

Unexplained infertility: prevalence, possible causes and treatment options. A review of the literature

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Abstract

The diagnosis of unexplained infertility established when all the standard infertility investigations are normal, including tubal patency (hysterosalpingogram and/or laparoscopy), normal ovulatory function (basal body temperature, cervical mucus changes, serum luteinizing hormone surge or mid-luteal progesterone), and normal semen analysis. The prognosis of unexplained infertility is good without therapy in women < 35 years and when the duration of infertility is < 2 years. Clomiphene citrate did not show any advantage over placebo in the treatment of unexplained infertility. The role of intrauterine insemination in treatment of unexplained infertility still raises many questions, particularly regarding its superiority in un-stimulated cycles over stimulated cycles or timed intercourse. *In-vitro* fertilization increases the pregnancy rate in women with unexplained infertility, and the present environment is in favor of single embryo transfer to reduce the multiple pregnancy rate. There is no definite answer for the question what is the best management approach for couples with unexplained infertility?

Key words: unexplained, infertility, prevalence, causes, treatment.

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Introduction

Unexplained infertility usually refers to a diagnosis (or lack of diagnosis) made in couples in whom all the infertility standard investigations such as tests of ovulation, tubal patency, and semen analysis are normal [1].

The prognosis of unexplained infertility is good without therapy in women < 35 years, when the duration of infertility is < 2 years, and treatment of unexplained infertility is indicated if the duration of infertility is > 2 years and/or the female age is > 35 years [2].

Schwartz *et al.* reported a significant slight decrease in fecundability (conception rate per cycle) as a function of a woman's age after 30 years of age, and a significant marked decrease after 35 years [3].

The American Society of Reproductive Medicine (ASRM) standard infertility evaluation tests were: semen analysis, post-coital test, assessment of ovulation, hysterosalpingogram, and laparoscopy if indicated. However, the Practice Committee bulletin on unexplained infertility mentioned that the basic evaluation should provide evidence of ovulation, adequate sperm production, and patency of fallopian tubes [4].

Definition

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 [5].

In general, 84% of women will conceive after 1 year, and 92% will conceive after 2 years of regular unprotected intercourse, and each additional month of infertility beyond the average reduces the chance of pregnancy by 2%, or about 25% each year.

The diagnosis of unexplained infertility established when the tubal patency (hysterosalpingogram and/or laparoscopy), normal ovulatory function (basal body temperature, cervical mucus changes, serum luteinizing hormone (LH) surge or mid-luteal progesterone), and normal semen analysis are confirmed.

Unexplained infertility may arise because of some subtle, undetected defect in the reproductive process or because of the couple's lower fecundity.

Prevalence

The prevalence of unexplained infertility is still debatable due to the lack of a specific test needed for the diagnosis of unexplained infertility and/or misdiagnosis.

In a study of 11 Canadian centers where a uniform protocol had been used, the proportion of unexplained infertility ranged from 8% to 37% [6].

Greenwood *et al.* conducted a multicentre cross-sectional study to test the hypothesis that women with unexplained infertility demonstrate evidence of diminished ovarian reserve compared with controls [7]. Greenwood *et al.* found that the anti-Mullerian hormone (AMH), antral

follicle count (AFC), and AMH/AFC ovarian reserve indices did not differ between infertile women and controls, after controlling for age, race, body mass index, smoking history, and study site. In addition, they concluded that women with unexplained infertility did not show evidence of decreased ovarian reserve as measured by AMH and AFC [7].

Possible causes

The current knowledge of the reproductive system assessment is far from complete, because there are many steps or functions not evaluated including cervical mucus, capacitation or the ability of spermatozoa to negotiate the utero-tubal junction. Defective oocytes, especially in ageing patients, are an important cause of infertility, which is difficult to assess. Tubal patency does not assess the characteristics of bidirectional tubal motility, which is important for embryo transport.

In addition, tests for the evaluation of the chance for successful implantation are not available.

Unexplained infertility may arise because of some subtle, undetected defect in the reproductive process or because of the couple's lower fecundity. Therefore, the ideal definition for unexplained infertility should be a couple with a real but unobservable defect leading to infertility, which may be prolonged, and permanent.

Treatment options

Expectant management

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 [9].

Evers *et al.* recorded a spontaneous pregnancy rate of 5.9% in an unexplained infertility group waiting for *in-vitro* fertilization (IVF) [10]. Therefore, the chance of spontaneous pregnancy with expectant management is low but never zero, and Wordsworth *et al.* concluded that empirical clomiphene citrate and intrauterine insemination (IUI) did not offer superior live birth rates compared to expectant management in unexplained infertility [11]. Therefore, expectant management plays an important role in a situation where limited resources are available.

Tubal flushing

Tubal flushing proved to increase the chance of pregnancy in unexplained infertility and early stages of endometriosis, and the effect of tubal flushing can be mechanical as well as immunological [12].

A prospective randomized trial by Nugent *et al.* showed that there is a significantly higher pregnancy rate in infertile couples randomized to single tubal flush with lipiodol com-

pared to no treatment [13]. It has been postulated that an increased pregnancy rate after oil-based tubal flushing may be due to removal of tubal debris; it also affects the peritoneal cytokines and prevents peritoneal mast cell phagocytosis of the spermatozoa [14].

Edelstam *et al.* concluded that the absolute pregnancy rate increased after combined treatment of clomiphene citrate, tubal flushing, and insemination. In addition, they recommended combined clomiphene citrate, tubal flushing, and insemination as the first-line treatment in unexplained infertility [15].

Fallopian tube sperm perfusion

Fallopian tube sperm perfusion consists of flushing the uterine cavity and the tubes with a sperm-enriched suspension. It helps spermatozoa to pass through the uterine cavity, to the fallopian tubes, and ultimately to the pouch of Douglas.

Fallopian tube sperm perfusion with a sperm-containing medium is done either laparoscopically or vaginally using a trans-vaginal catheter.

A randomized controlled trial (RCT) showed that fallopian sperm perfusion performed using a Foley catheter is significantly less effective than traditional IUI when associated with ovarian stimulation in the treatment of unexplained infertility [16].

However, the RCT by Ricci *et al.* showed that sperm perfusion yields higher pregnancy rates than traditional IUI [17].

NICE guidelines recommended fallopian sperm perfusion with a large volume (4 ml) to manage unexplained fertility problems rather than the standard insemination techniques [5].

Ovulation-inducing agents

Clomiphene citrate

Clomiphene citrate is commonly used ovulation-inducing agent. The effectiveness of the treatment is judged by the evidence of RCTs where placebo or no treatment is used in the controls. The latest RCT showed that clomiphene citrate offered no better (and even inferior) live-birth rates than expectant management (14% vs. 17%, respectively) [3].

There were four previous clomiphene citrate trials, and all of the trials showed that clomiphene citrate may improve fertility as much as 2-fold among couples with the duration of unexplained infertility > 3 years. However, the most reliable evidence comes from a systematic review by Hughes *et al.* which showed that there was no evidence that clomiphene citrate randomized with IUI or without IUI was more effective than no treatment or placebo for live birth or for clinical pregnancy rates [18].

Gonadotropins

Athallah *et al.* reviewed the evidence of oral versus injectable ovulation-inducing agents in the treatment of unexplained infertility, and concluded that there was insufficient evidence to prefer either one of them when comparing pregnancy or live birth rates [19].

Echochard *et al.* compared clomiphene citrate with human menopausal gonadotropins (hMG), and found no sig-

nificant difference in live-birth rate/couple [20]. Although gonadotropins seem to have higher pregnancy rates compared to clomiphene citrate, the cost of treatment, and patient's convenience should be considered before choosing any treatment method.

Aromatase inhibitors

Aromatase inhibitors suppress estrogen production but do not have the anti-estrogenic effect of clomiphene citrate in the late follicular phase, and they may have fewer side effects than clomiphene citrate [21].

A meta-analysis and systematic review was performed by Polyzos *et al.* comparing the efficacy of aromatase inhibitors (letrozole, anastrozole) versus clomiphene citrate for unexplained infertility [22].

Five eligible trials were included in this meta-analysis, which supports the role of aromatase inhibitors in unexplained infertility, in spite of non-significant difference between the compared arms regarding the pregnancy rates [22].

Intrauterine insemination (IUI)

The role of IUI in treatment of unexplained infertility still raises many questions, particularly regarding its superiority in un-stimulated cycles over stimulated cycles or timed intercourse. There is a hypothesis that ovulation induction with IUI in couples with unexplained infertility, increasing the density of the motile spermatozoa available to these eggs, may further increase the monthly probability of pregnancy [18].

A Cochrane review of the role of IUI in unexplained infertility reviewed the data available up to 2011, and concluded that a significant increase was found in pregnancy rate/woman in favor of the stimulated cycle [23].

Although all these previous studies showed improved pregnancy rates with ovulation induction and IUI, recent studies seriously questioned the effect of IUI with or without ovarian stimulation when compared with 6 months of expectant management [3, 24].

Bagist *et al.* found that there is no clear benefit of double over single inseminations in the overall clinical pregnancy rate in couples with unexplained infertility [25].

In unexplained infertility, there is controversy regarding the best treatment option. In the case of unexplained infertility, ovarian stimulation and IUI was stated as 'effective treatment' by the RCOG (1998). Later, these recommendations were described as 'not a natural choice' and the recommendations made by the guideline were questioned [26].

Because both stimulated and un-stimulated IUI are more effective than no treatment in unexplained infertility cases, the NICE guidelines suggested that ovarian stimulation should not be offered, in spite of associated higher pregnancy rates than un-stimulated IUI, because it carries a risk of multiple pregnancies [5].

Women with unexplained infertility are often offered IUI with ovarian stimulation as an alternative to IVF. However, little evidence exists that IUI is an effective treatment. In 2013, the NICE recommended that IUI should not be routinely offered for couples with unexplained infertility. For this reason, Farquhar *et al.* conducted an open-label,

randomized, controlled, two-centre study, for women attending two fertility clinics in New Zealand with unexplained infertility, and an unfavorable prognosis of natural conception [27].

Farquhar *et al.* concluded that IUI with ovarian stimulation is safe, effective treatment for women with unexplained infertility and an unfavorable prognosis for natural conception [27].

Gamete intra-fallopian transfer (GIFT)

Gamete intra-fallopian transfer involves transfer of the collected oocytes and spermatozoa directly into the fallopian tube. The hypothesis behind transferring the gametes directly into the fallopian tube is provision of a more physiological environment than in an *in-vitro* culture medium. GIFT is not used anymore after the introduction of ICSI [6].

Intracytoplasmic injection (ICSI)

Intracytoplasmic injection is a technique used within the *in-vitro* fertilization (IVF) treatment process where it is necessary to use micromanipulation to achieve fertilization. Intracytoplasmic injection is usually required when the numbers of sperm are too low for fertilization to occur through the incubation of motile sperm with an egg, which is the standard approach in IVF. As a result, ICSI makes possible fertilization of an egg with a single spermatozoon, and therefore it has become the standard approach to treatment where there is very poor semen quality or where spermatozoa have to be retrieved surgically because the man has azoospermia [5].

In-vitro fertilization (IVF)

In-vitro fertilization is an expensive, invasive, and the most effective method of treatment for unexplained infertility. The average success rate for IVF treatment using fresh eggs in the UK is 28.2% for women < 35, 23.6% for women aged 35–37, 18.3% for women aged 38–39, and 10.6% for women aged 40–42 [6].

Similarly, the ASRM/SART (Society of Assisted Reproductive Technology) reported a live-birth rate among women with unexplained infertility of 30.4% [4]. The IVF helps to overcome the ovarian dysfunction, cervical factors, sperm and egg interaction, and transport.

However, the increased success rate with IVF comes with a price of high multiple pregnancy rates (25%). The Human Fertilization and Embryology Authority (HFEA) and European Society of Human Reproduction and Embryology (ESHRE) declared that the maximum multiple-birth rate should not be more than 24% [28].

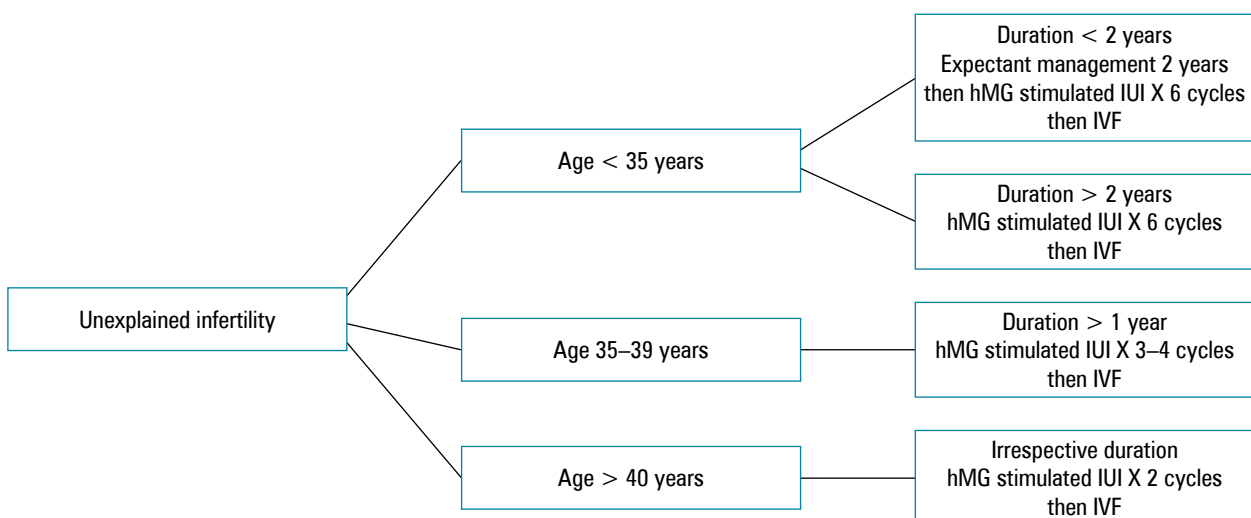
Ovarian hyper-stimulation syndrome (OHSS) is another serious life-threatening complication of IVF, and occurs in 6–14% of the gonadotropin-releasing hormone agonist cycle [6].

A Cochrane review on the role of IVF in unexplained infertility showed higher pregnancy rates than expectant management [29]. The live-birth rate/woman with a single cycle of IVF is significantly higher than with expectant management [30].

The role of IVF in unexplained infertility has not been properly evaluated. The physician should clearly mention the cost effectiveness of different treatment modalities before coming to any conclusion. Tsafirir *et al.* concluded that the chance of pregnancy decreased every year, and women over 40 years should be referred for IVF after a short trial of gonadotropins and IUI [31].

Conclusions

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



hMG – human menopausal gonadotropins, IUI – intrauterine insemination, IVF – *in-vitro* fertilization.

Figure 1. Suggested unexplained infertility management protocol

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 [32]. 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] (Figure 1).

Conflict of interest

The authors declare no conflict of interest.

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