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Review

Unexplained subfertility: diagnosis and management

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Key content

- Unexplained subfertility is diagnosed when standard investigations (tests for ovulation, tubal patency and semen analysis) are all normal. Between 30% and 40% of subfertile couples fall into this category.
- In some couples, unexplained subfertility may result from subtle undetectable factors; in other couples, it may be associated with a genuine absence of any abnormality.
- There is currently much controversy about the selection of appropriate management options for such couples, especially following the National Institute for Health and Care Excellence (NICE) guideline published in 2013. Therefore, a clear understanding of the available evidence is essential for the management of couples with unexplained subfertility.
- The potential contributing factors, diagnosis and management of unexplained subfertility are discussed.

Learning objectives

- To summarise the available recent evidence and help the reader obtain a clear understanding of the continuing debates in this field.
- To help clinicians in counselling couples with unexplained subfertility.

Ethical issues

- Should couples be advised to try to conceive naturally for 2 years (regardless of their age) before they are offered treatment, even though fecundity declines with age?
- What does the evidence suggest should be the first line of management for couples with unexplained subfertility: intrauterine insemination or in vitro fertilisation?

Keywords: IUI / IVF / unexplained infertility / unexplained subfertility

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Introduction

Unexplained subfertility is usually diagnosed if a couple fails to conceive after 1 year of regular unprotected sexual intercourse even though investigations for ovulation, tubal patency and semen analysis are normal.[1,2] For as many as 30–40% of couples experiencing subfertility, their subfertility remains unexplained.[3,4] While the average cycle fecundity without treatment in women with unexplained subfertility is 1.3–4.1%,[5] prognosis depends on the age of the female partner, duration of subfertility and previous obstetric history.[6,7] Differences of opinion exist among fertility specialists regarding the optimal treatment for couples experiencing unexplained subfertility.[8] This review aims to discuss the diagnosis and management of unexplained subfertility and highlight the continuing controversies in this field.

Potential contributing factors

The diagnosis of unexplained subfertility is made by exclusion. However, there are various potential contributing factors that can be responsible for subfertility (Box 1).

Increased age of the female partner

As the female partner's age increases, there is a decline in the total number of remaining oocytes and their quality.[9] Because of the decline in oocyte quality, there is an increase in the embryonic aneuploidy rate in older women,

Box 1. Potential contributing factors for subfertility

1. Low ovarian reserve
2. Increased age (over 35 years) and low oocyte quality
3. Lifestyle factors
4. Tubal function defects
5. Fertilisation defects
6. Implantation defects
7. Metabolic disorders, immunological and genetic factors
8. Endometriosis
9. Fibroids
10. Adenomyosis

which leads to nonimplantation and subfertility.[10,11] A study by Maheshwari et al.[12] showed that women over 35 years of age were more likely to have unexplained subfertility than their younger counterparts (OR 1.8, 95% CI 1.4–2.2).

Lifestyle factors and unexplained subfertility

Smoking

Both active and passive smoking can adversely affect the potential to conceive by reducing the ovarian reserve and by altering the tubal function and the uterine environment.[13] In men, smoking impairs the fertilising capacity of the sperm by reducing the mitochondrial activity and increasing the DNA damage.[14]

Weight

Both obesity (defined as a body mass index above 30) and being underweight (defined as a body mass index below 19) can impair fertility even in young and regularly ovulating women.[15] Obesity can alter the follicular environment and lead to oocyte incompetence and suboptimal embryo quality,[16] impairing implantation by negatively influencing the endometrium.[17] Obesity in men can contribute to subfertility by causing DNA damage to sperm,[18] decreased libido and erectile dysfunction.[19]

Excessive alcohol intake

In men, even habitual consumption of over 5 units per week has an adverse effect on sperm quality,[20] although the true impact on male fertility is unclear. Similarly, excessive alcohol consumption in women may affect fertility by decreasing the implantation rate, and causing luteal phase dysfunction and abnormal embryo development.[21] However, there is still no universal agreement on the safe limit of alcohol consumption.[22]

Other factors

Other factors that may have an impact on fecundity are psychological stress, environmental exposure to pollutants and use of illicit drugs and caffeine.[23]

Ovarian reserve

Ovarian reserve is the size of the remaining follicle pool in the ovary at any given time. This often indicates the capacity of the ovary to produce an oocyte that can be fertilised and that results in a successful pregnancy. The rate of follicular depletion varies between individuals, hence the ovarian reserve.[1] A woman's age remains the single most important factor in determining reproductive outcome; ovarian reserve can only predict ovarian response in an assisted reproductive technology cycle.[24] Younger women with low ovarian reserve are more likely to have cycle cancellation caused by poor oocyte yield in in vitro fertilisation (IVF), but once oocytes are retrieved they have almost normal pregnancy rates.[25]

Tubal function defects

In addition to tubal patency, tubal function is important to achieve successful pregnancy. Optimal tubal functions, such as adequate ciliary motion and muscular activity, are required for sperm–oocyte interaction and transport of the embryo to the uterine cavity for implantation.[26] Milder forms of gonorrhoea and chlamydia infection can cause tubal function defect without causing overt occlusion.[27] Impaired tubal function in otherwise patent tubes can lead to subfertility.

Fertilisation defects

Subtle defects in oocyte and sperm leading to defective fertilisation are possible causes of unexplained subfertility. Sperm defects, such as abnormal acrosomes resulting in poor or no zona pellucida binding[28] and defects in acrosome reaction resulting in failure of sperm–zona pellucida penetration, are possible factors leading to subfertility.[29] Sperm DNA integrity may be a prerequisite for normal fertilisation.[30] An otherwise normal semen analysis (as per the World Health Organization criteria) may include sperm with altered genetic material induced by various factors, such as defects in chromatin remodelling at the time of meiotic division, post-testicular oxidative stress, various environmental factors or advanced male age.[31] High levels of sperm DNA fragmentation can lead to reduced fertilisation and increased miscarriage rates.[32] A variety of in vitro tests are available to detect sperm function defects, such as the ability of sperm to penetrate cervical mucus surrogate, quantification of sperm–zona binding using hemizona pellucidae and hyaluronan binding assay.[33] The methods used to detect sperm DNA fragmentation include the sperm chromatin structure assay, the single-cell gel electrophoresis assay and the terminal uridine nick-end labelling assay.[34] However, the clinical utility of these tests has been undermined by the introduction of intracytoplasmic sperm injection (ICSI).[32] Hence, these tests do not form a part of routine investigations.[2,35]

Implantation defects

A receptive endometrium is undoubtedly essential for successful implantation and pregnancy. Various biochemical factors like cytokines, leukemia inhibitory factor, interleukin-1 and some chemokines (e.g. CX3CL1, CCL14) may be involved in endometrial receptivity.[36,37] Alterations of these factors in the endometrium can cause subfertility. There are no standard tests to detect these defects.

Immunological, metabolic and genetic factors

Dysregulation of the immune system and increased production of autoantibodies have been suggested as possible causes of unexplained subfertility. Autoimmune antibodies like anti-thyroid, anti-ovarian, antinuclear, antiphospholipid and anti-smooth muscle antibodies have been associated with unexplained subfertility.[38] Although the exact role of these autoantibodies in the pathogenesis of unexplained subfertility is unclear, various theories have been proposed, such as the reduction of fertilisation rate, interference with early implantation and modulation of follicle-stimulating hormone (FSH) function, thereby influencing ovarian function.[39] In addition to altered immune response, thrombophilic gene polymorphisms (e.g. methylenetetrahydrofolate reductase gene polymorphism) could be a cause of unexplained subfertility.[40] The possible mechanism could be the causation of early implantation failure; however, more evidence is needed to confirm this.[41]

Oxidative stress owing to an imbalance between reactive oxygen species and antioxidants can be caused by factors such as obesity, smoking, alcohol, recreational drug use and environmental exposure to various toxins. Oxidative stress has been linked both with male subfertility (as it causes damaged sperm[42]) and with female subfertility, although the mechanism of its action in females is not clear.[43]

Endometriosis

About 30% of asymptomatic women with otherwise unexplained subfertility will be diagnosed with mild endometriosis if laparoscopy is undertaken.[44] The fecundity of women with mild endometriosis is similar to that of women with unexplained subfertility.[45] There is no evidence that medical treatment of mild endometriosis improves fertility, and laparoscopic ablation can improve the live birth rate only minimally.[46–48] Hence, it is debatable whether mild endometriosis in women with unexplained subfertility is responsible for their subfertility.

Fibroids

The role of fibroids in causing subfertility is unclear. The submucosal component of fibroids could be associated with reduced conception but evidence remains scarce.[49] There is insufficient evidence that myomectomy for intramural or subserous fibroids improves pregnancy rates.[50]

Adenomyosis

The impact of adenomyosis or its treatment on fertility remains unsubstantiated because of a paucity of data.[51] Therefore, subfertility in women with adenomyosis remains unexplained for now.

Investigations for unexplained subfertility

Box 2 lists the tests performed to diagnose unexplained subfertility. However, they have limitations and even the most sophisticated tests can fail to detect subtle causes of subfertility.

Detection of ovulation

Although there are various strategies to detect ovulation, none of these tests can detect the quality of the oocyte. Tests like urinary luteinising hormone estimation, midluteal phase progesterone levels and ultrasound monitoring of follicular growth might detect ovulation; however, they may fail to do so if not performed at the right time of the menstrual cycle.[2,52] The presence of a regular menstrual cycle in itself is a fair indicator of regular ovulation, and the chances of anovulation in a woman with a regular menstrual cycle are low.[2,53]

Tubal patency test

Assessment of tubal patency can be achieved by various methods, such as hysterosalpingogram, hysterocontrast sonosalpingography and laparoscopy and dye tests. None of these methods, however, can detect tubal function defects, which can potentially contribute to a couple's subfertility.

Semen analysis

This remains the most important investigation of the male partner. In 2010, new World Health Organization criteria for semen analysis using lower reference limits were released (Table 1).[2,54] Although semen analysis results provide evidence of the concentration, motility and morphology of

Box 2. Investigations for unexplained subfertility

1. Detection of ovulation
   a. Urinary luteinising hormone estimation
   b. Midluteal progesterone
   c. Ultrasound monitoring of follicular growth and confirmation of follicular rupture.
2. Tubal patency test
   a. Hysterosalpingogram
   b. Hysterocontrast sonosalpingography
   c. Laparoscopy and dye test
3. Semen analysis
4. Pelvic ultrasound and saline infusion sonography
5. Ovarian reserve testing
6. Laparoscopy in symptomatic women
7. Hysteroscopy in known uterine anomaly or pathology

Table 1. World Health Organization 2010 criteria for normal semen analysis

Criteria	Parameters
Volume	≥1.5 ml
pH	≥7.2
Sperm concentration	≥15 × 10^6/mL spermatozoa
Total sperm count	≥39 × 10^6 spermatozoa
Total motility	≥40%
Progressive motility	≥32%
Vitality	≥58% live spermatozoa
Morphology	≥4% with normal morphology

sperm, they do not assess sperm function,[55] which potentially affects fertility.

Ovarian reserve tests

Tests available for ovarian reserve estimate basal FSH (early follicular phase: day 2–5 of the menstrual cycle), inhibin A and B, anti-müllerian hormone, antral follicle count and ovarian volume. The clomiphene citrate challenge test and the exogenous FSH ovarian reserve test[56] are also used. Although the basal FSH test is the most frequently used, it has significant intra- and intercycle variability, which limits its reliability. In contrast, the anti-müllerian hormone test can be applied at any time during the menstrual cycle and both this test and the antral follicle count have good predictive value for ovarian stimulation response.[57] Although these tests predict the response to ovarian stimulation during IVF, they are quite limited in their accuracy to predict the chances of spontaneous conception.[58,59] According to the American College of Obstetricians and Gynecologists, it is reasonable to encourage a woman to attempt to conceive sooner rather than later if her ovarian reserve is found to be diminished, as her window of opportunity to conceive might be shorter than anticipated.[60]

Diagnostic laparoscopy

Women with unexplained subfertility with tubal patency confirmed by normal hysterosalpingogram findings can still have peritubal adhesions and/or endometriosis, which can lower the chances of spontaneous conception.[61] However, it is difficult to predict which women would benefit most from surgery and the concerns are increased cost, surgical risks and women's anxiety about potential surgery. Both the American Society for Reproductive Medicine and the National Institute for Health and Care Excellence (NICE) suggest laparoscopy only in women with symptoms of comorbidities.[2,62] In 2010, Badawy et al.[63] showed in a prospective randomised controlled trial that diagnostic laparoscopy could be postponed until after 3–6 failed cycles of ovarian stimulation and timed sexual intercourse. While it is reasonable to postpone laparoscopy in asymptomatic women with normal hysterosalpingogram and no previous history of pelvic infection or surgery, it might be useful in selected women with multiple failed ovarian stimulation with or without intrauterine insemination (IUI).[64,65]

Hysteroscopy

Hysteroscopy is a reliable way to diagnose and treat uterine cavity anomalies like fibroids, polyps, septum and adhesions.[66] Women with unexplained subfertility might benefit from hysteroscopic removal of submucous fibroids and polyps to improve their chances of conceiving.[67] Where facilities are available, saline infusion sonography together with 3D ultrasound can offer a less invasive outpatient method to assess the uterine cavity with accuracy similar to that of hysteroscopy.[68]

Treatment options for unexplained subfertility

In the absence of a definitive diagnosis, the treatment of unexplained subfertility remains empirical.[4] Although various treatment strategies are available, evidence is lacking to confirm the superiority of one over the other (Box 3).

Expectant management

The chances of spontaneous conception remain high in couples with unexplained subfertility. In a multicentre cohort study of 437 couples with unexplained subfertility, 74% of couples conceived spontaneously.[7] A Dutch multicentre trial randomised 253 couples with unexplained subfertility and intermediate prognosis of natural conception within 12 months, into an expectant management group and an intervention group receiving IUI with controlled ovarian hyperstimulation (COH) for 6 months. Similar continuing pregnancy rates between the two groups were found (23% for the intervention group and 27% for the expectant management group)[69] and there was a saving of €2,616 per couple in favour of expectant management.[70] Although expectant management is a valid option for couples with a favourable prognosis, it

Box 3. Treatments for unexplained subfertility

1. Expectant management
2. Ovulation induction (clomiphene citrate, letrozole, gonadotrophins)
3. Intrauterine insemination (IUI) with or without ovarian stimulation
4. In vitro fertilisation (IVF)

NICE Guideline recommendations 2013: Do not offer IUI routinely for people with unexplained subfertility who have regular unprotected sexual intercourse. Consider IVF after 2 years of expectant management.

remains challenging for clinicians to choose the best candidates for this treatment. Twenty-nine prediction models have been developed to help clinicians in this regard. However, they have been developed for different patient profiles and lack thorough external validation.[71] Although these models can be used for decision making in couples similar to the populations they were developed for, there remain concerns regarding their generalisability across different patient profiles. Moreover, expectant management might not be acceptable to many couples, as further attempts of natural conception add to already existing stress and frustration.[72] This leads to overtreatment in many of these cases.[73]

Tubal flushing or perturbation

A possible therapeutic benefit of tubal flushing during hysterosalpingogram has been known to gynaecologists for over half a century. A range of oil-soluble and water-soluble contrast media have been used for hysterosalpingogram and have been linked to an increased chance of pregnancy. A 2007 Cochrane review summarised 12 trials involving 2079 participants and concluded that oil-soluble contrast media increase the odds of live birth in comparison with no treatment (Peto OR 2.98, 95% CI 1.40–6.37), but could not confirm any benefit of oil-soluble versus water-soluble media because of the lack of an appropriate trial.[74] Possible mechanisms of action are mechanical (removal of tubal debris), immunological (affecting peritoneal cytokines and preventing peritoneal mast cell phagocytosis of spermatozoa) or an effect on the endometrium to promote implantation.[75] Oil-soluble contrast media have now been widely replaced by water-soluble contrast media because of better image quality, early dissipation that removes the need for delayed films and the possibility of granuloma formation with oil-soluble media.

Clomiphene citrate with or without intrauterine insemination

Clomiphene citrate acts as an anti-estrogen; it increases endogenous FSH and thereby stimulates multiple follicular developments. Although its effectiveness has been described in cases of oligo-ovulation, questions have been raised regarding its usefulness in otherwise ovulatory women.[76] A Cochrane review that summarised 14 clinical trials (1159 participants) found no clinical benefit of clomiphene citrate for unexplained subfertility.[77]

Intrauterine insemination

IUI plus COH is widely used in cases of unexplained subfertility before resorting to more invasive options like IVF. It involves placement of washed sperms into the uterine cavity around the time of ovulation. It has been used both with and without ovarian stimulation. Two studies have failed to show any benefit of IUI with or without COH over expectant management in terms of live birth rates in couples with unexplained subfertility.[69,76] A 2012 Cochrane review demonstrated that IUI plus COH increases the live birth rate more than two-fold compared with IUI in a natural cycle (OR 2.07, 95% CI 1.22–3.5).[78] COH may correct subtle ovulation problems and slightly increase the number of oocytes available for fertilisation, thereby increasing the chances of pregnancy.[79] However, a major concern with multiple follicle development in IUI plus COH is multiple pregnancies.[80] It has been demonstrated that by using mild ovarian hyperstimulation and strict cancellation policies, multiple pregnancy rates can be kept to approximately 10% without reducing pregnancy rates.[81] The 2013 NICE fertility guideline recommends not routinely offering IUI to couples with unexplained subfertility but proceeding directly to IVF after 2 years of subfertility[2]. However, the success of IUI depends on multiple factors[82] and many clinics continue to provide IUI plus COH for patients with unexplained subfertility despite the NICE recommendation.[83]

In vitro fertilisation

With advances in assisted reproductive techniques, IVF has emerged as a safe and successful treatment option. However, debate continues about whether it should be the sole treatment for couples with unexplained subfertility.

The first randomised controlled trial by Goverde et al.[84] in 2000, compared six cycles of IUI in a natural cycle versus six cycles of IUI plus COH versus six cycles of IVF in 258 couples with unexplained and mild male factor subfertility. They found that although pregnancy rate per cycle was better with IVF compared with IUI in natural cycle or IUI plus COH (12.2% versus 7.45% and 8.7%, respectively), there was no difference in cumulative pregnancy rates (38% versus 31% and 37%, respectively). However, pregnancy rates from IVF have continued to improve and the current UK IVF success rates are 27–32% for women under 37 years of age.[85] One might argue that the pregnancy rate reported by Goverde et al.[84] is outdated.

Reindollar et al.,[86] in a large randomised controlled trial in 2010, demonstrated the effectiveness of moving to IVF after a course of clomiphene citrate and IUI compared with conventional treatments of clomiphene citrate and IUI, followed by FSH and IUI, followed by IVF. Pregnancy rates were not only higher, but moving to IVF sooner allowed women to conceive 3 months earlier. However, the use of clomiphene citrate and IUI prior to IVF in this trial can be questioned, as there is much evidence against the use of clomiphene citrate in ovulating women.[77] The same group compared two cycles of clomiphene citrate and IUI versus two cycles of FSH and IUI versus immediate IVF in 154 couples with older women (38–42 years) and demonstrated superior pregnancy rates and fewer treatment cycles with immediate IVF.[87]

In 2011, Custers et al.[88] randomised 116 couples with unexplained and mild male factor subfertility and unfavourable prognosis of natural conception, to one cycle of IVF-eSET (elective single embryo transfer) and three cycles of IUI plus COH. They found similar live birth rates: 24% in the IVF-eSET group and 21% in the IUI plus COH group (relative ratio 1.17; 95% CI 0.60–2.30). Custers and colleagues have also found IUI plus COH to be more cost effective.[89]

In 2012, a Cochrane review summarised the trials for unexplained subfertility treatment and found no evidence for the effectiveness of IVF over IUI as a first line treatment. No significant differences in multiple pregnancy or ovarian hyperstimulation syndrome rate between the two treatments were found.[90]

Bensdorp et al.[91] shed new light on the effectiveness of IUI and IVF for couples with subfertility in their 2015 study. In this multicentre randomised controlled trial involving 17 centres in The Netherlands, 602 couples with unexplained and mild male factor subfertility and unfavourable prognosis for natural conception were randomised to three groups: three cycles of IVF and single embryo transfer, six cycles of IVF in a modified natural cycle, and six cycles of IUI plus COH. The researchers found comparable singleton live birth rates (52% versus 43% and 47%, respectively) and comparable multiple pregnancy rates (6% versus 5% and 7%, respectively) between the treatment arms.

The literature indicates that although the per-cycle success rate of IUI is lower than that of IVF (9% versus 22%),[92] cumulative IUI success rates are comparable to those of IVF.[91] From the perspective of couples, IUI remains less invasive, less stressful and less time consuming than IVF. Perinatal outcome for singletons is better with IUI than with IVF.[93] Hence, IUI plus COH remains a very realistic treatment option.

Intracytoplasmic sperm injection

In 5–25% of cases of unexplained subfertility, no fertilisation has been reported with conventional IVF procedures.[94] This could be due to occult abnormalities in sperm or oocytes.[95,96] ICSI has been advocated for these couples.[97] However, studies have failed to show any benefits of ICSI over IVF in terms of clinical pregnancy rates (33% IVF versus 26% ICSI)[98] or live birth rates (46.7% IVF versus 50% ICSI).[99] A 2013 systematic review summarised 11 studies with a total of 901 couples and showed a higher fertilisation rate with ICSI compared with IVF (RR 1.49, 95% CI 1.35–1.65) and the need to treat five participants with ICSI to prevent one case of fertilisation failure.[100] Because of the paucity of data, the review authors could not analyse the pregnancy outcome from ICSI compared with IVF. Both the American Society for

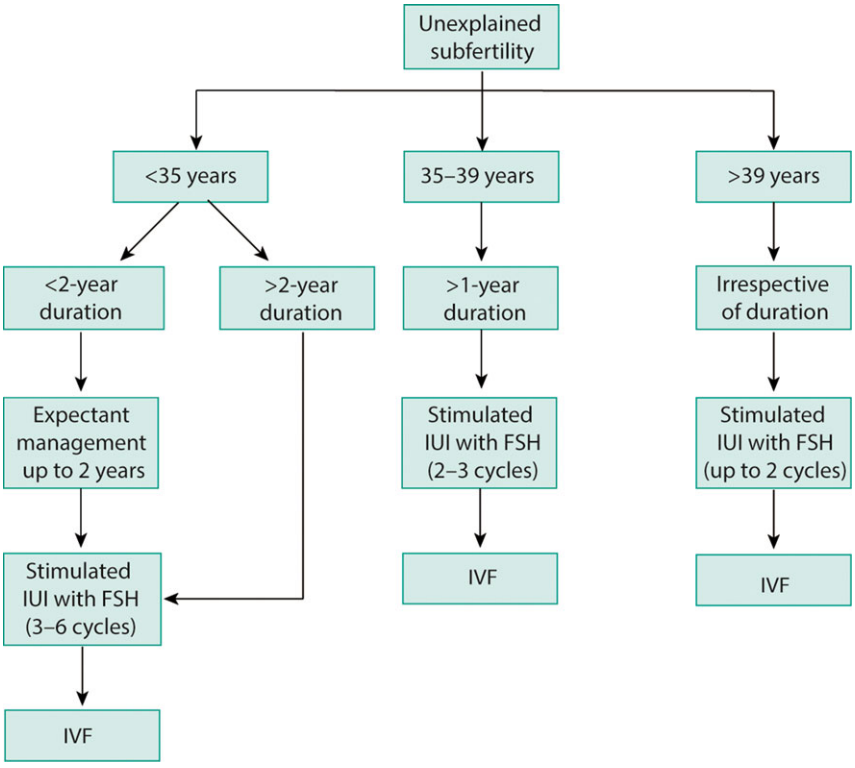

Figure 1. The authors' suggested algorithm on the best treatments for unexplained subfertility. FSH = follicle-stimulating hormone, IUI = intrauterine insemination, IVF = in vitro fertilisation.

Reproductive Medicine and the NICE practice committees do not recommend routine ICSI for unexplained subfertility.[2,101] However, use of ICSI for at least some oocytes (split IVF–ICSI) offers several benefits. It allows detection of fertilisation defects, reduces the risk of failure to fertilise and identifies couples that would need ICSI in subsequent cycles.

Cost analyses

One of the important factors to consider is the cost of treatments. It is difficult to perform this kind of analysis because of differences in the cost of treatment between different countries and different regions in the same country. The study by Reindollar et al.[86] in 2010 found a saving of $2,624 per couple in the immediate IVF arm. However, the cost they analysed was the insurer's charge data, which could be quite different from the cost of fertility treatment when it is government funded. Similarly, a cost-effectiveness analysis by Chambers et al.[102] in 2010 showed IVF to be cost effective. However, this study can be criticised because it was a cohort study and the study population was drawn from private clinics. In contrast, van Rumste et al.[89] showed cost saving with three cycles of IUI plus COH in comparison to one cycle of IVF-eSET in a randomised controlled trial from The Netherlands, where fertility treatments are covered by healthcare insurance. These differences between private and government-funded treatment reduce the generalised applicability of this kind of analysis.

Conclusions

A range of treatment options is available for unexplained subfertility; however, the right treatment strategy needs to be tailored according to the individual circumstances. Factors like the age of the female partner, duration of subfertility and previous pregnancies should be considered in choosing the optimal treatment protocol. One suggested algorithm is presented in Figure 1. There is a lack of agreement between clinicians regarding management and this is aggravated by a lack of strong evidence, impatience on the part of practitioners and couples and financial considerations. This frequently leads to overtreatment in cases suitable for expectant management or IUI with gonadotrophic ovarian stimulation. While clomiphene with or without IUI is not suitable for unexplained subfertility, 3–4 cycles of IUI and ovarian stimulation with gonadotrophins could be beneficial for many suitable couples. IVF should remain the first choice of treatment only for those with a long duration of subfertility, where ovarian reserve is deteriorating or when conservative treatment has failed.

Disclosure of interests

There are no interests to disclose.

Contribution to authorship

AN carried out the literature search and wrote the draft article. RH contributed to the final version of the article.

Supporting Information

Single Best Answer questions are available for this article at https://stratog.rcog.org.uk/tutorial/tog-online-sba-resource

References

1 Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2011. p. 1185.
2 National Institute for Health and Care Excellence. *Fertility: Assessment and Treatment for People with Fertility Problems*. NICE Clinical Guideline 156. London and Manchester: NICE; 2013.
3 Smith S, Pfiefer SM, Collins J. Diagnosis and management of female infertility. *JAMA* 2003;**290**:1767–70.
4 The Practice Committee of the American Society for Reproductive Medicine: Effectiveness and treatment for unexplained infertility. *Fertil Steril* 2006;**86**:S111–4.
5 Guzick DS, Michael W, Sullivan G, Adamson D, Marcelle I, Cedars RJ, et al. Efficacy of treatment for unexplained infertility. *Fertil Steril* 1998;**70**:207–13.
6 Collins JA, Burrows EA, Willan AR. The prognosis for live birth among untreated infertile couples. *Fertil Steril* 1995;**64**:22–8.
7 Brandes M, Hamilton CJ, van der Steen JO, de Bruin JP, Bots RS, Nelen WL, et al. Unexplained infertility: overall ongoing pregnancy rate and mode of conception. *Human Reprod* 2011;**26**:360–8.
8 Nandi A, Gudi A, Shah A, Homburg R. An online survey of specialists' opinion on first line management options for unexplained subfertility. *Hum Fertil* 2015;**18**:48–53.
9 Baird DT, Collins J, Egozcue J, Evers LH, Gianaroli L, Leridon H, et al. Fertility and ageing. *Hum Reprod Update* 2005;**11**:261–76.
10 Munne S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities. *Fertil Steril* 1995;**64**:382–91.
11 Balasch J, Gratacos E. Delayed childbearing effects on fertility and the outcome of pregnancy. *Curr Opin Obstet Gynaecol* 2012;**24**:187–93.
12 Maheshwari A, Hamilton M, Bhattacharya S. Effect of female age on the diagnostic categories of infertility. *Hum Reprod* 2008;**23**:538–42.
13 Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S, et al. Effects of cigarette smoking on reproduction. *Hum Reprod Update* 2011;**17**:76–95.
14 Calogero A, Polosa R, Perdichizzi A, Guarino F, La Vignera S, Scarfia A, et al. Cigarette smoke extract immobilizes human spermatozoa and induces sperm apoptosis. *Reprod Biomed Online* 2009;**19**:564–71.
15 Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, et al. Physical activity, body mass index and ovulatory disorder infertility. *Epidemiology* 2002;**13**:184–90.
16 Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. *Reprod Biomed Online* 2007;**15**:532–8.
17 Bellver J, Melo MA, Bosch E, Serra V, Remohi J, Pellicer A. Obesity and poor reproductive outcome: the potential role of the endometrium. *Fertil Steril* 2007;**88**:446–51.
18 Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril* 2010;**93**:2222–31.
19 Hammoud AO, Meikle AW, Reis LO, Gibson M, Peterson CM, Carrell DT. Obesity and male infertility: a practical approach. *Semin Reprod Med* 2012;**30**:486–95.
20 Jensen TK, Gottschau M, Madsen JOB, Andersson AM, Harmer Lassen T, Skakkebaek NE, et al. Habitual alcohol consumption associated with

reduced semen quality and changes in reproductive hormones; a cross-sectional study among 1221 young Danish men. *BMJ Open* 2014;**4**:e005462.
21 Gill J. The effects of moderate alcohol consumption on female hormone levels and reproductive function. *Alcohol Alcohol* 2000;**35**:417–23.
22 Eggert J, Theobald H, Engfeldt P. Effects of alcohol consumption on female fertility during an 18-year period. *Fertil Steril* 2004;**81**:379–83.
23 Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. *Hum Reprod Update* 2007;**13**:209–23.
24 Broer SL, van Disseldrop J, Broeze KA, Dolleman M, Opmeer BC, Bossuyt P, et al. Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach. *Hum Reprod Update* 2013;**19**:26–36.
25 van Rooij IA, Bancsi LF, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. Women older than 40 years of age and those with elevated follicle-stimulating hormone levels differ in poor response rate and embryo quality in in vitro fertilization. *Fertil Steril* 2003;**3**:482–8.
26 Jansen RP. Endocrine response in the fallopian tube. *Endocr Rev* 1984;**5**:525–51.
27 Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB. Risk of sequelae after Chlamydia trachomatis genital infection in women. *J Infect Dis* 2010;**201** Suppl 2:S134–55.
28 Liu DY, Baker HW. Disordered zona pellucida-induced acrosome reaction and failure of in vitro fertilization in patients with unexplained infertility. *Fertil Steril* 2003;**79**:74–80.
29 Baker HWG, Liu DY, Garrett C, Martic M. The human acrosome reaction. *Asian J Androl* 2000;**2**:172–8.
30 Evangelini E, Charalabopoulos K, Asimakopoulos B. Human sperm DNA fragmentation and its correlation with conventional semen parameters. *J Reprod Infertil* 2014;**15**:2–14.
31 Zhao J, Zhang Q, Wang Y, Li Y. Whether sperm deoxyribonucleic acid fragmentation has an effect on pregnancy and miscarriage after in vitro fertilization/intracytoplasmic sperm injection: a systematic review and meta-analysis. *Fertil Steril* 2014;**102**:998–1005.
32 Osman A, Alsomait H, Seshadri S, El-Toukhy T, Khalaf Y. The effect of sperm DNA fragmentation on live birth rate after IVF or ICSI: a systematic review and meta-analysis. *Reprod Biomed Online* 2015;**30**:120–7.
33 Oehninger S, Franken DR, Ombelet W. Sperm functional tests. *Fertil Steril* 2014;**102**:1528–33.
34 Aitken RJ. Sperm function tests and fertility. *Int J Androl* 2006;**29**: 69–75.
35 Practice Committee of American Society for Reproductive Medicine. The clinical utility of sperm DNA integrity testing. *Fertil Steril* 2008; **90** Suppl 5: S178–80.
36 Salleh N, Giribabu N. Leukemia inhibitory factor: roles in embryo implantation and in nonhormonal contraception. *Scientific World Journal* 2014; 201514.
37 Dimitriadis E, Nie G, Hannan NJ, Paiva P, Salamonsen LA. Local regulation of implantation at the human fetal-maternal interface. *Int J Dev Biol* 2010;**54**:313–22.
38 Haller-Kikkatalo K, Salumets A, Uibo R. Review on autoimmune reactions in female infertility: antibodies to follicle stimulating hormone. *Clin Dev Immunol* 2012;762541.
39 Jefferys A, Vanderpump M, Yasmin E. Thyroid dysfunction and reproductive health. *The Obstetrician and Gynaecologist* 2015;**17**:39–45.
40 Coulam CB, Jeyendran RS. Thrombophilic gene polymorphism are risk factors for unexplained infertility. *Fertil Steril* 2009;**91**:1516–7.
41 Casadei L, Puca F, Privitera L, Zamaro V, Emidi E. Inherited thrombophilia in infertile women: implication in unexplained infertility. *Fertil Steril* 2010;**94**:755–7.
42 Aitken RJ, Baker MA. Oxidative stress, sperm survival and fertility control. *Mol Cell Endocrinol* 2006;**250**:66–9.
43 Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. *Reprod Biol Endocrinol* 2012;**10**:49.
44 The Practice Committee of the American Society for Reproductive Medicine: Endometriosis and infertility: a committee opinion. *Fertil Steril* 2012;**98**:591–8.
45 Sylvie B, Sylvie M, Langevin M, Maheux R, Canadian Collaborative Group on Endometriosis. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. *Fertil Steril* 1998;**69**:1034–41.
46 Parazzini F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. *Hum Reprod* 1999;**14**:1332–4.
47 Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Jacobson TZ, et al. Laparoscopic surgery for endometriosis. *Cochrane database Syst Rev* 2014;(4):CD011031.
48 Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. *Fertil Steril* 2006;**86**:566–71.
49 Pritts EA, William HP, David LO. Fibroids and infertility: an updated systematic review of the evidence. *Fertil Steril* 2009;**91**:1215–23.
50 Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. *Cochrane Database Syst Rev* 2012;(11):CD003857.
51 Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. *Hum Reprod Update* 2012;**18**:374–92.
52 Garcia JE, Jones GS, Wright GL, Jr. Prediction of the time of ovulation. *Fertil Steril* 1981;**36**:308–15.
53 Malcolm CE, Cumming DC. Does anovulation exist in eumenorrheic women? *Obstet Gynecol* 2003;**102**:317–8.
54 World Health Organization. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. Geneva: World Health Organization; 2010.
55 Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HW, Behre HM, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update* 2010;**16**:231–45.
56 Coccia ME, Rizzello F. Ovarian reserve. *Ann NY Acad Sci* 2008;**1127**: 27–30.
57 The Practice Committee of the American Society for Reproductive Medicine: Testing, interpreting measures of ovarian reserve: a committee opinion. *Fertil Steril* 2015;**103**:e9–e17.
58 Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update* 2006;**12**:685–718.
59 Maheshwari A, Fowler P, Bhattacharya S. Assessment of ovarian reserve—should we perform tests of ovarian reserve routinely? *Hum Reprod* 2006;**21**:2729–35.
60 Committee on Gynecologic Practice. Committee opinion no. 618: Ovarian reserve testing. *Obstet Gynecol* 2015;**125**:268–73.
61 Nakagawa K, Ohqi S, Horikawa T, Kojima R, Ito M, Saito H. Laparoscopy should be strongly considered for women with unexplained infertility. *J Obstet Gynaecol Res* 2007;**33**:665–70.
62 The Practice Committee of the American Society for Reproductive Medicine: Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril* 2012;**98**:302–7.
63 Badawy A, Khiary M, Raqab A, Hassan M, Sherif L. Laparoscopy– or not–for management of unexplained infertility. *J Obstetet Gynaecol* 2010;**30**:712–5.
64 Bonneau C, Chanelles O, Sifer C, Poncelet C. Use of laparoscopy in unexplained infertility. *Eur J Obstet Gynecol Reprod Biol* 2012;**163**:57–61.
65 Kahyaoglu S. Does diagnostic laparoscopy have value in unexplained infertile couple? A review of the current literature *J Minim Invasive Surg Sci* 2013;**2**:124–8.
66 Elbareg A, Essadi F, Anwar K, Elmehashi M. Value of hysteroscopy in management of unexplained infertility. *Asian Pacific Journal of Reproduction* 2014;**3**:295–8.
67 Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database Syst Rev* 2015;(2): CD009461.
68 Brown SE, Coddington CC, Schnorr J, Toner JP, Gibbons W, Oehninger S. Evaluation of outpatient hysteroscopy, saline infusion hysterosonography, and hysterosalpingography in infertile women: a prospective, randomized study. *Fertil Steril* 2000;**74**:1029–34.

69 Steures P, van der Steeg JW, Hompes P, Habbema J, Eijkemans M, Broekmans F, et al. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. *Lancet* 2006;**368**:216–21.

70 Custers IM, van Rumste M, van der Steeg JW, van Wely M, Hompes P, Bossuyt P, et al. Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. *Hum Reprod* 2012;**27**:444–50.

71 Leushuis E, van der Steeg JW, Steures P, Bossuyt P, Eijkemans M, van der Veen F, et al. Prediction models in reproductive medicine: a critical appraisal. *Hum Reprod Update* 2009;**15**:537–52.

72 Steures P, Berkhout JC, Hompes P, van der Steeg JW, Bossuyt PM, van der Veen F, et al. Patients' preferences in deciding between intrauterine insemination and expectant management. *Hum Reprod* 2005;**20**:752–5.

73 Kersten FAM, Hermens RPGM, Braat DDM, Hoek A, Mol BW, Goddijn M, et al. Overtreatment in couples with unexplained infertility. *Hum Reprod* 2015;**30**:71–80.

74 Luttjeboer F, Harada T, Hughes E, Johnson N, Lilford R, Mol BW. Tubal flushing for subfertility. *Cochrane Database Syst Rev* 2007;(3):CD003718.

75 Johnson NP. Review of lipiodol treatment for infertility - an innovative treatment for endometriosis-related infertility? *Aust NZ J Obstet Gynaecol* 2014;**54**:9–12.

76 Bhattacharya S, Harrild K, Mollison J, Wordsworth S, Tay C, Harrold A, et al. Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. *BMJ* 2008;**337**:a716.

77 Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. *Cochrane Database Syst Rev* 2010;(1): CD000057.

78 Veltman-Verhulst SM, Cohlen BJ, Hughes E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. *Cochrane Database Syst Rev* 2012;(9):CD001838.

79 van Rumste MME, Custers IM, van der Veen F, van Wely M, Evers JLH, Mol BWJ. The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis. *Hum Reprod Update* 2008;**14**:563–70.

80 Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. *Lancet* 2005;**365**:1807–16.

81 Ragni G, Caliari I, Nicolosi AE, Arnoldi M, Somigliana E, Crosignani PG. Preventing high-order multiple pregnancies during controlled ovarian hyperstimulation and intrauterine insemination: 3 years' experience using low-dose recombinant follicle-stimulating hormone and gonadotropin-releasing hormone antagonists. *Fertil Steril* 2006;**85**:619–24.

82 Merviel P, Heraud MH, Grenier N, Lourdel E, Sanquinet P, Copin H. Predictive factors for pregnancy after intrauterine insemination (IUI): an analysis of 1038 cycles and a review of the literature. *Fertil Steril* 2010;**93**:79–88.

83 Kim D, Child T, Farquhar C. Intrauterine insemination: a UK survey on the adherence to NICE clinical guidelines by fertility clinics. *BMJ Open* 2015;**15**:e007588.

84 Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. *Lancet* 2000;**355**:13–8.

85 Human Fertilisation & Embryology Authority Latest UK IVF figures: 2010 and 2011 [http://www.hfea.gov.uk/ivf-figures-2006.html].

86 Reindollar R, Regan M, Neumann P, Levine B, Thornton K, Alper M, et al. A randomized clinical trial to evaluate optimal treatment for unexplained subfertility: the fast track and standard treatment (FASTT) trial. *Fertil Steril* 2010;**94**:888–9.

87 Goldman MB, Thornton KL, Ryley D, Alper MM, Fung JL, Hornstein MD, et al. A randomised clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment (FORT-T). *Fertil Steril* 2014;**101**:1574–81.

88 Custers I, Konig T, Broekmans F, Hompes P, Kaaijik E, Oosterhuis J, et al. Couples with unexplained subfertility and unfavourable prognosis: a randomised pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. *Fertil Steril* 2011;**5**:1107–11.

89 van RM, Custers I, van WM, Koks C, van WH, Beckers N, et al. IVF with planned single-embryo transfer vs intrauterine insemination with ovarian stimulation in couples with unexplained subfertility: an economic analysis. *Reprod BioMed Online* 2014;**28**:336–42.

90 Pandian Z, Gibreel A, Bhattacharya S. In vitro fertilisation for unexplained subfertility. *Cochrane Database Syst Rev* 2012;(4):CD003357.

91 Bensdorp A, Tjon-Kon-Fat R, Bossuyt P, Koks CM, Oosterhuis GJ, Hoek A, et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. *BMJ* 2015;**350**:g7771.

92 Kupka MS, Ferraretti AP, de Mouzon J, Erb K, D'Hooghe T, Castilla JA, et al., for the European Society of Human Reproduction and Embryology. Assisted reproductive technology in Europe, 2010: results generated from European registers by ESHRE. *Hum Reprod* 2014;**29**:2099–113.

93 Malchau SS, Loft A, Henningsen AK, Nyboe Andersen A, Pinborg A. Perinatal outcomes in 6,338 singletons born after intrauterine insemination in Denmark, 2007 to 2012: the influence of ovarian stimulation. *Fertil Steril* 2014;**102**:1110–6.

94 Bungum L, Bungum M, Humaidan P, Yding Anderson C. A strategy for treat-ment of couples with unexplained infertility who failed to conceive after in- trauterine insemination. *Reprod Biomed Online* 2004;**8**:584–9.

95 Mackenna A. Contribution of the male factor to unexplained infertility: a review. *Int J Androl* 1995;**18** Suppl 1:58–61.

96 Ezra Y, Simon A, Laufer N. Defective oocytes: a new subgroup of unexplained infertility. *Fertil Steril* 1992;**58**:24–7.

97 Jaroudi K, Al-Hassan S, Al-Sufayan H, Al-Mayman H, Qeba M, Coskun S. In- tracytoplasmic sperm injection and conventional in vitro fertilization are complementary techniques in management of unexplained infertility. *J Assist Reprod Genet* 2003;**20**:377–81.

98 Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, Ghobara T, et al. Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. *Lancet* 2001;**357**:2075–9.

99 Foong SC, Fleetham JA, O'Keane JA, Scott SG, Tough SC, Greene CA. A prospective randomized trial of conventional *in vitro* fertilization versus intracytoplasmic sperm injection in unexplained infertility. *J Assist Reprod Genet* 2006;**23**:137–40.

100 Johnson NL, Sasson IE, Sammel MD, Dokras A. Does intracytoplasmic sperm injection improve the fertilization rate and decrease the total fertilization failure rate in couples with well-defined unexplained infertility? A systematic review and meta-analysis. *Fertil Steril* 2013;**100**:704–11.

101 The Practice Committees of the American Society for Reproductive Medicine and Society for Assisted Reproductive Technology. Intracytoplasmic sperm injection (ICSI) for non-male factor infertility: a committee opinion. *Fertil Steril* 2012;**98**:1395–9.

102 Chambers G, Sullivan E, Shanahan M, Ho M, Priester K, Chapman G. Is in vitro fertilisation more effective than intrauterine insemination as a first line therapy for subfertility? A cohort analysis *Aust N Z J Obstet Gynaecol* 2010;**50**:280–8.

