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Literature Review on Unexplained Infertility: An update and Review of Practice

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ABSTRACT

Of the couples unable to conceive without any identifiable cause, 30% are defined as having unexplained infertility. Management depends on duration of infertility and age of female partner. This review describes and comments on the definition and evidence for the management of unexplained infertility. A literature search was conducted in EMBASE, Medline, Ovid and Cochrane Database of Systematic reviews using the terms 'infertility', 'unexplained infertility', 'idiopathic infertility', 'definition of infertility', 'treatment options', 'intrauterine insemination', 'ovulation induction', 'Fallopian tubAe sperm', 'GIFT' and 'IVF'. There is no uniform definition for unexplained infertility. This varies in the literature depending on the duration of infertility and the age of the female partner. Although additional investigations are reported to explain or define other causes of infertility, these have high false-positive results and therefore cannot be recommended for routine clinical practice. Couples with unexplained infertility might be reassured that even after 12 months of unsuccessful attempts, 50% will conceive in the following 12 months and another 12% in the year after the treatment of unexplained infertility is empirical and many different regimens have been used. Among these are expectant management, ovulation stimulation with clomiphene citrate, gonadotrophins and aromatase inhibitors, Fallopian tube sperm perfusion, tubal flushing, intrauterine insemination, gamete intra-Fallopian transfer and IVF. The standard protocol is to progress from low-technology to high-technology treatment options. On the best available evidence, an algorithm for management is suggested. There is a definite need for multicentre randomized controlled trials to identify the best treatment option in unexplained infertility using a standard definition.

Of the couples unable to conceive without any identifiable cause, 30% are defined as having unexplained infertility. The management for unexplained infertility is empirical. There is no uniform definition for unexplained infertility. The timely access to effective treatment for subfertility is important as many couples have a narrow window of opportunity before the age-related effects of subfertility limit the likelihood of success. Assisted reproduction can overcome the barriers to fertility caused by tubal disease and low sperm count, but little progress has been made in reducing the effect of increasing age on ovarian function. The next 5–10 years will likely see further increases in birth rates in women with subfertility, a greater awareness of

lifestyle factors and a possible refinement of current assisted reproduction techniques and the development of new ones. The treatment of unexplained infertility is empirical and many different regimens have been used. Among these various treatment options are expectant management, ovulation stimulation with clomiphene citrate, gonadotrophins and other agents, Fallopian tube sperm perfusion, tubal flushing, intrauterine insemination, gamete intra-Fallopian transfer and IVF. There is no definite evidence to show that any one treatment is better than the other. Treatment of unexplained infertility is very much dependent on availability of resources and patients' age and duration of infertility.

There is a definite need for multicentre randomized controlled trials to identify the best treatment option in unexplained infertility.

INTRODUCTION

Infertility is generally defined as failure of conception after 1 year of regular unprotected intercourse in the fertile phase of the menstrual cycle. However, NICE guidelines considered infertility after at least two years of regular unprotected intercourse in the fertile phase of the menstrual cycle [8].

Unexplained infertility usually refers to a diagnosis (or lack of diagnosis) made in couples in whom all the standard investigations such as tests of ovulation, tubal patency and semen analysis are normal. Unexplained infertility is a term that has been applied to as many as 30–40% of infertile couples (Smith et al., 2003). The potential causes of unexplained infertility have been described as disturbances in endocrinological balance, immunology and genetic and reproductive physiology (Pellicer et al., 1998).

Approximately 1 in 8 women aged 15 to 49 years receive infertility services. Although success rates vary by age and diagnosis, accurate diagnosis and effective therapy along with shared decision-making can facilitate achievement of fertility goals in many couples treated for infertility. [9]

The inability to apply a specific infertility diagnosis is clearly related to the depth of testing applied to couples and rather than unexplained infertility being a true diagnosis it can be seen as an exclusion of proven pathology and an acknowledgement that generic rather than specific treatment strategies should be applied. Unexplained infertility can be either primary or secondary and it is possible that the underlying contributory factors may differ between these two. [1]

The infertility evaluation is typically initiated after 1 year of trying to conceive, but in couples with advanced female age (> 35 years), most practitioners initiate diagnostic evaluation after an inability to conceive for 6 months. The Practice Committee of the American Society for Reproductive Medicine (ASRM) has published guidelines for a standard infertility evaluation.[5] It includes a semen analysis, assessment of ovulation, a hysterosalpingogram, and, if indicated, tests for ovarian reserve and laparoscopy. When the results of a standard infertility evaluation are normal, practitioners assign a diagnosis of unexplained infertility. Although estimates vary, the likelihood that all such test results for an infertile couple are normal (ie, that the couple has unexplained infertility) is approximately 15% to 30%.[5]

physicians should be better able to identify the epidemiology of unexplained infertility and standard investigations for infertile couples and to consider other possible causes of infertility before making a diagnosis of unexplained infertility. [3]

The biggest debate in the treatment of unexplained infertility is the decision between expectant management, stimulated intrauterine insemination or in vitro fertilisation as a first-line treatment option.2
Unfortunately, improved efficacy in live births following therapeutic interventions for unexplained infertility may be associated with an increase in undesired outcomes. For example, the recent National Institute of Child Health and Human Development Cooperative Reproductive Medicine Network study of couples with unexplained infertility [53 identified the highest live birth rate in couples in whom the female partner received gonadotropins (as opposed to clomiphene citrate or letrozole), although those receiving gonadotropins also had the highest rates of multiple gestations. Thus, for couples with unexplained infertility, care providers and the couples they counsel will need to determine risks and benefits of therapeutic interventions. [4]

The Royal College of Obstetricians and Gynecologists (RCOG) guidelines recommended that couples with unexplained infertility should try expectant treatment before assisted reproductive treatment (ART). The chance of such a pregnancy depends mainly on the patient's age, duration of infertility, and history of any other pregnancy in the same relationship [8].

The average cycle fecundity in the untreated group of unexplained infertility was 3.8% in 6 randomized studies, and 1.8% in 11 non-randomized trials [8].
There is a need for randomized controlled trials to evaluate empiric therapies because conception may occur even without treatment. This summary of treatment for unexplained infertility relies mainly on level I evidence from randomized clinical trials. [6]

Management of unexplained infertility includes intrauterine insemination (IUI), ovulation induction with clomiphene citrate (CC) or gonadotropins, and assisted reproductive technology (ART), particularly in vitro fertilization (IVF).

Evidence suggests that IUI alone provides only a modest improvement in pregnancy rates compared with timed intercourse, with approximately one additional pregnancy achieved per 37 treatment cycles. Although statistically significant, the clinical benefit of IUI alone remains limited.
Active intervention methods, such as intrauterine insemination (IUI) or in vitro fertilisation (IVF), are often sought. Despite the National Institute for Health and Care Excellence (NICE) recommending IVF for unexplained infertility, this recommendation has generated an ongoing debate, with few fertility clinics discontinuing the use of IUI as the first-line management of choice. In contrast to

NICE, recent guidance released from the European Society for Human Reproduction and Embryology (ESHRE) in August 2023 supports the use of IUI as first-line. High-quality evidence behind such interventions is lacking, with current literature providing conflicting results. [11]

Clomiphene citrate has been widely used as an empirical treatment for unexplained infertility; however, studies demonstrate inconsistent benefits. Randomized controlled trials showed only a small increase in pregnancy rates with CC compared with placebo or no treatment, and some studies reported no significant advantage. Overall, CC alone appears to offer minimal improvement in fecundity among ovulatory women with unexplained infertility.

The combination of CC with IUI has been investigated to determine whether combining ovulation stimulation with insemination improves outcomes. Some studies reported higher pregnancy rates with CC/IUI compared with intercourse or IUI alone, whereas others failed to show significant benefit. Due to methodological limitations such as crossover designs and unequal follow-up, evidence regarding CC/IUI remains inconclusive.

Gonadotropin therapy, particularly when combined with IUI, demonstrates better effectiveness than CC-based regimens. Studies consistently report higher cycle fecundity and pregnancy rates with gonadotropin/IUI protocols compared with expectant management, CC/IUI, or gonadotropin therapy alone. The addition of IUI significantly enhances outcomes, with evidence suggesting approximately one additional pregnancy for every 15 gonadotropin/IUI cycles performed. However, gonadotropin therapy is associated with increased risks of multiple pregnancy and ovarian hyperstimulation syndrome.

Assisted reproductive technology, especially IVF, provides the highest pregnancy and live birth rates among treatment options for unexplained infertility. Large studies and registry data report live birth rates of approximately 30% per cycle with IVF. Comparative trials suggest IVF is more effective than IUI-based treatments, although cumulative pregnancy rates may become similar after multiple treatment cycles due to treatment discontinuation. Current evidence also indicates that intracytoplasmic sperm injection (ICSI) offers no additional advantage over conventional IVF in couples with unexplained infertility.

Adverse effects vary according to treatment modality. CC is associated mainly with multiple pregnancy and ovarian cyst formation, while gonadotropin therapy and IVF carry higher risks of multiple gestation and ovarian hyperstimulation syndrome. IVF is additionally associated with increased perinatal morbidity, particularly due to multiple pregnancies.

Evidence from randomized data regarding the use of aromatase inhibitors is fragmented and weak. Aromatase inhibitors may have a role in the treatment of women with unexplained infertility desiring pregnancy. However, meticulous reporting and study design should be a priority in this field and large, registered, and properly designed randomized trials are essential to test whether aromatase inhibitors can be introduced as a first-line treatment in carefully selected subgroups of women with unexplained infertility [12]

Cost-effectiveness analyses indicate that less invasive treatments such as IUI and CC/IUI are less expensive but also less effective than IVF. IVF achieves higher pregnancy rates but at substantially greater financial cost.

Therefore, treatment decisions in unexplained infertility should balance effectiveness, safety, patient preference, and economic considerations. [6] However, with estimated live-birth rates per cycle varying between 13% and 28%, its effectiveness has not been rigorously evaluated in comparison with other treatments. With increasing awareness of the role of expectant management and less invasive procedures such as intrauterine insemination, concerns about multiple complications and costs associated with IVF, it is extremely important to evaluate the effectiveness of IVF against other treatment options in couples with unexplained infertility. [10]

The decision to offer IUI with ovarian stimulation (IUI-OS) or IVF should be based upon patient prognostic factors. We suggest that IUI-OS could be offered as first-line treatment for unexplained infertility for women < 38 years, with good prognosis, and

IVF could be offered first to those > 38 years. Patients should be appropriately counselled to enable informed decision making. [11]

Expectant treatment is the option of choice for young patients with short period of infertility. The spontaneous pregnancy rate is very high in this group of patients. [7]

CONCLUSIONS

A thorough but time-efficient investigation of the infertile couple is required prior to a diagnosis of unexplained infertility. Couples should undergo a semen analysis, ovulation testing, assessment of ovarian reserve, and imaging to assess for tubal and uterine factors before a diagnosis of unexplained infertility is made. This workup can be completed within 1 menstrual cycle. In the couples with unexplained infertility, various treatment modalities are available, including expectant management with lifestyle changes, operative laparoscopy, COH (clomiphene citrate or gonadotropins) with IUI, and IVF (with or without ICSI). The optimal treatment strategy needs to be based on individual patient characteristics such as age, treatment efficacy, side-effect profile such as multiple pregnancy, and cost considerations. Unexplained infertility is common diagnosis affecting up to 30% of infertile couples when all the infertility standard investigations are normal. Clomiphene citrate did not show any advantage over placebo in the treatment of unexplained infertility, and the NICE guidelines recommended IUI as a treatment option in unexplained infertility.

However, if ovarian stimulation for IUI is aimed at producing no more than two large follicles, the multiple pregnancy rates are reduced without seriously comprising the overall pregnancy rate. The IVF increases the pregnancy rate in patients with unexplained infertility, and the present environment is in favor of single embryo transfer to reduce the chance of multiple pregnancies. The most serious potential risk in the IVF procedure is OHSS, which can be minimized using an antagonist protocol, gonadotrophin-releasing hormone agonist trigger, and successful embryo-freezing programs [3]. There is no definite answer for the question what is the best management approach for couples with unexplained infertility? The treatment policy should follow a stepwise manner of expectant management followed by stimulated IUI, and a final resort to IVF if these options fail. The NICE guideline on fertility assessment recommended treatment with IUI in unexplained infertility for six cycles based on grade A recommendation [5]

Therefore, in the context of currently conflicting guidelines, this review aims to explore current evidence on the practise of IUI versus IVF as first-line treatment for unexplained infertility via comparison of pregnancy outcomes. The primary outcome is live birth (LB) rates as the preferred outcome for evaluation of infertility treatment recommended by the ESHRE [11]. Secondary outcomes are clinical pregnancy (CP) and ongoing pregnancy (OP) rates, to avoid exclusion of relevant studies given the large disparity in pregnancy outcomes reported within studies

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