

Evidence-based treatments for couples with unexplained infertility: a guideline

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Objective: To provide evidence-based recommendations to practicing physicians and others regarding the effectiveness and safety of therapies for unexplained infertility.

Methods: ASRM conducted a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and prospective and retrospective comparative observational studies published from 1968 through 2019. The ASRM Practice Committee and a task force of experts used available evidence and informal consensus to develop evidence-based guideline recommendations.

Main Outcome Measure(s): Outcomes of interest included: live-birth rate, clinical pregnancy rate, implantation rate, fertilization rate, multiple pregnancy rate, dose of treatment, rate of ovarian hyperstimulation, abortion rate, and ectopic pregnancy rate.

Result(s): The literature search identified 88 relevant studies to inform the evidence base for this guideline.

Recommendation(s): Evidence-based recommendations were developed for the following treatments for couples with unexplained infertility: natural cycle with intrauterine insemination (IUI); clomiphene citrate with intercourse; aromatase inhibitors with intercourse; gonadotropins with intercourse; clomiphene citrate with IUI; aromatase inhibitors with IUI; combination of clomiphene citrate or letrozole and gonadotropins (low dose and conventional dose) with IUI; low-dose gonadotropins with IUI; conventional-dose gonadotropins with IUI; timing of IUI; and in vitro fertilization and treatment paradigms.

Conclusion(s): The treatment of unexplained infertility is by necessity empiric. For most couples, the best initial therapy is a course (typically 3 or 4 cycles) of ovarian stimulation with oral medications and intrauterine insemination (OS-IUI) followed by in vitro fertilization for those unsuccessful with OS-IUI treatments. (Fertil Steril® 2020;113:305–22. ©2019 by American Society for Reproductive Medicine.)

Key Words: Unexplained infertility, ovarian stimulation, intrauterine insemination, in vitro fertilization, multiple pregnancy

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Of couples experiencing infertility, up to 30% are diagnosed with unexplained infertility after a standard evaluation (1). This evaluation would typically include the demonstration of at least one patent fallopian tube, documentation of ovulation of the female partner, and a semen analysis with an adequate number of motile sperm for the male partner. Since no treatable cause is identified in the setting of unexplained infertility, treatment is by necessity empiric. Commonly used treatments include ovarian stimulation (OS) with oral medications or injectable gonado-

tropins with intrauterine insemination (IUI). OS refers to pharmacological treatment with the intent of inducing development of multiple mature ovarian follicles and is the preferred term for treatment previously described as “superovulation,” “ovarian hyperstimulation,” and “controlled ovarian hyperstimulation” (2). OS should be distinguished from ovulation induction, which refers to the pharmacological treatment of the anovulatory woman to induce ovulation. OS-IUI is believed to improve cycle fecundity by increasing the number of oocytes that are available for fertilization while

increasing the number of motile sperm in the uterus through IUI at the time of ovulation. Other proposed treatments for unexplained infertility include IUI in unstimulated (that is, natural) cycles and OS with timed intercourse.

Treatment paradigms for unexplained infertility have typically involved OS-IUI, initially with oral medications, then gonadotropins, followed by in vitro fertilization (IVF) for those unsuccessful in achieving pregnancy with OS-IUI. While success rates in IVF have increased dramatically over the last 20 years, non-assisted reproductive technology (ART) treatments are associated with relatively low and unchanged live-birth rates per cycle (3–5). Developing a modern, evidence-based approach to couples with unexplained infertility requires a full

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understanding of not only the effectiveness of individual treatments, but also the risks such as ovarian hyperstimulation syndrome (OHSS) and multiple-gestation pregnancies. Furthermore, treatment decisions should be made in consideration of the significant unassisted pregnancy rate observed in couples with unexplained infertility (6, 7) and desired family size. The present guideline is based on a systematic review of the literature with the goal of informing practitioners about the effectiveness and risks of treatments for unexplained infertility.

LIMITATIONS OF THE LITERATURE

Multiple challenges exist in interpreting the literature related to the effectiveness and safety of treatments for unexplained infertility. Most studies do not include an untreated or placebo control group, which is problematic given the significant rate of unassisted pregnancies with expectant management. Unexplained infertility is also variably defined, such that some studies include patients with early-stage endometriosis and couples with mild male-factor infertility. Many investigations are underpowered, and some report only surrogate outcomes such as clinical or ongoing pregnancy rather than live birth. In many studies, the rate of side effects or harms from treatment such as OHSS or multiple-pregnancy rates are not reported or incompletely reported. Multiple investigations are of a crossover design, which may be biased due to carryover or order effects. Many investigations vary in the duration of infertility at trial entry, which makes comparisons between trials difficult given the strong correlation between infertility duration and treatment outcomes (8). Trials involving gonadotropin treatment are often problematic in that dosing is frequently inadequately reported. In many European investigations, couples are categorized and enrolled in trials based on the prognosis of unassisted pregnancy using the prediction model of Hunault (9). This model incorporates prognostic factors such as the woman's age, duration of subfertility, primary or secondary subfertility, and percentage of progressive motile sperm as variables to predict the probability of unassisted pregnancy. Since most US trials do not stratify patients by prognosis, study populations are different at baseline, making direct comparisons between US and European trials problematic. Finally, for some of the reviewed therapies there are limited well-designed, adequately powered randomized controlled trials (RCTs) to address effectiveness and harms associated with treatment.

METHODS

This clinical practice guideline followed a methodological protocol established by ASRM staff and executive leadership, the ASRM Practice Committee, and an independent consulting epidemiologist. The ASRM Practice Committee identified the necessity of this guideline on unexplained infertility and empaneled a task force of experts to engage in its development. Members of the task force applied the PICO (Population, Interventions, Comparisons, and Outcomes) framework to formulate a focused question related to clinical practice and evidence-based treatments for unexplained infertility, as well as preliminary inclusion/exclusion criteria.

This guideline provides evidence-based recommendations for the following treatments for couples with unexplained infertility: natural cycle with IUI; clomiphene citrate with intercourse; aromatase inhibitors with intercourse; gonadotropins with intercourse; clomiphene citrate with IUI; aromatase inhibitors with IUI combination of clomiphene citrate or letrozole and gonadotropins (low dose and conventional dose) with IUI; low-dose gonadotropins with IUI; conventional-dose gonadotropins with IUI; timing of IUI; and IVF and treatment paradigms.

A comprehensive systematic review of the literature using the MEDLINE® database through PubMed® was conducted on December 19, 2017, with updates on October 3, 2018, February 26, 2019, and August 7, 2019 to identify peer-reviewed studies relevant to treatments for unexplained infertility. No limit or filter was used for the time period covered or English language, but articles were subsequently culled for English language. The literature search and examination of reference lists from primary and review articles yielded 2,546 studies, of which 83 studies met inclusion criteria. This guideline's summary statements and recommendations were based on included studies.

Per inclusion/exclusion criteria that the task force agreed upon (Table 1), included for assessment were randomized controlled trials (RCTs); systematic reviews or meta-analyses of RCTs; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; cohort studies; and case-control studies. Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees were excluded from this guideline.

Titles and abstracts of potentially relevant articles were screened and reviewed initially according to preliminary inclusion/exclusion criteria determined by members of the task force. Only studies that met the inclusion criteria were assessed in the final analysis. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure (pregnancy or live-birth rates); meta-analyses; and relevant articles from bibliographies of identified articles. Four members of the task force reviewed the full articles of all citations that potentially matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and resolved by consensus or arbitration after consultation with an independent reviewer/epidemiologist. Studies with multiple diagnoses of infertility were included only if data for patients with unexplained infertility were reported separately from the entire cohort.

Quality of Evidence

A methodological specialist extracted data from included studies into an evidence table for outcomes identified by the task force, including: live-birth rate, clinical pregnancy rate, implantation rate, fertilization rate, multiple pregnancy rate, dose of treatment, rate of ovarian hyperstimulation, abortion rate, and ectopic pregnancy rate. Nonconflicted

TABLE 1

Summary of inclusion/exclusion criteria.

Include

Randomized controlled trials (RCTs); systematic reviews or meta-analyses of RCTs; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; cohort studies; case-control studies
 Human studies
 English
 Studies with a comparison group
 Early/minimal endometriosis (stage 1 or 2)
 Patients with intracytoplasmic sperm injection (ICSI) for non-male factor; >5 million total motile sperm (TMS) count
 Spontaneous ovulatory cycles
 Outcomes: Primary or secondary: pregnancy rate, live-birth rate
 Studies that compare a low dose (<150 IU) and conventional dose (≥ 150 IU) of gonadotropins in patients who received IUI

Exclude

Descriptive studies, case series, case reports, letters, nonsystematic reviews, opinions based on clinical experience, and reports of expert committees

 Animal studies
 Non-English
 Studies without a comparison group
 Studies in which treatment/intervention is not clearly stated
 Stage-3 or -4 endometriosis

 Hysteroscopy/"endometrial scratch" focus
 Modeling studies
 Focus on passive uterine straightening

 Severe male factor <5 million/ml TMS count on semen analysis
 Tubal factor infertility
 Polycystic ovary syndrome (PCOS) or anovulation
 Focus on luteal progesterone/luteal support
 Studies with patients who received IUI and overlapping doses (low and high doses) of gonadotropins in the same arm
 Studies that did not specify dose of gonadotropin, or systematic reviews that included studies with great variability in dose of gonadotropin
 Treatment with tamoxifen
 IUI with gonadotropin-releasing hormone (GnRH) agonists or antagonists for suppression
 Acupuncture as treatment
 Hysterosalpingo-foam sonography (HyFoSy)
 Hysterosalpingography (HSG)
 Diagnostic rather than therapeutic studies
 Dexamethasone as adjunctive therapy

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members of the task force critically assessed the strengths and limitations of available evidence that met inclusion/exclusion criteria to rate the quality of each study and assign a quality grade based on the rating scale below, which was recorded in the evidence table ([Supplemental Table 1](#), available online).

Assessment of the quality of the evidence allowed the task force to make distinctions among studies. The quality of the evidence was evaluated using the following grading system. The task force chair reviewed grades of quality assigned by members of the task force and provided oversight throughout the entire development process. If no grade was assigned, the task force chair determined a grade of quality based on a study's strengths and limitations. Study design was evaluated and quality of methodology was assessed based on components including blinding, allocation concealment, appropriate control groups, intention-to-treat analysis, generalizability and risk of bias. The consulting epidemiologist and chair of the task force confirmed agreement with the expert task force's assessment of quality, based on the definitions presented in [Table 2](#).

The task force summarized data from the evidence table in narrative form to include the characteristics, quality, benefit, and conclusions of studies relevant to answer each treatment related to the question. The expert task force convened via email to review literature and summarize findings. The chair of the task force presented these summaries of evidence and draft con-

clusions to the ASRM Practice Committee for deliberation of the strength of the evidence and the strength of the recommendations and approval of summary statements and recommendations. The quality of the evidence informed the strength of the guideline's evidence ([Table 3](#)).

Not all topics are appropriate for a systematic review. In some cases, literature is not yet available and documents based on expert consensus must summarize suggested best practice in the context of available literature. ASRM guidelines, however, follow a rigorous developmental process based on documented, verifiable systematic reviews of the scientific literature. ASRM task forces for guideline development must follow a strict methodology to objectively evaluate available scientific literature on their assigned topic to make evidence-based recommendations for clinical practice. Included evidence related to treatments for couples with unexplained infertility was searched for and collected systematically, objectively assessed, and described clearly and succinctly to inform readers relying on ASRM guidelines with trusted recommendations that were guided by the quality of available evidence. These evidence-based recommendations are intended to optimize patient care and help guide medical practice in the field of reproductive medicine. The strengths of recommendations in this guideline were based on both the quality and strength (confidence/certainty) of evidence, risks and benefits, and expert judgment of the

TABLE 2**Rating for quality of evidence.**

Quality of evidence	Definition
High	Target population clearly identified Sufficient sample size for the study design Clear description of study design Appropriate control(s) Generalizable results Definitive conclusions Minimal risk of bias Limitations do not invalidate conclusions Evidence primarily based on well-designed systematic reviews or meta-analyses of randomized controlled trials
Intermediate	Target population Sufficient sample size for the study design but could benefit from larger studies Control group identified Reasonably consistent results which limitations do not invalidate Fairly definitive conclusions Low risk of bias Evidence primarily based on small randomized controlled trials; systematic reviews or meta-analyses of a combination of RCTs, controlled trials without randomization, and cohort studies; controlled trials without randomization; and/or well-designed observational studies
Low	Insufficient sample size for the study design Discrepancies among reported data Errors in study design or analysis Missing significant information Unclear or inconsistent results High risk of bias due to multiple flaws so that conclusions cannot be drawn High uncertainty about validity of conclusions

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TABLE 3**Rating for strength of evidence.**

Strength of Evidence	Definition
Grade A	High confidence in evidence. Larger or further study very unlikely to change reported effect. Majority of evidence supported by well-constructed RCTs or extremely strong and consistent observational studies with generalizable results, sufficient sample sizes for the study design, adequate controls, definitive conclusions, and minimal risk of bias.
Grade B	Moderate confidence in evidence. Larger or further studies not likely to change reported effect but may more precisely identify magnitude of effect. Majority of evidence comprised of RCTs with potential weaknesses including small sample size or generalizability or moderately strong and consistent observational studies with reasonably consistent results, sufficient sample sizes for the study designs, identified appropriate controls, fairly definitive conclusions, low risk of bias.
Grade C	Low confidence in evidence. Evidence lacking to support reported effect. Evidence comprised of observational studies with significant methodological flaws and/or inconsistent findings based on poor evidence, inconsistent results, insufficient sample size for study design, conclusions that cannot be drawn, and/or high risk of bias.

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Practice Committee and task force (Table 4). Patient perspective and feedback were elicited during review and prior to publication of guideline.

INTRAUTERINE INSEMINATION (IUI), NATURAL CYCLE

Intrauterine insemination (IUI) is often considered first-line treatment for couples with unexplained or mild male-factor infertility because it is less invasive and less costly than IVF. IUI can be performed in a natural ovulatory cycle or it can be combined with OS, which is intended to induce multiple follicular development in an effort to improve the chances of pregnancy. Because OS increases the risk of multiple pregnancy, which is associated with significantly higher

maternal and neonatal morbidities, some clinicians favor natural-cycle IUI over IUI with OS.

This guideline includes seven randomized trials (10–16), one cost-effectiveness study (17), and six cohort studies (18–23) that assessed treatment with IUI in natural (i.e., unstimulated) cycles in patients with unexplained infertility. Some investigations compared natural-cycle IUI to OS with oral medications or gonadotropins with IUI.

In a high-quality RCT of 580 couples with unexplained or mild male-factor infertility, couples randomized to 6 cycles of IUI alone were not significantly more likely to achieve a live birth than those randomized to expectant management (23% [43/191], and 17% [32/193] live-birth rates, respectively, $P=.16$) (14). A post hoc per-protocol analysis of live-birth rates similarly did not show an improvement with

TABLE 4

Rating for strength of recommendations.	
Strength of Recommendation	Definition
Strong	Strong degree of confidence that stated recommendation reflects best practice approach. Recommendation based on consistent evidence of high quality, consideration that benefit of stated recommendation outweighs potential risks, and consensus of expert task force and Practice Committee review.
Moderate	Moderate degree of confidence that stated recommendation reflects best practice approach. Recommendation based on limited evidence of high quality or mix of evidence of high and intermediate quality or consistent body of evidence mostly of intermediate quality, consideration that benefit of stated recommendation outweighs potential risks, and consensus of expert task force and Practice Committee review.
Weak/Conditional	Low degree of confidence in stated recommendation. Low quality or insufficient evidence to assess true measure of effect. Limited ability to assess benefit vs. risk of intervention. Inability of expert task force or Practice Committee to reach evidence-based consensus.
No recommendation	Insufficient available evidence, lack of confidence or consensus to provide a recommendation for clinical practice.

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natural-cycle IUI over expectant management (live birth adjusted odds ratio [OR] 1.25, 95% confidence interval [CI] 0.71–2.18, $P=.44$). Live-birth rates were similar and also not significantly different excluding couples with mild male-factor infertility (14). Treatment with IUI was also determined to not be cost-effective compared to expectant management (17).

Several other studies also directly compared the use of natural-cycle IUI with expectant management for unexplained infertility. One RCT of high quality (11) that included 932 couples with unexplained or mild male-factor infertility demonstrated higher clinical pregnancy rates with IUI alone compared with intracervical insemination (ICI), which could be considered a surrogate treatment for expectant management. However, live-birth rates were not significantly different between the two treatments (12.8% vs. 7.7% over four treatment cycles, IUI vs. ICI, respectively, $P=.09$; post-hoc calculation by the Practice Committee). In this same study, OS with gonadotropins with IUI was three times more likely to result in pregnancy than ICI alone and twice as likely to result in pregnancy than OS with gonadotropins with ICI or natural cycle IUI (11). Two randomized trials included in this guideline of intermediate and low quality (12, 15), respectively, also demonstrated no significant difference in clinical pregnancy rates.

The majority of studies included in this guideline concluded that OS combined with IUI was associated with higher clinical pregnancy rates than IUI alone (10, 11, 13, 16, 18–23) and OS alone (11, 18, 23). The one exception was an RCT of 48 infertile patients which compared injectable gonadotropins with IUI to IUI alone and found no difference in pregnancy rates (12). However, in this older study of intermediate quality, only 32 couples had unexplained infertility, and pregnancy rates in all groups were low (12). A large retrospective cohort study that assessed 14,519 IUI cycles in 8,583 couples with unexplained infertility also found that, compared with natural-cycle IUI (live-birth rate, 6.2%), adjusted live-birth rates were significantly higher with OS using clomiphene citrate with IUI (8.9%, risk ratio [RR] 1.4, 95% CI 1.2–1.6), letrozole with IUI (9.4%, RR 1.5, 95% CI 1.3–1.7), and gonadotropins with IUI (9.5%, RR 1.5, 95% CI 1.3–1.8) (19).

Summary Statement

- There is strong evidence that IUI in unstimulated cycles is less effective than OS with IUI and it is not significantly more effective than expectant management.

Recommendation

- It is not recommended to perform IUI in natural cycles for the treatment of unexplained infertility. It is less effective than OS with IUI and likely no more effective than expectant management. (Strength of Evidence: A; Strength of recommendation: Strong)

CLOMIPHENE CITRATE WITH INTERCOURSE

Clomiphene citrate is an oral selective estrogen receptor modulator and is a commonly used treatment for anovulatory infertility. By antagonizing the action of estrogen at the level of the hypothalamus and pituitary, clomiphene increases secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, which may lead to the development of more than a single ovulatory follicle (24). However, it is uncertain if this mechanism increases an ovulatory woman's fecundity.

This guideline includes four RCTs (14, 25–27) and three systematic reviews of RCTs (28–30) that assessed clomiphene citrate with intercourse for the treatment of couples with unexplained infertility. Most investigations demonstrated no difference in pregnancy outcomes comparing clomiphene vs. placebo with timed intercourse or clomiphene vs. expectant management (14, 29). In a 2008 high-quality RCT, the adjusted OR for live birth for OS with clomiphene with timed intercourse compared to expectant management was 0.80 (0.45–1.42), $P=.45$ (14). One low-quality RCT conducted in the 1980s suggested higher pregnancy rates with clomiphene and timed intercourse, with or without human chorionic gonadotropin (hCG) supplementation in the luteal phase vs. placebo with timed intercourse, with or without HCG supplementation (27); however, these differences were not statistically significant (10/76 vs. 4/72 over 4 treatment cycles;

clomiphene vs. placebo, respectively, $P=.16$; post-hoc calculation by the Practice Committee). Additionally, live-birth rate by treatment group was not reported, and some pregnancies in this trial occurred outside of treatment. One low-quality RCT reported greater pregnancy rates in clomiphene with timed intercourse than in clomiphene with IUI treatments (28/69 [40%] vs. 8/44 [18%], respectively, $P=.014$) (25). However, the overall high and uneven dropout rate between groups (26 in the IUI group) limits conclusions from this investigation.

One RCT comparing clomiphene vs. letrozole with timed intercourse determined no difference in clinical pregnancy rate or risk of multiple-gestation pregnancy (clinical pregnancy rate: letrozole 11.1%, clomiphene citrate 12.1%, $P=NS$; multiple-pregnancy rate: letrozole 8.3%, clomiphene 9.1%, $P=NS$) (26). Two systematic reviews of RCTs were consistent with these findings (28, 30); however, both reported significant heterogeneity in the data and included studies with both timed intercourse and IUI treatments.

Summary Statement

- There is good evidence that clomiphene citrate with timed intercourse is no more effective than expectant management.

Recommendation

- It is not recommended to use clomiphene citrate with timed intercourse as a treatment for unexplained infertility, as it is no more effective than expectant management. (Strength of Evidence: B; Strength of Recommendation: Moderate)

AROMATASE INHIBITORS WITH INTERCOURSE

Aromatase inhibitors comprise a class of drugs commonly used in the treatment of breast cancer in women. These medications inhibit the aromatase enzyme, thereby decreasing serum levels of estrogen. The resulting hypoestrogenism causes an increase in the release of FSH and LH from the anterior pituitary leading to follicular development. Aromatase inhibitors, particularly letrozole, are commonly used off-label (i.e., a non-FDA approved indication) for the purpose of ovulation induction in anovulatory women. A recent multicenter RCT demonstrated that letrozole was more effective than clomiphene citrate for this purpose (31). However, aromatase inhibitors are also frequently used for OS, with and without IUI, as treatment for couples with unexplained infertility.

There are many types of selective aromatase inhibitors such as anastrozole, exemestane, vorozole, formestane, fadrozole, and, the most common aromatase inhibitor in fertility treatment, letrozole. Animal studies have shown that letrozole can cause birth defects if taken during pregnancy, prompting Food and Drug Administration (FDA) warnings for its usage in pregnancy, but there is evidence to support its safety when used to induce ovulation or OS (4, 31, 32).

This guideline includes two randomized trials (26, 33) and two systematic reviews of RCTs (28, 30) that assessed aromatase inhibitors with intercourse as treatment for couples with unexplained infertility. In one high-quality RCT which included 996 patients, clinical pregnancy rate was no different between letrozole cycles with timed intercourse vs. medically unassisted age-matched controls who conceived (11.1% vs. 7.0%, respectively, $P=NS$) (26). Letrozole was also associated with no significant advantage in pregnancy rates as compared to clomiphene citrate with timed intercourse (11.1% letrozole vs. 12.1% clomiphene) (26). Both systematic reviews demonstrated no difference in outcomes including clinical pregnancy, live-birth, miscarriage, and multiple pregnancy rates comparing letrozole to clomiphene citrate. However, both noted significant heterogeneity in the data and included some studies which added IUI to the ovarian stimulation (28, 30). Pregnancy rates in an earlier trial were equivalent (and low) across doses of letrozole ranging from 2.5 to 7.5 mg (pregnancy rate/cycle: 2.5 mg, 4.8%; 5 mg, 4.3%; 7.5 mg, 6.5%), $P=NS$) (33). Subgroup analyses in both systematic reviews found that treatment with 2.5 mg letrozole resulted in a higher pregnancy rate when compared with treatment with clomiphene citrate (28, 30). However, these findings must be interpreted with caution because of the inability to determine how many cycles a patient was treated at a given dose (28).

Summary Statement

- There is good evidence that letrozole with timed intercourse is no more effective than clomiphene citrate with timed intercourse or expectant management in the treatment of unexplained infertility.

Recommendation

- It is not recommended to use letrozole with timed intercourse as a treatment for unexplained infertility, as it is no more effective than expectant management. (Strength of Evidence: B; Strength of Recommendation: Moderate)

GONADOTROPINS WITH INTERCOURSE

The gonadotropins FSH and LH are polypeptide hormones secreted by the anterior pituitary. These hormones act directly on the ovaries, regulating follicular development and hormone secretion. Gonadotropins have a dose-dependent action on the ovaries, with greater doses resulting in the maturation of additional follicles (unless limited by decreased ovarian reserve). OS with gonadotropins is considered more aggressive treatment than OS with letrozole or clomiphene. The more potent action of gonadotropins compared with oral medications frequently results in the development of more ovulatory-sized follicles during treatment than achieved with letrozole or clomiphene (34). This increase in follicle number following treatment would be anticipated to increase pregnancy rates at the expense of an increase in the risk of multiple-gestation pregnancy.

This guideline includes four randomized trials (11, 12, 35, 36), one systematic review of RCTs (37), and three cohort studies (18, 23, 38) that assess treatment with gonadotropins and intercourse for couples with unexplained infertility. Most trials do not directly compare gonadotropin treatment with timed intercourse vs. expectant management; rather, they compare gonadotropin treatment with timed intercourse vs. gonadotropins with IUI, or gonadotropin treatment with timed intercourse vs. oral medications with timed intercourse.

There are conflicting data regarding pregnancy rates when comparing IUI with *low-dose* gonadotropins (<150 IU) to low-dose gonadotropins with timed intercourse. Two older RCTs of intermediate quality showed higher pregnancy rates in their IUI arms compared with timed intercourse, one with statistically significantly higher pregnancy rates per cycle with IUI (25.7% vs. 8.9%, with IUI vs. timed intercourse, $P < .05$) (35), while the other trial showed a difference that was higher with IUI but not statistically significant (8.7% vs. 4.3% with IUI vs. timed intercourse, $P = .30$) (12). Both studies were limited by small sample sizes (less than 50 couples) and crossover study design. The multiple-gestation pregnancy rate in the 1995 RCT was 9.1% in the gonadotropin with IUI treatment arm and not reported in the gonadotropin with timed intercourse arm (35). No multiple pregnancies were reported in the 1991 RCT.

Conventional-dose gonadotropins (≥ 150 IU) with timed intercourse were not associated with higher pregnancy rates as compared to oral agents in a systematic review (37). One RCT of intermediate quality demonstrated no significant difference in pregnancy outcomes comparing timed intercourse with IUI and conventional-dose gonadotropins in patients with unexplained or male-factor infertility; however, the per-cycle pregnancy rate was significantly lower in the male-factor group than the unexplained infertility group ($P < .05$) (36). A high-quality RCT determined that conventional-dose gonadotropins with ICI (which could be considered a proxy for timed intercourse) resulted in a higher live-birth rate than ICI alone ($P = .01$) (11). Patients treated with gonadotropins and ICI were almost twice as likely to conceive as patients treated with ICI alone (19% vs. 10%, respectively, per couple rate; $P = .006$) (11). However, $\geq 20\%$ of live births in the group treated with conventional-dose gonadotropins plus ICI were multiple gestations, with one triplet and one quadruplet pregnancy (11). Two cohort studies of low quality demonstrated higher pregnancy rates in conventional-dose gonadotropin cycles with IUI, compared with natural-cycle IUI or gonadotropins with timed intercourse (18, 23). Multiple-gestation pregnancy rates ranged from 6.5% (18) to 22% (23) in gonadotropins with IUI treatments. A third cohort study of low quality reported significantly improved pregnancy (12.4%) and live-birth (8.2%) outcomes in treatment with gonadotropins and timed intercourse compared with medically unassisted outcomes in the study group (1%; $P < .003$) or among controls (4%; $P < .07$); however, the multiple-gestation pregnancy rate was not reported (38).

Summary Statement

- There is insufficient evidence that gonadotropins with timed intercourse is superior to expectant management in the treatment of unexplained infertility, and there is moderate evidence that treatment outcomes with gonadotropins are similar to oral medications in timed-intercourse cycles. Most studies report no difference in pregnancy outcomes comparing gonadotropins to OS with oral agents or higher pregnancy rates at the expense of increased risk of multiple-gestation pregnancy. Differences in outcomes between investigations are likely due to different patient populations, dosing, and cancellation criteria.

Recommendation

- It is not recommended to use gonadotropins with timed intercourse in the treatment of unexplained infertility. Studies report either no difference in pregnancy outcomes compared to OS with oral agents or higher pregnancy rates associated with a higher risk of multiple-gestation pregnancy. (Strength of Evidence: B; Strength of Recommendation: Moderate)

CLOMIPHENE CITRATE WITH INTRAUTERINE INSEMINATION (IUI)

Ovarian stimulation (OS) with IUI is a mainstay of fertility treatment for couples with unexplained infertility and is commonly utilized as an alternative or antecedent to IVF. The treatment is based on the premise that increasing the number of oocytes ovulated in a single cycle and positioning more sperm in closer proximity to the site of fertilization improves the chance of conception. Significant investigation has been done to explore this treatment. This guideline includes 19 randomized trials (4, 13, 25, 34, 39–53) and 4 systematic reviews of RCTs (28–30, 54) and 3 cohort studies (19, 20, 22) that assess treatment of clomiphene citrate with IUI compared with other treatment modalities in patients with unexplained infertility.

Two randomized trials evaluated efficacy of clomiphene citrate with IUI compared with expectant management. One recent trial of 201 couples with unexplained infertility treated with clomiphene and IUI over 3 treatment cycles determined a significantly increased live-birth rate compared with expectant management (31% vs. 9% respectively, $P = .0003$) (48). A strict per-protocol analysis similarly demonstrated improved live-birth outcome with OS and IUI vs. expectant management (24% vs. 7%, $P = .005$). It should be noted that 7 of 101 patients in the clomiphene group were treated with letrozole in this study (48). An intermediate-quality RCT similarly demonstrated a higher pregnancy rate in clomiphene-IUI cycles among patients with unexplained infertility compared with untreated cycles (9.7% vs. 3.3%, respectively, $P = .049$; post-hoc calculation by the Practice Committee); however, this trial did not report live-birth outcome by diagnosis (45). In contrast, two systematic reviews failed to show a statistical

improvement in pregnancy rate or live-birth rate when using clomiphene and IUI (29, 54). In particular, the 2010 systematic review (29) did not detect a significant difference in live birth with clomiphene plus IUI compared with expectant management or placebo (OR 0.79, 95% CI 0.45–1.38; $P=.41$). Importantly, both reviews were published prior to the 2018 RCT (48).

One randomized trial of intermediate quality and one cohort study of intermediate quality showed an improved pregnancy rate with clomiphene-IUI compared with IUI alone: 6 pregnancies of 23 cycles (26.1%) vs. 1 pregnancy of 20 cycles (5%), respectively, ($P<.05$) in the RCT (13), and 15 pregnancies of 34 couples (44.1%) vs. 4 pregnancies of 34 couples (11.7%), respectively, ($P=.006$) in the cohort study (20). A smaller retrospective study showed no difference (22). A low-quality RCT of 113 patients suggested higher pregnancy rates with clomiphene with timed intercourse than with clomiphene with IUI (25). However, the high and uneven dropout rate limits conclusions from this study.

When comparing clomiphene-IUI vs. letrozole-IUI, four randomized trials (4, 39, 40, 42) and two systematic reviews of RCTs (28, 30) did not show any difference in pregnancy rates. A single intermediate-quality RCT suggested higher ongoing (OR 2.09, 95% CI 1.11–3.95, $P=.02$) and cumulative pregnancy rates (OR 2.05, 1.12–3.73, $P=.019$) with letrozole 2.5 mg vs. clomiphene 100 mg, with no differences in multiple pregnancy rates (OR 0.78, 0.16–3.82, $P=.756$) (49). A large retrospective cohort study of 14,519 cycles demonstrated similar live-birth rates for clomiphene-IUI and letrozole-IUI, both of which were greater than natural-cycle IUI (natural-cycle IUI 6.2% vs. clomiphene-IUI 8.9% [RR 1.4, 95% CI 1.2–1.7, adjusted RR 1.2–1.6]; letrozole 9.4% [RR 1.5, 95% CI 1.3–1.8, adjusted RR 1.3–1.7]) (19).

Seven randomized trials compared *low-dose* gonadotropins (<150 IU per day) and IUI to clomiphene and IUI. A recent high-quality RCT demonstrated similar ongoing pregnancy rates following up to 4 cycles of low-dose FSH with IUI vs. clomiphene with IUI (31% vs. 26%, FSH vs. clomiphene, respectively, $P=NS$) (43). This study, which included strict cycle-cancellation criteria, also reported similar and low multiple-gestation pregnancy rates between the treatments (1.4% vs. 2.2%, FSH vs. clomiphene, respectively, $P=NS$) (43). Of the six other trials, three found significantly higher pregnancy rates with FSH plus IUI compared with clomiphene and IUI (41, 47, 52), while three other RCTs showed no difference (34, 44, 46). The multiple-pregnancy rate, which was reported in all but one trial (46), was not significantly different between treatment groups (range 0–12.5%). Differences in the outcomes of these trials may be due to different dosing protocols (both gonadotropin and clomiphene), patient populations, and cancellation criteria. A recent large retrospective cohort study also showed similar live-birth rates comparing clomiphene with IUI to low-dose gonadotropins with IUI (8.9% vs. 9.5%, clomiphene vs. gonadotropins, respectively, $P=NS$) (19).

Four trials comparing *conventional-dose* gonadotropins (≥ 150 IU per day) plus IUI also produced conflicting results. Comparing gonadotropins plus IUI with clomiphene plus IUI, two high-quality RCTs reported significantly higher clinical pregnancy rate 27% vs. 14%, respectively, ($P<.001$) (51), as

well as live-birth rate over 4 cycles (32.2% vs. 23.3%, respectively, $P<.02$) and multiple-pregnancy rate (31.8% vs. 9.4%, $P<.001$) (4). Conversely, two other high-quality RCTs showed no difference in either outcome (live-birth rate over 2 cycles 13.5% vs. 15.7%, gonadotropins vs. clomiphene, respectively, $P=NS$) (50), and per cycle pregnancy rate 9.8% vs. 7.6%, gonadotropins vs. clomiphene, respectively, $P=NS$) (53). As above, differences in the outcomes of these trials may reflect differences in patient populations, gonadotropin dosing, and cancellation criteria.

Summary Statement

- There is strong evidence that clomiphene citrate with IUI is superior to expectant management and natural-cycle IUI for the outcome of live-birth rate in couples with unexplained infertility. Multiple gestation pregnancy rates with clomiphene citrate with IUI treatment range from 0 to 12.5%. Differences in multiple gestation outcomes between investigations are likely due to different patient populations, dosing, and cancellation criteria.

Recommendation

- It is recommended to use clomiphene citrate with IUI in the treatment of couples with unexplained infertility. (Strength of Evidence: A; Strength of Recommendation: Strong)

AROMATASE INHIBITORS WITH INTRAUTERINE INSEMINATION (IUI)

Ovarian stimulation (OS) has traditionally been achieved using clomiphene citrate and/or injectable gonadotropins. More recently, aromatase inhibitors have entered clinical practice as an alternative method of OS. However, it is unclear whether aromatase inhibitors with IUI are an effective form of treatment. This guideline reviews the evidence evaluating the efficacy of aromatase inhibitors with IUI compared to expectant management and compared to other OS agents including clomiphene and injectable gonadotropins. This guideline includes eight randomized trials (4, 39, 40, 42, 48, 49, 55, 56), two systematic reviews/meta-analyses of RCTs (28, 30), and one cohort study (19) that assess the use of aromatase inhibitors for OS with IUI in patients with unexplained infertility.

A high-quality RCT of 201 women with unexplained infertility randomized patients to 3 cycles of OS with IUI (either oral clomiphene 50–150 mg, days 2–6, or oral letrozole 2.5–7.5 mg, days 2–6) or 3 cycles of expectant management (48). These authors reported significantly higher clinical pregnancy rates (RR 3.33, 95% CI 1.80–6.15; $P<.0001$) and cumulative live-birth rates (RR 3.41, 95% CI 1.71–6.79; $P=.0003$) in the OS–IUI group compared with expectant management. However, only seven women in this study received letrozole (48). A recent retrospective cohort study of 14,519 IUI cycles in 8,583 couples with unexplained infertility included larger numbers of natural cycles ($n=6,746$), clomiphene cycles ($n=3,205$), letrozole-stimulated cycles ($n=1,989$), and gonadotropin-stimulated cycles ($n=2,579$) (19).

Compared with natural-cycle IUI (live-birth rate 6.2%), adjusted live-birth rates were significantly higher with clomiphene (8.9%, RR 1.4, 95% CI 1.2–1.6), letrozole (9.4%, RR 1.5, 95% CI 1.3–1.7), and gonadotropins (9.5%, RR 1.5, 95% CI 1.3–1.8). Multiple-pregnancy rates were significantly higher in the clomiphene (4.6%, RR 6.2, 95% CI 2.1–18.3) and gonadotropin (3.9%, RR 5.3, 95% CI 1.7–16.1) groups compared with natural cycles (0.7%), but not in the letrozole group (1.3%, RR 1.7, 95% CI 0.4–7.7) (19).

One systematic review compared letrozole to clomiphene citrate for unexplained infertility, including six RCTs of 1,776 women, ages 21–33, with unexplained infertility (30). One of the included studies compared letrozole to clomiphene with intercourse, while four others compared these treatments combined with IUI. There were no differences in pregnancy, miscarriage, multiple-pregnancy rates, adverse events, number of dominant follicles (>18 mm), or endometrial thickness. Clinical pregnancy rates were not significantly different overall between letrozole (199/809 [24.5%]) and clomiphene (201/967 [20.8%]), RR 1.26, 95% CI 0.89–1.80, $P=.20$; six studies; heterogeneity $P=.01$. However, a subgroup of 2.5 mg of letrozole (74/261, 28.4%) compared to 100 mg clomiphene (39/260, 15%) suggested higher clinical pregnancy rates with the low dose of letrozole (RR 1.85, 95% CI 1.31–2.60, $P=.0004$; no heterogeneity, $P=.60$) (30). A second systematic review with broader inclusion criteria and assessing the outcome of live birth also demonstrated similar outcomes with letrozole compared to clomiphene (live birth: RR 0.94, 95% CI 0.83–1.08; spontaneous miscarriage: RR 0.92, 95% CI 0.61–1.38; or twin gestation: RR 0.81, 95% CI 0.39–1.68) (28).

Several other RCTs have compared varying doses of letrozole (ranging from 2.5 mg–7.5 mg) to 100 mg clomiphene combined with IUI, and all found no significant differences in pregnancy rates between letrozole and clomiphene (39, 40, 42). One RCT of 214 patients evaluated the use of extended letrozole (2.5 mg from day 1–9) compared with clomiphene (100 mg days 3–7) and reported significantly higher ongoing pregnancy rates in the letrozole group (35/106, 33%) than the clomiphene group (20/105, 19%) (OR 2.09, 95% CI 1.11–3.95, $P=.02$) (49).

In two studies comparing letrozole to injectable gonadotropins, pregnancy rates were comparable. A small RCT randomized 80 women to 5 mg letrozole or 75 IU vs. 150 IU of human menopausal gonadotropins (hMG) for women <30 and >30 years old, respectively, and found that clinical pregnancy rates were similar (letrozole 18.42% [7/38]; hMG 15.78% [6/38], NS) (55). In another RCT, which included 50 couples who previously failed to conceive after 3 cycles of clomiphene with IUI, live-birth rates were also similar between letrozole (20%) and injectable gonadotropins (28%) ($P>.05$) (56). A high-quality RCT randomized 900 couples with unexplained infertility up to 4 cycles of OS with injectable gonadotropins, letrozole, or clomiphene with IUI (4). Compared with the gonadotropin group, use of letrozole resulted in lower rates of live birth, but those rates did not differ significantly between letrozole and clomiphene (gonadotropins 32.2% [97/301]; letrozole 18.7% [56/299], $P<.001$ vs. gonadotropins; clomiphene 23.3% [70/300], $P=.02$ vs.

gonadotropins). The rate of multiple gestations among live births was highest in women receiving gonadotropins (gonadotropins 32% [31/97]; clomiphene 5.7% [4/70]; letrozole 14.3% [8/56]) (4).

Summary Statement

- There is strong evidence that there is no significant difference in pregnancy rates or multiple-gestation pregnancy rate following letrozole with IUI as compared to clomiphene citrate with IUI. Both are superior to expectant management and natural-cycle IUI.

Recommendation

- It is recommended that letrozole with IUI treatments be considered as an alternative regimen for couples with unexplained infertility, as studies to date suggest similar efficacy. Of note, letrozole is not FDA approved for treatment of unexplained infertility, but is considered an effective and well tolerated option. (Strength of Evidence: A; Strength of Recommendation: Strong)

INTRAUTERINE INSEMINATION (IUI) WITH COMBINATION OF CLOMIPHENE CITRATE OR LETROZOLE AND GONADOTROPINS (LOW DOSE AND CONVENTIONAL DOSE)

Combination therapy of oral agents for OS, such as clomiphene citrate and letrozole, with gonadotropins has been explored to improve pregnancy success beyond oral agents alone. This guideline includes six RCTs (57–62) and six cohort studies (22, 63–67) that assess patients with unexplained infertility treated with clomiphene citrate and low-dose gonadotropins with IUI compared with two other treatments: (1) letrozole and IUI and (2) letrozole and low-dose gonadotropins with IUI. Among included studies, one RCT compared clomiphene plus hMG with IUI to clomiphene plus FSH with IUI (60). Five cohort studies (22, 63–65, 67) compared clomiphene citrate plus hMG or FSH with various treatment modalities.

One intermediate-quality RCT demonstrated no difference in live-birth outcome in treatments of clomiphene with IUI, low-dose FSH with IUI, or sequential clomiphene plus low-dose FSH with IUI (8.3%, 12.1%, and 13.6%, respectively ($P=NS$)) (57). Three randomized trials suggested no difference in fecundity between clomiphene and low-dose gonadotropins with IUI compared to letrozole and low-dose gonadotropins with IUI (58, 59, 62). A cohort study reported higher pregnancy rates with clomiphene and gonadotropins than letrozole and gonadotropins, but these differences were not statistically significant (66). Conversely, one RCT found that letrozole-IUI alone resulted in higher clinical pregnancy rates per cycle than clomiphene combined with gonadotropins-IUI, but this study reported an unusually high pregnancy rate with letrozole plus IUI (23/70, 32.8%) vs. clomiphene with low-dose hMG plus IUI (10/70, 14.3%) (61). Additionally, there was a high risk for bias in the randomization strategy.

In a cohort study, clomiphene and conventional-dose gonadotropins with IUI was superior to expectant management (pregnancy rate 34.7% vs. 8.9%, respectively, $P < .001$) (64). However, 16% of pregnancies following gonadotropin treatment were multiple-gestation pregnancies with two sets of triplets, and 3.7% developed moderate OHSS (64). A cohort study by the same authors compared pregnancy rates with IVF and intracytoplasmic sperm injection (ICSI) to clomiphene and conventional-dose gonadotropins with IUI in couples that had failed 3 prior cycles with the same treatment. Pregnancy rates were significantly higher per cycle with IVF-ICSI compared with clomiphene plus gonadotropins and IUI (36.6% vs. 5.6% per cycle, respectively, $P < .001$) (63). A third cohort study suggested higher pregnancy rates with clomiphene plus FSH with IUI treatments compared to natural-cycle IUI or clomiphene with IUI treatments (22). However, only three total conceptions occurred in the unexplained infertility group in this study.

The type of gonadotropin does not appear to be associated with outcomes. An RCT comparing clomiphene with low-dose recombinant FSH vs. low-dose menopausal gonadotropins with IUI found no difference in clinical pregnancy, multiple pregnancy, abortion, live birth, and OHSS (live-birth rate 14.4% vs. 12.6%, recombinant FSH vs. menopausal gonadotropins, respectively, $P = \text{NS}$) (60). A cohort study similarly found no difference in pregnancy rates comparing clomiphene with one dose (150 IU) of gonadotropins with IUI vs. the same protocol with 75–150 IU of hMG on days 5–9 (65). Interestingly, a quasi-randomized study comparing clomiphene and gonadotropins with IUI, direct intraperitoneal insemination, and timed intercourse, found similar pregnancy rates per cycle across all treatments with similarly high multiple-pregnancy rates in all three treatment groups (30% of all pregnancies and 40% of all deliveries) (67).

Summary Statement

- There is fair evidence that clomiphene citrate and conventional-dose gonadotropins with IUI treatments are associated with higher pregnancy rates than expectant management.
- There is good evidence that clomiphene citrate with conventional-dose gonadotropins with IUI treatments are associated with an increased risk of multiple-gestation pregnancy.
- There is good evidence that clinical pregnancy and live-birth rate are similar when comparing letrozole and low-dose gonadotropins with IUI vs. clomiphene citrate and low-dose gonadotropins with IUI.

Recommendation

- It is not recommended to use letrozole or clomiphene citrate plus conventional-dose gonadotropins with IUI, as most studies associated with improved pregnancy rate over OS-IUI with oral medications are also associated with an increased risk of multiple-gestation pregnancy. (Strength of Evidence: B; Strength of Recommendation: Moderate)

INTRAUTERINE INSEMINATION (IUI) WITH LOW-DOSE GONADOTROPINS

IUI with *low-dose* gonadotropins (<150 IU daily) has been suggested as an alternative to IUI with conventional-dose gonadotropins to reduce the risk of multiple-gestation pregnancy and OHSS (68). This guideline includes 13 randomized trials (7, 10, 12, 34, 35, 41, 43, 44, 46, 47, 52, 56, 69), 1 systematic review of RCTs (54) and 1 cohort study (19) that assessed the outcomes of treatment with IUI with low-dose gonadotropins in patients with unexplained infertility.

In couples with unexplained infertility and a good or intermediate prognosis for unassisted conception, two included RCTs showed that expectant management resulted in similar pregnancy rates and similar time to pregnancy compared to IUI with low-dose gonadotropins (7, 69). Both RCTs calculated the prognosis of unassisted pregnancy using the prediction model of Hunault (9). A systematic review was generally consistent with the findings of these studies (54). A cost analysis conducted as part of a 2012 RCT also showed that IUI with low-dose gonadotropins had a significantly higher cost per ongoing pregnancy compared with 6 months of expectant management (69). One RCT showed no difference in pregnancy rates comparing natural-cycle IUI to low-dose FSH with IUI up to 6 treatment cycles (23.7% vs. 36.1%, respectively $P = .17$, post hoc calculation by the Practice Committee) (10).

There are conflicting data regarding pregnancy rates when comparing IUI with low-dose gonadotropins to timed intercourse with low-dose gonadotropins. One small RCT of 46 couples with unexplained infertility showed higher pregnancy rates per treatment cycle with IUI compared with timed intercourse (25.7% and 8.9%, respectively, $P < .05$) (35). However, a second small RCT ($n = 48$) with low-dose gonadotropins demonstrated no difference in pregnancy rates between IUI and timed-intercourse groups (12).

Seven randomized trials compared low-dose gonadotropins with IUI to clomiphene citrate with IUI. Three of these trials found higher pregnancy rates with gonadotropins plus IUI compared with clomiphene citrate and IUI (41, 47, 52), while four other RCTs (34, 43, 44, 46) showed no difference in pregnancy rate. Differences in the outcomes of these trials may be due to different dosing protocols (gonadotropins and oral medications), patient populations, and cancellation criteria. The multiple-pregnancy rate, which was reported in all but one trial (46), was not significantly different between treatment groups in any of these seven studies.

One RCT (56) and one cohort study (19) of low-dose gonadotropins plus IUI vs. letrozole plus IUI also demonstrated no significant difference in pregnancy rates or multiple-pregnancy rate.

Summary Statement

- There is insufficient evidence that treatment with low-dose gonadotropins with IUI is associated with a higher pregnancy rate than clomiphene citrate or letrozole with IUI. Differences in the outcomes of these trials may be due to different dosing protocols, patient populations, and cancellation criteria.

- In couples with unexplained infertility who have a good or intermediate prognosis for unassisted conception, there is fair evidence that treatment with low-dose gonadotropins with IUI is no more effective than 6 months of expectant management
- There is no difference in multiple-pregnancy rates between clomiphene citrate or letrozole with IUI treatments compared to low-dose gonadotropins with IUI.

Recommendation

- It is not recommended to use low-dose gonadotropins with IUI in the treatment of unexplained infertility, as it is more complex and expensive, and likely no more effective than OS with oral medications with IUI. (Strength of Evidence: B; Strength of Recommendation: Moderate)

INTRAUTERINE INSEMINATION (IUI) WITH CONVENTIONAL-DOSE GONADOTROPINS

Intrauterine insemination and OS with gonadotropins have been used as empiric treatment for unexplained infertility. Theoretical mechanisms by which gonadotropin stimulation may be of benefit include increasing the number of oocytes ovulated (4, 19, 70), correcting subtle ovulatory dysfunction (70), and improving implantation through hormonal effects on the endometrium (4). Since both human hMG and recombinant human follicle-stimulating hormone (rhFSH) have similar effects (71), they are both treated as the general class of gonadotropins for the purpose of this guideline.

This guideline includes eight randomized trials (4, 11, 16, 36, 50, 53, 68, 72) and two cohort studies (18, 23) that assessed treatment of IUI with conventional-dose (≥ 150 IU) gonadotropins in patients with unexplained infertility.

Two included RCTs compared IUI in unstimulated cycles to IUI with conventional-dose gonadotropin stimulation. Both studies showed a significant increase in pregnancy rates with gonadotropin stimulation but also significantly higher multiple-gestation pregnancy rates (11, 16). In the largest of these two studies, the pregnancy rate following four treatment cycles was 18% in the natural-cycle IUI group and 33% in the gonadotropin with IUI group ($P < .001$) (11). The multiple-pregnancy rate in this RCT was at least 20% (estimate based on data available in the published study) in the gonadotropin group including two quadruplet and three triplet pregnancies (11). Additionally, 18% of pregnancies achieved in this group delivered preterm. Two retrospective cohort studies also showed similar increased pregnancy and multiple-pregnancy rates in patients treated with conventional-dose gonadotropins with IUI (18, 23).

Three RCTs compared IUI with gonadotropin stimulation to timed intercourse or ICI with gonadotropin stimulation (11, 36, 72). These studies showed conflicting results, with two RCTs (11, 72) showing significantly higher pregnancy rates with IUI while the third showed no difference in outcome (36). In the largest of these RCTs (932 couples), pregnancy rates following 4 treatment cycles in the IUI-gonadotropin group was significantly higher compared with the

ICI-gonadotropin group (33% and 19%, respectively, $P < .001$) (11).

One RCT which compared low-dose vs. conventional-dose gonadotropins with IUI found a similar pregnancy rate with both protocols (14.3% vs. 14.6%, respectively, $P = \text{NS}$) (68). The risk of moderate OHSS requiring hospitalization was significantly lower in the low-dose protocol (0% vs. 16.7%, low-dose vs. conventional dose, respectively, $P < .01$); however, the difference in multiple-gestation pregnancy rates did not reach statistical significance (1/7 low dose vs. 2/7 conventional dose, $P = \text{NS}$) (68).

One RCT ($n = 900$) was designed specifically to assess the effect of conventional-dose gonadotropins with IUI vs. oral medications with IUI treatments on live-birth and multiple-pregnancy rates (4). It found a significantly higher live-birth rate with gonadotropins and IUI compared to either clomiphene citrate with IUI or letrozole with IUI (32.2%, 23.3%, and 18.7%, respectively, $P = .02$ gonadotropins with IUI vs. clomiphene citrate with IUI, $P < .001$ gonadotropins with IUI vs. letrozole with IUI). It also found a significantly higher risk of multiple gestations among live births with IUI and gonadotropins compared to either IUI with clomiphene citrate or letrozole (32%, 5.7%, and 14.3%, respectively) (4). However, another RCT ($n = 154$) showed no difference in live-birth rates between gonadotropins with IUI vs. clomiphene with IUI following two treatment cycles (13.5% vs. 15.7%, gonadotropin with IUI vs. clomiphene with IUI, respectively, $P = .79$) (50). This study also showed no difference in multiple-gestation live-birth rates between the two treatments (14.3% vs. 12.5% of live births, gonadotropin with IUI vs. clomiphene with IUI, respectively, $P = 1.0$) (50). A third RCT ($n = 503$) also reported similar live-birth rates per cycle between the two treatments (9.8% vs. 7.6% ongoing pregnancy per initiated cycle, gonadotropin with IUI vs. clomiphene with IUI, respectively, $P = .40$) (53). Differences in outcomes of these trials may reflect differences in patient populations, dosing, and cancellation criteria.

A well-designed RCT compared conventional and accelerated treatment protocols in 503 women < 40 years of age with unexplained infertility. The conventional protocol consisted of ≤ 3 cycles of clomiphene-IUI, followed by ≤ 3 cycles of gonadotropins-IUI, followed by ≤ 6 cycles of IVF. The accelerated protocol was identical but with the omission of treatment with gonadotropins-IUI (53). This study reported the following per-cycle pregnancy rates: clomiphene-IUI=7.6%, FSH-IUI=9.8%, IVF=30.7%. The women treated with the accelerated protocol had a shorter time to pregnancy than those treated with the conventional protocol (8 vs. 11 months; hazard ratio [HR] 1.25, 95% CI 1.00–1.56, $P = .045$). The authors concluded that, in women < 40 years of age, treatment with an accelerated protocol resulted in a shorter time to pregnancy, with fewer treatment cycles, and cost savings compared to a conventional protocol.

Summary Statement

- There is insufficient evidence that treatment with conventional-dose gonadotropins with IUI is associated with a higher pregnancy rate than clomiphene citrate or

letrozole with IUI based on mixed findings from well designed studies. Treatment with conventional-dose gonadotropins with IUI demonstrates either no difference in pregnancy outcomes with similar multiple-gestation pregnancy rates compared to OS with clomiphene citrate or letrozole with IUI, or higher pregnancy rates associated with a higher rate of multiple-gestation pregnancy. Differences in both outcomes between investigations are likely due to different patient populations, dosing, and cancellation criteria.

Recommendation

- It is not recommended to use conventional-dose gonadotropins with IUI, as most studies associated with improved pregnancy rate over OS-IUI with oral medications are also associated with a high multiple-gestation pregnancy rate. (Strength of Evidence: A; Strength of Recommendation: Strong)

TIMING OF INTRAUTERINE INSEMINATION (IUI)

Intrauterine insemination (IUI) with and without OS is a standard component of treatment for unexplained infertility. However, the most effective method of timing inseminations and the optimal number of inseminations to perform per cycle have been debated. A single IUI can be performed after a spontaneous LH surge or after ovulation is initiated with exogenous hCG. A second IUI can be performed the following day, but it is debated whether double IUI yields a higher chance of pregnancy compared with single IUI. This guideline includes seven randomized trials that assessed the timing and number of IUIs in patients with unexplained infertility (73–79).

Two included RCTs evaluated the timing of IUI relative to hCG injection. One RCT of infertile couples undergoing gonadotropin stimulation compared 106 cycles in which IUI was performed 34–36 hours after hCG to 98 cycles in which IUI was performed simultaneously with hCG administration (73). In this study, there was no difference in clinical pregnancy rates based on the timing of IUI (IUI simultaneously with hCG 12.2% vs. IUI 34–36 hours after hCG 9.4%, $P=.523$, OR 1.35, 95% CI .53–3.42) (73). In another RCT of 204 couples with mild male-factor or unexplained infertility, patients were randomized to undergo IUI at 24 hours or 36 hours after hCG injection in cycles utilizing clomiphene for OS (77). Live-birth rates per cycle were higher in the 36-hour IUI group (13.4% [31/231]) than the 24-hour IUI group (7.8% [18/230]), but this difference was not statistically significant ($P=.07$, 77).

One small RCT suggested that ultrasound monitoring of follicular development and hCG induction of ovulation achieved no improvement in pregnancy rates over urinary LH monitoring in patients receiving clomiphene citrate (79). This was a study of poor quality which acknowledged its low power.

Several RCTs have compared single IUI at 34–36 hours after hCG to double IUI with the studies varying widely in the timing intervals between the first and second IUIs. Three

studies demonstrated no differences in pregnancy rates between single and double IUIs after OS in unexplained infertility (12/95 [12.6%] vs. 9/43 [20.9%], $P=.21$) (74) (23/195 [11.8%] vs. 21/204 [10.3%], $P=.64$) (78), and (26/247 [10.5%] vs. 29/243 [11.9%], $P=.68$) (75). A single RCT ($n = 273$) determined higher clinical pregnancy rates following double insemination compared with single IUI following OS with clomiphene 100 mg plus conventional-dose gonadotropins in patients with unexplained infertility (21.9% vs. 10.9%, double vs. single IUI, $P<.05$) (76). However, this study did not describe the method of randomization and reported an overall high multiple-pregnancy rate (25.4%) (76).

Summary Statement

- There is fair evidence that the timing of IUI relative to hCG injection between 0 and 36 hours does not impact pregnancy rates in OS with IUI treatments.
- There is fair evidence that live-birth rate following single IUI is not significantly different than double IUI in treatment cycles with clomiphene citrate.
- There is insufficient evidence that ultrasound monitoring for timing of IUI improves pregnancy outcomes compared to urinary LH monitoring in clomiphene citrate-IUI treatments.

Recommendation

- It is recommended that a single IUI be performed between 0 and 36 hours relative to hCG injection in OS with IUI treatments. (Strength of Evidence: B; Strength of Recommendation: Moderate)

IN VITRO FERTILIZATION (IVF) AND TREATMENT PARADIGMS

Due to steady improvements in IVF technology over the past two decades, IVF has become the most effective form of treatment for nearly all causes of infertility, but is substantially more invasive and more costly than other methods of treatment. For patients with unexplained infertility, OS-IUI with oral medications is generally considered first-line therapy, followed by IVF only if OS-IUI with oral medications is unsuccessful after several attempts. However, expedited treatment with IVF could reduce the emotional and physical burden to patients by shortening the overall time required to achieve pregnancy. This guideline reviews evidence which evaluated the efficacy of IVF and assessed its suitability as a first-line option for unexplained infertility. This guideline includes 12 randomized trials (10, 50, 53, 69, 80–87) and 8 cohort studies (88–95) that assessed IVF in patients with unexplained infertility.

Some studies suggested that there is no benefit to immediate treatment with IVF compared with expectant management or OS-IUI treatments for 6 months (69, 86). One RCT randomized infertile couples to “early IVF” within 6 months of initiating treatment to “late IVF” performed after 6 months of OS and found no differences in clinical pregnancy rates in unexplained infertility (early IVF 4.7% vs. late IVF 14.2%, $P=.32$), live-birth rates ($P=.13$), or time to pregnancy

($P=.85$) (86). This study was limited by its low pregnancy rates with IVF (overall 12% per cycle), which is not representative of modern-day IVF pregnancy rates. A more recent RCT of 253 couples with an intermediate prognosis of natural conception compared expectant management for 6 months to immediate treatment, which included 6 months of OS with either clomiphene citrate or low dose gonadotropins with IUI followed by up to 3 cycles of IVF (69). Couples randomized to expectant management also underwent up to 6 cycles of OS with IUI followed by IVF if not pregnant during the expectant management phase. After 3 years, there was no difference in pregnancy rates between expectant management and immediate treatment (cumulative ongoing pregnancy rate: RR 0.99; 95% CI 0.85–1.1) (69). However, in couples with long-standing unexplained infertility of ≥ 2 years, a cohort study comparing 131 women who were waiting to receive IVF with 119 women who underwent IVF immediately found higher clinical pregnancy rates in the IVF group compared with expectant management (38% vs. 13%, respectively) (93).

There are several RCTs that compare the conventional approach of 3 cycles of OS with IUI to the alternative of IVF as first-line treatment for unexplained infertility. Three such studies included in this guideline that assessed women with a mean age of <35 years reported no significant difference in pregnancy rates between OS with low dose gonadotropins with IUI and IVF (10, 81, 84). A secondary analysis of Custers 2011 suggested that 3 cycles of OS-IUI was also cost-effective compared to immediate IVF treatment (87). The previously described FASTT trial demonstrated that in couples who fail to achieve a pregnancy following a course of clomiphene citrate with IUI treatment, immediate IVF results in a shorter time to pregnancy and lower cost per pregnancy than a strategy that incorporates gonadotropins with IUI treatments in women ≤ 40 years (53).

In women ages 38–42 years, there is one RCT evaluating OS with IUI to IVF for unexplained infertility (mean age 40 years). This study determined that immediate treatment with IVF yielded superior live-birth rates compared to IUI with clomiphene or FSH-induced OS in this population (50). Live-birth rates per couple after the first two treatment cycles were 15.7% in the clomiphene-IUI group, 13.5% in the FSH-IUI group, and 31.4% in the immediate IVF group ($P=.035$) (50).

Three randomized trials and two observational studies suggested that there are no differences in clinical pregnancy rates or live-birth rates when comparing conventional IVF to IVF with ICSI for couples with unexplained infertility (80, 82, 83, 89, 92). One RCT (85), six cohort studies (88–92, 94), and one systematic review of cohort studies (95) provided evidence that ICSI results in higher fertilization rates than IVF and/or reduced the risk of complete fertilization failure.

Some studies reported increased implantation and clinical pregnancy rates in the non-ICSI groups (80, 90, 91). Two retrospective studies by the same group also reported higher live-birth rate with conventional fertilization compared with ICSI (90, 91). In an RCT of 415 couples with non-male-factor infertility randomized to conventional fertilization or ICSI, fertilization rates per oocyte retrieved favored conventional fertilization (IVF 61% vs. ICSI 50%,

95% CI 5–17), whereas fertilization rate per oocyte inseminated favored ICSI (IVF 61% vs. ICSI 70%, 95% CI 2–14) (80). This suggests that the improved fertilization rates with ICSI may be attributable to the number of mature oocytes included in the denominator, rather than to the ICSI procedure itself. In this RCT, implantation rates were higher in the IVF group (IVF 30% [95/318] vs. ICSI 22% [72/325], RR 1.35, 95% CI 1.04–1.76), but clinical pregnancy rates were not significantly different (IVF 72 [33%] vs. ICSI 53 [26%], RR 1.27, 95% CI 0.95–1.72) (80).

Summary Statement

- Current evidence does not support IVF as a first-line therapy for unexplained infertility over expectant management for 6 months or a limited course of treatment of OS with IUI in women <38 years of age. However, it is important to note that many of the included studies were conducted in an era of lower IVF success rates than those currently observed.
- There is good evidence that immediate IVF in women ≥ 38 years of age may be associated with a higher pregnancy rate and shorter time to pregnancy as compared to a strategy consisting of OS with IUI treatments with either oral medications or gonadotropins prior to IVF.
- There is good evidence that in couples who fail to achieve a pregnancy following a course of clomiphene citrate with IUI treatment, immediate IVF results in a shorter time to pregnancy and lower cost per pregnancy than a strategy that incorporates gonadotropins with IUI treatments in women ≤ 40 years.
- There is good evidence that there is no reported difference in clinical pregnancy and live-birth rates when comparing IVF with conventional fertilization to IVF with ICSI in the setting of unexplained infertility. However, ICSI has been associated with higher fertilization rates and a reduced risk of complete fertilization failure as compared to conventional fertilization.

Recommendation

- It is recommended that couples with unexplained infertility initially undergo a course (typically 3 or 4 cycles) of OS and IUI with oral agents. For those unsuccessful with OS and IUI treatments with oral agents, IVF is recommended rather than OS and IUI with gonadotropins. (Strength of Evidence: B; Strength of Recommendation: Moderate)

RISK CONSIDERATIONS

The major risks associated with therapies for the treatment of unexplained infertility are directly related to the OS process. With the development and ovulation of multiple follicles, there is inevitably an increased risk of OHSS and, importantly, multiple-gestation pregnancy, with its associated risks of pre-term delivery and low birth weight. While these risks exist with OS-IUI treatments with oral medications and IVF, they are less common with oral medications, and in the setting of IVF, can be mitigated with elective single-embryo transfer. The risk of multiple-gestation pregnancy is most clearly present with gonadotropin-OS treatments, with and without IUI.

These risks are best demonstrated in two large prospective RCTs conducted by the Reproductive Medicine Network. In one RCT conducted in 2015, the risk of multiple-gestation pregnancy associated with conventional-dose gonadotropin-IUI treatments was 32%, including 10 sets of triplets in this treatment arm (107 pregnancies) (4). In the other 1999 RCT, of 72 live births in the gonadotropin-OS arms, 24 were multiple-gestation pregnancies (33%) with 17 twin, 4 triplet, and 3 quadruplet pregnancies (3). Although the risk of multiple-gestation pregnancy is consistently lower in low-dose gonadotropin protocols, the evidence would suggest that these treatments are no more effective than less complex and less expensive OS-IUI treatments with oral medications and may be no more effective than expectant management.

There is potential harm and cost associated with the treatment of unexplained infertility in general, as even OS-IUI treatments with oral medications are associated with an increased risk of multiple-gestation pregnancy. Given that some studies report significant pregnancy rates associated with expectant management (6, 7), care to avoid overtreatment is important. Nevertheless, it is clear that a strategy of expectant management is not preferred by couples with unexplained infertility (14) and is associated with low pregnancy rates per cycle. Additionally, age of the female partner, duration of infertility, and overall desired family size are important considerations in the decision to initiate or delay treatment.

CONCLUSIONS

For most couples with unexplained infertility there is no role for OS with gonadotropins, with or without IUI. Pregnancy rates associated with these treatments are dose dependent, and meaningful improvements over outcomes seen with OS-IUI with oral medications are only achieved at doses associated with a high risk for multiple-gestation pregnancy. Together with compelling evidence that a strategy of 3 cycles of clomiphene citrate-IUI followed immediately by IVF results in a shorter time to pregnancy at lower cost than a strategy that includes an intervening gonadotropin-IUI course, gonadotropin-IUI cycles should be rare. While IVF is an effective treatment for unexplained infertility, it is also associated with risks of multiple-gestation pregnancy, preterm delivery, and low birth weight. Furthermore, it is cost prohibitive for many couples. There is a pressing need for investigations to evaluate treatments to bridge the gap between the effectiveness of IVF and the low (and unchanging) success rates associated with OS-IUI treatments with oral medications. Additionally, further research is needed regarding barriers to the access of treatments such as ART, including social, cultural, and economic factors.

UNANSWERED QUESTIONS

- Future investigations of therapies for unexplained infertility should clearly report adverse outcomes, including OHSS and multiple-gestation pregnancies.
- Investigations into alternative treatment strategies or adjuvants to lessen the gap in effectiveness between OS-IUI

with oral agents and IVF in the treatment of unexplained infertility are needed.

- In addition to comparative effectiveness trials, additional RCTs which compare a sequence or course of treatments for unexplained infertility to another treatment strategy are needed.
- Studies directed toward treatment options for the male partner of a couple diagnosed with unexplained infertility are needed.

RECOMMENDATIONS

- It is not recommended to perform IUI in natural cycles for the treatment of unexplained infertility. It is less effective than OS with IUI and likely no more effective than expectant management. (Strength of Evidence: A; Strength of Recommendation: Strong)
- It is not recommended to use clomiphene citrate with timed intercourse as a treatment for unexplained infertility, as it is no more effective than expectant management. (Strength of Evidence: B; Strength of Recommendation: Moderate)
- It is not recommended to use letrozole with timed intercourse as a treatment for unexplained infertility, as it is no more effective than expectant management. (Strength of Evidence: B; Strength of Recommendation: Moderate)
- It is not recommended to use gonadotropins with timed intercourse in the treatment of unexplained infertility. Studies report either no difference in pregnancy outcomes compared to OS with oral agents or higher pregnancy rates associated with a higher risk of multiple-gestation pregnancy. (Strength of Evidence: B; Strength of Recommendation: Moderate)
- It is recommended to use clomiphene citrate with IUI in the treatment of couples with unexplained infertility. (Strength of Evidence: A; Strength of Recommendation: Strong)
- It is recommended that letrozole with IUI treatments be considered as an alternative regimen for couples with unexplained infertility, as studies to date suggest similar efficacy. Of note, letrozole is not FDA approved for treatment of unexplained infertility but is considered an effective and well tolerated option. (Strength of Evidence: A; Strength of Recommendation: Strong)
- It is not recommended to use letrozole or clomiphene citrate plus conventional-dose gonadotropins with IUI, as most studies associated with improved pregnancy rate over OS-IUI with oral medications are also associated with an increased risk of multiple-gestation pregnancy. (Strength of Evidence: B; Strength of Recommendation: Moderate)
- It is not recommended to use low-dose gonadotropins with IUI in the treatment of unexplained infertility, as it is more complex and expensive, and likely no more effective than OS with oral medications with IUI.

(Strength of Evidence: B; Strength of Recommendation: Moderate)

- It is not recommended to use conventional-dose gonadotropins with IUI, as most studies associated with improved pregnancy rate over OS-IUI with oral medications are also associated with a high multiple-gestation pregnancy rate. (Strength of Evidence: A; Strength of Recommendation: Strong)
- It is recommended that a single IUI be performed between 0 and 36 hours relative to hCG injection in OS with IUI treatments. (Strength of Evidence: B; Strength of Recommendation: Moderate)
- It is recommended that couples with unexplained infertility initially undergo a course (typically 3 or 4 cycles) of OS and IUI with oral agents. For those unsuccessful with OS and IUI treatments with oral agents, IVF is recommended rather than OS and IUI with gonadotropins. (Strength of Evidence: B; Strength of Recommendation: Moderate)

SUMMARY RECOMMENDATIONS AND FUTURE DIRECTIONS

- For most couples with unexplained infertility, the best initial therapy is a course (typically 3 or 4 cycles) of OS and IUI, either with clomiphene or letrozole, followed by IVF for those couples unsuccessful in achieving a pregnancy with OS and IUI.
- There is a pressing need for additional therapies to bridge the wide gap in effectiveness between OS and IUI with oral medications and IVF.
- Further research is needed into methods to improve access to care, including ART treatments.

ABOUT THIS DOCUMENT

Disclaimer. This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM) as a service to its members and other practicing clinicians. Although 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. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Disclosures and Conflicts of Interest. Per ASRM policy, all members of ASRM task forces and the Practice Committee disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients for the preceding 12 months. Committee members were reminded to update potential disclosures annually and if new potential conflicts arose during their appointments. Before live discussions or meetings, Committee members were reminded verbally and in writing to disclose any new or previ-

ously undisclosed relationships. Disclosures were reviewed for conflicts by the ASRM Chief Medical Officer and the Chair of the Practice Committee. Task force members for whom conflicts were identified were excused from this project. Members of the Practice Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of the document.

Panel. This evidence-based guideline with recommendations for clinicians was developed by a multidisciplinary group, comprised of the ASRM Practice Committee and a task force of medical experts, which included specialists in obstetrics and gynecology, reproductive endocrinology and infertility, fertility preservation, reproductive surgery, endometriosis, uterine anomalies, fibroids, assisted reproductive technology, in vitro fertilization, and epidemiology/biostatistics. Members of the task force for this clinical practice guideline consisted of medical professionals at various levels of training, including fellows and senior experts, as well as experts with less than 10 years of post-training, CREST (Clinical Reproductive Scientist Training) Program scholars, a clinical epidemiologist who is also a reproductive medicine subspecialist, and a methodologic specialist. In addition, a select group of patients participated in document scoping and review.

Review Process. The Practice Committee, a multidisciplinary body, reviewed this document at various stages of development. After thorough review of the final draft by the task force for this guideline as well as the Practice Committee, this document was reviewed by ASRM executive leadership. The document then proceeded to a 15-day period of open review by ASRM members, which includes patient advocates, genetic counselors, mental health professionals, nursing professionals, legal professionals, laboratory personnel, research scientists, and physicians boarded in one or more specialties. The ASRM Board of Directors also reviewed the document over a period of 15 days. The input of all was considered in the preparation of the final document.

Patient/Public Perspective. To incorporate perspectives of those who might be affected most by the recommendations in this guideline, a group of patient volunteers and lay stakeholders in reproductive medicine who were not involved in the scoping or development of this guideline reviewed the document. Their feedback was considered in the preparation of the final document.

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Updating Policy. Document expiration: March 2024

ASRM reviews and updates or retires its evidence-based guidelines every 5 years or after significant scientific developments or change in public policy as determined by the ASRM Practice Committee.

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