

# Test tube fertilisation

## - in vitro fertilisation IVF

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## Definition

### 1. In vitro fertilisation?

In Vitro Fertilisation is also called *In Vitro* Fertilisation (IVF). In IVF, mature eggs are retrieved from the ovaries and fertilised with sperm outside the body in the laboratory. *In vitro* is Latin for *in glass*. Once the eggs have been fertilised, they are transferred to the uterus.

IVF treatment is efficient: within three periods of treatment, 70 percent of our patients are pregnant with at least one child if the women's ages is below 40 years.

We recommend IVF if:

- the woman has blocked tubes
- the male has poor quality of semen
- unexplained infertility after failed IUI

## The process

### 1.2 IVF step by step:

1. Consultation with your doctor
2. Examination to identify the cause for infertility
3. Hormone stimulation
4. Ultrasound scan of the follicles
5. Semen sample
6. Egg aspiration
7. Fertilisation of the egg
8. Embryo transfer
9. Pregnancy test
10. Pregnancy scan

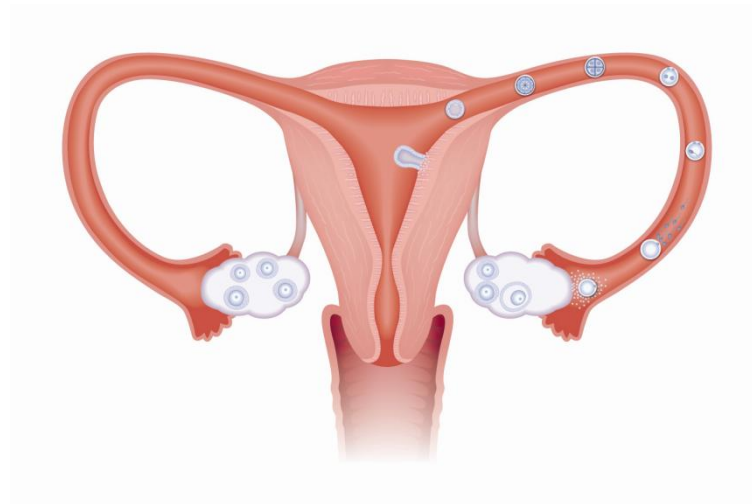
If you have any questions, please do not hesitate to contact Copenhagen Fertility Center.

### 1.3 Before IVF treatment the following aspects has to be controlled.

- that the woman has a normal uterus. We will examine this by an ultrasound scan or a water scan.
- that the woman is ovulating, either by herself or assisted by hormonal treatment.
- that the man is producing sperm cells. Or the sperm cells can be recovered from the testicle or the by-testicle. There is also the option of using donor semen.
- that the woman either has had or has been inoculated against rubella within at least the past three months. This can be examined by a blood sample.
- That you have received counselling about possible hereditary genetic diseases.
- That both the woman and her partner have been tested for HIV and Hepatitis B and C prior to the treatment. The tests which needs to be taken are:

HbsAg, Anti-HBc, anti HCV and anti-HIV 1 + 2

See the below illustration of the normally functioning uterus:



*The illustration shows a normally functioning uterus.*

*Kindly provided by Ferring*

## 2. About the female reproductive system

In this chapter you can read more about how the hormonal system interacts and the impacts on the reproductive system. The chapter is meant as help to understand the treatment you are about to have.

The female reproduction system is, somewhat simplified, constructed through the interplay of three elements:

- The hormonal interplay between the pituitary gland in the brain and the ovaries, where the eggs mature and the ovulation takes place.
- The uterine tubes, where the egg is fertilised and transported to the uterus.
- The uterus, where the fertilised egg adheres to the endometrium and becomes a pregnancy.

### 2.1 The development of the follicle

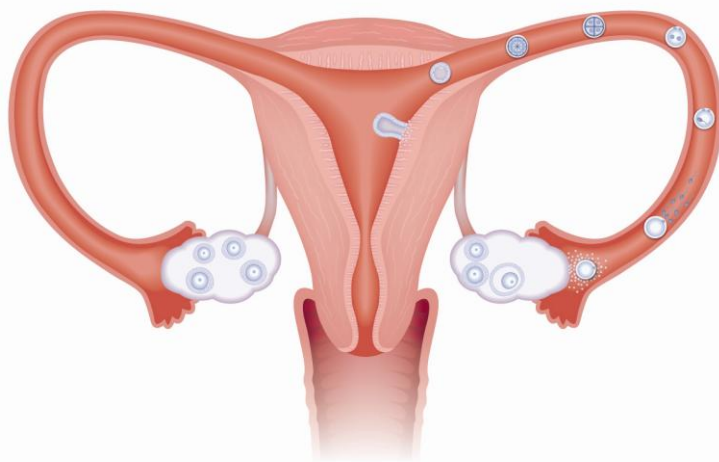
In the ovaries the egg is matured and fully developed prior to the ovulation. The egg is caught by the uterine tube, which leads the egg to the uterus. If the egg is fertilised, it will adhere to the endometrium in the uterus and further develop.

This process is coordinated by the hormones.

The development of the follicle and the embryo is illustrated below:

The illustration shows the development of the follicle, ovulation, fertilisation, embryo development and finally the adherence of the embryo to the endometrium of the uterus.

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## 2.2 The interplay of the hormones

Most of the superior sex hormones are formed in the pituitary gland, which is a gland in the brain. The hormone is transported via the blood to its destination (the organ), where a reaction takes place and a signal is sent back to the pituitary gland

Below the functions of the individual hormones are briefly described.

**GnRH-Gonadotropin releasing hormone.** GnRH causes release of FSH and LH in the pituitary gland.

**FSH (Follicle stimulating hormone)** - is formed in the pituitary gland and stimulates the growth of the follicles, which mature the eggs.

**LH-Luteinizing hormone** - is formed in the pituitary gland and causes ovulation.

**Prolactine** is formed in the pituitary gland and is in interplay with the breasts and the ovaries. Prolactine causes growth of the mammary gland during pregnancy and stimulate the milk production after childbirth. A too high level of prolactine can restrain the ovulation.

**Estradiol** is formed in the ovaries. During a menstrual cycle estradiol causes growth of the endometrium in uterus. A high level of estradiol in the middle of the cycle results in an increase of LH, which leads to ovulation.

**Progesterone.** During the menstruation progesterone together with estradiol prepare the endometrium in uterus to receive the fertilised eggs. During a pregnancy progesterone restrains the contractions of the uterus.

**Androgens** are formed in the ovaries and stimulate growth of the hair and the sexual instinct. An overproduction of androgens restrains ovulation.

**HCG (human chorion gonadotropin)** is formed in the placenta and prevents that the follicles are destroyed during pregnancy. We analyse this hormone to find out if you are pregnant.

During the menstruation the ovaries contain several small follicles, each of them containing an egg. The pituitary gland releases the hormone FSH, which leads to development of one single follicle to be approximately 20 mm in size. When the follicle is mature, the ovulating hormone LH is released. The hormones are interdependent, and for some hormones the rule is that an increase in one hormone results in a decrease in another.

Below you can see how the hormones normally develop during each menstruation cycle. At the very top of the illustration you can see how the follicle develops and matures throughout the cycle.

### 3. Treatment - long down regulation

Copenhagen Fertility Centre's long course of treatment with test tube fertilisation normally takes 45-50 days. We divide the treatment into four phases:

#### Down regulation

#### Stimulation

#### Laboratory

1. **Down regulation** with Synarela® or Suprefact® takes approximately 16-19 days.
2. **Stimulation** with Puregon®, Gonal F® or Menopur® takes on average 15 days.
3. **The laboratory work** with egg aspiration, fertilisation *in vitro* and transferral of the fertilised egg/eggs takes 2 days
4. **After-treatment** with Progestan® for 14 days. The after-treatment is completed by a pregnancy test.

Blocks the hormones that normally regulate the function of the uterus. The ovaries come to a stop, no eggs are developed and therefore there is no ovulation.

Now the ovaries only react to the hormone that is supplied from outside. The hormone FSH (follicle stimulating hormone) helps the follicles grow, and when a suitable number have reached a size of 18-20 mm, the maturation of the eggs is induced with another hormone hCG (human chorion gonadotrophin = ordinary pregnancy hormone).

After 37 hours, the eggs are aspirated from the follicles (aspiration) and become fertilised in the laboratory. Two days later 2-3 of the best fertilised eggs (embryos) are transferred to the uterus (embryo transfer).

For the following 14 days a supplement of the hormone progesterone is given. This hormone stabilises the mucous membrane in the uterus and this helps the embryos to adhere. Finally, on day 14, a pregnancy test is done.

#### How to get started on the treatment

One of the first days of your menstrual cycle you call the nurse at the Copenhagen Fertility Centre and get the 1<sup>st</sup> appointment for day 19-23 in the cycle. The telephone number is 3325 7000, and the telephone is open on weekdays between 10 am and 1pm and weekends between 9 and 12am.

#### 1<sup>st</sup> appointment on day 19-23 in the cycle – down regulation

We perform an ultrasound scan, and if everything is in order you can start the down regulation. The down regulation is carried out with either Synarela® nasal spray, 3 puffs 3 times daily, i.e. with an interval of 8 hours, or with Suprefact® injection, 0,5 mg subcutaneous once daily. The down regulation must be continued until the aspiration.

The nurse will explain the treatment in details and together you will discuss and make arrangements for possible egg donation and freezing of fertilised eggs. Should any questions arise, you should feel free to ask during this or future consultations. You will receive

various forms, which we kindly ask you to read thoroughly and bring back signed for the next consultation. Also, you will get a written treatment schedule with all relevant information. Finally, we supply you with all medication, syringes and needles, and we keep a careful record of your medicine. Later on you will receive an invoice directly from the pharmacy.

Please note that you inject the medicine yourself. After careful instructions from the nurse most patients are able to inject themselves, but of course you can attend the clinic for injections, if you wish.

### Menstruation

Your menstruation will typically begin 8-10 days after starting down regulation and will probably last a little longer than usually. In some cases, menstruation can be up to 8-14 days overdue. If the menstruation has not yet started on the date where the stimulation is scheduled to start, please contact the clinic.

### Stimulation

Stimulation with Puregon starts after 16-19 days of down regulation and when you have had your menstruation. The injections are made daily before 12am. Be sure to continue using Synarela® / Suprefact®, but now it is only necessary to use the nasal spray twice a day: 1 puff 2 times daily, i.e. with an interval of 12 hours and Suprefact® 0,2 mm daily.

### 2<sup>nd</sup> appointment after 8 days of stimulation

Nine days later we perform another ultrasound scan. We measure the thickness of the mucous membrane in the uterus, the number of follicles and their size. We often perform an extra scan a couple of days later.

When a suitable number of follicles have reached a size of 18-20 mm, we plan the egg aspiration and the time for the ovulating injection. We use 250 micrograms of Ovitrelle®. The egg aspiration is performed 37 hours after you have taken Pregnyl® and on average 15 days after the stimulation was started.

### Egg aspiration

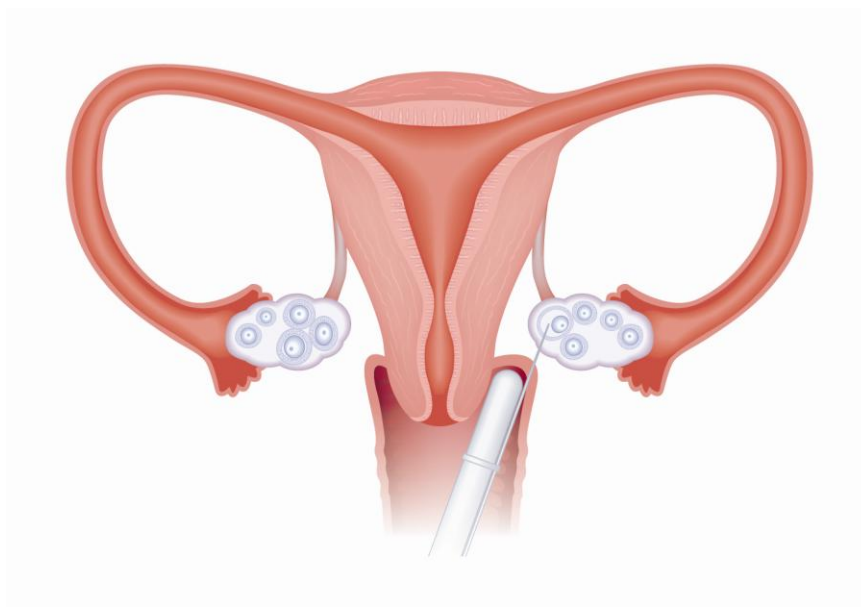
The aspiration takes place between 9 and 11am on weekdays and in the weekend. It will take about 10-20 minutes. You don't have to be fasting, but please refrain from eating anymore than a light meal before aspiration.

You can take two Panodil tablets one hour prior to your a appointment at the clinic.

Immediately before the egg aspiration you will get an injection of the painkiller Rapifen® through a plastic canola which is inserted in your hand. Furthermore, the doctor will administer a local anaesthetic in the vagina wall.

The egg aspiration is performed through the vagina wall. Making use of ultrasound, a thin needle is inserted into the follicles. Each follicle is drained of fluid and at the same time the egg is sucked out. On our screen you are able to follow the whole procedure. The aspiration takes approximately 10-20 minutes.

*Aspiration is performed with a thin needle through the vagina wall.*  
Kindly provided by Ferring



After the aspiration you will get something to drink and rest for an hour in the clinic. The next couple of days there might be some minor bleeding from the vagina. There might also be some pain, and you can take some pain-killing Panodil tablets, but not more than 1 g = 2 tablets 4 times daily.

You are always welcome to call the clinic, should any problems occur or should you have further questions.

Finally, you need someone to escort you home and stay with you for the rest of the day, and you are still not allowed to drive a car yourself. Moreover, we advise you to rest that day.

### **Sperm sample**

When you attend for the aspiration you bring a sperm sample. It is important that the sample has your full name and d. o. b. on it. You can either make the sample at home or at the clinic. In either case, the sperm sample must not be more than two hours old, when you hand it in. After aspiration we will use the sperm sample to inseminate the egg.

### **Fertilisation *in vitro***

Approximately 100.000 sperm cells are added to each egg. The next day the eggs are sorted and controlled, and we monitor whether the development is normal. During the next two days and nights the fertilised eggs (embryos) will develop from being 1 cell to being 2-6 cells. We follow this development daily, but it is only after 48 hours that we know for certain how many of the eggs have developed satisfactorily.

### **Aspiration of sperm from the testicle – TESA**

We use TESA if the man cannot naturally produce sperm cells. The procedure is performed under local anaesthesia. A fine needle is introduced directly into the testicle, and suck out a tissue sample containing sperm cells. The sperm cells of which there are only few, are at first completely immobile, but after 3-4 hours they can be used for fertilisation by microinsemination (ICSI).

## Fertilisation by microinsemination – ICSI

At microinsemination the sperm cell is injected directly into the egg. This method is used when only very few sperm cells are available or when the sperm cells are quite immobile.

Microinsemination does not reduce the chance of pregnancy.

## Embryo transfer

The next day, i.e. 2 days after the egg aspiration, the fertilised eggs (embryos) are transferred to the uterus. Routinely, only one or two fertilised eggs are transferred, but if the woman is more than 38 years of age three fertilised eggs can be transferred. The fertilised eggs are transferred to the uterus through a thin plastic catheter, which is inserted into the cervix. The embryo transfer is usually a quite simple procedure and completely painless; you will probably feel nothing at all.

## Freezing of surplus embryos

After the embryo transfer, surplus embryos might be frozen and later on be transferred to uterus. Of course, this only applies for embryos that are considered suitable for freezing.

## After-treatment

For the following 14 days you will take Progestan® vaginal suppositories 100 mg, 2 suppositories 3 times daily. Progestan® contains the hormone progesterone, which stabilises the mucous membrane in the uterus. You will not need any time off from work. If you use your common sense, you can live quite normally.

## The pregnancy test

14 days after the embryo transfer take a pregnancy test. The pregnancy hormone is determined in a blood sample. The pregnancy test has to be performed, also if you have started to bleed. The test is performed at Copenhagen fertility Centre all weekdays, and the result will be given by telephone after 1 hour. If the test is positive, we will offer you a pregnancy scan three weeks later (the 7th week of pregnancy).

If the test is negative, we recommend you to make an appointment with the doctor, where we can evaluate your course of treatment and maybe reschedule.

If you live far away from the clinic, your general practitioner can do the pregnancy test or you can do a sample of morning urine with a test supplied by us. We kindly ask you to telephone the result to Copenhagen Fertility Center on week days between 10am and 1pm.

## 4. Treatment - Short down regulation

Nordica Fertility Centre's short course of treatment normally takes 30 days, and can be divided into three phases:

- **Stimulation (FHS)** with Puregon®, Gonal-F® or Menopur®. Approximately 10-15 days.
  - **Preventing ovulation** with Orgalutran® 0,25 milligrams once daily from the 7th day for 3.8 days.
- **The laboratory phase** with aspiration, fertilisation *in vitro* and transfer takes 2 days.

- **After-treatment** with Progestan® for 14 days and finally a pregnancy test.

We use the hormone FSH (follicle stimulating hormone) that helps the follicles grow. When the follicles have reached a size of about 12-14 mm, (around day 7), you must also take Orgalutran®, which prevents ovulation. When a suitable amount of follicles have reached the size of 18-20 mm, the maturation of the eggs is induced with ordinary pregnancy hormone hCG, called Ovitrelle®.

After 37 hours, the eggs are aspirated from the follicles (aspiration) and become fertilised in the laboratory. Two days later 2-3 of the best fertilised eggs (embryos) are transferred to the uterus (embryo transfer).

For the following 14 days a supplement of the hormone progesterone is given. This hormone stabilises the mucous membrane in the uterus and this helps the embryos to adhere. Finally, on day 14, a pregnancy test is done, and this is hopefully positive.

### How to get started on the treatment

On the first day of your menstrual cycle you call our nurse and schedule an appointment for the second or third day. Our telephone is open on weekdays from 10am to 1pm and the telephone number is 3325 7000.

### 1<sup>st</sup> appointment on day 2 in the cycle

We perform an ultrasound scan, and if everything is in order you can start stimulation with Gonal-F or Puregon. You must take the injections every day before 12am.

The nurse will explain the treatment in details and together you will discuss and make arrangements for possible egg donation and freezing of fertilised eggs. Should any questions arise, you should feel free to ask during this or future consultations. You will receive various forms, which we kindly ask you to read thoroughly and bring back signed for the next consultation. Also, you will get a written treatment schedule with all relevant information. Finally, we supply you with all medication, syringes and needles, and we keep a careful record of your medicine. Later on you will receive an invoice directly from the pharmacy.

Please note that you inject the medicine yourself. After careful instructions from the nurse most patients are able to inject themselves, but of course you can attend the clinic for injections, if you wish.

### 2<sup>nd</sup> appointment on day 7 or 8 of your cycle

We perform an ultrasound scan on the 7th day of your cycle. We measure the thickness of the mucous membrane in the uterus, the number of follicles and their size. You must begin taking injections with Orgalutran® whilst continuing with FHS, when the follicles have reached the size of 12-14 mm.

### 3<sup>rd</sup> appointment

When a suitable number of follicles have reached a size of 18-20 mm, we plan the egg aspiration and the time for the ovulating injection. We use 250 micrograms of Ovitrelle®. The egg

aspiration is performed 37 hours after you have taken Pregnyl® and on average 15 days after the stimulation was started.

### Egg aspiration

This takes place as mention in the chapter for long protocol see page 8.

## 5. Treatment - Low Stimulation

With this treatment only a few eggs are matured and this is why it is only suitable for young women who are in IVF treatment.

### The treatment

Mild hormone stimulation with Clomivid tablets (Pergotime®) is given: 3 tablets daily starting on the 3<sup>rd</sup> day to the 7<sup>th</sup> day of the menstrual cycle. In addition, daily injections of 100 units of Puregon® from day 8 of the cycle, which will make your follicles grow. With this treatment, 1-5 eggs will mature. Ultrasound scan of the follicles is performed to determine the optimal time for aspiration. When the follicles are 18 mm in diameter, you must take Ovitrelle® to provoke ovulation. 34 hours later the eggs are aspirated from the follicles (aspiration).

The eggs are fertilised in the laboratory, and two days later the best fertilised eggs are transferred to the uterus (embryo transfer)

### The treatment day by day

One of the first days of your menstrual cycle you call Nordica Fertility Centre and get an appointment for an ultrasound scan on the 11<sup>th</sup> day of the cycle. Our phone number is +45 3325 7000.

From the 3<sup>rd</sup> day of the menstrual cycle to the 7<sup>th</sup> day included, you take 3 Clomivid (Pergotime®) tablets daily.

From the 8<sup>th</sup> day of the menstrual cycle to the 10<sup>th</sup> day included, you take 1 Puregon® injection daily.

On the 11<sup>th</sup> day of the menstrual cycle you attend Nordica Fertility Centre for the ultrasound scan appointment.

The exact time is arranged for the injection with Ovitrelle® to induce ovulation, and 34 hours later the eggs are aspirated from the follicles (aspiration). The eggs are fertilised in the laboratory and two days later the best fertilised eggs are transferred to the uterus (embryo transfer).

### Egg aspiration

This takes place as mentioned in the chapter for long protocol see page 8.

## 6. Crash

*Crash* treatment combines *the short variant* and *the long variant*. Treatment normally takes 45-50 days and can be divided into four phases:

1. **Injection** with 3 milligrams of Cetrotide® on the 21st day of your cycle.
2. **Stimulation (FHS)** with Puregon®, Gonal F® or Menopur® from day 2 or 3 of your cycle for on average 15 days. **Preventing ovulation** with Orgalutran®, 0,25 milligrams, once daily for 3-8 days from day 7.
3. **The laboratory phase** with egg aspiration, fertilisation *in vitro* and transferral of the fertilised egg/eggs takes 2 days.
4. **After-treatment** with Progestan® for 14 days. The after-treatment is completed by a pregnancy test.

### **Injection Cetrotide®**

We give an injection Cetrotide® three milligrams on approximately the 21<sup>st</sup> day of the cycle. By suppressing the ovulating hormone (LH) we expect the egg-stimulating hormone (FSH) to have a stronger effect.

### **Stimulation**

We use the hormone FSH (follicle stimulating hormone) that helps the follicles grow. When the follicles have reached a size of about 12-14 mm, (around day 7), you must also take Orgalutran®, which prevents ovulation. When a suitable amount of follicles have reached the size of 18-20 mm, the maturation of the eggs is induced with ordinary pregnancy hormone hCG, called Ovitrelle®.

After 37 hours, the eggs are aspirated from the follicles (aspiration) and become fertilised in the laboratory. Two days later 2-3 of the best fertilised eggs (embryos) are transferred to the uterus (embryo transfer).

For the following 14 days a supplement of the hormone progesterone is given. This hormone stabilises the mucous membrane in the uterus and this helps the embryos to adhere. Finally, on day 14, a pregnancy test is done, and this is hopefully positive.

### **How to get started on the treatment**

One of the first days of your menstrual cycle you call the nurse at the Nordica Fertility Centre and get the 1<sup>st</sup> appointment for day 19-23 in the cycle. The telephone number is 33 25 70 00, and the telephone is open on weekdays between 10 am and 1pm and weekends between 9 and 12am.

### **1<sup>st</sup> appointment on day 19-23 in the cycle – down regulation**

We perform an ultrasound scan, and if everything is in order you get an injection with 3 milligrams of Cetrotide®. This will suppress the ovulating hormone endemic to the female body. If menstruation hasn't occurred within 5 days, the Cetrotide® injection is repeated.

The nurse will explain the treatment in details and together you will discuss and make arrangements for possible egg donation and freezing of fertilised eggs. Should any questions arise, you should feel free to ask during this or future consultations. You will receive various forms, which we kindly ask you to read thoroughly and bring back signed for the next consultation. Also, you will get a written treatment schedule with all relevant information. Finally, we supply you with all medication, syringes and needles, and we keep a careful record of your medicine. Later on you will receive an invoice directly from the pharmacy. Please note that you inject the medicine yourself. After careful instructions from the nurse most patients are able to inject themselves, but of course you can attend the clinic for injections, if you wish.

### Menstruation

Your menstruation should begin 1-5 days after the injection with Cetrotide®. If menstruation doesn't occur within 5 days, please contact the clinic and reschedule a new appointment. If you do get your menstruation within the 5 days, please also contact the clinic. Our phone number is 3325 7000 and you can call any weekday between 10am and 1pm. We will then tell you when to start Puregon® and FSH and when your next appointment at the clinic is. (approximately day 7-8 of your cycle).

### 2<sup>nd</sup> appointment on day 7-8 of your cycle

On day 7-8 of your cycle we perform another ultrasound scan. We measure the thickness of the mucous membrane in the uterus, the number of follicles and their size. When the follicles have reached 12-14 mm in diameter, you will get injections with Orgalutran®.

### Third appointment

When a suitable number of follicles have reached a size of 18-20 mm, we plan the egg aspiration and the time for the ovulating injection. We use 250 micrograms of Ovitrelle®. The egg aspiration is performed 37 hours after you have taken Ovitrelle® and on average 10-15 days after the beginning of menstruation.

### Egg aspiration

This takes place as mentioned in the chapter for long protocol see page 8

## 7. Treatment with thawed fertilised eggs

Before starting the treatment, you should have a consultation with the doctor and plan the transfer of the thawed eggs. In some cases minor hormone stimulation is given, in the form of pills. The mucous membrane in the uterus is thus stimulated with hormones. The frozen eggs are thawed, and a maximum of 3 thawed eggs are transferred to uterus.

Please note the following:

- According to prevailing law frozen eggs must be destroyed after 2 years.
- Frozen eggs will only be thawed if we have your permission in writing.
- As a principal rule we only thaw 6 frozen fertilised eggs at a time.
- Approx. 40 % of frozen eggs do not survive the thawing, but will not know with certainty until the day after the thawing.

### The treatment day by day

#### Day 1

You call the clinic between 10am and 1pm and get an appointment for an ultrasound scan on the 11<sup>th</sup> day of the cycle. Our phone number is 3325 7000.

#### Day 2

You take Estrofem® 2 mg, 1 tablet 3 times daily = 6 mg daily from the 2<sup>nd</sup> day in the cycle. In this dosage, Estrofem® acts like a contraceptive pill.

#### Day 11-14

You continue with Estrofem® and in addition you take Progestan® 100 mg, 2 vaginal suppositories 3 times daily = 600 mg daily.

#### Day 14

The frozen eggs are thawed. You are welcome to call the clinic after 8am. The phone number is 3325 7000.

#### Day 15

If possible, we transfer three thawed eggs. After the embryo transfer you continue with Estrofem® and Progestan®

#### Pregnancy test

14 days after the embryo transfer a pregnancy test is performed in the clinic. If the test is positive, it is important that you continue with Estrofem® and Progestan® until the 11th week of your pregnancy.

## 8. Laser assisted hatching

Assisted hatching is a technology that helps embryos to attach to the womb of the woman. Pregnancy cannot occur unless the human embryo hatches.

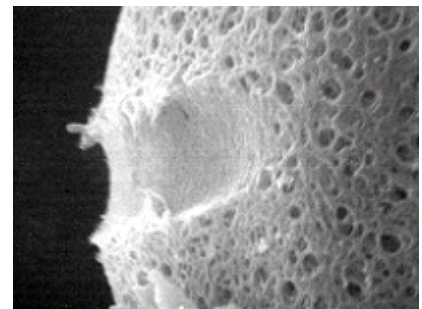
The unfertilised egg is surrounded by a shell called zona pellucida. The zona pellucida ensures that only one sperm cell enters and thus fertilises the egg. After fertilisation of the egg, zona pellucida keeps the cells of the embryo together. Now the cell begins to cleave into a two-cell, then a four-cell and so on.

During the cleavage of the early foetus, zona pellucida hardens. This development is normal and the purpose is to keep the cells in the egg together. Removing the egg for in vitro fertilisation and micro insemination takes it out of its natural environment. This procedure tends to lead to egg shells that harden faster those of normally fertilised eggs.

Especially women older than 37 years of age, have a tendency to produce eggs with a harder zona pellucida than younger women. The same goes for women with a high level of follicle stimulating hormone (FSH). This can be diagnosed from a blood sample.

The problem of a harder zona pellucida is that the egg may not hatch and thus not attach to the woman's womb. Hatching of the egg is necessary to become pregnant. We know that eggs from older women have problems hatching, explaining why some older women have problems becoming pregnant.

Laser assisted hatching is one out of several methods to help the fertilised egg hatch and attach to the womb. Other methods are acid or mechanical hatching of one a part of zona pellucida. At Nordica we offer laser assisted hatching, which is a gentle and safe way to weaken a part of zona pellucida. After treating the fertilised egg with laser assisted hatching, we transfer the embryo into the woman's womb. In most cases the embryo will attach for normal growth and development.



Scientific experiments have shown that one method of assisted hatching is not superior to another. Nor does assisted hatching damage eggs. On the contrary, different studies on assisted hatching show better pregnancy results, mainly among women over 37 years of age. Other studies do not report significantly better results using assisted hatching on "normal" IVF patients or patients treated with micro insemination. At Nordica we offer laser assisted hatching for patients who have undergone repeated treatments without conceiving, and/or in cases where the woman is over 37 years of age.

We also recommend that thawed embryos be treated with laser assisted hatching. It is our experience that thawed embryos have difficulty attaching to the womb. The likelihood of improved chances for pregnancy is assessed medically before recommending laser assisted hatching.

## 9. Egg Donation

We offer egg donation to couples if the woman has no ovaries or her ovaries do not function normally. For these women the only possibility of achieving pregnancy is to receive unfertilised eggs from another woman.

The precondition for egg donation is:

- that the woman donating the eggs is below 35 years of age.
- that the woman donating the eggs has no hereditary diseases in her family.
- that the woman donating the eggs must be tested for HIV and hepatitis B + C and syphilis.

During the IVF procedure you can consider whether you would like anonymously to donate a small number of unfertilised eggs to another involuntary infertile woman.

You can give written consent to the donation, and prior to that you will be informed about the consequences of the donation. Your anonymity is secured, and you cannot get information about the identity of the recipient or the child.

### Which women can be helped through egg donation:

- Women who are in a premature menopause. This can set in as early as the age of 20-25 years.
- Women who are unable to get pregnant because of genetic reasons, for instance Turner patients (women with no ovarian function).
- Women who have had their ovaries removed at an operation because of infection, endometriosis or cancer.
- Women who repeatedly have failed to respond to ovarian hyper stimulation.
- Women who produce abnormal eggs.

The woman who is to receive the eggs must not be more than 40 years of age, and her husband's sperm must be suitable for fertilisation of the donated eggs, as the sperm must not be from a donor.

When at a consultation with the doctor it is decided that egg donation is the right treatment for you, you will be put on a waiting list. The period of waiting depends on the number of couples who can/are willing to donate eggs. The period of waiting might be up to 2-3 years.

## 10. Possible adverse effects of IVF

The patient as well as the doctor can cancel the treatment. Before the aspiration there are three reasons for cancelling the treatment:

1. development of few or no follicles, i.e. under-stimulation/*low response*.
2. development of too many follicles, i.e. over-stimulation.
3. one of the parties becomes ill.

After the aspiration there are also three reasons for cancelling the treatment:

1. no eggs at the aspiration.
2. none of the eggs are fertilised.
3. none of the fertilised eggs cleave.

### Over stimulation

The primary adverse effect of the treatment is over stimulation of the ovaries, i.e. too many follicles are developed. The probability of over stimulation is 0,5 percent. Over stimulation will occur 2-14 days after injection of Ovitrelle®. The symptoms are abdominal pain and abdominal distension, which in the worst case can result in hospital admission.

If there is a risk of over stimulation we usually stop the stimulation with Gonal-F® / Puregon® but continue the down regulation with Synarela® / Suprefact®, and control the level of the female sex hormone daily. We give Ovitrelle® when the female sex hormone level has fallen again. This might take a few days.

### Bleeding

Usually there is a minor bleeding or a bloodstained discharge from the vagina after the aspiration. A heavy bleeding during and right after the aspiration is caused by a ruptured blood vessel in the vagina wall. The bleeding will stop after compression with a pad of gauze for 5 minutes. Should heavy bleeding occur after you have returned home, please contact the clinic or the nearest doctor or hospital.

### Pain

There might be some abdominal pain, especially the day after the aspiration. The pain will disappear within a few days. You can take Panodil, 2 tablets 3 times a day, if necessary.

### Infection

Infection as a consequence of the treatment is very rare. It could be infection in one of the ovaries following the aspiration or infection in a collection of blood (haematoma) in the vagina wall. The symptoms would be fever and some soreness or pain.

### Extra-uterine pregnancy

A pregnancy outside uterus occurs if the fertilised egg adheres in the uterine tube. It is a serious condition and involves hospital admission. In the worst case an operation is necessary. In case of extra-uterine pregnancy, the uterine tube is often removed.

## 11. Medicine

### Rules of medicine subsidy

Nordica Fertility Clinic always applies to The Danish Medicines Agency for the so-called *kronikertilskud* (State-subsidized grants) for medicine. This means that the subsidies for the medicine mentioned below amount to 100% of expenditures exceeding 3.800 kroner. With *kronikertilskud*, therefore, the cost of medicine will amount to no more than 3.800 annually. The *kronikertilskud* is valid for two years. The Danish National Health Service annually subsidizes the medicine as follows:

- No subsidy at expenditure up to 500 Dkr.
- 50% subsidy at expenditure between 500 Dkr. and 1.200 Dkr.
- 75% subsidy at expenditure between 1.200 Dkr. and 2.800 Dkr.
- 85% subsidy at expenditure above 2.800 Dkr.

### Down regulation

#### **Centrotide® (cetorelix) injection**

*Effect:* Prevents ovulation by inhibiting the excretion of the luteinizing hormone (LH) from the pituitary gland. Is injected in the subcutis on the abdominal wall, 0,25 mg = 1 ampoule in the morning.

*Adverse effects:* Local irritation on the injection site is normal and completely harmless.

*Price:* Approx. 400 Dkr. for 1 vial and approx. 1.270 Dkr. for 7 vials with dry-matter + powder 0,25 mg

#### **Orgalutran® (ganirelix) injection**

*Effect:* Prevents ovulation by inhibiting the excretion of the luteinizing hormone (LH) from the pituitary gland. Is injected in the subcutis on the abdominal wall, 0,25 milligrams = ½ ml in the morning.

*Adverse effects:* Local irritation on the injection site is normal and completely harmless.

*Price:* Approx. 500 Dkr. for 1 vial and approx. 1270 Dkr. for 7 vials with dry-matter + powder 0,25 milligrams.

#### **Suprefact (buserelin) injection**

*Effect:* Down regulates the superior sex hormones by inhibiting their excretion in the pituitary gland. Ovulation at the wrong moment is thus prevented. Is injected in the subcutis on the abdominal wall 0,5 milligrams = ½ ml once daily.

*Adverse effects:* Induces a short false menopause, and slight hot flushes, sweats and headache might occur.

*Price:* approx. 550 Dkr. for vials with 2 x 5,5 ml injection fluid 1 milligram /ml

#### **Synarela® (nafarelin) nasal spray**

*Effect:* Down regulates the superior sex hormones by inhibiting their excretion in the pituitary gland. Ovulation at the wrong moment is thus prevented. Nasal spray, 1 puff in the nose 2 or 3 times daily.

*Adverse effects:* Induces a short false menopause, and slight hot flushes, sweats and headache might occur, and moreover dryness and irritation of the nasal mucosa.

*Price:* approx. 800 Dkr. for 1 bottle with 60 doses.

**Gonal F® (Follicle Stimulating Hormone, FSH) injection**

**Stimulation**

*Effect:* Stimulates the ovaries and causes the largest follicles to grow further. Is injected in the subcutis on the abdominal wall.

Dosage varies.

*Adverse effects:* Local irritation on the injection site. Can cause over stimulation.

*Price:* approx. 770 Dkr for 3 ampoules and approx. 1.350 for 10 ampoules dry matter + saline of 75 units. Is also available as injection pen.

**Puregon® (Follicle Stimulating Hormone, FSH) injection**

*Effect:* Stimulates the ovaries and causes the largest follicles to grow further. Is injected in the subcutis on the abdominal wall.

Dosage varies. Can be given by dosage pen. The pen is handed out for free at the clinic.

*Adverse effects:* Local irritation on the injection site. Can cause over stimulation.

*Price:* approx. 275 Dkr for 1 vial and approx. 870 Dkr for 5 vials of 50 units.

*Price:* approx. 515 Dkr for 1 vial and approx. 1180 Dkr for 10 vials of 100 units.

*Price:* approx. 1.500 Dkr for 1 ampoule with 300 units and approx. 2.950 Dkr

for an ampoule with 600 units for injection with dosage pen.

**Menopur® (Follikel stimulerende Hormon, FSH) injection**

*Effect:* Stimulates the ovaries and the largest follicles to grow further. Is injected in the subcutis on the abdominal wall. Dosage varies.

*Adverse effects:* Can cause over stimulation, especially at PCO.

*Price:* Approximately 1.340 Dkr for 5 vials of 75 units.

*Price:* Approximately 2.350 Dkr for 10 vials of 75 units.

**Ovitrelle® injection**

*Effect:* Stimulates the ovaries and cause the largest follicles to ovulate. Is injected in the subcutis on the abdominal wall. Dosage varies.

*Adverse effects:* Over stimulation can be caused by hCG after over stimulation by FSH. Local irritation on the injection site, headache, tiredness, vomiting, abdominal pain and nausea.

*Price:* Approx. 350 Dkr disposable syringe of 250 micrograms.

*Price:* Approx. 350 Dkr for a vial of 250 micrograms.

**Panodil® (paracetamol) tablets**

*Effect:* Has a light pain-killing effect. Tablets 1 g = 2 tablets, not more than 4 times daily. Administered as premedication prior to aspiration. In the morning before the aspiration you take 1 g Panodil® = 2 tablets. The clinic will supply you with the tablets.

*Adverse effects:* Very rare.

*Price:* approx. 50 Dkr for 100 tablets, sold over-the-counter.

**Rapifen® injection**

*Effect:* A morphine-like drug, which has a strong pain-killing effect. During the aspiration 50 mg = 1 ml Rapifen is administered as an intravenous injection.

*Adverse effects:* nausea and tiredness.

### After-treatment

#### **Progestan (progesterone) tablets**

*Effect:* Stabilises the mucosa membrane in uterus and creates optimal conditions for the fertilised egg to adhere. Administered as tablets inserted into the vagina, 100 milligrams = 1 tablet 3 times daily for 2 weeks, until the result of the pregnancy test is available.

*Adverse effects:* mild nausea, bloating and tautness of the breasts

*Price:* approx. 250 Dkr for 30 tablets.

### Treatment with thawed fertilised eggs

#### **Estrofem® (oestradiol) tablets**

*Effect:* Stimulates the growth of the mucosa membrane in the uterus. Administered as tablets 2 milligrams = 1 tablet 3 times daily from the 2<sup>nd</sup> day of the cycle.

*Adverse effects:* mild nausea, tautness of the breasts, and a tendency to oedema.

*Price:* approx. 160 Dkr for 3 x 28 tablets.

### “Low stimulation” IVF-treatment

#### **Pergotime® tablets, 50 milligram**

*Effect:* Stimulates the ovaries and causes the largest follicles to grow further and mature the eggs.

*Dosage:* Normally three tablets = 150 milligrams daily from day 3 to 7 in the cycle.

*Price:* Approx. 60 Dkr for five tablets (without subsidies).

#### **Puregon® injection fluid 300 units / Gonal F 7 IE x 3**

*Effect:* Stimulates the ovaries and causes the largest follicles to grow further and mature the eggs.

*Dosage:* 100/75 units daily from the 8<sup>th</sup> to the 10<sup>th</sup> day of the cycle. Is injected in the subcutis, for instance on the lower abdominal wall.

*Price:* approx. 1.500 Dkr.

#### **Ovitrelle® injection**

*Effect:* Stimulates the ovaries and cause the largest follicles to ovulate. Is injected in the subcutis on the abdominal wall. Dosage varies.

*Adverse effects:* Over stimulation can be caused by hCG after over stimulation by FSH. Local irritation on the injection site, headache, tiredness, vomiting, abdominal pain and nausea.

*Price:* Approx. 350 Dkr disposable syringe of 250 micrograms.

*Price:* Approx. 350 Dkr for a vial of 250 micrograms.

## 12. Prices and treatments

Prices are in Dkr. and exclusive medicine

### **IVF-treatment**

**Dkr. 17.500**

*(Includes all consultations, pregnancy test and ultrasound examination in the 7th week of pregnancy)*

### **Contract on 3 standard IVF-treatments**

**Dkr. 36.500**

*(The offer concerns 3 completed treatments, i.e. treatments with egg aspiration and egg transfer; the contract terminates with the birth of a living child.)*

### **Bloodtests: HIV, hep B, hep C**

**Dkr. 1.250**

### **Interrupted IVF-treatment**

**Dkr. 4.000**

*(i.e. treatment interruption before egg aspiration)*

### **Supplementary payment in connection with IVF:**

Microinsemination (ICSI)	Dkr. 3.500
Aspiration of sperm from the testis (TESA)	Dkr. 4.000
Assisted hatching (Zona drilling)	Dkr. 2.500
Utilisation of donor sperm	Dkr. 900
Freezing and storage of sperm per year	Dkr. 1.000
Freezing of fertilized eggs	Dkr. 2.500
Transfer of thawed, fertilized eggs	Dkr. 4.000

### **Treatment with donor egg (Egg donation)**

**Dkr. 35.000**

### **Insemination treatment**

*(includes pregnancy test and ultrasound scan in 7th week of pregnancy)*

Insemination with sperm from partner (IUIH) per day	Dkr. 1.800
Insemination with sperm from donor (IUID) per day	Dkr. 2.300

### **Examination for infertility**

**Dkr. 2.700**

*(Includes consultations, hormone analysis, scanning of ovaries, water scanning (ultrasound guided rinse out of uterus and fallopian tubes), sperm analysis and if convenient, scanning of testicles)*

Hysteroscopy	Dkr. 5.000
Water scanning (HSU)	Dkr. 2.400
Sperm analysis	Dkr. 900
Hormone analysis each	Dkr. 200

### **Prenatal diagnostic**

Placenta- or amniocentesis	Dkr. 7.000
Pregnancy scan 1 <sup>st</sup> trimester (7 <sup>th</sup> – 12 <sup>th</sup> week)	Dkr. 1.000
Nuchal Translucency	Dkr. 2.000
Pregnancy scan 2 <sup>nd</sup> trimester	Dkr. 2.500

Prices are of April 2008. We reserve the right for correcting errors and misprints.

According to present Danish law concerning in vitro fertilisation, - all patients treated in a Danish fertility clinic must have the following tests taken by their own doctor:

A cell-sample (ex. PAP smear) from the cervix which is not more than 3 year old at the start of the treatment .

Blood tests for the following less than 3 month old:

Hepatitis B and C. i.e.: HbsAg, Anti-HBc and anti HCV from the woman and her partner.

HIV tests; which is the following: anti-HIV 1+2.

These tests cannot be more than 3 months old at the start of the treatment and are to be renewed every 24 months when in treatment.

This note is supposed to be given to your doctor if you have not had these tests taken already. The doctor can send the results directly to the Fertility clinic or you can bring them with you when you come. According to European rules of analysis of human tissue, it must be very clear in which lab the tests have been analysed.

Kind regards

Svend Lindenberg  
Professor. Dr. med.