ORIGINAL ARTICLE: INFERTILITY

Evidence-based approach to unexplained infertility: a systematic review

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Objective: To summarize the available evidence for the efficacy of various treatments for unexplained infertility.
Design: Systematic review.
Setting: Randomized, controlled trials in the English language literature from 1989 to present.
Patient(s): Patients aged 18–40 years with unexplained infertility.
Intervention(s): Clomiphene citrate, letrozole, timed intercourse, IUI, gonadotropins, IVF, and IVF–intracytoplasmic sperm injection.
Main Outcome Measure(s): Clinical pregnancy rate, ongoing pregnancy rate, and live birth rate.
Result(s): Thirteen studies with a total of 3,081 patients were identified by systematic search and met inclusion criteria. The available literature demonstrates that expectant management may be comparable to treatment with clomiphene and timed intercourse or IUI. Clomiphene may be more effective than letrozole, and treatment with gonadotropins seems more effective, albeit with significantly higher risk of multiple gestations than either oral agent. On the basis of current data, IVF, with or without intracytoplasmic sperm injection, is no more effective than gonadotropins with IUI for unexplained infertility.
Conclusion(s): Adequately powered, randomized controlled trials that compare all of the available treatments for unexplained infertility are needed. Until such data are available, clinicians should individualize the management of unexplained infertility with appropriate counseling regarding the empiric nature of current treatment options including IVF. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Intrauterine insemination, in vitro fertilization, superovulation, unexplained infertility

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The diagnosis of unexplained infertility encompasses an important subset of couples seeking treatment for infertility. After evaluation of ovulatory function, tubal patency, and semen analysis, no etiology is identified in 10%–30% of couples seeking treatment for infertility (1, 2). Any treatment for unknown infertility is empiric by default, and the broad range of treatment, including expectant management, superovulation, and IVF, reflects the uncertainty with this diagnosis. However, there are limited data to support the efficacy of many of these treatments in the management of unexplained infertility, and no uniform protocol exists in clinical practice.

One must take into account that unexplained infertility is perhaps best characterized as subfertility (3). This nomenclature is significant in that some couples will conceive without intervention. In one randomized trial of 253 patients with unexplained infertility, a 27% ongoing pregnancy rate was observed in the expectant management group (4). Others observed a 13% spontaneous pregnancy rate in a group of patients awaiting IVF, although this cohort consisted of patients with unexplained subfertility of 2 years' duration or more and may represent a poorer prognostic subgroup (5). Another cohort experienced only a 5.9% cumulative pregnancy rate over 12 months in an untreated group of patients awaiting IVF (6). Despite this variability, it is evident that a proportion of couples will achieve pregnancy with no intervention.

Superovulation, which induces the development of more than one follicle per cycle, combined with either timed intercourse or IUI, is commonly used to treat unexplained infertility. The use of oral or injectable agents may increase the number of dominant follicles

Received September 23, 2015; revised and accepted February 1, 2016.
D.D.G. has nothing to disclose. G.W.B. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.02.001

available for fertilization (7) and correct subclinical ovulatory dysfunction (8). Many argue that the addition of IUI ensures that sufficient numbers of sperm overcome any cervical barrier (8). Disadvantages of treatment with gonadotropins and IUI include significant cost, ovarian hyperstimulation syndrome, and higher rates of multiple pregnancy (9). In vitro fertilization has also been used to treat unexplained infertility. According to 2013 Society for Assisted Reproductive Technology data, live birth rates per cycle of IVF ranged from 25% to 43% in patients with unexplained infertility aged ≤40 years (10).

Ideally a randomized controlled trial would be performed to compare expectant management with oral superovulation, superovulation with gonadotropins, and IVF, with a secondary analysis of whether IUI is of benefit. No such trial has yet been performed. The purpose of this review, therefore, is to summarize the available evidence from clinical trials regarding the relative efficacy of various treatments for unexplained infertility.

MATERIALS AND METHODS

The systematic literature search and qualitative review were performed according to PRISMA guidelines (11). All of the data were obtained from previously published studies, and therefore institutional review board approval was not obtained.

Search Strategy

A systematic literature search was conducted, with studies identified by searching MEDLINE (1966–September 2015). Results were limited to peer-reviewed, English-language, and human studies only. The search strategy included the terms "unexplained infertility," "subfertility," "natural cycle," "expectant management," "conservative management," "clomiphene citrate," "letrozole," "gonadotropins," "intercourse," "insemination," and "in vitro fertilization."

Retrieved records were screened by title and abstract for relevance by one reviewer (D.D.G.). Full-text review of the remaining articles was performed by the same reviewer. A second reviewer (G.W.B.) confirmed the validity of the review and verified the accuracy of the data extraction. Assessment of eligibility for inclusion in the systematic review was determined by consensus between the two authors.

A data extraction form was developed before data collection. Data extracted from each study included [1] characteristics of trial participants (including diagnostic subtype of infertility), [2] type of intervention and comparison groups, [3] type of outcome measures, and [4] type of study and level of evidence.

Eligibility and Outcome Measures

Patients with unexplained infertility/subfertility aged 18–40 years were considered in this analysis. Unexplained infertility/subfertility was defined as normal ovulatory status, tubal patency, normal semen analysis, and attempt at conception for duration of at least 1 year. Types of interventions studied included the following: expectant management, clomiphene citrate (CC) with or without IUI, letrozole with or without IUI, natural-cycle IUI, gonadotropins with or without IUI, IVF, and IVF with intracytoplasmic sperm injection (IVF-ICSI). Primary outcome measures were per-couple live birth rate (LBR), ongoing pregnancy rate (OPR), and clinical pregnancy rate (CPR). Studies with a primary outcome other than LBR, OPR, or CPR were included if these data were reported as secondary outcomes. Only randomized controlled trials were included in this analysis. Trials that did not report data separately for patients with unexplained infertility or subfertility were excluded.

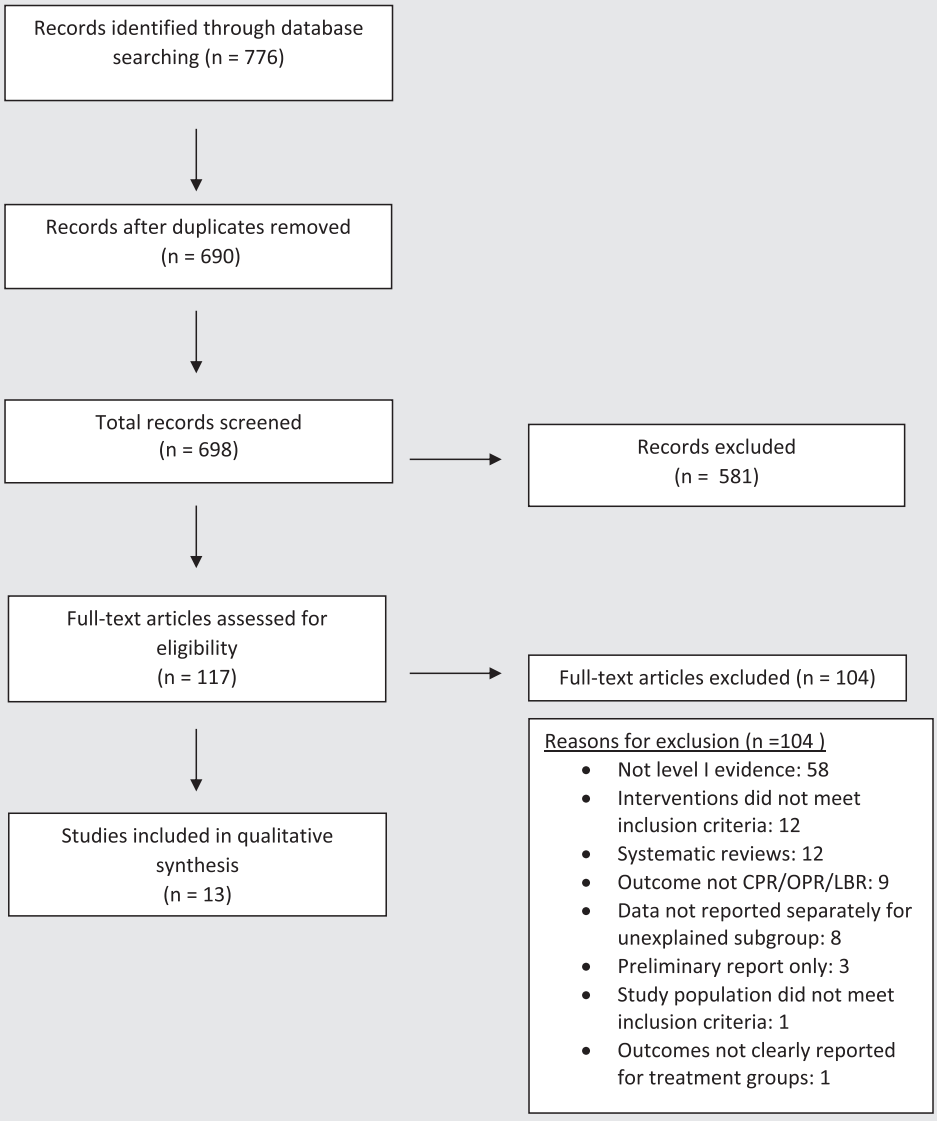
RESULTS

The systematic search produced 776 results (Fig. 1). After exclusion of duplicates, 690 records remained. Abstracts of these records were screened, resulting in the exclusion of an additional 581 records that clearly did not meet criteria for this review. Additional articles were identified through review of reference lists of screened articles. Full text of 117 articles was then reviewed. Of these, only 13 studies met the inclusion criteria. The 13 studies included in this review comprised a total of 3,081 patients. These studies, including interventions, methodology, and outcome measures, are summarized in Tables 1–3. Demographic data of study participants are summarized in Supplemental Table 1 (available online). Interventions examined in this review include the following: expectant management (four studies: Fisch, Bhattacharya, Deaton, Steures); CC with or without IUI (eight studies: Fisch, Bhattacharya, Deaton, Fouda, Diamond, Dankert, Berker, Reindollar); letrozole with or without IUI (four studies: Fouda, Diamond, Baysoy, Gregoriou); natural-cycle IUI (two studies: Bhattacharya, Goverde); gonadotropins with or without IUI (eight studies: Steures, Diamond, Dankert, Berker, Baysoy, Gregoriou, Goverde, Reindollar); IVF (three studies: Goverde, Foong, Reindollar); and IVF-ICSI (one study: Foong).

CC with Timed Intercourse vs. Expectant Management

Two trials addressed CC with timed intercourse vs. expectant management. In the Fisch study (3), 148 patients in a multicenter trial were randomized to one of four treatment groups for four consecutive cycles. Study arms included the following: placebo on cycle days 5–9 followed by saline injections on cycle days 19, 22, 25, and 28; placebo on cycle days 5–9 followed by hCG (5,000 IU) on cycle days 19, 22, 25, and 28 for luteal support; CC (100 mg) on cycle days 5–9 followed by saline injections in the luteal phase as above; and CC (100 mg) on cycle days 5–9 followed by hCG injections as above. For the purposes of this review, the placebo/placebo group constituted "expectant management" compared with the CC/placebo intervention. The mean age of the patients was 30 years, with a mean duration of infertility of 4.3 years. The placebo/placebo group had no clinical pregnancies during the study period, whereas the CC/placebo group had a CPR of 19%, a statistically significant difference. Of note, there were 25 treatment-independent pregnancies in the trial,

FIGURE 1



Flowchart of included studies.

Gunn. Systematic review of unexplained infertility. Fertil Steril 2016.

7 before the study and 18 after completion, representing 16% of all pregnancies in the study population.

Conversely, Bhattacharya et al. (8) in a larger trial of 580 patients (507 with unexplained infertility) at four centers found no benefit of therapy, with a 16% LBR with expectant management vs. 13% after CC therapy. This trial randomized patients to one of three arms for a treatment period of 6 months: [1] expectant management, consisting of no visits or interventions; [2] CC at a starting dose of 50 mg on cycle days 2–6 with timed intercourse on cycle days 12–18 (initial cycle monitored with ultrasound and mid-luteal serum P, with subsequent cycles monitored only with mid-luteal progesterone); and [3] IUI in the spontaneous cycle, with monitoring by urine LH kit starting on cycle day 12, with a single IUI performed at 20–30 hours after surge. Patients in the study had a mean duration of infertility of 30 months and a mean age of 32 years. The median number of treatment cycles was five in the CC/timed intercourse group and four in the natural-cycle IUI group. Spontaneous pregnancies occurred in 2% of women in the CC group and 7% of women in the IUI group, but it was unclear whether these were unexplained infertility patients. The authors planned a comparison of expectant management with CC/timed intercourse and with unstimulated IUI, and therefore no direct comparison was made between the CC/timed intercourse and unstimulated IUI groups.

CC with IUI vs. Expectant Management

Only one study, by Deaton et al. (12), examined CC with IUI in comparison with expectant management, and it found no

TABLE 1

Studies comparing oral superovulation methods. Q6

Study (reference)	No. of patients with unexplained infertility randomized	Maximum no. of treatment cycles per couple	Interventions	Outcome measures	Conclusion
Fisch 1989 (3)	148	4	CC with TI vs. expectant	CPR	CC with TI more effective
Deaton 1990	24	8	CC + IUI vs. expectant	OPR	No significant difference
Bhattacharya 2008	507	6 mo	CC with TI vs. expectant; natural-cycle IUI vs. expectant	LBR	CC with TI or natural-cycle IUI were not superior to expectant management
Fouda 2011	214	3	CC + IUI vs. letrozole + IUI	OPR	Letrozole + IUI more effective
Diamond 2015	900 (599 in oral treatment arms)	4	CC + IUI vs. letrozole + IUI[a]	CPR, OPR, LBR	No significant difference between CC + IUI and letrozole + IUI[a]

[a] See Table 2; this trial includes a gonadotropin treatment arm, which was superior to both oral interventions.

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TABLE 2

Studies comparing gonadotropin treatment with oral superovulation or IVF.

Study (reference)	No. of patients with unexplained infertility randomized	Maximum no. of treatment cycles per couple	Interventions	Outcome measures	Conclusion
Goverde 2000	181	6	GND + IUI vs. natural-cycle IUI vs. IVF	LBR	No significant difference
Steures 2006	253	6 mo	GND + IUI vs. expectant	OPR	No significant difference
Baysoy 2006	80	1	GND + IUI vs. letrozole + IUI	CPR	No significant difference
Dankert 2007	68	4	GND + IUI vs. CC + IUI	OPR, LBR	No significant difference
Gregoriou 2008	50	3	GND + IUI vs. letrozole + IUI	CPR, LBR	No significant difference
Berker 2011	93	1	GND + IUI vs. CC + IUI	OPR	No significant difference
Diamond 2015	900	4	GND + IUI vs. CC + IUI vs. letrozole + IUI[a]	CPR, OPR, LBR	GND + IUI more effective than CC + IUI or letrozole + IUI

Note: GND = gonadotropin.
[a] See Table 1 for comparison of oral agents in this study.

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TABLE 3

Studies with IVF comparison group.

Study (reference)	No. of patients with unexplained infertility randomized	Maximum no. of treatment cycles per couple	Interventions	Outcome measures	Conclusion
Goverde 2000	181	6	GND + IUI vs. natural-cycle IUI vs. IVF	LBR	No significant difference
Foong 2006	60	1	IVF vs. IVF-ICSI	LBR	No significant difference
Reindollar 2010	503	–	Conventional arm (CC + IUI, GND + IUI, and IVF) vs. accelerated arm (CC + IUI, IVF)	Time to pregnancy with a live birth; per-cycle pregnancy rate	No difference in per-cycle PR of CC + IUI vs. GND + IUI; significantly higher PR with IVF and shorter time to live birth

Note: GND = gonadotropin.

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significant difference. Of the 51 patients included in the data analysis of this trial, 24 patients had unexplained infertility, and 27 patients had endometriosis. This study had a cross-over design whereby patients were randomized to either four treatment cycles or four control cycles and would then cross over to the other arm if pregnancy did not occur in the first four cycles. Mean age was 33 years, with a mean duration of infertility of 3.5 years. In the treatment cycles, patients received CC (50 mg) on cycle days 5–9 (or days 4–8 if the patient's average cycle length was <27 days), with hCG (10,000 IU) given when the lead follicle was 18 mm on ultrasound. Intrauterine insemination was performed 36 hours after hCG administration. In the control cycles, patients were instructed to have intercourse during the periovulatory period. The ongoing pregnancy rate in the treatment cycles (defined in this study as >20 weeks' gestation) was 10 of 46 (21%), and OPR in the control cycles was 5 of 40 (12%). Because of the cross-over design of the study, some patients were counted twice in this analysis.

IUI (in Natural Cycle) vs. Expectant Management

One study compared IUI in the natural, unstimulated cycle with expectant management. Bhattacharya et al. (8) noted a 23% LBR with natural-cycle IUI vs. 16% with expectant management, a difference that was not statistically significant.

Gonadotropins with IUI vs. Expectant Management

Only one trial, by Steures et al. (4), involving 253 patients compared gonadotropins and IUI with expectant management, and it found no significant difference in ongoing pregnancy rate over the 6-month study period. In the treatment arm, patients received FSH or hMG (average 75 IU, range 37–150 IU) starting on cycle day 3 until the lead follicle measured 16 mm, when hCG was administered at a dose of either 5,000 or 10,000 IU, with IUI performed 36–40 hours later. If there were three or more follicles >16 mm or five follicles >12 mm, hCG was withheld. Patients' mean age was 33 years, with a mean duration of 2 years of infertility and baseline mean FSH of 7.0 and 6.7 IU/L in the gonadotropin and expectant management groups, respectively. Of note, 11% of the treatment cycles involved stimulation with CC instead of gonadotropins as specified by study protocol. Multiple gestations in the treatment arm consisted of one set of twins and one set of triplets selectively reduced to twins. Of the 127 patients assigned to the treatment arm, there were 29 ongoing pregnancies (23%) and 26 live births. In the expectant management arm, there were 34 ongoing pregnancies (27%) among 126 patients, and 30 live births. There was no significant difference in OPR in the treatment arm compared with expectant management. However, a total of 13 of 42 pregnancies occurred spontaneously in the treatment Q1 arm, and in the expectant management arm 20% of the patients underwent treatment with gonadotropins/IUI before the end of the study period. Fourteen percent of cycles were canceled in the intervention group (i.e., for over-response), and a further limitation was the monofollicular response

seen in 58% of the treatment cycles (4). The deviations from study protocol (use of CC instead of gonadotropins; use of gonadotropins in the expectant group), high number of spontaneous pregnancies in the treatment group, low rate of multiple follicular recruitment on gonadotropins, and high cancellation rate all limit interpretation of this study's findings.

CC with IUI vs. Letrozole with IUI

Two trials examined CC with IUI vs. letrozole with IUI. In a trial of 214 patients, Fouda et al. (13) demonstrated an improved ongoing pregnancy rate with letrozole plus IUI (33%) compared with CC plus IUI (19%), which was statistically significant. Mean age of patients was 26 years, with a mean duration of infertility of 3.7 years in the letrozole group and 3.4 in the CC group (no statistical difference); mean baseline FSH was 5.7 and 5.5 IU/L, respectively. Patients underwent up to three cycles of treatment. The letrozole arm consisted of an extended letrozole regimen of 2.5 mg daily on cycle days 1–9, and in the CC group, patients received CC (100 mg) on cycle days 3–7. Ultrasound monitoring was performed, and IUI was done 36–40 hours after administration of hCG (10,000 IU). The number of multiple gestations (all twins) was four and three in the letrozole and CC groups, respectively.

In the Diamond trial (14), 900 patients were randomized to one of three treatment arms for a total of four cycles: [1] letrozole (5 mg) on cycle days 3–7; [2] CC (100 mg) on cycle days 3–7; and [3] FSH (150 IU) starting on cycle day 3 through the day of hCG administration. Mean age of patients in this trial was 32 years, and mean duration of infertility was 35 months. The mean antimüllerian hormone level was the same (2.6 ng/mL) and baseline FSH was similar at 7.0, 7.2, and 6.9 mIU/mL, respectively (15). The oral intervention arms included a combined 599 patients and demonstrated a higher live birth rate in the clomiphene group (23.3%) compared with the letrozole group (18.7%), although the result was not statistically significant. Rates for ongoing clinical pregnancy and multiple gestation were also not significantly different between these two interventions, although this study was powered for a comparison of the letrozole group with the combined gonadotropin and clomiphene groups, not for individual comparisons (15, 16).

Gonadotropins with IUI vs. CC with IUI

Three trials compared gonadotropins with clomiphene. The Berker et al. trial (17) randomized 93 patients with unexplained infertility to one treatment cycle. Patients had a mean age of 28 years and baseline FSH of 6.7 mIU/mL in both groups, with a mean duration of infertility of 44 months and 48 months in the CC and FSH groups, respectively (no statistical difference). Interventions included CC (100 mg) beginning on cycle days 2–4, or FSH at a starting dose of 75 or 100 IU according to body mass index; both groups were monitored with ultrasound and serum E_2 measurements, and hCG (10,000 IU) was administered at a follicle size of 18 mm, with IUI 36–40 hours later. No luteal support was given. Ongoing pregnancy occurred in 5 of 43 patients (11.6%) in the clomiphene arm vs. 9 of 50 (18%) in the gonadotropin arm, which was not a statistically significant difference. Data on ovarian hyperstimulation syndrome (OHSS) and multiple gestations was provided for the overall study population but not separately reported for the unexplained infertility subgroup.

In the Dankert et al. trial (18), a total of 138 patients (68 with unexplained infertility) were randomized to CC/IUI or FSH/IUI for up to four cycles. Clomiphene citrate was given at a starting dose of 100 mg on cycle days 3–7, and FSH was given at a starting dose of 75 IU. Ultrasound monitoring was performed, and a 5,000-IU hCG dose was administered when the lead follicle reached 18 mm, followed by IUI 38–40 hours later. Administration of hCG was withheld if there were more than three follicles >14 mm. Mean age of the study population was 31 years, with a mean duration of infertility of 33 months. This trial, like the Berker et al. study, showed no difference in these treatments, with a LBR of 31.4% in the CC group and 30.3% in the FSH group. Of note, neither of these studies achieved statistical power.

The Diamond et al. trial (16) also directly compared these two interventions but showed a statistically significant difference in LBR, with 32.2% in the gonadotropin group compared with 23.3% in the clomiphene group. The rate of multiple gestations was also higher in the gonadotropin group, with 10 triplets and 24 twins, vs. 0 and 8, respectively, in the CC group. One patient in the gonadotropin group developed OHSS, compared with none in the CC group.

Gonadotropins with IUI vs. Letrozole with IUI

Three trials assessed the efficacy of gonadotropins with IUI vs. letrozole with IUI. In the Baysoy et al. (19) and Gregoriou et al. (20) studies, the efficacy of letrozole with IUI was comparable to that of gonadotropins with IUI. Of note, the Baysoy trial was characterized as a pilot study and did not calculate a sample size needed to detect a significant difference in pregnancy rates. This trial (19) randomized 80 patients to one cycle of either letrozole (5 mg) on cycle days 3–7 or hMG (75 or 150 IU; dose based on age). Mean age was 28 years, and mean baseline FSH was 6.4 and 6.1 IU/L, with a mean duration of infertility of 5.3 years in the letrozole group and 5.9 years in the gonadotropin group. The primary outcome was clinical pregnancy rate, which was 18.4% for letrozole and 15.7% for gonadotropins. One triplet gestation occurred in the letrozole group, and a twin gestation in the gonadotropin group. One case of moderate OHSS occurred in the gonadotropin group.

Gregoriou et al. (20) studied 50 patients and similarly found no significant difference in the efficacy of letrozole vs. gonadotropins, with respect either to clinical pregnancy rate per cycle (the primary outcome) or live birth rate per couple. In this study, 50 patients were randomized to receive either FSH at a starting dose of 150 IU on cycle day 3, or letrozole (5 mg) on cycle days 3–7, for a maximum of three cycles. Mean age was 32 years, and all patients had failed three prior cycles of CC/IUI. Mean duration of infertility and baseline FSH in the two groups was similar: 3.9 years and 7.4 IU/L in the FSH group, and 3.6 years and 6.9 IU/L in the letrozole group. All patients underwent ultrasound monitoring, with

serial E_2 measurements in the gonadotropin group only, and hCG was administered at a dose of 10,000 IU in both groups. Intrauterine insemination was done 36 hours after hCG trigger. Live birth rate in the gonadotropin group was 28%, compared with 20% in the letrozole group, which did not reach statistical significance, and there were no multiple gestations in either group.

In contrast to the Baysoy and Gregoriou studies, the Diamond trial (16) showed a significantly higher live birth rate in the gonadotropin group (32.2%) compared with the letrozole group (18.7%). The letrozole group had 9 twin pregnancies and no higher-order multiples, compared with 24 and 10, respectively, in the gonadotropin group.

Gonadotropins with IUI vs. IVF

One study, by Goverde et al. (21), that met inclusion criteria for this review examined the efficacy of gonadotropins with IUI compared with IVF and did not show a statistically significant difference in LBR. The authors also included a cost-effectiveness analysis in their study, concluding that IUI cycles were more cost-effective than IVF. This trial randomized 181 patients with unexplained infertility to one of three interventions for up to six treatment cycles: IUI in spontaneous/natural cycles, IUI in FSH-stimulated cycles (at a starting dose of 75 IU beginning on cycle day 3), and IVF (variable treatment protocol based on age). Mean age of patients was 32 years, and the mean duration of infertility was 3.9, 4.2, and 4.4 years in the three groups, respectively. In the stimulated IUI group, patients were monitored by ultrasound and urine LH testing, and hCG was given at a dose of 10,000 IU when the lead follicle reached 18 mm if no endogenous surge had been detected. Intrauterine insemination was done 40–42 hours after hCG administration. In the IVF group the same dose of hCG was used for trigger, followed by oocyte retrieval 35 hours later, and then ET 48–72 hours after retrieval. A maximum of two embryos were transferred in patients aged <35 years, and up to three embryos were transferred in patients aged >35 years.

Of note, this trial included some male-factor patients but did report pregnancy data by subgroup, so live birth rates for the unexplained infertility patients could be calculated from the reported data. The authors noted that the results for the overall study population did not differ by diagnostic subgroup. In the unexplained infertility subgroup assigned to natural-cycle IUI, the LBR was 24%, compared with 36% in the stimulated-cycle IUI group and 39% in the IVF group. There was also no difference between the pregnancy rates of either of the IUI groups compared with IVF. The per-cycle pregnancy rate was higher in the IVF group compared with the IUI groups. There were 18 spontaneous conceptions between treatment cycles in this study, all of which led to live births. The rate of multiple gestation was 4% in the natural-cycle IUI group (one twin pregnancy), 29% in the stimulated IUI group (nine twin pregnancies), and 21% in the IVF group (one triplet and six twin pregnancies). Mild OHSS occurred in two of the stimulated IUI cycles, and three patients in the IVF group had severe OHSS.

Gonadotropins with IUI vs. IUI (in Natural Cycle)

The Goverde trial (21), as described above, was the only study included in this review that examined gonadotropins with IUI vs. natural-cycle IUI. The LBR for natural-cycle IUI was 24%, compared with 36% in the gonadotropin/IUI group, a difference that did not achieve statistical significance.

IVF vs. IUI (in Natural Cycle)

The Goverde trial (21) also included IVF and natural-cycle IUI treatment arms, and there was no significant difference in live birth rates (39% vs. 24%). As described above, the per-cycle pregnancy rate was higher for IVF compared with IUI.

IVF vs. IVF with ICSI

One study, by Foong et al. (22), was identified that compared IVF with IVF-ICSI in 60 patients with unexplained infertility undergoing one treatment cycle. The mean age of study participants was 33 years; in the conventional IVF group, mean baseline FSH was 6.2 IU/L, and duration of infertility was 57 months, vs. mean FSH of 6.5 IU/L and duration of infertility of 64 months in the IVF-ICSI group (no statistical difference). Patients underwent GnRH agonist suppression followed by stimulation with Gonal-F at variable dosing, Q2 with hCG (unspecified dose) given for trigger followed by retrieval 35 hours later. A maximum of four embryos were transferred on day 3 after retrieval. The primary outcome was fertilization rate, although other outcomes were reported, including clinical pregnancy rate and live birth rate. Live birth rate in the IVF group was 46.7%, compared with 50% in the IVF-ICSI group, a difference which was not statistically significant. There was also no significant difference in any of the other outcomes studied.

The FASTT Trial

The fast track and standard treatment (FASTT) trial demonstrated a shorter time to pregnancy and higher per-cycle pregnancy rates for IVF compared with treatment with oral agents or gonadotropins in patients with unexplained infertility (23). Although the FASTT trial does not directly compare CC/IUI, GND/IUI, and IVF in a parallel fashion with respect to live Q3 birth rate, the study does report per-cycle pregnancy rates and also demonstrates a shorter time to pregnancy in the accelerated arm, with the interesting finding of no benefit to gonadotropin treatment in the case of failed oral superovulation.

In this trial, Reindollar et al. (23) randomized patients to one of two arms: [1] a conventional arm with three cycles of CC (at a starting dose of 100 mg on cycle days 3–7, with LH kit monitoring or ultrasound monitoring if no surge by cycle day 15) followed by three cycles of gonadotropins (at a starting dose of FSH 150 IU) and then up to six cycles of IVF; or [2] an accelerated arm with three cycles of CC followed by up to six cycles of IVF. The dose of hCG was 10,000 IU in each group (used in CC group if ultrasound monitoring was required). Intrauterine insemination was done 36 hours later. In the IVF group, GnRH agonist suppression was followed by

administration of FSH (225 IU) as a starting dose. Oocyte retrieval occurred 36 hours after hCG trigger, with ICSI done in cases of failed fertilization or $<10 \times 10^6$ sperm available. Embryo transfer occurred on day 3 after retrieval, with the number transferred based on American Society for Reproductive Medicine guidelines. Mean age of patients was 33 years, with a mean baseline FSH of 6.6 and 6.7 mIU/mL in the conventional and accelerated groups, respectively. Duration of infertility was not reported. The primary endpoint was length of time from date of randomization to the date a pregnancy was established that led to a live birth. Per-cycle pregnancy rates for CC/IUI, FSH/IUI, and IVF were 7.6%, 9.8%, and 30.7%, respectively. Median time to pregnancy was 8 months in the accelerated arm, compared with 11 months in the conventional arm. Of the clinical pregnancies, 52 were treatment-independent (14%).

DISCUSSION

In this systematic review, we examined the available evidence from clinical trials for the relative efficacy of various treatments for unexplained infertility with respect to the outcomes of clinical or ongoing pregnancy rate or live birth rate per couple. Among the 13 studies that met criteria for inclusion in this review, the following interventions were studied: [1] CC with timed intercourse vs. expectant management (3, 8); [2] CC with IUI vs. expectant management (12); [3] natural-cycle IUI vs. expectant management (8); [4] gonadotropins with IUI vs. expectant management (4); [5] CC with IUI vs. letrozole with IUI (13, 16); [6] gonadotropins with IUI vs. CC with IUI (16–18); [7] gonadotropins with IUI vs. letrozole with IUI (16, 19, 20); [8] gonadotropins with IUI vs. IVF (21); [9] gonadotropins with IUI vs. natural-cycle IUI (21); [10] IVF vs. natural-cycle IUI (21); and [11] IVF vs. IVF/ICSI (22). Another study was included, which compared a stepwise, conventional approach including CC + IUI, gonadotropins + IUI, and IVF vs. an accelerated approach of CC + IUI followed by IVF (23).

Although there is considerable clinical heterogeneity among the included studies that precluded performance of a meta-analysis, this review demonstrates the following findings. Clomiphene citrate with timed intercourse was more effective than expectant management in an older study (3), although a larger, more recent trial found no benefit (8). When expectant management was compared either with CC with IUI (12) or with gonadotropins with IUI (4), it was as effective as either intervention. Applicability of the Steures gonadotropin IUI trial (4) to clinical practice is limited, given its clear potential for underestimation of pregnancy due to a high cycle cancellation rate (14.9%), in addition to underestimation of multiple gestation rates due to the incidence of monofollicular recruitment (58%). Conversely, in a multicenter Reproductive Medicine Network trial in 1999 (excluded in this review because it included male-factor patients without separate data reporting), a clear benefit was found for gonadotropins compared with natural-cycle IUI (7). When CC and letrozole (both with IUI) were compared, letrozole with IUI was superior in one study (13); the larger, more recent Diamond trial (16) showed a higher ongoing pregnancy rate and live birth rate with CC, although the difference was not statistically significant. Two studies that examined letrozole with IUI vs. gonadotropins with IUI showed these interventions to be equally effective (19, 20), as did two other studies that examined clomiphene with IUI vs. gonadotropins (17, 18). However, Diamond demonstrated that gonadotropins were significantly more effective than either letrozole or clomiphene, despite a higher cycle cancellation rate of 6.9% vs. 3.7% and 3.3%, respectively. Nonetheless, it may be argued that the increase in cumulative pregnancy rate may not be justified with the high rate of multiple pregnancies (32%), including triplet pregnancies (6.2%) (16). Natural-cycle IUI was comparable to expectant management in one study (8), and with gonadotropins/IUI and IVF in another study, although the Goverde trial (21) did show a higher per-cycle pregnancy rate for IVF vs. IUI.

Direct comparisons between oral agents, gonadotropins, and IVF are limited. Goverde et al. (21) showed no difference in efficacy when IVF was compared with gonadotropins with IUI for unexplained infertility (although the per-cycle pregnancy rate was higher). The Reindollar study (23) also demonstrated an increased per-cycle pregnancy rate with IVF compared with gonadotropin treatment. There was also no significant difference in treatment outcome when IVF-ICSI was compared with IVF in one study (22). Additionally, an accelerated approach involving CC plus IUI followed by IVF seems to shorten the median time to pregnancy when compared with a conventional stepwise method of CC plus IUI, gonadotropins plus IUI, then IVF (23).

The strength of this review is the systematic search strategy used and the large number of patients (more than 3,000) included in the 13 studies. In addition, this review included only studies with clear diagnosis of unexplained infertility and separate data reporting for this subgroup of infertility. With these strict criteria, however, some of the individual comparison groups did not include more than one or two studies examining that particular intervention. Although this approach limits the quantity of data available for review, it more precisely reflects the characteristics of unexplained infertility, including the benefit of expectant management in this patient population. Any discussion of unexplained infertility must bear in mind that many of the reports contain treatment-independent pregnancies, highlighting the fact that "subfertility" is a better descriptor for this patient population. This review was limited by the clinical heterogeneity of the included studies. There were variable numbers of treatment cycles per intervention across studies, different monitoring methods, and different starting dosages of medications. There were also some studies that did not adequately describe randomization and allocation. Although all of the studies included mean age of participants, and all but one included duration of infertility, only 8 of the 13 reported baseline serum measurements of ovarian reserve (FSH or antimüllerian hormone). Many of the individual studies had small sample sizes and lacked the statistical power to detect significant differences between interventions.

In conclusion, on the basis of the currently available literature, expectant management may be comparable to

treatment with CC and timed intercourse or IUI in patients with unexplained infertility. For patients who undergo superovulation with oral agents, clomiphene may be more effective than letrozole. Treatment with gonadotropins seems to be more effective than either oral agent, although its attendant risk of multiple gestations is an obvious disadvantage that should limit utilization. Despite its cost and widespread utilization, IVF was no more effective than gonadotropins with IUI but may accelerate the time to clinical pregnancy.

Well-designed prospective trials with adequate sample size are needed to directly compare superovulation with oral agents and gonadotropins, as well as the role of IUI and IVF, with careful assessment of the risk and benefit profiles. Until such data are available, clinicians should individualize the management of unexplained infertility for each patient with appropriate counseling regarding the empiric nature of their treatment.

Acknowledgments: The authors thank Andrew R. LaBarbera, Ph.D., and Jessica Goldstein, R.N., of the American Society for Reproductive Medicine for their assistance in the systematic search and assessment of the literature.

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SUPPLEMENTAL TABLE 1

Demographics of included studies.

Study (reference)	Interventions	Mean age in each group (y)	Mean FSH in each group (IU/L or mIU/mL)	Duration of infertility in each group
Fisch 1989	CC with TI vs. expectant	30	Not available	4.3 y
Bhattacharya 2008	CC with TI vs. expectant; natural-cycle IUI vs. expectant	32	Not available	30 mo
Deaton 1990	CC + IUI vs. expectant	33	Not available	3.5 y
Steures 2006	GND + IUI vs. expectant	33	7.0, 6.7	2.0, 1.9 y
Fouda 2011	CC + IUI vs. letrozole + IUI	26.1, 26.7	5.5, 5.7	3.4, 3.7 y
Diamond 2015	CC + IUI vs. letrozole + IUI vs. GND + IUI	32.0, 32.2, 32.3	7.2, 7.0, 6.9	34.2, 35.2, 34.8 mo
Dankert 2007	CC + IUI vs. GND + IUI	31.0, 31.6	Not available	33.4, 34.0 mo
Berker 2011	CC + IUI vs. GND + IUI	28.0, 28.2	6.7, 6.7	44.4, 47.9 mo
Baysoy 2006	Letrozole + IUI vs. GND + IUI	27.2, 28.1	6.4, 6.1	5.3, 5.9 y
Gregoriou 2008	Letrozole + IUI vs. GND + IUI	32.1, 31.5	6.9, 7.4	3.6, 3.9 y
Goverde 2000	GND + IUI vs. natural-cycle IUI vs. IVF	31.7, 31.6, 32.0	Not available	4.2, 3.9, 4.4 y
Foong 2006	IVF vs. IVF-ICSI	33.0, 33.7	6.2, 6.5	57.2, 64.5 mo
Reindollar 2010	Conventional arm (CC + IUI, GND + IUI, and IVF) vs. accelerated arm (CC + IUI, IVF)	33	6.6, 6.7	Not available

Note: GND = gonadotropin.

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