

Fertility and Infertility

How and Why?



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Foreword

The birth of Louise Brown, now nearly two decades ago, signalled a milestone in the development of possible treatments in reproductive medicine. It opened up new avenues for many married couples to explore in their heartfelt desire to have children. Sometimes it created the wrong impression, put forth by the media, that in vitro fertilisation was the one and only existing method of treatment that almost always resulted in a pregnancy. Unfortunately this remains to this day an illusion.

In this information brochure you will find a concise explanation of the normal cycle and conception and you will be given a brief introduction to the various treatment options. It is our job as doctors to select with you the best treatment for you. This means the treatment that in your specific situation gives the greatest chance of pregnancy, in the context of the physical and mental burden of the treatment and bearing in mind the cost efficiency of the treatment.

Every kind of treatment requires effort from you as a married couple and you will sometimes feel it is onerous. This is not surprising considering that getting pregnant is pretty well regarded as something that can be taken for granted. If it doesn't happen it is often met with a lack of understanding not only by you as a couple but also and in particular by those close to you - family, friends or acquaintances. Consequently for these reasons a psychologist works permanently with the centre and can be contacted whenever you need.

Treatment for fertility problems can only work best if a lot of different people work together: a specialist in male fertility, a psychologist, the technicians in the laboratory, the nurses and the administrative staff. Although we work as a team we try to approach each couple individually.

When going through the practicalities of your treatment the secretaries and the nurses will do their best to assist you. If some aspects of your treatment are not entirely clear, you can always ask them to explain.

We hope this booklet will make your treatment and what happens in practice clearer to you and we wish you every success.

The Normal Sequence

The desire for children is a very distinct and intimate expression of the affection that a couple feels for one another. However from the biological point of view, reproduction is the process of mingling the hereditary material of the man and woman. In this way a unique new individual can be created. Human beings use specialised cells for this: the reproductive cells or gametes. In men these are the sperm (spermatozoa) and in the woman they are the egg cells or ova (oocytes). The fusion of the sperm and the ovum (egg cell) creates a foetus, an embryo, which contains a new combination of genes (inherited characteristics). When the baby is finally born and grows up, you can very often recognise traits of the father and mother. "Mummy's blue eyes and Daddy's curly hair".

You can see below a diagram showing the most important stages of reproduction (Figure 2). Following the release of sperm (ejaculation) the millions of sperm try to find their way to the ovum. However a great many of them will not get past the many obstacles that they encounter on their journey. The first big barrier is access to the inside of the uterus (womb): the neck of the uterus (cervix). This is sealed with a plug of mucus. Next they must travel the entire length of the uterus and only then can they start their journey along the fallopian tubes. There they might find an ovum (oocyte).

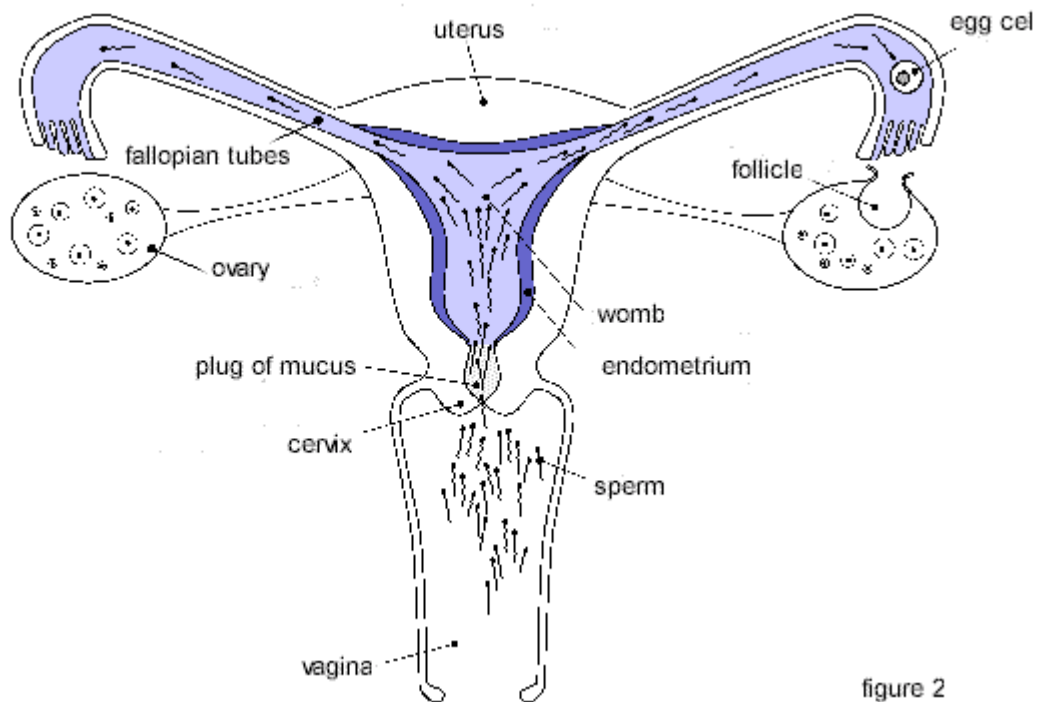


figure 2

In about the middle of the menstrual cycle the ovum is released from the follicle, a fluid-filled cavity in the ovary in which the ovum has matured. After ovulation the ovum is taken up by the fallopian tube and carried in the direction of the uterus.

So providing the sperm were released around the time that ovulation occurred, the best sperm will finally meet the ovum. The ovum allows one sperm to penetrate the membrane surrounding the egg, and that can fertilise the ovum.

During fertilisation the genetic material from the woman and the man fuses and the embryo begins to develop. The embryo divides during development, and every time a single cell becomes two. So first the embryo goes from a one-cell stage to a 2-cell stage, then from a 2-cell to a 4-cell stage, and so on (Figure 3). While the embryo continues to develop in this way, it is slowly transported to the cavity of the uterus by the fallopian tube.

At around the fourth day after fertilisation it comes to the uterus. The endometrium, or mucous membrane that covers the inside of the uterus, has been prepared for the arrival of a foetus after ovulation. The young embryo breaks through the membrane surrounding the egg, attaches itself to the endometrium and around the sixth day after fertilisation gradually starts to implant (nestle into) the wall of the uterus. If the uterus does not reject this new, foreign tissue and if the embryo continues to develop normally, the pregnancy has got under way.

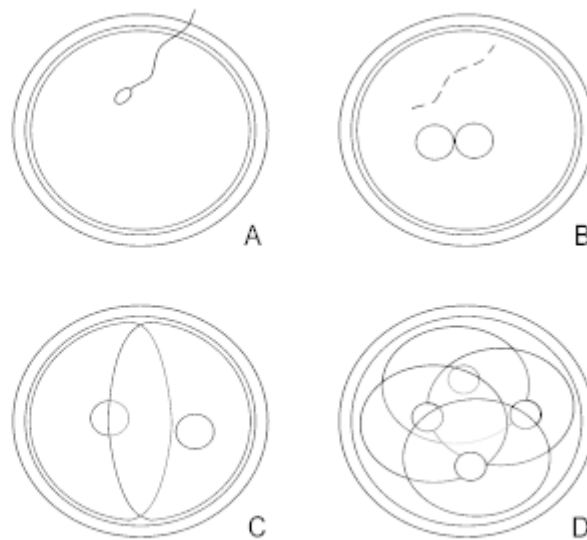


figure 3

- A. The sperm has just penetrated the membrane surrounding the egg and has fertilised the ovum.
- B. The genetic material of the man and woman is ready to combine. It is now shown collected into 2 spherical sacs (the pro-nuclei). A female and male pro-nucleus are shown. The tail of the sperm slowly disintegrates.
- C. The embryo has divided for the first time. There are now 2 cells (blastomeres).
- D. The embryo has divided for a second time. You can now see 4 cells.

How do your hormones work?

Many of the medicines you might have to take during the treatment have an important effect on the action of the hormone glands in your body. So it is a good idea to pause for a moment on the role of the most important hormones. By doing this you will understand even better why you have to follow a particular course of treatment.

2 important hormones are made in the ovaries: oestradiol and progesterone. The production of oestradiol rises strongly during the first half of the menstrual cycle (the follicular phase) and reaches a peak just before ovulation. Oestradiol makes the endometrium grow. It also makes the vagina moister and the mucus plug more accessible for sperm, so that around ovulation the chance of fertilisation is greatest. After ovulation the follicle in the ovary is transformed into the corpus luteum ("yellow body"). This produces the progesterone during the second half of the menstrual cycle (the luteal phase). The progesterone stops the growth of the endometrium and now makes it store nutrients. These are needed by the embryo during implantation.

How does the ovary know when and which hormone to make? And how does it know when sufficient has been made?

A very complicated process lies behind this. In simple terms it comes down to this. A hormone is produced in the brain that we call gonadotropin-releasing hormone (GnRH). The name refers to the fact that this hormone stimulates the release of two "gonadotrophins" in the pituitary, a gland that lies behind the nose, and below the brain (see Figure 4). Gonadotrophins are hormones that stimulate the activity of the ovaries. There are two gonadotrophins: **f**ollicle-**s**timulating hormone (FSH) and **l**uteinizing hormone (LH). As the name says, follicle-stimulating hormone promotes the growth of the follicle. The luteinizing hormone activates the ovary in preparation for the luteal phase. This is done by a sudden release of large quantities of LH in the middle of the cycle. This makes the follicle mature, followed by ovulation, 36 hours after the LH peak. The corpus luteum, which forms after ovulation, is stimulated by the LH to make progesterone.

The oestradiol and the progesterone can slow the release of GnRH, FSH and LH if necessary. So the loop is completed and the ovaries are prevented from making too little or too much oestradiol or progesterone at any time.

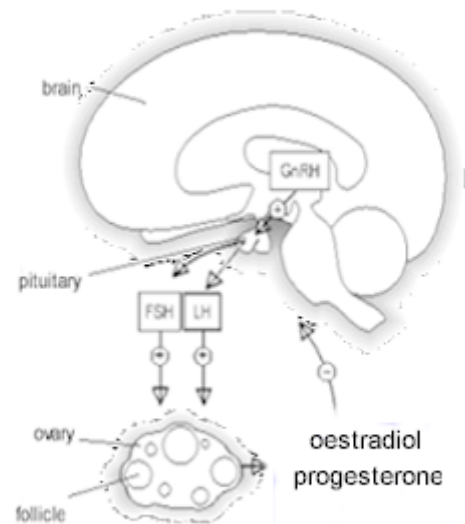


figure 4

When are you infertile?

Many couples are faced with difficulties in having children. On average it is estimated that 1 in 7 couples who want children experience fertility problems. For some couples it is really impossible to have children without treatment. For other couples a spontaneous pregnancy is not impossible, but it could take a lot longer than normal until the woman becomes pregnant. Therefore it would be better to talk generally of reduced fertility (sub-fertility) than infertility.

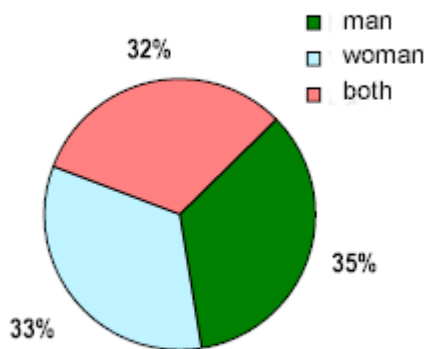
Nevertheless the word infertility is so well established that we will continue to use it, but we take it to include reduced fertility as well.

The relative nature of the concept of "normal fertility" is demonstrated by the fact that 1 in 7 of women with children have had to try for longer than 1 year. So it is not easy to define infertility. For example are you infertile after wanting to become pregnant for 1 year, or only after 2 years? Most infertility specialists advise you to try to become pregnant in a regular way for at least 1 year. Of course this doesn't apply to couples where a clear problem is already present, such as the absence of periods or the impossibility of obtaining an erection. In such cases and in all doubtful cases advice from an infertility specialist is certainly indicated. Likewise women with infertility who are older than 35 would do well to arrange an appointment with a specialist at an early date.

Why are you infertile?

Infertility could be caused by many things, and they could affect the man, the woman, or both. The frequency of the causes is spread over these three groups. (figure 5)

To get a better understanding of what problems can occur, it is important to understand how a normal pregnancy comes about. In the following section we will try in a simple way to present again the different steps in human reproduction.



From the previous summary it is already apparent that very many difficulties can arise. Below we will first discuss the possible problems men can have, and then those women can have. It is important to grasp that there can sometimes be more than one problem. A third, somewhat separate group, concerns couples with unexplained infertility.

Fertility problems in the man

In men a distinction is made between 1) abnormalities in the composition of the ejaculate 2) sexual and ejaculatory disturbances

So where do problems arise?

In the first case abnormalities are found when the semen is examined, which among other things can have an effect on the following properties of the ejaculate:

- volume of the ejaculate
- number of sperm in the ejaculate (concentration)
- number of sperm with normal movements (motility) and number of sperm with a normal appearance (morphology)
- number of white blood cells in the ejaculate
- the presence of antibodies on the sperm

Abnormalities that come to light when the semen is examined must always be confirmed by at least 1 confirmatory examination. If indeed there are abnormalities, then the first step is to look at the cause. This is important because sometimes a poor lifestyle is the basis for the abnormality. So it is known that smoking, alcohol and hot baths can cause a variation in the sperm picture. A recent illness can however also give a disturbed sperm picture. In other cases the cause is an abnormality in the functioning of the male reproductive organs. In this case a thorough physical examination by a specialist in the male reproductive system can bring clarity.

In approximately 2 out of 100 couples the man has sexual or ejaculation problems. Although there is usually a psychological cause, there are also certain diseases that can cause these problems.

Fertility problems in the woman

For the sake of clarity we will discuss female infertility problems based on the following breakdown:

1. the neck of the uterus (cervix)
2. the uterine cavity
3. the fallopian tubes
4. the ovaries
5. endometriosis

1. The neck of the uterus (cervix)

The mucus plug in the cervix acts a bit like a filter for the poor sperm. However if the mucus plug is too tenacious, it can even prove an impossible task even for good sperm to get through the cervix.

The most important causes of an abnormal mucus plug are:

- an infection in the cervix
- a shortage of the female hormone oestradiol, for example when ovulation is not forthcoming

- an earlier intervention on the cervix

2. The uterine cavity

The main reason for the existence of the uterine cavity is to receive the foetus. In order to do this the endometrium undergoes a number of important changes every month. During the first two weeks after the period the endometrium grows to a thickness of about 4 to 5 mm. This growth is promoted by the female hormone oestradiol, which is excreted into the blood by the ovary. After ovulation the ovary mostly makes the hormone progesterone.

Progesterone makes the endometrium accumulate nutrients before the arrival of the embryo. So hormonal disturbances can cause unfavourable changes in the endometrium, making implantation impossible.

Problems of quite a different kind can occur if the uterine cavity has an abnormal shape. This might be an inherited defect, such as a uterine cavity with a separating wall or it could be an abnormality that has developed in later life, such as a fibroma. It must be mentioned here that not all abnormalities always give rise to infertility. Women with a double womb can sometimes become pregnant without any problem and fall pregnant without treatment.

In a small number of patients there is a problem of an immunological nature, in other words the woman's defence system is not working properly. Usually the mother's defence system tolerates the presence of foreign tissue, which is what the foetus actually is. Sometimes the defence system mobilises against the young embryo, obstructing implantation. In women where this happens, the problem is sometimes expressed by repeated early miscarriages.

3. The fallopian tubes

The fallopian tubes also have an important task: they ensure that the ovum is transported to the uterine cavity. The ovum is also fertilised in the fallopian tubes. If the fallopian tubes are completely blocked by adhesions from previous infections, the ovum and the sperm can never meet: fertilisation is then impossible. If the obstruction is incomplete, it can still be very difficult for the fertilised ovum to reach the uterine cavity. There is then an increased risk of an extra-uterine (ectopic) pregnancy. The foetus no longer develops in the uterus, but for example, in the fallopian tube. Since the fallopian tube is lacking the muscular wall of the uterus, it is possible for the pregnancy to easily tear through the wall, which can lead to serious complications.

4. The ovaries

In the ovaries the female hormones are made and the egg cells grow. Most women have a large number of egg cells, sufficient for their whole life until they reach the menopause. However some women exhaust their whole stock of egg cells before they reach the normal age of the menopause. This is known as premature menopause. The egg cells can also be of less good quality. For example it is known that clearly more chromosomal abnormalities (the chromosomes bear the genes) can occur in the egg cells in older women than in the egg cells of younger women. The presence of an abnormally thick membrane around the egg can also sometimes cause difficulties when the embryo is ready to implant. However it is not always easy to detect these problems. We have already outlined above why the female hormones play such an important role in reproduction. For the female reproductive organs to work well the ovaries have to produce the right amounts of these hormones at the right time. Small deviations can sometimes cause major consequences. If it is suspected that

there is a hormonal imbalance, a series of blood samples will be taken and based on them the specialist can catch up with the problem and choose the best treatment.

5. Endometriosis

The term endometriosis is used whenever the mucous membrane is also present in a different place in the body from the inside of the uterus. Endometriosis is a very common condition in women of reproductive age. It is estimated that this condition appears in 1 in 5 women with infertility problems. Foci of endometriosis are mostly found on the peritoneum, on the ovaries and on the fallopian tubes. These areas of endometrium, just like the normal uterine membrane, also go through the monthly cycle of growing and bleeding, which can give rise to serious adhesions in the abdominal cavity. They can seal the fallopian tubes. The ovaries can similarly become encapsulated (surrounded by endometrial tissue) so that the ovum cannot be released at ovulation. These are the serious forms of endometriosis. In the mild forms of endometriosis, if there are only small patches of endometrium here and there, the connection with infertility is not so pronounced.

6. Unexplained infertility

If all avenues have been explored and nothing abnormal has been found, the infertile couple is often left with the unpleasant feeling that the specialist doesn't know what is wrong. That is actually true. In about 15% of infertile couples no clear cause of the infertility can be demonstrated.

Luckily scientific research is advancing rapidly, so in the future the number of cases where the reason for the infertility cannot be explained will reduce sharply. This is not to say that there is as yet no treatment for them at this time.

A little word about lifestyle

1. Smoking

You have probably already heard of the harmful effects of smoking. Smoking causes lung cancer, everyone knows that. But did you know that it takes longer for women to smoke to fall pregnant? Did you know that the stock of egg cells in women who smoke is more rapidly used up? Did you know that women who smoke run a higher risk of miscarrying? And did you know that the babies carried by women who smoke have a much lower weight at birth? Men who smoke also strongly compromise their fertility. It has been demonstrated that the sperm of smokers is of poorer quality than that of non-smokers.

2. Alcohol

A glass of wine now and then certainly does you no harm. But excessive use of alcohol is harmful. It diminishes the quality of sperm and the ability to maintain an erection. The effects of alcohol on a woman's fertility have not yet been proven beyond doubt. But we confidently advise you to keep your alcohol consumption reasonable. Especially since consuming alcohol during pregnancy can give rise to malformations.

3. Body weight

To help you decide whether your body weight lies within the normal limits, we have drawn up the following table for you. Find your height in the first column and then read off between which two values your weight should lie.

Why are these values so important?

Well, women who weigh more than normal for their height often have great disturbances in their ovulation. If you are overweight and you don't have periods or they are very irregular this can have an adverse effect on the pattern of ovulation. It is very encouraging to know that the great majority of these women return to a regular pattern of menstruation if they lose at least 5% of their weight. In other words, you can expect a beneficial effect if you lose 1 kg for every 20 kg that you weigh. Typical height values: A small number of women can indeed have a perfectly normal pattern of ovulation with a weight that lies outside the boundary values. Nevertheless we cannot advise you more strongly to try and get to your normal weight. After all, the risks of the surgical interventions that you might have to undergo during the treatment of your infertility increase sharply with your weight.

Women whose weight is clearly less than what is normal for their height, can funnily enough also have problems in the regularity of their periods. They should try to reach a sufficient weight, so that the body weight falls within the normal limits again.

The figures in the table are nevertheless only typical values. A small number of women can indeed have a perfectly normal pattern of ovulation with a weight that lies above the boundary limit. Nevertheless we could not recommend more highly that you try to get to your normal weight. As you know, this is because the risks of surgical interventions that you might have to undergo during treatment of your infertility rise steeply as your weight increases above normal values.

Have you heard of these tests?

1. Blood tests

The investigations that are done on the blood can vary from patient to patient. The most common tests are the following:

Hormone determinations

Determinations of antibody levels against certain infectious diseases

Chromosome determinations

2. Vaginal echography

Vaginal echography is a way of getting pictures of the internal sexual organs of the woman. The examination is painless and is done with a vaginal probe. The sound waves that are used for this are harmless to the human body, even during pregnancy. It is routinely used to monitor the growth of the follicles in the ovaries and also to follow a beginning pregnancy.

3. Hysteroscopy

The best images of the uterine cavity are obtained with hysteroscopy. During this ambulant and painless examination a fine endoscope (the hysteroscope) is inserted through the cervix into the uterus.

4. Laparoscopy

As with hysteroscopy, an endoscope (a laparoscope) is used. Under a general anaesthetic a very small incision (< 1 cm) is made in the navel and the endoscope is inserted into the abdominal cavity. All the organs in the abdominal cavity can be inspected thoroughly. At the same time the free passage through the fallopian tubes can be examined.

5. Transvaginal hydrolaparoscopy

This method of investigation was developed in our centre and provides us with the same information as laparoscopy. The procedure is performed through the vagina and has the big advantage that it can be formed on a conscious patient so it is much less invasive than the standard laparoscopy.

Hysterosalpingograph (HSG)

In this investigation a contrast medium (a substance that does not allow X-rays to pass through) is injected into the uterus. In this way we can get a picture of the inside of the uterine cavity and the fallopian tubes. This technique can also reveal whether there is free passage through the fallopian tubes. This investigation is only performed rarely in our centre.

Postcoital test (PCT)

The postcoital test is one of the older tests in the investigation of infertility. The test takes place a few days before ovulation is expected. The couple are asked to make love 6 to 12 hours before the investigation is scheduled. A sample is examined under the microscope to determine how many motile sperm are to be found in the mucous of the neck of the uterus.

Sperm analysis

The examination of a sample of sperm is an important element in investigating infertility in men. The semen is produced by masturbation after a period of 2-3 days' abstinence. The sample can be produced in the centre or at home, but in the latter case, it must be brought to the lab within an hour. It is important not to let the sample get cold while it is being transported. The best way of doing this is to carry the closed container in your trouser pocket or in the inside pocket of a jacket.

Possible treatments

The right diagnosis is very important for the treatment of infertility. Unless there is a diagnosis a treatment plan cannot be discussed with the couple. For example some causes of infertility require a purely surgical approach while other causes are better treated by IVF. In each case the choice of the treatment is a decision-making process in which the couple is closely involved. The treatment is in itself often very arduous. If in addition the couple still have the feeling of not knowing exactly what has to be done, the feeling of helplessness can become great. Therefore the infertility team tries to explain all the steps in the proposed treatment as well as they can. To explain what lies before you there follows a brief summary of the different types of treatment, so that armed with this knowledge you are better able to prepare questions to ask the doctor.

1. Surgery

These techniques are always performed under general anaesthetic. For some of the more complicated interventions it is not unusual for you to be admitted the evening before the operation.

1a. Laparoscopic surgery

Many of the surgically treated causes of infertility can today be tackled using a laparoscope. The advantage of this is that the incision through the skin is much smaller than in the "usual" surgery, so patients are not upset so much by the operation and can often even go home the same day.

1b. Microsurgery

Some surgical interventions require special technical precision, which can only be achieved by the use of an operating microscope.

2. Hormone therapy

In this category we discuss treatments in which medication alone is prescribed. This type of treatment is indicated for couples in which the only problem is disturbed ovulation, for example in irregular or absent periods. As the monthly ovulation is an important prerequisite for rapidly achieving pregnancy, an obvious first step for these women is to restore the pattern of ovulation. A number of medicines are available to the doctor, which we will go over shortly. In each of the different possibilities the doctor will try to increase the amount of FSH that reaches the ovaries. After all this is the hormone that stimulates the growth of the follicles.

2a. Tablets

Clomid is the best known of this group. When Clomid is taken, the body gets the false impression that there is a serious shortage of oestradiol ("anti-oestrogen"). The body reacts to this by an indirect stimulation of the ovaries. However the fact is that this treatment does not definitively restore the rhythm of ovulation in most cases, therefore the treatment must be re-started every month as long as it is required.

2b. Injections

A more direct approach is to inject substances that stimulate the ovaries directly. The injections are given in a muscle or subcutaneously depending on the substances used.

2c. The pump

This method uses a small pump by which small amounts of hormone are injected into the skin at regular points in time. This is a way by which a normal cycle can be restored in patients with a complete absence of cycle by direct stimulation of the pituitary.

2d. The nasal spray

This medication is primarily used during treatment by in vitro fertilisation and prevents a premature ovulatory response.

3. Medically assisted reproduction

This category contains technologies that can help to bring about fertilisation in a more intrusive way. Stimulatory treatment is usually combined with these techniques, which can differ depending on the technique used.

3a. IUI

This abbreviation stands for intra-uterine insemination. This means that the man's semen is prepared in the laboratory, after which it is injected directly into the uterine cavity. This has two advantages: the sperm no longer have to get past the plug of mucus in the neck of the womb and the sperm in the prepared sample are already a selection of the best sperm.

The most important prerequisite for being able to use this technique is free passage through the fallopian tubes. If they are closed, it is impossible for the sperm to reach the ovum. The stimulation treatment given with this technique is quite gentle. The goal of the stimulation is to obtain 1 to 3

mature follicles (with egg cells). With more egg cells the risk of multiple pregnancy would be unacceptably high.

3b. IVF

This abbreviation stands for in vitro fertilisation.

After the follicles have been strongly stimulated follicle puncture is performed (to collect mature egg cells from the ovary). The ova obtained are mixed in the laboratory in a dish with prepared sperm (insemination) and then placed in an incubator. The incubator keeps the culture fluid at the right temperature and degree of acidity. As this technique places the best sperm in the immediate vicinity of the ova, it is usually not long before a sperm has penetrated the membrane of an ovum and fertilised it. If all goes well a large proportion of the eggs cells will be fertilised. If absolutely none or very few of the ova obtained are fertilised, this could indicate a problem with the ova, the sperm, or both. This is always disappointing news, but the information can be used to try another, more complicated, technique in the following cycle.

After the fertilisation the embryos are regularly checked to see if the development of the embryo is normal. Usually on the second or third day following the puncture one or two embryos are placed back in the uterine cavity. This is called embryo transfer. It is a simple and painless procedure whereby a catheter (small tube) is inserted through the cervix to the uterine cavity so that the embryos and a small quantity of culture fluid can be transferred here (see Figure 6). In the uterine cavity the embryos continue to develop further until they are big enough to break through the egg membrane and implant themselves in the endometrium.

Embryos that are not returned to the uterus and show no signs of serious disturbance in their development are frozen. The frozen embryos can later be thawed and placed in the uterus.

3c. GIFT

his abbreviation stands for gamete intra-fallopian transfer.

At first this treatment proceeds in the same way as in vitro fertilisation. After the egg cells have been aspirated (sucked up) the second step follows whereby a laparoscopy is performed to place ova and sperm in the fallopian tubes.

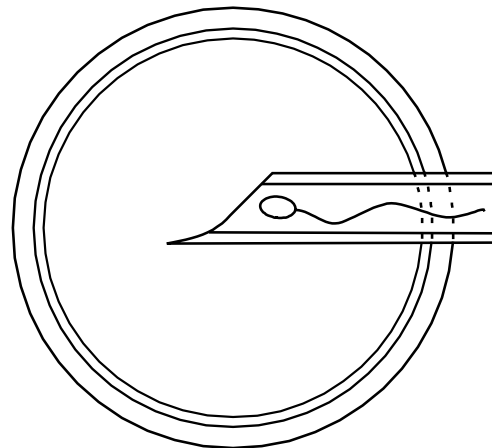
So in GIFT fertilisation does not take place in the laboratory but in the fallopian tubes. This distinction can be important for a number of reasons. For people with certain religious convictions this is a more acceptable solution than IVF, where fertilisation takes place in the lab. This technique is more invasive than IVF, does not offer any additional advantages and is not used as often at the moment.

3d. Special techniques

1. ICSI

This abbreviation stands for intracytoplasmic sperm injection.

If there are serious abnormalities in the sperm picture IVF can often not offer a solution. Although a sample is prepared for IVF using only the best sperm, in some men even the best of these is not good enough to penetrate the egg membrane “under its own steam”. If only a very low number of egg cells was fertilised in a previous attempt at IVF, there is little point in continuing. In these cases ICSI can sometimes be the way forward. The principle of ICSI is to inject a single sperm directly into each ovum using a very powerful microscope and an ultra-fine glass needle (see Figure 7).



Figuur 7

After the sperm has been injected the genetic material has to be released into the nucleus of the ovum and pair with that of the ovum. If that does not happen, the fertilisation is incomplete. In other words, injecting the sperm is the first step in the (in this case assisted) fertilisation, but it is only complete if the hereditary material of the man and woman fuses. That is a condition for the normal development of the embryo. So injecting the sperm into the egg is no guarantee that embryos will be obtained. After the sperm has been injected the rest proceeds as for IVF: two or three days after the ova are obtained the best embryos are replaced in the woman's body.

2. MESA, TESA and TESE

In some men it can be difficult to extract sufficient good sperm from a typical ejaculation for the ICSI procedure. If this is the case, there exists the possibility of obtaining sufficient sperms directly from the epididymis (a structure associated with the testis) or the testis (testicle). It is frequently possible to obtain sufficient sperm from the epididymis or testis under local anaesthetic using a very fine needle. These procedures are known as MESA and TESA respectively and from there an ICSI procedure can be performed.

In a very small number of cases aspiration using a needle is insufficient and a small incision must be made in the testis (TESE) in order to remove a small amount of tissue. The embryologist can then extract the sperm from this tissue.

3. Assisted hatching

The term “assisted hatching” refers to a technique by which the embryo is given a helping hand to break through the egg membrane. In some women the egg cells are enclosed by an unusually thick or hard membrane, so it is not inconceivable that the infertility is being partly caused by this. With the special microscope that is also used for ICSI a small opening is made very carefully in the egg cell membrane so the embryo can attach itself at this point. The value of this technique has been strongly criticised by many doctors however.

4. Pre-implantation screening

In this embryos are examined for possible genetic defects. We know that there is a direct connection between the number of genetically abnormal ova and the woman's age. If such ova do become fertilised these embryos would not usually implant or might result in a miscarriage.

Techniques have recently been developed that make it possible to detect these genetically abnormal embryos before the fertilised eggs are replaced in the woman's body. In other words the test can be performed on embryos that are created by IVF or ICSI. In this test a single cell is removed from the embryo for further examination. This does not threaten the continued normal development of the

embryo. It enables us to only insert genetically normal embryos, resulting in an increased likelihood that the pregnancy will develop normally. This method can be used for women over the age of 37. The same method is used in couples who are known to have an increased risk of known hereditary defects. Until recently there were only two ways of preventing a known hereditary disease or condition being transferred: advise the couple not to have any children or perform an abortion at the start of the second term of pregnancy if amniocentesis or chorionic villus sampling indicates that the disease has indeed been passed to the child. If the embryos are examined before they are returned to the woman, only those that have not inherited a disease can be used.

This technique enables couples to have their own children safely without having to wait a long time for the result of the amniocentesis or chorionic villus sampling tests. Furthermore a second-term abortion is always a very traumatic experience from both a physical and emotional point of view. It is obvious that when testing for hereditary diseases these techniques are only possible due to close co-operation with a centre for genetic diagnosis.

4. Alternative forms of treatment

4a. Egg cell donation

Some women cannot use their own ova for medically assisted reproduction. This may be because the woman has no more egg cells, for example if she has undergone a premature menopause. In a particular case it might be that a woman carries a disease or condition that can be inherited by the children. Although these women are not infertile, if they want to have children the donation of an egg by a healthy woman can offer a way out.

The woman who provides the ova (the donor) is treated to stimulate her ovaries then has eggs removed by the puncture technique. The donor cells are then fertilised by sperm from the recipient's husband. The embryos are placed in the recipient's uterus in the same way as with IVF. If however the recipient no longer has periods, she must have replacement therapy, by which the hormones she no longer makes herself are compensated for by tablets or injections. This technique has already helped many couples. Nevertheless the demand for donor egg cells is always much higher than the supply. Consequently the waiting time is long, unless the patient finds a donor herself.

4b Sperm donation

If it appears impossible to obtain sperm from the man, the doctor can suggest that the couple use sperm from a donor. We call this artificial inseminate by donor (AID). If this is an acceptable option for the couple, fertilisation with donor sperm can take place by the IUI as described above. In some cases the use of donor sperm can be recommended for IVF or ICSI.