TOPIC 11 · UNEXPLAINED INFERTILITY

What “unexplained” really means, when active treatment is appropriate, and what we know about expectant management, IUI, IVF and ICSI.

Why 8 core sources?

Eight is the ideal number. The topic does not need dozens of isolated trials, but a clear framework built from the two major international guidelines, systematic reviews of IUI/IVF, evidence on ovarian stimulation, prognosis-based management and the latest position on routine ICSI. This covers definition, prognosis and the main treatment decisions without overload.

The evidence in context

Unexplained infertility is a diagnosis of exclusion: standard evaluation has not identified a clear cause, but that does not mean the biology is fully understood or that “nothing is wrong.” A meaningful proportion of couples may still conceive without treatment, so age, duration of infertility and predicted probability of natural conception should influence when active treatment begins. For many couples, oral ovarian stimulation with IUI is a reasonable first step before IVF, whereas older age or poorer prognosis may justify faster escalation. The diagnosis also provides no scientific basis for attributing the cause to stress, emotional “blocks” or other unproven explanations.

1. ESHRE Guideline Group (2023)

Evidence-based guideline: unexplained infertility

Original source

What it studied → The European evidence-based guideline on the definition, diagnosis and management of unexplained infertility, comprising 52 recommendations.

What it found → Unexplained infertility is a diagnosis of exclusion after standard evaluation, and the decision to initiate active treatment should take prognosis for natural conception, age, infertility duration and couple preferences into account.

What it means in practice → “Unexplained” does not mean there is no biological reason; it means routine clinical evaluation has not identified a specific cause. Management should not be automatic or identical for everyone.

Limitations → A guideline synthesising heterogeneous evidence; many individual questions remain supported by low- or moderate-certainty evidence.

2. ASRM Practice Committee (2020)

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

Original source

What it studied → An ASRM guideline drawing on 88 relevant studies of expectant management, ovarian stimulation, IUI and IVF.

What it found → For most couples it recommends an initial course of 3–4 cycles of ovarian stimulation with oral agents plus IUI, followed by IVF if unsuccessful. It also highlights meaningful unassisted pregnancy rates and the multiple-pregnancy risks of more aggressive stimulation.

What it means in practice → Management is necessarily empirical because no specific treatable cause has been identified. Strategy should balance success probability, time, age, cost and treatment risks.

Limitations → Variable definitions of unexplained infertility, many underpowered studies and frequent reliance on surrogate rather than live-birth outcomes.

3. Wang et al. (2019)

Interventions for unexplained infertility: a systematic review and network meta-analysis

Original source

What it studied → A systematic review and network meta-analysis comparing expectant management with multiple active treatments for unexplained infertility.

What it found → No single treatment emerged as universally superior for all couples. Relative effectiveness depended on comparator, outcome and couple characteristics, while certainty was often low.

What it means in practice → It supports prognosis-based, individualised management rather than one universal escalation pathway.

Limitations → Heterogeneous interventions and populations, limited direct head-to-head data and low certainty for several comparisons.

4. Nandi et al. (2022)

IUI with controlled ovarian hyperstimulation versus IVF in unexplained infertility: a systematic review and meta-analysis

Original source

What it studied → A systematic review comparing IUI with controlled ovarian hyperstimulation against IVF in couples with unexplained infertility.

What it found → IVF may offer higher per-cycle effectiveness, but cumulative outcomes, cost, invasiveness and time-to-pregnancy require individualised interpretation.

What it means in practice → Going straight to IVF is not automatically the best option for every couple; age, prognosis and time horizon matter.

Limitations → Limited direct comparisons and variation in IUI/IVF protocols and reported outcomes.

5. Ayeleke et al. / Cochrane (2020)

Intra-uterine insemination for unexplained subfertility

Original source

What it studied → A Cochrane review of IUI in natural and stimulated cycles, including comparisons with expectant management and other strategies.

What it found → Stimulated-cycle IUI may increase cumulative live birth in some comparisons, but certainty was often low and multiple-pregnancy risk remains important.

What it means in practice → IUI may have a role in selected couples, but benefit and risk depend on the stimulation protocol and underlying prognosis.

Limitations → Low-certainty evidence for many comparisons, few trials and uncertainty regarding adverse outcomes such as multiple pregnancy.

6. Wessel et al. (2022)

Ovarian stimulation strategies for intrauterine insemination in unexplained infertility

Original source

What it studied → An analysis of ovarian-stimulation strategies before IUI in couples with unexplained infertility.

What it found → Gonadotropins may increase live birth and shorten time to conception versus clomiphene in some strategies, but at the cost of a higher multiple-pregnancy risk.

What it means in practice → More stimulation is not necessarily better overall care; any potential benefit must be weighed against multiple-pregnancy risk.

Limitations → Results depend on dose and cancellation policies and on how stimulation is implemented in practice.

7. Shingshetty et al. (2024)

Prognosis-based management of unexplained infertility—why and when?

Original source

What it studied → A contemporary review focusing on prognosis models to decide when expectant management is appropriate and when IUI/IVF should be considered.

What it found → Couples with a good probability of natural conception may avoid immediate treatment, whereas those with poorer prognosis appear more likely to benefit from active treatment such as stimulated IUI.

What it means in practice → The same diagnosis does not imply the same prognosis. Age, duration of trying, primary versus secondary infertility and semen parameters can materially change management.

Limitations → A review rather than a new RCT. Prognostic models require appropriate use and are not equally validated in every population.

8. ASRM Practice Committee (2026)

Intracytoplasmic sperm injection for nonmale factor indications: a Committee opinion

Original source

What it studied → The latest ASRM guidance on routine ICSI in the absence of male-factor infertility, with a specific section on unexplained infertility.

What it found → ICSI may reduce fertilisation failure and may increase fertilisation rates in some studies, but it has not been shown to improve live birth in unexplained infertility. ASRM does not recommend routine ICSI without male factor.

What it means in practice → A better laboratory surrogate outcome does not necessarily mean more babies. Live birth remains the outcome that matters most.

Limitations → Limited evidence, potentially unrepresentative fertilisation-failure rates in some older studies, and insufficient robust live-birth data.

Library conclusion

The key message is that “unexplained” does not mean “psychological”, nor does it mean a woman must discover a hidden cause on her own. It means standard evaluation has not identified a specific mechanism. Prognosis varies substantially between couples, and management should reflect age, duration of trying, reproductive history, semen parameters, desired family size and personal preferences. Complementary interventions may support well-being, but should not be presented as the “explanation” for unexplained infertility.

Template for future maintenance

Maintain separate evidence categories for definition/diagnosis, prognosis and expectant management, OS-IUI, IVF, ICSI/add-ons and harms/costs. For every update distinguish clinical pregnancy from cumulative live birth and identify whether the study concerns good or poor prognosis for natural conception. For each new source: Full citation + link → What it studied → What it found → What it means in practice → Limitations → Date last reviewed.