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In Vitro Fertilization

Ann Fullick

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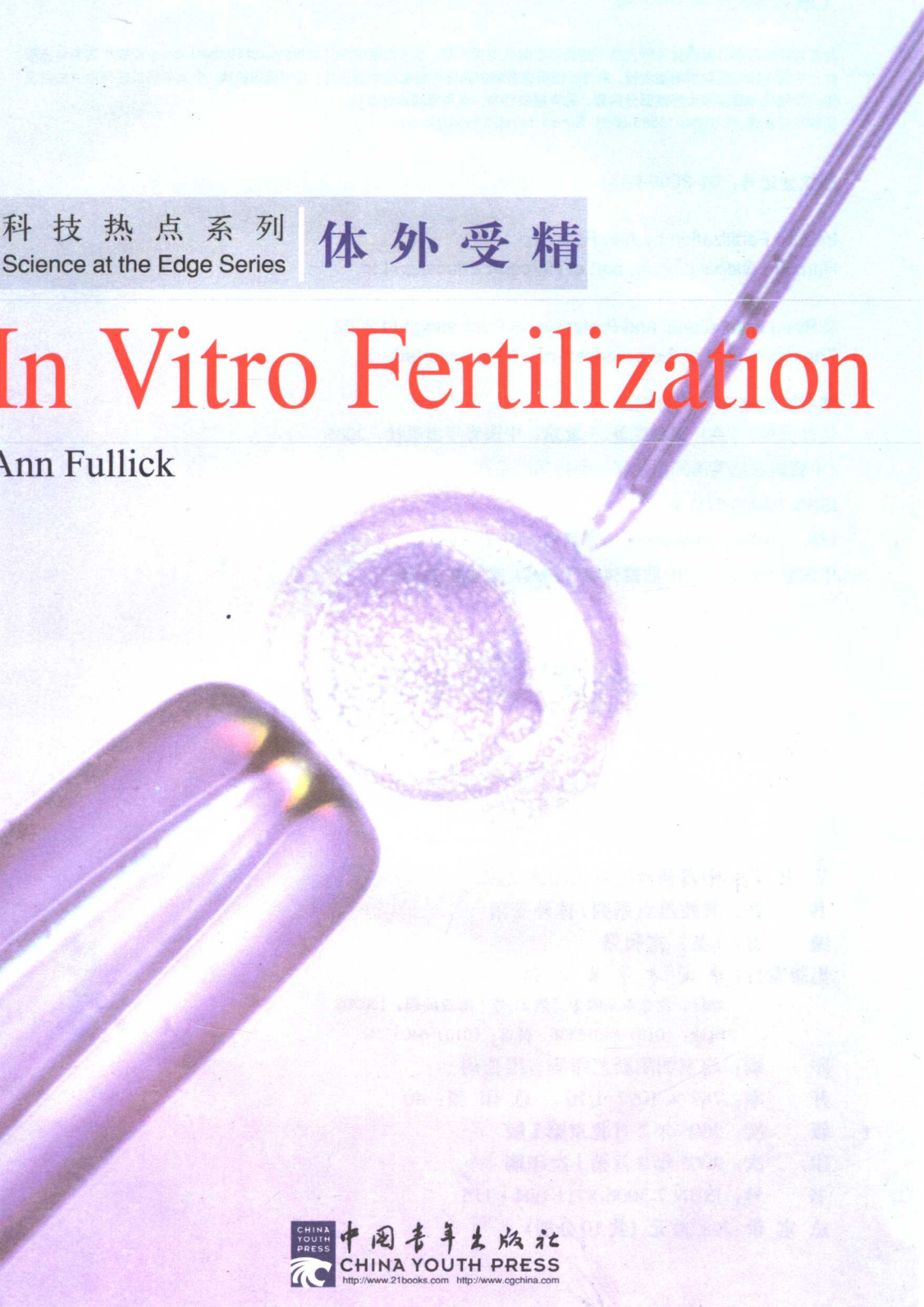
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An everyday miracle?

Every moment of every day a baby is born somewhere around the world. Each new human being comes into existence as the result of the joining of two minute cells from the parents to form a single new cell. It is this cell which then grows and divides to form the billions of cells that make up the body of a newborn baby.



Although it happens every day, the safe arrival of a baby – which has grown over the course of nine months from a single **fertilized** human egg cell – is still an amazing event.

Infertility

For lots of people, having babies is very easy. There is a time each month when, if the couple make love, there is a chance that an **ovum** (egg) in the body of the woman will be fertilized by a **sperm** from the man and nine months later a new baby will be born. In fact many people spend years trying to avoid pregnancy, using different methods

of **contraception** to make sure that sperm and eggs don't meet. But what happens if pregnancy and babies don't happen when they are wanted?

Infertility has always been an issue – King Henry VIII got rid of several wives who could not produce him the son and heir he so desperately wanted! The lives of many ordinary people have also been blighted by the inability to have a much-wanted child. Although there are many different causes of infertility, for centuries the solutions were few and far between – adopting a child or becoming resigned to childlessness were the main options.

'Not being able to have a baby of your own is the most heart-breaking experience.'

Jilly Cooper, journalist and writer

So what can we do about it today? In the last 50 years, it has become increasingly possible to treat and overcome at least some forms of infertility. A wide variety of options are now available for couples who cannot produce a child naturally. These range from simple tests that make it possible to pinpoint when a woman is most likely to get pregnant, to complex techniques such as *in vitro* fertilization or IVF. This is a form of treatment where an egg and sperm are brought together outside the mother's body. They are usually mixed in a glass **Petri dish**, hence the name *in vitro* fertilization – *in vitro* is Latin for 'in glass'. The developing **embryo** is then replaced into the mother's body. The development of IVF has resulted in the births of thousands of babies around the world to people who would otherwise have had no hope of becoming pregnant. And IVF has led the way for the development of other methods to help couples have babies. These even include injecting a single sperm into an egg before replacing it in the mother's body.

Like most scientific breakthroughs, our increased ability to control human **fertility** is something of a mixed blessing. It can bring great personal happiness to couples who would otherwise be unable to have a child. At the same time it also opens up many questions about embryos which are created and then not needed, and the possibilities for changing the inherited material of an embryo before it is returned to the mother. As new and ever more sophisticated treatments for infertility are discovered, the ethics of each need to be discussed. Yet the driving force behind the whole technology remains the desperate desire of infertile couples to have a child of their own.

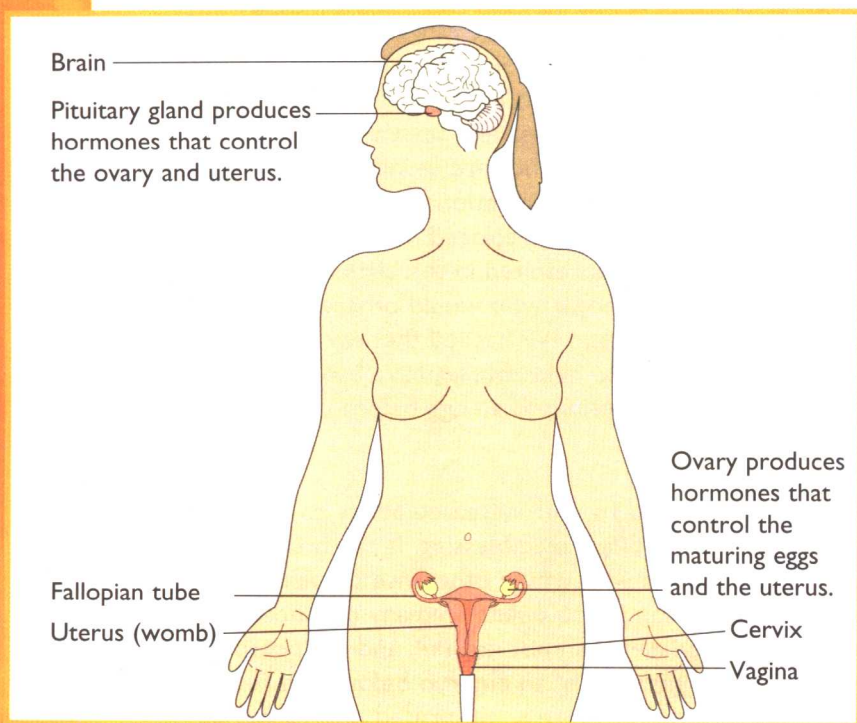
The biology of reproduction

Young children cannot have children of their own, but as we grow and mature the parts of the body involved in making babies – technically known as **reproduction** – become active. These include the sexual organs and a **gland** in the brain. For many people these systems start up and run fairly smoothly, but for a growing number, things don't quite work as they should. So how does the body of a healthy, **fertile** woman or man work?

The fertile female

For about two days in every month a woman is fertile – she has produced an egg that is mature and ready to meet a sperm. The events leading up to and following this special time form a 28-day cycle of fertility, called the **menstrual cycle**.

Inside the body of every newborn baby girl are the eggs (called ova) that will form her future children. Once the girl goes through **puberty**, the **ovaries**, which contain the eggs, become active in response to chemical signals called **hormones**.

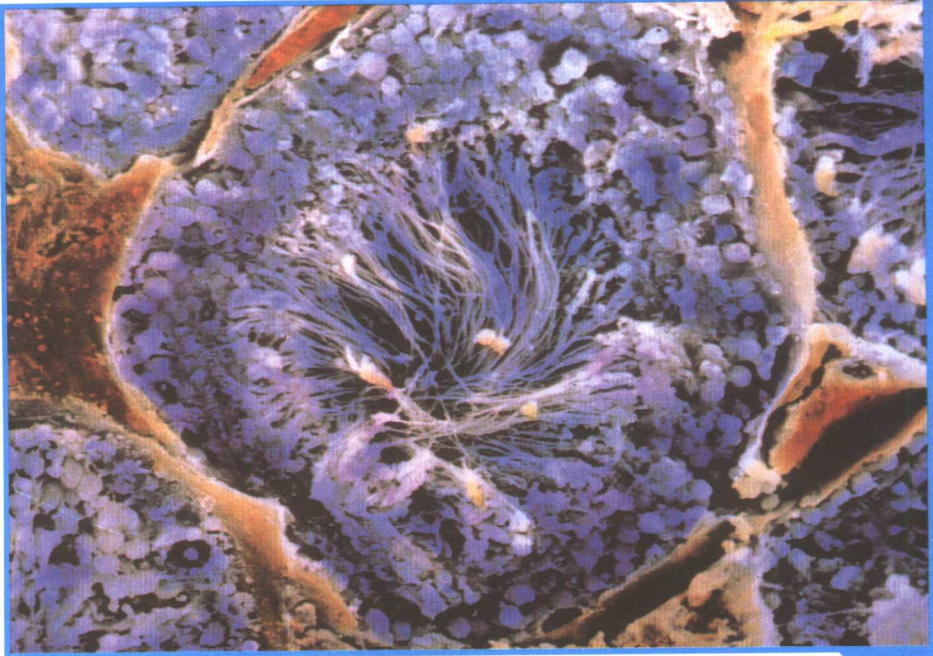


A delicate balance of hormones controls the reproductive system in a woman.

Follicle Stimulating Hormone (FSH) is made by the **pituitary gland** in the brain and it has a direct effect on the ovaries. It makes some of the eggs grow and mature, ready for release. FSH also makes the ovary produce another female hormone, **oestrogen**. This triggers the build-up of the lining of the **uterus** (the organ in which the baby grows and develops) ready to nurture a pregnancy. After about fourteen days an egg is released – this is known as **ovulation** – and it leaves the ovary. The egg travels through the **Fallopian tube** towards the uterus. If it meets some sperm on the way up, it may be fertilized and a pregnancy begins. If not, the lining of the uterus gradually breaks down and passes out of the body. This is called menstruation.

Reproduction in the male

Men do not have a reproductive cycle as women do, but they do have male reproductive hormones produced by the pituitary gland and by the male sex organs, the **testes**. In response to these hormones the testes make a constant supply of sperm, and other glands make the various **secretions** which are mixed with the sperm to form **semen**.



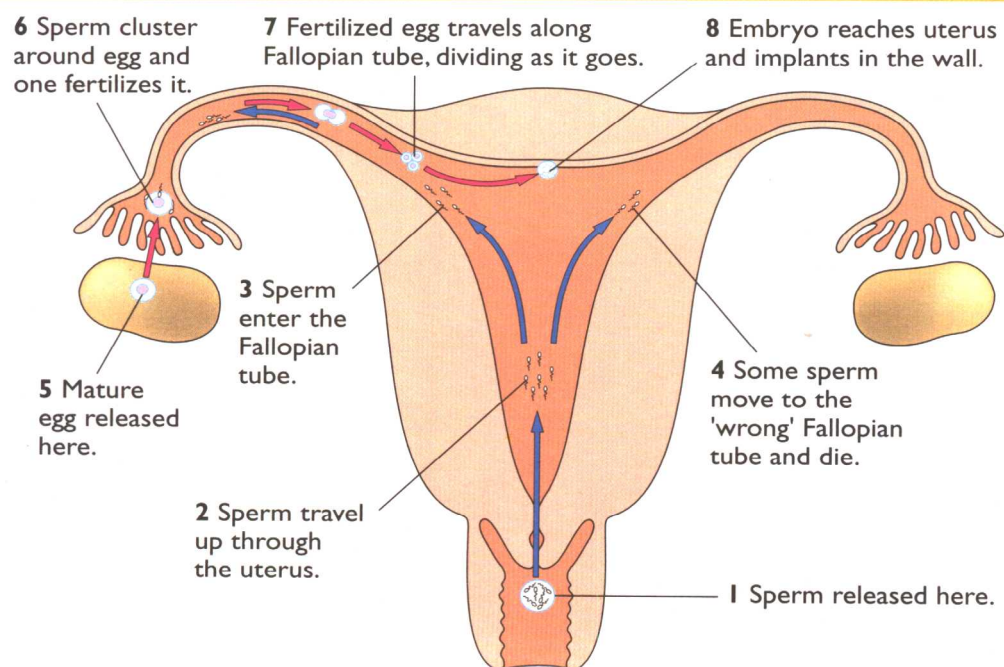
Whereas women usually produce a single mature egg each month, millions of sperm are produced all the time in the testes. The tails of hundreds of developing sperm can be seen here, in a tiny tube in the testes.

From conception to birth

Once a couple decide that they want a baby they need to try and make sure that sperm are present when a mature egg is released from the woman's ovary. Every time they make love the man releases semen containing millions of sperm into the woman's vagina. At around the same time, if the woman is at the fertile point in her menstrual cycle, an egg will be released from the ovary and begin its journey along the Fallopian tube. How do the egg and the sperm meet?

The egg cannot move – it is **wafted** along the Fallopian tube by the beating of millions of tiny hair-like **cilia** which move it slowly away from the ovary towards the uterus. After ovulation the egg only lives for around 48 hours.

The sperm, on the other hand, have an enormously long journey to make as they travel through **mucus** and other secretions in the vagina and **cervix**, up through the uterus and on into the Fallopian tube which contains the egg. The journey of a single sperm can be compared to a person setting off from Britain and swimming to the USA – through **treacle**!



The Fallopian tubes are the site where the egg and the sperm meet at fertilization, and where the first divisions of the newly formed embryo take place.

Each sperm makes frantic **lashing** movements with its tail, which keep it suspended in the liquids, and it is moved to the egg by natural muscle movements of the uterus. Some sperm reach the Fallopian tubes very quickly – in a matter of minutes – but millions are lost along the way. This is why so many sperm are produced in the first place, because the odds against any of them reaching the egg are so high!

Fertilization

Once the sperm reach the egg, how is the egg actually fertilized? The sperm cluster round the egg, attracted by chemical messages it sends out. Special digestive **enzymes** in the head of the sperm act to dissolve away the protective jelly coating of the egg. Finally one sperm manages to break through and get inside the egg – after that no other sperm can get in. The **nucleus** of the sperm contains **genetic** information from the man while the nucleus of the egg contains genetic information from the woman. Once they fuse together, fertilization has taken place – a new genetic individual is formed and a potential new life has begun!

After fertilization the single cell begins to grow and divide as it continues to travel along the Fallopian tube to the uterus. By the time it reaches the uterus it is a small ball of cells ready to implant in the blood-rich lining that has developed in order to support it.



Once the fertilized egg has implanted in the uterus, cell divisions, the specialization of tissue and lots of growth take place. After nine months, a fully formed baby human being is ready to emerge and take a place in the world.

What causes infertility?

When a couple decide that they want to start a family and begin to try to have a baby, most expect to get pregnant straight away. After all, many of them have spent years trying very hard not to get pregnant by mistake! Even if a young, fertile couple have unprotected intercourse at the right stage of the monthly cycle there is no guarantee that they will become pregnant. The percentage chance that they will conceive gets steadily lower as they get older, and it is also reduced by lifestyle factors such as smoking, drinking and being overweight.



For an increasing number of couples, the months without a positive pregnancy test turn into years. When infertility seems to be staring people in the face, it becomes very important to understand why pregnancy is not happening, and what, if anything, can be done about it.

When pregnancy doesn't happen, every monthly **period** comes as a bitter disappointment. Even children's clothes in a shop window can make it seem as if everyone else has a baby.

Whose problem?

It is almost inevitable that, if a couple cannot have a child, they wonder whose 'fault' it is. For centuries it was assumed that childlessness was the woman's fault. We now know better! Failing to get pregnant can be the result of problems in either partner, or even both.

In about a third of all cases of infertility there is indeed a problem in the way that the body of the woman is working. However, in over a third of the cases, it is the reproductive system of the man which is not functioning as it should. The final group of infertility cases are either the result of both the man and the woman in a couple being a bit less fertile than normal or – the most puzzling of all – both partners are theoretically healthy but pregnancy just doesn't happen.

Finding out

IVF has been successful in helping to overcome some forms of infertility, but it is still a very specialized area of medicine. A couple who are having problems in **conceiving** a baby do not start their quest for a child with the IVF specialist – they begin with the family doctor.

Typically a doctor will check the general health of the couple in case there are any other causes of infertility not related to their reproductive systems. The doctor will also check that the woman is not taking the **contraceptive** pill and whether the couple are having sexual intercourse at the time of the month when the woman is most fertile. Another check will be on any other medications either partner may be taking, and whether either of them smoke or drink. Sometimes this allows the doctors to find a simple solution to fertility problems so that medical intervention is not needed to start a family.

For many the solution is not quite so simple, and doctors will refer a couple to an infertility specialist when it becomes apparent that they are having real difficulty in conceiving. For older couples, especially, the 'biological clock' is ticking away fast, as a woman's fertility begins to fall as she approaches 40. It is important that they start working with an infertility specialist as soon as possible. However, most specialists would rather see all couples with fertility problems sooner rather than later, to try and find a successful solution to their problems.

An infertile woman...

When a couple can't have a baby a number of different tests are carried out on both partners to try and find out the cause of the infertility, because different causes need different solutions.

Ovulation problems

To find out why a woman is not conceiving, doctors look for both physical and chemical causes. One of the first checks will be to see if ovulation is occurring – because no egg equals no baby!



By measuring the levels of different hormones in the blood, doctors can build up a pretty good picture of what is going on and whether ovulation is taking place.

'It is estimated that problems with ovulation occur in 25 per cent of infertile couples. This is an important problem to identify, as most of these patients can be treated successfully.'

Susan Smith, Deputy Medical Director, Bridge Fertility Centre

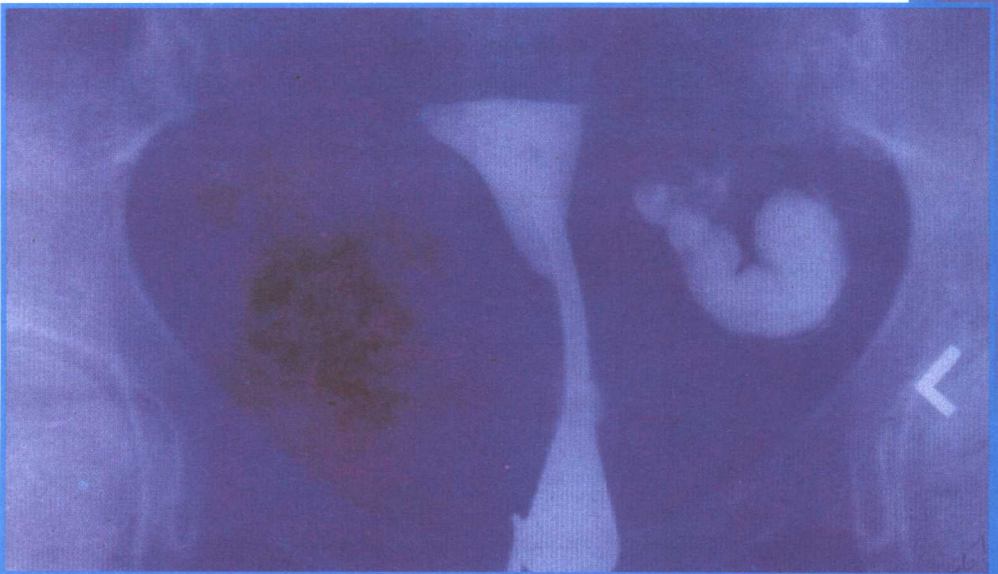
There can be several explanations for a lack of ovulation. Sometimes the situation is very stark – there are no eggs in the ovaries. However, this is relatively rare and is the cause of infertility in only one to two per cent of the women who have difficulty in conceiving. If there are no eggs then the woman will never conceive naturally. IVF can help provide her only chance of motherhood. Some women who

have had families of their own are prepared to act as egg donors. This means they allow eggs to be collected from their ovaries and given to other, infertile women. A donated egg can be fertilized by sperm from the man and placed in the infertile woman's body to develop.

However, in many women who do not ovulate the cause is easier to deal with. Some women don't make enough FSH to stimulate the release of the mature eggs from the ovary and others don't make any at all. Synthetic (laboratory-created) hormones can be used that will replace natural FSH, bringing about ovulation and so, hopefully, pregnancy (see page 16).

Tangled tubes?

The most common female physical problem preventing pregnancy is that the Fallopian tubes are twisted, scarred or blocked in some way. The Fallopian tubes are inside the body, hidden to human eyes. About 11cm long, they lead from the ovaries to the uterus. If the tubes are damaged, this prevents the sperm from meeting the egg and even more importantly, stops the egg, fertilized or not, from travelling along to the uterus. Thirty per cent of female infertility is the result of damaged Fallopian tubes.



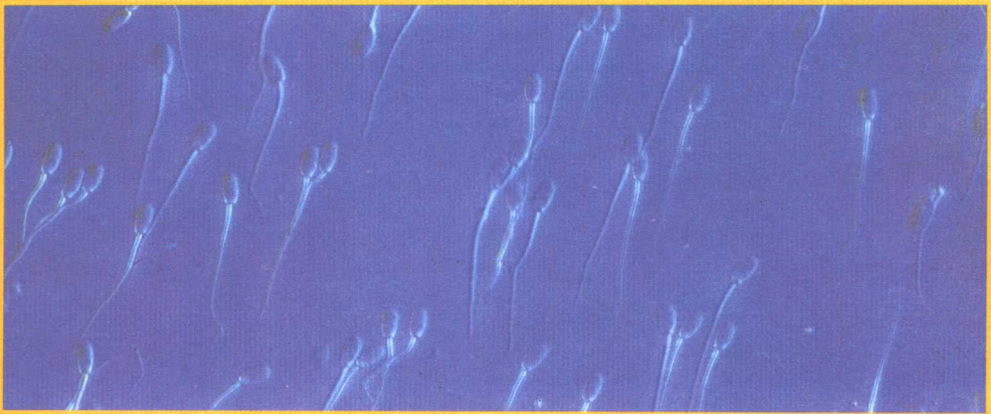
Techniques like this hysterosalpingogram help doctors decide whether IVF is necessary – if the Fallopian tubes are damaged, as these are, a normal **conception** is impossible. The uterus is the pale, **triangular** shape in the centre. The Fallopian tube on the left of the picture is not visible meaning that no dye has passed into it from the uterus. This shows that it is blocked. The tube on the right is damaged.

Damage to the tubes is revealed during an investigation known as a **laparoscopy**, usually combined with a dye test. During a laparoscopy a fine telescope is inserted into the abdominal cavity so doctors can look at the Fallopian tubes from the outside. Not surprisingly the woman is given a general **anaesthetic** so that she is unconscious during this procedure. For the dye test, a coloured dye is injected through the cervix and the doctors watch to see how the dye progresses through the Fallopian tubes – if the tubes are clear, the dye will spill out of the ends of them. These tests give a good first idea of whether or not the tubes are blocked or if there are any abnormalities in the uterus itself. If there seems to be problems the investigation can be taken further with a hysterosalpingogram. For this a special dye that shows up on X-rays is injected up into the cervix. The dye shows up blockages in the Fallopian tubes on the X-rays that are taken.

Sometimes a technique that involves tiny instruments placed into the Fallopian tubes can be used to try and reopen them, but the technique itself can damage the very delicate tubes. When the tubes are badly damaged or blocked then the only hope of a solution is IVF.

... or an infertile man

When a couple visit their doctor about fertility problems, investigations will be made into the fertility of the man as well as the woman. There are two crucial factors. Is the man producing sperm in his semen, and are they normal, healthy and active? The answer to both of these questions comes from a careful examination of the man's semen.



Using a microscope to view a fresh sample of semen reveals just what state the sperm are in, and how many of them there are.

In normal healthy semen there will be hundreds of millions of sperm. In fact the lowest number of sperm counted as normal is 20 million sperm per 1 cm³ of semen! Once the sperm count falls below this level it begins to affect fertility – remember that only one out of every 2000 sperm will make it from the cervix to the Fallopian tubes. If the sperm count is just a bit below normal there are certain things that the man can do to increase the numbers – all of them very low tech! If the testes get too warm, the level of sperm production falls, so cool showers or baths, baggy underwear and loose clothing can help to increase the sperm count. Smoking and drinking alcohol are known to lower the sperm count, so reducing or stopping these habits can also help increase sperm numbers. If the count is really low, it gets more difficult.

Numbers aren't everything

The overall sperm count is important, but the ability of sperm to **fertilize** eggs successfully depends on more than numbers. The **motility** of the sperm is very important too – in other words, how active are they and how well do they swim? For the man to be fertile his sperm needs to have actively lashing tails and around 50 per cent of them must swim forward in straight lines rather than round and round in circles.

Even if a man has lots of active sperm it isn't quite enough to be sure that he is fertile. It is also very important that the semen doesn't contain too many abnormal sperm. Every man produces a certain number of sperm with two heads instead of one, or with two tails, or broken necks. But if the percentage of these abnormal sperm gets too high, then the chances of a successful pregnancy fall.

Overcoming male infertility is not easy. Until recently the best hope was for the woman to be treated with healthy sperm given by an unknown donor, often mixed with some of her partner's sperm. However, some of the latest developments of IVF involve using a single normal sperm and injecting it into the woman's egg cell which is then implanted in her uterus. This exciting new development is leading to potential treatment for almost all men with fertility problems, as the numbers of men who produce no healthy sperm at all is relatively small.

*'There are very few cases of male infertility or sub-fertility that can actually be cured. Generally when we refer to treatment we mean techniques that enable us to **circumvent** the problem.'*

Sue Avery, Scientific Director, Bourn Hall Clinic

Treating infertility without IVF

The best known treatment for infertility is, without a doubt, IVF. It is never far away from the news headlines, not least because of the many new treatments that have followed in its wake. But when a couple first have fertility problems, the way they are treated will not always involve IVF.

Smoking, drinking alcohol, being very overweight or underweight, eating an unhealthy diet or having a lack of **follic acid** (a type of vitamin B) in the diet can make it difficult or impossible to conceive. For a surprising number of people, simple changes in lifestyle can make conception possible and result in the birth of a baby.

'Without very overweight or very underweight patients – in other words, if everyone was within the ideal weight range – the number of patients in my infertility clinic would be significantly reduced.'

Mr Michael Dooley, Consultant,
Winterbourne Hospital Infertility Clinic

One of the most common ways of treating fertility problems involves fertility drugs. These are not only remarkably successful in their own right, but have also paved the way for the development of IVF. One of the main reasons women fail to get pregnant is because they do not produce mature eggs. Fertility drugs are chemicals that work in different ways to stimulate the woman's body to produce and release a mature egg from the ovary.

The most widely used drug is clomiphene citrate. This drug works by fooling the body into making extra FSH and so stimulating the production of eggs by the ovaries. When women do not make any of their own FSH they can be given different drugs which actually contain human hormones. These stimulate the ovaries directly. Other fertility drugs can be used if the mature eggs are not released from the ovaries.

The use of these drugs has been very successful in helping many infertile couples to have children, and it has been vital in the development of IVF. To carry out this technique doctors need to harvest a number of eggs to fertilize outside the body. Even with fertile women, only