its use alone in couples with unexplained infertility has been evaluated against intercourse in only one randomized trial (5). In the one trial comparing IUI with intercourse, each was performed 40 hours after the detection of a rise in serum LH, in 73 couples with unexplained infertility. Conceptions occurred in 6 of 145 (4.1%) IUI cycles and 3 of 123 (2.4%) intercourse cycles ( $P=.46$ ) (5). Another trial compared IUI with intracervical insemination (ICI) (6). Although the study was not ideal for the evaluation of unexplained infertility because 25% of male partners had oligospermia, the majority had unexplained infertility; preg-

nancies occurred in 35 of 717 (4.9%) IUI cycles and 14 of 706 (2.0%) ICI cycles ( $P=.005$ ).

The aggregate fecundity in the two trials was 4.76% with IUI and 2.05% with controls, and the absolute treatment effect was  $4.76 - 2.05$  or 2.71 (95% confidence interval [CI], 0.99–4.42). The number needed to treat is the inverse of the absolute treatment effect (7). Thus, one would need to provide  $100/2.71$  or 37 cycles of IUI therapy to obtain a single additional pregnancy compared with control cycles. In summary, based on these two trials, there is a significant but small effect of IUI therapy: 1 additional pregnancy in 37 IUI cycles (95% CI, 23–101) compared with control cycles.

## CLOMIPHENE CITRATE THERAPY

Clomiphene citrate is a common treatment for unexplained infertility, although it has been suggested that the empiric use of CC in ovulatory women can cause alterations in the normal endocrinology of ovulation (8). CC combined with intercourse has been evaluated in four trials. A randomized double-blind placebo-controlled 4-month trial involving 564 cycles in 148 couples compared empiric CC treatment (100 mg daily, cycle days 5–9) with placebo. Ten of 290 (3.4%) cycles in those receiving CC treatment resulted in pregnancy compared with 4 of 274 (1.5%) of cycles in women receiving placebo ( $P=.15$ ) (9). In a randomized crossover placebo-controlled trial involving 118 couples, pregnancies occurred in 24 of 295 cycles (8.1%) treated with CC 100 mg and in 15 of 295 (5.1%) placebo cycles ( $P=.17$ ) (10). Another trial involved CC treatment with hCG-triggered ovulation; conceptions occurred in 5 of 159 treated cycles (3.1%) and in 1 of 158 (0.6%) placebo cycles ( $P=.15$ ) (11).

In one trial, clomiphene 50 mg was not effective in the treatment of unexplained infertility. Eighteen CC users were compared with 15 control patients (12). Pregnancies occurred in 4 of 66 (6.1%) treated cycles and in 11 of 51 (21.5%) control cycles ( $P=.04$ ). Note that the control group fecundity in this trial is similar to that of young couples with normal fertility (12).

Based on the first 3 homogeneous trials, the overall effect of CC treatment is significant but small: one additional pregnancy in 40 CC cycles (95% CI, 20–202) compared with untreated control cycles. Including the fourth trial introduces significant heterogeneity ( $P=.003$ ). Based on the 4 trials, the overall effect of CC treatment is smaller and nonsignificant: 1 additional pregnancy in 76 CC cycles compared with untreated control cycles and the confidence interval includes infinity.

### Educational Bulletin

Revised June 2006.

Received and accepted September 5, 2006.

Reprints will not be available.

## CLOMIPHENE CITRATE AND IUI

In a literature review of 8 studies involving 932 cycles, the cycle fecundity rates were 5.6% with CC and 8.3% with CC/IUI (3). Empiric CC treatment combined with IUI has been evaluated in three randomized controlled trials. The trials had three different control groups, and in each trial, CC cycles included hCG administration when mature follicles were observed by ultrasound examinations. The first was a 1990 crossover trial of CC/IUI versus timed intercourse, involving 298 treatment cycles and 67 couples. Before crossover, there were 8 pregnancies in 73 CC/IUI cycles (11%) compared with 4 in 103 timed intercourse cycles (3.9%); the difference was not significant ( $P=.08$ ) (13). The second was a 1994 crossover trial of CC/IUI versus IUI alone that involved 26 couples with unexplained infertility and 30 with male infertility with treatments alternated in each cycle after the first randomized cycle. In the first cycle among those with unexplained infertility, there were 3 pregnancies in 10 CC/IUI cycles (30%) compared with 1 in 16 CC cycles (6.3%) (14); the before-crossover comparison was not significant ( $P=.15$ ). The third trial in 2004 compared CC/IUI with CC treatment alone in 556 cycles among 140 couples. Cycle fecundity was 3.4% with CC/IUI and 8.8% with CC alone, but this result was flawed by the loss of 29 couples from the CC/IUI group and only one from the CC group (15).

Although it is logical that two effective treatments would have greater value when combined, the data on CC/IUI are contradictory and the reported effects are compromised by crossover designs and unequal loss to follow-up. The combination of CC with IUI may be useful, but the current evidence indicates only that CC/IUI should be evaluated in a four-arm factorial trial (placebo, CC, IUI, and CC/IUI) with adequate power.

## GONADOTROPIN THERAPY

A review of descriptive and randomized studies suggested that empiric gonadotropin therapy is an effective therapy for unexplained infertility, especially when combined with IUI (3). For example, improved fecundity was observed in a group of 97 couples awaiting IVF who were treated with gonadotropins and IUI compared with 48 untreated control couples (16). Also, a study involving 492 couples found that both cycle fecundity and pregnancy rate per patient were superior when gonadotropin therapy plus IUI was compared with expectant management (17).

A few trials comparing various stimulation regimens have been reported. In one randomized clinical trial, gonadotropin/IUI was found superior to CC/IUI (cycle fecundity 0.19 vs. 0.04,  $P<.05$ ) (18). The addition of a GnRH agonist to the gonadotropin treatment regimen does not appear to improve fertility (19).

In contrast, the addition of IUI to empiric gonadotropin therapy does improve fertility. In a review of 27 studies

involving 2,939 cycles, the pregnancy rate per cycle was 8% with gonadotropin treatment alone and 18% when IUI was added to gonadotropin stimulation (3). The effect was confirmed in a trial among patients stimulated with gonadotropins who were randomly allocated to receive IUI (20). In yet another randomized clinical trial, IUI improved fertility in cycles in which CC was combined with gonadotropins (21).

In a large randomized multicenter trial, FSH combined with IUI yielded higher cumulative pregnancy rates (33%) than FSH treatment alone (19%), IUI alone (18%), or intracervical insemination (ICI) (10%) (6). Among those receiving FSH and IUI, there were 54 pregnancies in 618 cycles (9%) compared with 14 in 706 ICI cycles (2%). The trial included patients with stage I or II endometriosis if 6 months had elapsed after surgical therapy or return of menses after medical therapy. Based on the results of this trial, the effect of gonadotropin/IUI treatment is one additional pregnancy in 15 FSH and IUI cycles (95% CI, 11–23) compared with ICI cycles.

## ASSISTED REPRODUCTIVE TECHNOLOGY

ART is advocated by many clinicians based on evidence from retrospective and/or uncontrolled trials. In the Centers for Disease Control and Prevention (CDC), the American Society for Reproductive Medicine (ASRM), and the Society for Assisted Reproductive Technology (SART) report on ART results for 2003, the live birth rate among women with unexplained infertility was 30.4% (22).

Although numerous randomized trials have evaluated ART treatment protocols, very few have compared the live birth rates achieved with ART with placebo treatment for unexplained infertility. The results of a trial comparing immediate IVF to a 90-day delay among women with tubal patency and nonsevere male factor infertility are relevant to unexplained infertility because the outcomes were not affected by semen variables. The live birth rates were 20 of 68 (29%) and 1 of 71 (1%), respectively, and the NNT was 4 (95% CI, 3–6) (23). Two other trials indicate that there is no advantage to the use of intracytoplasmic sperm injection (ICSI) over conventional fertilization when ART is used for the treatment of unexplained infertility (24, 25).

Among trials that compared IVF with other treatments for unexplained infertility, the European Society for Human Reproduction and Embryology Multicentre Trial reported that pregnancy rates per cycle were 15.2% in gonadotropin-only cycles, 27.4% in gonadotropin and IUI cycles, and 25.7% in IVF cycles (26). In another trial, live birth rates per cycle initiated in the unexplained subgroup were 6.0% in IUI only cycles, 8.7% in gonadotropin and IUI cycles, and 13.0% in IVF cycles (27). However, after six cycles, the cumulative success rates associated with IUI, stimulated IUI, and IVF were similar because few couples continued through six cycles of stimulated IUI or IVF treatment, even though the cost of these cycles was not borne by the patients.

## Adverse Effects

Adverse events after IUI treatment with prepared sperm are reported infrequently. Intrauterine placement of prepared spermatozoa does not alter the frequency of antisperm antibodies (28). CC has been used widely over more than 3 decades, and its side effects are reasonably predictable; multiple pregnancy in 8% to 10% of cases and ovarian cysts in 5% to 10% are the most common (29). Although earlier studies implied that CC was associated with increased ovarian cancer risk after 12 cycles of treatment use, more recent studies have observed no increased ovarian cancer risk related to the use of ovulation-inducing drugs (30, 31). In any case, there is no need for prolonged treatment because none of the unexplained infertility trials offers evidence that ovulation stimulation is effective after six cycles.

Gonadotropin therapy is associated with multiple pregnancy and ovarian hyperstimulation syndrome. In a large multicenter trial in the United States, 33% of live births were multiple pregnancies (3 quadruplet, 4 triplet, and 17 twin pregnancies delivered as 5 triplet births and 19 twin births among the 72 live births) (6). Severe ovarian hyperstimulation occurred in 1.3% (6 of 465 women in the FSH treatment groups required hospitalization).

IVF is associated with multiple pregnancy, ovarian hyperstimulation, and increased perinatal morbidity and mortality (32). In the 2003 CDC, ASRM and SART ART report, multiple pregnancy accounted for 34.2% of all IVF/ICSI births, comprising 31.0% twins and 3.2% triplet or higher order births (22). Severe ovarian hyperstimulation occurs in approximately 2% of cycles (32). Preterm delivery rates and small-for-gestational-age births are higher, in part, because of multiple pregnancies (32).

## Cost-effectiveness

Numerous cost analyses of infertility treatment have been published, although few have focused on treatment for unexplained infertility. Moreover, few cost analyses estimate cost-effectiveness, that is, the incremental cost per live birth when a given treatment is compared with an alternative treatment, preferably determined in the setting of a randomized clinical trial. A review of 45 reports on unexplained infertility estimated the marginal costs of treatment, assuming that the baseline untreated pregnancy rate was 1.3% per month (3). The marginal costs were \$7,143, \$15,823, and \$46,391, respectively, for CC and IUI, gonadotropins and IUI, and IVF treatment. One randomized clinical trial estimated that the cost per pregnancy was \$57,161 in a group treated initially with IVF and \$20,019 in a standard treatment group in which IVF was the ultimate treatment (33). The marginal cost was \$37,142 per pregnancy higher in the initial IVF group, but only 8% of the initial IVF group and 12% of the standard treatment group had unexplained infertility. In another randomized clinical trial that estimated costs per live birth in Dutch guilders, the equivalent costs in U.S. dollars

were \$4,511, \$5,710, and \$14,679, respectively, for IUI, gonadotropins and IUI, and IVF (27). The marginal cost per live birth was \$10,168 greater with IVF than with IUI alone.

## SUMMARY AND CONCLUSIONS

- The treatment effects with non-ART treatment for unexplained infertility generally are small. Empiric treatment may do no more than hasten conception in those couples who would conceive eventually without treatment.
- Level I evidence from randomized clinical trials supports short-term use of IUI, CC, gonadotropins and IUI, and ART treatment for unexplained infertility but is insufficient for conclusions regarding CC/IUI treatment.
- ART therapies are considerably more costly than CC and IUI.
- Adverse effects of ART and ovarian stimulation include multiple pregnancy and ovarian hyperstimulation.
- When considering treatment options for couples with unexplained infertility, it is prudent to consider simple treatment before complex treatment and to balance what is known about effectiveness against the cost and adverse effects of different treatments.

*Acknowledgments:* This report was developed under the direction of the ASRM Practice Committee as a service to its members and other practicing clinicians. While this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. This bulletin was approved by the ASRM Practice Committee in January 2000 and the ASRM Board of Directors in March 2000.

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