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IUI or IVF as First-Line Treatment of Unexplained Subfertility

El Helw B*

Consultant Assisted Reproduction, Middle East Fertility Center, Egypt

***Corresponding author:** Bassam El Helw, Consultant Assisted Reproduction, Middle East Fertility Center, Egypt, Email: bassam@cairoivf.com

Short Communication

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Short Communication

Unexplained subfertility refers to a subset of couples where investigations of ovulatory function, tubal patency, and semen analysis are normal [1]. No etiology is identified in 10%-40% of couples seeking treatment for infertility [1]. Any treatment for unknown infertility is empiric by default, and the broad range of treatment, including expectant management, superovulation, IUI and IVF, reflects the uncertainty with this diagnosis [2].

However, there are limited data to support the efficacy of many of these treatments in the management of unexplained subfertility, and no uniform protocol exists in clinical practice. Most studies do not include an untreated or placebo control group, which is problematic given the significant rate of unassisted pregnancies with expectant management. In a randomized trial of 253 patients with unexplained subfertility, a 27% on-going pregnancy rate was observed in the expectant management group [3].

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 on-going pregnancy rather than live birth.

In many studies, the rate of side effects 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 [4].

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.

An online survey of specialists' opinion showed a lack of agreement among fertility specialists with regard to the first line treatment of couples with unexplained subfertility [5].

In this article I would like to elicit the present available evidence regarding first-line treatment of unexplained subfertility

The National Institute for Health and Care Excellence (*NICE*) guideline "Fertility problems: assessment and treatment." were published in 2013 (*updated September 2017*) *stated that* [6]*:* For couples with unexplained infertility, who are having regular unprotected sexual intercourse.

Do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF). Advise them to try to conceive for a total of 2years before IVF will be considered (this can include up to 1year before their fertility investigations).

An online survey in the UK revealed that there are two main arguments being used against implementing the NICE recommendations:

- Firstly, the evidence on which the recommendation was made was generally regarded of low to very low quality, leading to many gynecologists being reluctant to discontinue the use of IUI;
- Secondly, IVF was not regarded as an established first-line option for unexplained subfertility compared to IUI [5], resulting in many gynecologists continuing to offer IUI, instead of IVF, as first-line treatment.

In 2015 a Cochrane Systematic Review on IVF for

unexplained subfertility was published [7]. Eight randomized parallel-group trials included 1622 women.

Some were multi-arm trials with several comparisons:

- *Two compared IVF with expectant management*
- *Two compared IVF with insemination alone (IUI) and*
- *Four compared IVF with insemination plus stimulation of the ovaries; 3 gonadotropin, 1 clomiphene.*

The Cochrane Systematic Review on IVF for unexplained subfertility *key results*:

- IVF may be associated with higher live birth rates than expectant management, and unstimulated IUI but there is insufficient evidence to draw firm conclusions.
- In women pre-treated with clomiphene + IUI, IVF appears to be associated with higher birth rates than IUI plus gonadotropins.
- However in women who are treatment-naive there is no conclusive evidence of a difference in live birth rates between IVF and IUI + gonadotrophins or between IVF and IUI + clomiphene.
- Adverse events associated with these interventions could not be adequately assessed owing to lack of evidence.
- *Quality of the evidence* ranged from very low to moderate.
- The main limitation was serious imprecision resulting from small study numbers and low event rates.

A recent Systematic review on IUI for unexplained subfertility was published in 2016; included 14 RCT (1867 women) and concluded that:

- There was no conclusive evidence of a difference between most treatment groups in live birth rates, multiple pregnancy rates and other adverse effects for couples with unexplained subfertility undergoing IUI when compared with timed intercourse (TI), both with and without ovarian hyperstimulation (OH).
- The evidence was of moderate quality for live birth and low to moderate quality for multiple pregnancies [8].
- A group from The Netherlands investigated the *cost-effectiveness* of IVF with conventional ovarian stimulation, single embryo transfer and subsequent cryocycles *or* IVF in a modified natural cycle compared with IUI-COH as a first-line treatment in couples with unexplained subfertility.

➢ They found no evidence in support of offering IVF as a first line treatment in couples with unexplained subfertility.
➢ Both IVF strategies are significantly more expensive when compared with IUI-COH, without being significantly more effective.

In 2017 the same group published a study to assess whether there is a differential effect of potential treatment selection markers on the chances of a healthy child with IVF-SET (201 couples) compared to IUI-OS (207 couples) as first-line treatment.

➢ They did not identify any potential treatment selection markers indicating better chances of a healthy child with IVF-SET as first-line treatment instead of IUI-OS.
➢ They concluded; IUI rather than IVF should remain the preferred first-line treatment for couples with unexplained and a female age between 18 and 38 years [9].

In June, 2017 Nandi A et al., published a RCT comparing three cycles of IUI + COH and one cycle of IVF for unexplained subfertility (207 couple instead of 250 due to NICE guidelines) [10];

➢ Their results suggest that there is no statistically significant difference in live birth rate between one cycle of IVF compared with three cycles of IUI+COH with FSH as per intention-to-treat and per-protocol analysis.
➢ However, due to the relative nature of subfertility in this patient population, reflected by the large number of naturally occurring pregnancies, it is possible that expectant management might have been as effective as IUI+COH in these patients.

Conclusion

The evidence available so far on the best first line management for couples with unexplained subfertility is inconsistent, controversial and differs considerably in their study design. 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.

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 includes gonadotropins with IUI treatment in women ≤40 years.

Clinicians should carefully balance the cost and invasiveness of IVF and take patient's wishes into consideration before choosing the right treatment modality.

Well-designed prospective trials with adequate sample size are needed to directly compare, the role of IUI and IVF in unexplained subfertility, with careful assessment of the risk and benefit profiles.

Until such data are available, clinicians should individualize the management of unexplained subfertility for each patient with appropriate counselling regarding the

empiric nature of their treatment.

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