



Information on Unexplained Infertility

Patient leaflet

based on the evidence-based guideline on Unexplained
Infertility

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Introduction

This booklet is for you if:

- You are initiating fertility investigations
- You have been diagnosed with unexplained infertility

This booklet is intended for patients but may also be useful for their family members and caregivers.

This booklet aims to

- Increase awareness of unexplained infertility (UI).
- Provide couples with information on appropriate tests and treatments.
- Provide couples with tools to discuss their options with their healthcare provider.

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This booklet and the information presented are entirely-based on the evidence-based Guideline on Unexplained Infertility. All the information and recommendations in the guideline are built upon the best available evidence from research. Where there is insufficient evidence from research, a group of experts has formulated recommendations based on their clinical expertise. The experts also formulated areas of research to improve future clinical care for couples with unexplained infertility.

We have added the following symbols to explain the strength of the recommendations and whether or not they are based on results from studies.



Recommendation based on research evidence



Recommendation based on considered opinion of the guideline development group

More information is available in the last pages of this booklet, including a list of medical and research terms and their meanings. The full guideline is available on the website of ESHRE (www.eshre.eu/guidelines).

What is Unexplained Infertility?

If you have tried to get pregnant for a year or more and you have not succeeded to get pregnant and your doctor has not found an obvious problem during fertility investigations, you receive the diagnosis of 'unexplained infertility'.

With increasing age of the female partner, the quality of her eggs decreases and fertility problems are more likely to occur. Therefore, the guideline development group has added a threshold of 40 years for the female partner to the definition of unexplained infertility.

Which tests should my doctor perform?

Investigations that are recommended

After 12 months of regular, unprotected intercourse without achieving a pregnancy, a fertility work-up can be initiated. Your doctor can recommend earlier investigation depending on your age.

The investigations discussed here are **recommended** for all couples undergoing a fertility work-up.

Confirmation of ovulation



First, your doctor will ask about your menstrual history to make sure you have a regular menstrual cycle. A regular menstrual cycle is 24 to 38 days, up to 8 days in duration and has a cycle variation of less than 7 to 9 days.

Pelvic examination (ultrasound)



Then, your doctor can do a pelvic ultrasound to check the shape and the wall of the uterus (womb) for any abnormalities, such as fibroids.

Semen analysis



A semen sample is analysed to make sure the quality is sufficient. During semen analysis, a sample is examined under the microscope to check the total number of sperm, the amount of live sperm, the motility of the sperm (are they able to swim toward an egg), and the size and shape of the sperm. Ideally, the semen analysis is done at this stage, to prevent any unnecessary further testing.

Tubal patency test (hysterosalpingography (HSG) or hysterosalpingo-contrast- sonography (HyCoSy)/hysterosalpingo-foam sonography (HyFoSy))



When the semen analysis is normal, the doctor can propose to do a test to check if your fallopian tubes are open. At ovulation, an egg is released from the ovary and it travels to the uterus (womb) via the fallopian tubes. Therefore, it is important to check that there is no obstruction in the fallopian tubes. During the test, a contrast agent (dye) is injected into your uterus. If your fallopian tubes are open, the dye can be seen passing through them with imaging (X-ray in case of HSG or ultrasound in case of HyCoSy).

If all of these tests are normal, the diagnosis of unexplained infertility is established.

Additional investigations that could be considered based on medical and family history

In the next section, we discuss an investigation that **might be considered** for some couples, based on medical and family history.

Coeliac disease



Coeliac disease is an autoimmune disease where ingestion of gluten causes damage to the small intestine. Classic symptoms of coeliac disease are associated with the gastro-intestinal tract, such as malabsorption, chronic diarrhoea, vomiting, bloating. However, you can also have coeliac disease without gastro-intestinal symptoms, making this a difficult disease to diagnose. In some women, coeliac disease can disturb fertility, for example a delay of puberty, early menopause and pregnancy complications. Studies have shown that there is a higher risk of having coeliac disease in women with unexplained infertility compared to women from the general population. If you are showing symptoms, your doctor could consider testing for coeliac disease.

Which investigations should not be routinely performed?

There are several tests that have been described and carried out in couples with unexplained infertility, but do not provide any useful information. This is because:

- They do not provide a cause for your infertility
- They do not help in estimating prognosis for successful reproductive outcome
- They do not help in selecting treatment

These tests are NOT routinely recommended for couples with unexplained infertility:

- Female
 - o Hysteroscopy/laparoscopy
 - o Post-coital test
 - o Vaginal microbiota testing
 - o Auto-immune tests other than for coeliac disease
 - o Thyroid hormones
 - o Thrombophilia
 - o Vitamin D
 - o Prolactin
- Male
 - o Scrotal ultrasound
 - o Sperm DNA fragmentation
 - o Sperm chromatin condensation test
 - o Hormonal testing
 - o Human Papilloma Virus (HPV) testing
 - o Sperm microbiology testing
- Couple
 - o Oxidative stress testing
 - o Genetic testing

Although these tests are not recommended for all patients with unexplained infertility, your doctor may suggest them, based on clinical symptoms (not necessarily related to unexplained infertility) or because of your medical or family history.

What are the options for treatment?

The guideline development group (GDG) advises to base the decision to start active treatment on prognosis in couples with unexplained infertility.

Couples presenting with unexplained infertility can get pregnant spontaneously. Models have been developed to predict the chance of spontaneous pregnancy, called prognosis. Important factors that influence your prognosis are the age of the female partner, the duration of your infertility, what previous treatments you underwent and if you had previous pregnancies. A good prognosis patient for example would be a young woman, who has been experiencing infertility for a short period of time, and who did not undergo fertility treatment and has no previous pregnancies.

Unfortunately, none of the currently available models are ideal for use in daily practice. Still, it is important to have an idea about your prognosis to achieve a spontaneous pregnancy. Studies have shown that in couples with a good prognosis, fertility treatments will not increase (or only have a limited benefit to) your chance of becoming pregnant.

Expectant management



Expectant management means having regular intercourse, every two to three days in the fertile window. If your prognosis to conceive spontaneously is good, your doctor may advise expectant management for up to six months before proceeding with fertility treatment. During expectant management, your doctor may suggest to monitor follow the growth of your follicles during the cycle with ultrasound, and/or triggering ovulation with an human chorionic gonadotropin (hCG) injection.

Intra-uterine insemination with ovarian stimulation



If expectant management is not an option for you, or if you have tried it for up to six months, your doctor may propose to proceed with fertility treatments (active treatment). Studies show that for couples with unexplained infertility, intra-uterine insemination (IUI) in combination with ovarian stimulation (hormones) is equally effective as IVF.

IUI is a technique where sperm is placed into a woman's womb through the cervix. IVF is a technique by which eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually, one embryo is transferred into the womb, in exceptional circumstances two embryos can be transferred. If an embryo implants successfully, it results in a pregnancy.

IVF is more expensive and the risk of complications and the emotional burden on the couple is higher compared to IUI. Therefore, the guideline group decided that IUI with ovarian stimulation is the best first-line strategy for couples with unexplained infertility.

There are couples with unexplained infertility for whom IVF is more suitable. Also, if you haven't conceived after three to six rounds of IUI, your doctor may suggest proceeding with IVF.

Which treatments are not recommended?

We note here treatments that we do not recommend for couples with unexplained infertility.

This is either:

- because there is not enough evidence that the treatment improves the chance of becoming pregnant if you have unexplained infertility, or
- because studies have shown that the treatment does not work, or that it might be harmful.

Treatments with insufficient proof (more research is needed/no proof of safety yet):

- Resection of polyps or fibroids not seen on routine imaging by ultrasound
- Antioxidants, both for the female and the male
- Acupuncture
- Nutraceuticals (inositol)
- Traditional Chinese medicine

Treatments that do NOT work for unexplained infertility:

- ICSI
- Endometrial injury/scratching

Where can I find more information or support?

More detailed information on each of the topics in this booklet can be found in the clinicians' edition of the guideline on the ESHRE website (www.eshre.eu/guidelines).

For more detailed information or support, you can contact your doctor or a patient organisation.

For contact details of national patient organisations for infertility, you can ask your doctor, or contact **Fertility Europe** (www.fertilityeurope.eu)

About this booklet

This booklet aims to involve patients in healthcare improvement by informing them about current standards of care, and by enabling them to make informed decisions on their health, supported by the best available evidence.

How this booklet was developed

This booklet was written by Dr. Nathalie Le Clef (methodological expert) and revised by the members of the guideline group. All the information provided is based on the recommendations in the evidence-based guideline on Unexplained Infertility.

Who developed the ESHRE guideline?

The evidence-based guideline on Unexplained Infertility, was developed by a multidisciplinary guideline development group including fertility specialists, an andrologist, a nurse/midwife, a patient representative and a research specialist.

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Glossary (explanation of medical or research terms)

Acupuncture: In acupuncture, fine needles are inserted at specific sites in the body for therapeutic purposes.

Antioxidants: Antioxidants, such as vitamin C and E, neutralise free radicals from the body cells. Free radicals are unstable molecules that can harm the cell.

DNA: Deoxy nucleic acid, a molecule that carries the genetic instructions to develop and maintain humans (and other organisms).

Endometrial injury/scratch: A technique where the lining of the uterus is gently 'scratched'. This superficial wounding of the uterus is thought to increase the chance of implantation of the embryo.

Fibroids: Benign growths in the uterus made of uterine muscle tissue.

GDG: guideline development group, the group of experts that developed this evidence-based guideline.

hCG: human chorionic gonadotropin, a hormone produced during pregnancy and needed to maintain the pregnancy.

HPV: Human Papilloma Virus.

HSG: Hysterosalpingography, a test that is used to verify that the fallopian tubes are open (patent). During the test, contrast medium (dye) is injected in the uterus. When the fallopian tubes are open, the dye can be seen passing through them using X-rays.

HyCoSy: Hysterosalpingo-contrast-sonography, a test that is used to verify that the fallopian tubes are open (patent). During the test, contrast medium (dye) is injected in the uterus. When the fallopian tubes are open, the dye can be seen passing through them using ultrasound.

Hysteroscopy: a procedure used to examine the inside of the womb (uterus). It is carried out using a hysteroscope, which is a narrow telescope with a light and camera at the end.

Infertility: The state of being not fertile and unable to become pregnant, usually defined as not becoming pregnant after 12 months or more of regular unprotected sexual contact.

Intracytoplasmic sperm injection (ICSI): a more specialised form of IVF, where one sperm is injected into the egg.

Intra-uterine insemination (IUI): A technique where sperm is placed into a woman's womb through the cervix.

In vitro fertilization (IVF): a technique by which eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually, one embryo is transferred into the womb, in exceptional circumstances two embryos can be transferred. If an embryo implants successfully, it results in a pregnancy.

Laparoscopy: a surgical procedure in which a thin, lighted telescope called a laparoscope is inserted through a small incision (cut) in the abdomen. The laparoscope is used to view the pelvic organs.

Microbiota: the community of microorganisms (such as fungi, bacteria and viruses) that exists in a particular environment.

Nutraceutical: Nutraceuticals is an umbrella term describing any product derived from food sources with extra health benefits in addition to the basic nutritional value found in foods.

PCT: A post-coital test assesses the interaction between sperm and cervical mucus after intercourse. This test was developed as an attempt to check whether sperm were able to swim through a woman's cervical mucus in order to enter the uterus.

Polyp: Polyps are usually benign growths in the uterus. They form as a result of cells in the lining of the uterus (endometrium) overgrowing. They can be small or large enough to fill the uterine cavity.

Prolactin: A hormone that enables females to produce milk but is also involved in many other processes in the body.

Thrombophilia: An abnormality in the clotting of blood, which causes the blood to clot more than it should.

Ultrasound: High frequency sound waves used to provide images of the body, tissues and internal organs.

Disclaimer

The European Society of Human Reproduction and Embryology (ESHRE) developed the current information booklet for patients based on the clinical practice guideline. The aim of clinical practice guidelines is to aid healthcare professionals in everyday clinical decisions about appropriate and effective care of their patients.

This booklet is in no way intended to replace, dictate or fully define evaluation and treatment by a qualified physician. It is intended solely as an aid for patients seeking general information on issues in reproductive medicine.

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