# Infertility

**Infertility means that couples cannot have children. There are many possible causes of infertility. However, intensive research by the pharmaceutical industry continues to increase the chances of family happiness for thousands of couples.**

### What is infertility?

Infertility is defined as 'the incapacity of a couple to achieve conception or to bring a pregnancy to term after a year or more of unprotected intercourse'.

### Who does infertility affect?

Any number of factors can cause infertility, as more than ten per cent of couples worldwide know all too well from their own experiences. In Europe, one in six couples faces infertility problems at some point in their lives.

Exclusively female or male problems account for 35 per cent each, 25 per cent are due to problems in both partners and five per cent remain unexplained. Advances in the area of infertility treatment now mean that around half of these couples can be successfully treated.

### Present treatments:

The yield of biotechnological research over the past ten years has resulted in a complete range of fertility medicines for each stage of the female reproductive cycle, from ovulation through to early pregnancy.

Today, recombinant human medicines are used in different settings, e.g. when there is a hormonal defect that inhibits ovulation. If low levels of natural hormone are produced, a woman may be prescribed an oestrogen antagonist for several days in each monthly cycle. This stimulates the pituitary gland to release gonadotrophin, which in turn stimulates ovulation.

If this fails or is inappropriate, the individual will be given recombinant follicle stimulating hormone (rFSH) and recombinant human chorionic gonadotrophin (rhCG). These mimic the natural hormonal cycle and prepare the woman for ovulation and implantation if the egg is fertilised.

Luteinising hormone is required to form follicles in the ovary, the production of an egg and the growth of the lining of the uterus. A small proportion of infertile women, estimated at about five per cent of the population, have a deficiency of the hormone because of hypogonadotrophic hypogonadism. However, correction of this deficiency alone does not ensure a successful pregnancy, as more factors are involved.

Where infertility has other causes than ovulation failure, such as tubal dysfunction, endometriosis, anti-sperm antibodies or low sperm counts or motility, couples may be offered outside the body or *in vitro* fertilisation (IVF), also termed assisted reproductive techniques or ART. An oestrogen antagonist and rhCG are used to induce ovarian hyperstimulation, oocytes (eggs) are then removed and fertilised *in vitro* and the resulting embryos re-implanted. Success rates lie in the order of magnitude of 25 per cent.

Diminished ovarian reserve, i.e. a reduced number of eggs that are still available in the ovary for fertilisation, is a major cause of infertility. Anti-Mullerian hormone (AMH) seems to be a promising candidate to assess ovarian reserve and predict the response to controlled ovarian hyperstimulation. Measurement of AMH supports clinical decisions, but alone it is not a suitable predictor of IVF success.

Another disorder which can cause infertility is hyperprolactinaemia, a disease state that suppresses ovulation because of excess levels of the hormone prolactin. If this is the case, the woman will be treated with a prolactin inhibitor.

Male infertility may be due to erectile dysfunction, low sperm production or defects in sperm motility or maturation. All causes of male infertility affect only one target organ, the testes. Semen analysis is the primary test used to determine male fertility. Results can be normal, moderately or severely abnormal or may show no semen at all, a condition called azoospermia.

Impaired testicular function or hypogonadism results in a lower concentration of testosterone in the blood, which leads to diminished sexual function, lethargy and reduced bone mass. Transdermal testosterone therapies are available to increase low hormone levels in the blood. A preparation containing a slow-releasing depot formulation of an androgen has improved treatment, as it can be administered by just four injections a year.

Erectile dysfunction is common in later life and is often due to physical causes such as progressive atherosclerosis or venous leaks, although it may also be related to medication. The introduction of oral phosphodiesterase-5 inhibitors has improved prospects for treating erectile dysfunction, although they are not effective in all cases.

The treatments have been shown to be effective in older men, as well as in those with diabetes - both groups that are likely to have an increased rate of impaired erectile function. Low sperm production may be improved by the use of rFSH.

Hospital- and institute-based research efforts in Europe have made valuable contributions to infertility treatment - for example, IVF was pioneered in the UK, France and Germany.

## What's in the development pipeline?

Research continues into improvements in assisted reproduction technology and fertility treatment. Approval has been received for recombinant forms of human luteinising hormone (LH) and human chorionic gonadotrophin (CG).

There is an emerging belief that combined treatment with rFSH together with rLH may offer therapeutic advantages, including increased pregnancy rates in some groups of women. "Chimerical" gonadotrophins, possessing both FSH and LH activities in a single protein molecule, are being developed. Such compounds which have recently entered the pre-clinical phase of development may be potent activators of the human FSH and LH receptors.

Recombinant leukaemia inhibitory factor (rLIF) is in Phase 3 trial for treatment of embryo implantation failure, as well as a microencapsulated form of rFSH. LIF is a protein believed to be important to the process of attachment of the embryo to the inner lining of the uterus. A few years ago, a gonadotrophin-releasing hormone antagonist was launched and has been used in ART that reduces the number of injections that must be given during ovarian stimulation.

Researchers are also investigating the efficacy and safety of a new treatment regimens with a recombinant gonadotrophin applied to initiate and sustain follicular stimulation in controlled ovarian stimulation for ART. For this regimen, patients

receive a single injection of the medicine and one week later, treatment is continued with daily recFSH up to the day of triggering final oocyte maturation. These studies are in clinical phase 3.

One major determinant for the success of IVF is the production of an adequate number of eggs from the woman in order to have acceptable pregnancy and delivery rates. Some women will not respond adequately to hormonal stimulation and are diagnosed as having low ovarian response. Currently, the understanding of low ovarian response is limited, and although many therapeutic approaches have been suggested, no treatment has been proven significantly efficient.

Dehydroepiandrosteron (DHEA) is a pro-hormone produced by the adrenal gland and the ovary. DHEA is involved in the regulation of follicular growth in the ovaries and may appear useful for improving IVF outcome. Prospective randomised studies on DHEA supplementation for IVF patients are underway, focusing on women with low ovarian response.

About ten per cent of all pregnancies end prematurely. Reducing uterine activity during pre-term labour could improve the outcome. An approach would be to switching off premature uterine contractions. Research in this area focuses on oxytocin receptor and prostaglandin receptor antagonists.

Lastly, research is ongoing to explore the usefulness of a selective $5HT_{1A}$ receptor agonist in counteracting the loss of libido seen in some patients taking antidepressants.

## The longer-term future

Prospects for successful treatment of infertility continue to improve and new findings, such as the discovery of a key protein that controls sperm motility, may provide better understanding of the various causes that can lead to infertility in couples.



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