Centre for Reproductive Medicine

In Vitro Fertilisation (IVF) / Intracytoplasmic Sperm Injection (ICSI) – Information for Patients

In Vitro Fertilisation (IVF) was first carried out successfully in 1978. Since then many thousands of babies have been born as a result of this treatment. Since it was first begun IVF has undergone a number of changes the most dramatic of which has been the option for microinjection of the sperm into the egg - Intra Cytoplasmic Sperm injection. Despite the long experience with IVF it remains a complex treatment.

IVF was originally applied to by-pass absent or severely damaged tubes. The scope for IVF has now widened especially with the development of Intra Cytoplasmic Sperm Injection (ICSI) in 1993 to help the treatment of severe sperm problems. IVF or ICSI may be advised in the following circumstances:

- **When tubal surgery has been unsuccessful**
- **When tubal surgery has less chance of working than IVF**
- **When the partner's sperm count is reduced or the quality is poor**
- **When both Fallopian Tubes have been removed**
- **Moderate and severe Endometriosis**
- **Unexplained infertility of long duration**
- **Egg donation**
- **Difficult anovulatory infertility (failure of ovulation unresponsive to conventional therapy)**
- **High levels of anti-sperm antibodies**
- **Combinations of any of the above**

Certain couples are unsuitable for treatment with IVF. These include:

- **Anyone who has had a hysterectomy (unless contemplating surrogacy)**
- **Anyone who has had an endometrial ablation or resection**
- **People with severe abnormalities of the uterus such that they cannot carry a child (unless contemplating surrogacy)**
- **People who have had Tuberculosis of the womb**
- **People from whom it is impossible, due to pelvic scarring, to collect eggs safely**
- **People for whom a pregnancy would be dangerous (unless contemplating surrogacy)**
- **Anyone for whom stimulation and anaesthetic for egg collection would be dangerous.**

There now follows a more detailed description of IVF. Small variations occur between patients, but these will be explained on an individual basis.

IVF involves:

1. Pre-treatment preparation and counselling
2. Reduction of the natural hormones - “down regulation”
3. Stimulation of the ovaries to produce a number of eggs
4. Monitoring the response to drug stimulation
5. Recovery of the eggs and fertilisation in the laboratory
6. Transfer of the fertilised eggs (the embryos) back inside the uterine cavity (womb)
7. Hormonal Support after embryo transfer
8. Follow up to carry out a pregnancy test
9. If pregnant - scans to assess pregnancy
10. If not pregnant - follow up clinic visit or summary letter to discuss reasons for failure

ICSI involves:

1. All the above steps with IVF
2. The laboratory procedure of injecting sperm into egg

IVF pre-treatment visit “pre-treatment information session”

A few weeks before your treatment is due to start you will be given an appointment to attend the clinic. At this visit you will be seen by an Infertility Nurse Practitioner who will discuss with you, in detail, the various steps involved in the treatment and plan your treatment start date. She will deal specifically with the following points:

- **Details of the treatment, drugs required and their administration**
- **Problems and complications of treatment that you will need to be aware of**
- **Ensure that all preliminary tests have been carried out**
- **Give you the opportunity to clarify any points in connection with the proposed treatment**
- **Arrange ovarian reserve testing in the form of an FSH blood test on day two of the cycle or AMH test (this is a self funded test) and an up to date sperm test if these have not already been done**
- **Give you the special consent forms that have to be read through and signed by both partners**
- **Obtaining drugs from a pharmacy depending on how your treatment is funded.**
- **Up-to-date Covid information**

To assist this visit it is most important that you have read through the written information provided to you and completed any consent or other forms given to you prior to the visit.

Some general points

a) Blood tests to measure the hormonal levels - Oestradiol

Although not routine, these may be carried out as part of the monitoring of the treatment. They reflect the degree of ovarian activity and are especially important if the ovaries are showing signs of over-response or under response.

b) Ultrasound scans

Ultrasound scanning is the main method of monitoring how the ovaries are responding to stimulation. By far the most accurate way of seeing the ovaries is vaginal scanning. This is accomplished by passing an ultrasound probe into the vagina. The examination takes just a few minutes and requires an empty bladder.

c) Hormonal injections

During the stimulation phase of the treatment, daily injections of Gonadotrophin drug are required. These are usually administered by yourself or your partner. You will be given instruction on how to give the injections. The injections use a very fine needle and are given just beneath the skin to make them easier and less uncomfortable.

Stages of IVF/ICSI

1. Pituitary Down Regulation or Desensitisation

Pituitary down regulation means giving a drug to lower the hormones, FSH and LH which are produced by the pituitary gland that normally stimulate the ovaries. This in turn lowers oestrogen levels.

The purpose of Down Regulation is:

- **To ensure that natural ovulation doesn't occur during the stimulation phase before the eggs have been collected**

Methods of giving Down Regulation

There are three methods, each of which may be advocated in specific circumstances which will be discussed with you at your pre-treatment counselling or consultation.

i) Long course - starting on day 21 of the cycle immediately preceding the treatment cycle. This is our <u>standard protocol.</u>

- Day 1 is the first day of the period
- The Down Regulation begins on day 21 of this cycle
- The next period should begin about 7 – 10 days after starting the Down Regulation
- The Baseline scan is carried out on the first available Monday after this next bleeding starts

ii) Long course - starting on day 2 of the cycle in which the treatment is going to occur.

- Day 1 is the first day of bleeding
- Down Regulation is commenced on day 2 (the next day)
- The Baseline scan is carried out at least 2 weeks later on a Monday

iii) Cetrotide / Fyremadel / Ganirelix (antagonist cycle)

- Day 1 is the first day of bleeding
- Scan carried out on day 1-3 of bleeding
- Stimulation will start on day 2-3 of bleeding

<u>Drugs for Down Regulation</u>

All drugs used for this purpose have a very similar action and have similar side effects which include hot flushes, sweats and vaginal dryness. The effects of the drug are completely reversible. The drug most commonly used is:

Buserelin injections once a day or Suprecur nasal spray 4 times a day

2. First visit - "Baseline scan" (Long Protocol)

The purpose of the Baseline Scan visit is:

- **To ensure that your Down Regulation has been effective and decide when the Gonadotrophin injections should begin.**

The Baseline scan is almost always carried out on a Monday. Which Monday will be determined by the Down Regulation regime you are on and the scan slot availability.

Down Regulation is confirmed by:

- **A scan showing a thin Endometrium and no cysts in the ovaries**
- **Sometimes we check the oestrogen level by a blood test if we are not sure that the hormone levels are low enough**

If Down Regulation is confirmed you will be:

- **Advised of the starting date of the Gonadotrophin injections (usually the next day)**
- **Told the dosage of the Gonadotrophin injections**
- **Given your appointments for subsequent visits**

If Down Regulation is not confirmed :

- **You will be asked to continue the Down Regulation drugs and attend for a further scan in 1 or 2 weeks**
- **Or alternative plans will be discussed with you**

Key point: It is most important that you DO NOT stop the Down Regulation drugs until your Gonadotrophin injections are completed. We will tell you when to stop.

3. Ovarian Stimulation

The purpose of Ovarian Stimulation is:

To produce a number of eggs simultaneously to give the best chance of having more than one embryo to select from.

Stimulation is by daily injection of Gonadotrophin (see Superovulation information sheet). The start of the injections will be advised at the Baseline Scan as detailed above. The starting dose will also be advised and may well have been indicated at your pre-treatment counselling.

The purpose of these injections is to stimulate the simultaneous development of multiple follicles. The active ingredient in all the preparations is Follicle Stimulating Hormone (FSH).

There are a number of different preparations which can be used for stimulation. Possible preparations include Menopur, Gonal F, Bemfola. Whichever preparation is used the outcome of the treatment is likely to be similar.

Monitoring the response to stimulation

The purpose of monitoring is:

- **To assess the development of the follicles which contain the eggs**
- **To detect under response**
- **To detect indications of over response - ovarian hyperstimulation syndrome**
- **To plan the timing of the collection of the eggs**

The responses of different people to the same Gonadotrophin drugs may vary considerably, and the response may vary from cycle to cycle in the same person. There are several factors which will affect the response, including:

- **A persons age**
- **Previous response to the drugs**
- **FSH level on day 2 of the menstrual cycle**
- **Appearance of the ovaries (polycystic ovaries may respond strongly)**
- **AMH result (if carried out)**

Even with this information the response is not always predictable, which makes it all the more important to monitor response.

a) Ultrasound scans on Long Protocol

The most important method of monitoring is by Ultrasound scans. These are carried out vaginally as discussed above. The scans are normally carried out in the morning on the following days:

Stimulation cycle day 8 (normally a Tuesday)
Stimulation cycle day 11 (normally a Friday)

Additional scans may be required according to response and you will be advised of the timing of these on an individual basis. The schedule of scans may alter if a different stimulation protocol is being used (i.e. Antagonist), but this will be advised on an individual basis.

b) Blood tests for Oestradiol

The level of Oestradiol reflects the numbers of follicles. The greater the number of follicles the higher the Oestradiol level.

We may measure the Oestradiol level in two circumstances:

- **If the scan shows too many follicles developing**
- **If the scan does not clearly show follicles developing at the correct rate**

If the Oestradiol level is particularly high this will indicate a high risk of developing Ovarian Hyperstimulation Syndrome in which case the stimulation will be reduced or stopped and the cycle may be cancelled.

5. Human Chorionic Gonadotrophin (HCG) injection

The purpose of the HCG injection is:

- **To cause the final maturing of the eggs**
- **To allow the eggs to be removed and to time their collection**

When the follicles have grown in size - three or more follicles with a mean diameter of at least 18 mm - the eggs are ready to be collected. Before the eggs can be removed the follicles have to be put through a final maturing process. The HCG injection mimics the natural hormone LH, which causes ovulation in the natural menstrual cycle.

HCG preparations : **Pregnyl or Ovitrelle**

It makes no difference to your treatment which one you use.

Key point: Once the HCG injection is given, the eggs must be removed 36 hours later. If the HCG has not been given at the correct time, we may not be able to obtain any eggs.

6. Collection of the eggs (Oocyte retrieval)

The purpose of Oocyte retrieval is:

To drain the fluid from the follicles and look for the egg in the fluid

At this stage you will have received a number of days of stimulation of the ovaries and will have a number of mature follicles developed in the ovary. The size and number of follicles varies from patient to patient. There are often a number of small follicles as well as large

follicles. During the egg collection we will try to aspirate all the follicles to obtain as many eggs as possible but the small follicles may not produce eggs.

Egg retrieval involves the following steps:

- **Nothing to eat or drink as advised by the nursing staff**
- **Please take a bath or shower at home on the morning of the procedure**
- **Bring with you dressing gown and slippers**
- **Bring with you any medication (other than your fertility medication) that you are taking**
- **Admission to the Centre at around 8 am on the morning of the egg recovery**
- **Medical check, consent form signed**
- **Pre-medication (antibiotics)**
- **Needle into back of hand**
- **Sedation anaesthetic**
- **Egg collection**
- **Home within 1-2 hours or when recovered**

The removal of the eggs is normally carried out by passing a needle under ultrasound guidance through the vaginal wall and into the ovary where the follicles are punctured and their fluid aspirated. The fluid is checked by the embryologist for the presence of an egg and if not present the follicle is flushed out with a small amount of irrigating fluid. If it is not possible to remove the eggs by this method it may be possible to remove them through the abdominal wall by carrying out laparoscopy but the reasons which may make it difficult to remove them through the vagina may also make it difficult to remove them through the vagina. Our failure rate in removing eggs is less than 0.5%.

Anaesthetic The type of anaesthetic used is a strong intravenous sedation. You will be virtually asleep and have no recollection of the procedure.

Procedure of egg collection

- Empty your bladder immediately before the procedure
- You are walked through to theatre
- Identity details checked
- Anaesthetist will connect you to the monitor and induce an anaesthetic
- Your legs are placed in stirrups
- Vaginal scan is carried out and the eggs are removed (takes about 20 minutes)
- The vagina is checked for bleeding from the puncture sites at the end of the procedure. Very occasionally a dissolving suture is required to stop bleeding
- Return to the recovery area

Recovery

- You will sleep off the immediate effects of the sedation in the day unit
- You should be able to go home in about 1-2 hours. Occasionally it may be necessary to keep you in hospital overnight if recovery from the anaesthetic is slow or if there are any concerns about the egg collection procedure. If this is necessary you will be admitted to the adjacent gynaecology department.
- You may experience some lower abdominal discomfort for a day or so after the removal of the eggs due to bruising in the ovaries
- You may also experience some brown discharge as a result of slight bleeding from the vaginal puncture sites
- You should not drive for 24 hours
- It is best to avoid sex for about 1 week although there is no evidence to support this advice
- Paracetamol can be taken regularly for discomfort
- You will start Progesterone (400 mgs twice daily from the evening of the egg collection day) rectally
- A responsible adult needs to accompany you home and stay with you all afternoon and overnight.
- We recommend that you do not go to work the following day.

7. Laboratory procedures

A number of processes are carried out in the laboratory to attempt to fertilise the egg(s) and nurture the embryo(s). The stages are as follows:

- **Identification of the egg**
- **Preparation of the sperm specimen**
- **Insemination of the eggs with the sperm - or in the case of ICSI, injection of a single sperm into each egg**
- **Assessment of the egg the following day for signs of fertilisation**
- **Culture of the fertilised egg for at least a further 24-48 hours or for up to a week to blastocyst stage**
- **Assessment of the division of the embryo and its quality**
- **Replacement of the embryo(s)**
- **Cryopreservation of spare embryos**

The embryologist will contact you by phone the day following the egg collection to advise you whether fertilisation has occurred. (see below under failed fertilization)

If there has been no fertilisation, arrangements will be made for you to attend the clinic to discuss the reasons for this and the possibilities for future treatment.

Key point: If the sperm quality on the day is unexpectedly poor and the prospect of fertilisation low, the possibility of carrying out ICSI may be suggested even though this may not have been previously discussed or considered

Failure of fertilisation

Unfortunately 10 - 15 % of all cycles of IVF will result in failed fertilization with no embryos available for transfer. It may be impossible to predict this situation as in most of these cases the male partner will have had a normal semen analysis and the eggs will have appeared normal (Unexplained infertility is common in these situations). If this happens the possible reasons and the options for further treatment will be discussed with you. In these cases intra cytoplasmic sperm injection (ICSI) may be the treatment recommended.

In some cases the semen analysis carried out before treatment will indicate a possible risk of failed fertilization and this will have been discussed with you. In such cases intra cytoplasmic sperm injection may have been suggested or the outcome may have been uncertain so that IVF was advised to provide diagnostic information. Where the sperm parameters are borderline we may suggest the possibility of half of the eggs being fertilised with ICSI and half with IVF. These are decisions taken on an individual basis and may be advised on the basis of the sperm produced on the day of egg collection.

8. Embryo transfer - ET

The purpose of embryo transfer is:

To load one or two embryos into a fine catheter and insert them as gently as possible into the cavity of the uterus

At this stage the fertilised egg has normally gone through at least two divisions – from 1 cell to 2 cells and again to 4 cells. If the transfer is carried out on day 3 we would expect the embryos to have divided to 6-8 cells. If the embryos are replaced as blastocysts they will have up to 150 cells although they are still microscopic.

The embryo(s) is/are replaced in a tiny amount of culture medium injected into the cavity of the womb through a very fine, soft tube passed through the cervix (neck of the womb). If more than one embryo is replaced they are replaced at the same time.

Embryo transfer is normally carried out two to three days or five days (for blastocysts) after the eggs are removed.

The process of embryo replacement is dealt with in detail in the sheet “Embryo transfer - information for patients”. The process involves:

- **Admission to the Centre (the time will be advised)**
- **No special preparation is required**
- **You should bring a clean night dress, dressing gown and slippers**
- **Please take a bath or shower at home on the morning of the procedure**
- **The embryologist / doctor or senior nurse will speak to you before the embryos are replaced to give you details about the embryos and whether there are any embryos left over for cryopreservation**

- **An identity label will be placed on your wrist**
- **We ask that your bladder is reasonably full to ease the passage of the catheter into the womb. Therefore you should not empty your bladder before the embryo transfer**
- **You will be walked through to the theatre where we carry out the embryo transfer**
- **No anaesthetic is required except in exceptional cases**
- **Your legs will be placed in stirrups**
- **A scan is carried out first to assess the position of the uterus and make measurements about its length**
- **A speculum is passed to look at the cervix**
- **Mucus is cleaned away from the entrance to the womb using a cotton tip**
- **A "dummy" catheter may be tried first to assess the likelihood of any difficulties**
- **The embryos are replaced by passing a fine catheter through the cervix**
- **The catheter is removed and checked by the embryologist to ensure the embryos have not come back in the catheter**
- **A brief resting period of up to 10 minutes**

Normally your partner will be encouraged to be with you when the embryos are replaced. If he is not able to, you have the ***choice to have another person with you*.**

9. Hormonal support after embryo transfer

The purpose of hormonal support after embryo transfer is:

To increase levels of progesterone hormone to give the embryo the best chance of implanting

Because of the administration of Down Regulation up to the time of the hCG injection, the progesterone - normally produced to cause the endometrium to be receptive to implantation - may be suppressed. We therefore need to supplement the progesterone - this is known as ***Luteal Phase Support.***

The preparation used is:

Cyclogest (400 mg by intravaginal pessary or suppository). The dose is normally 400 mg twice daily up until pregnancy test. If the pregnancy test is positive you will need to continue Cyclogest 400 mg twice a day until the 10th week of pregnancy.

The detailed schedule will be provided to you at the time of your treatment.

Key point: Luteal phase support must be continued until told otherwise by a nurse. If a pregnancy is confirmed then the progesterone should continue until 10 weeks.

What to expect and do after the embryos are replaced

1. The two weeks or so after the embryos are replaced is a difficult time emotionally as you have contradictory feelings of hope, expectation, fear and anxiety. Although you and your partner will prepare yourself it is not possible to avoid these difficult emotions. Please let us know if there is anything we can do to reassure you.

2. You will receive Progesterone pessaries to prepare for implantation. These can often give rise to some bloatedness.

3. The two weeks after egg collection and embryo transfer is the time when two key complications of this treatment may cause symptoms. Infection in the ovary will cause abdominal pain usually on one side or the other and a fever. The other important complication is ovarian hyperstimulation syndrome which you should have received separate information on. OHSS gives rise to symptoms of abdominal distension, discomfort (both sides), decreased urine production and shortness of breath. If you experience any of these symptoms you should call the Centre for advice.

4. It is not uncommon to experience some brown discharge for a day or so after the eggs are removed. This is from the puncture sites through which the eggs are obtained. This discharge can continue the day after the embryos are replaced. You should not be concerned by this as it will not affect the treatment.

5. If you get light blood stained discharge in the two weeks after the embryos are replaced do not be alarmed as this may be an indication of embryo implantation.

6. Activity levels can continue normally after the embryos are replaced although it probably makes sense to take the rest of the day of the embryo transfer off work.

7. If you exercise regularly you should ease off in the few days after the embryos are replaced.

8. Swimming should be avoided for 1 week (*although there is no evidence for this advice*)

9. Intercourse should be avoided for 48 hours after the embryos are replaced (*although there is no evidence for this advice*).

10. Bed rest is not helpful and should be avoided.

11. You should eat and drink normally although keeping yourself well hydrated is sensible. Some say you should drink plenty of milk although there is no evidence to support this view.

If you have any concerns we are happy to try to reassure you. Emergency numbers are available in your infertility booklet if you have a problem out of hours.

Partner's role

If the partner is male, they will be required to produce a fresh semen specimen on the morning of the egg collection.

It is important to abstain from ejaculation for two days prior to the day of egg collection. This is to ensure that the sperm sample will be at its best.

The instructions to follow are:

- **2 -3 days abstinence**
- **A sheath (condom) should not be used for collection**
- **The penis should be washed prior to production of the specimen**
- **The specimen should be produced in as hygienic a circumstance as possible**
- **The specimen should be collected in the container provided**

Sometimes a second sperm specimen is necessary if the quality of the first specimen is not adequate. It is therefore important that the partner is available to produce a second specimen later on the day of the egg collection if necessary.

Care following treatment

The outcome of all infertility treatment is indicated by the start or - hopefully not - of a period. The waiting time can seem very long when you are going through IVF treatment. After all the preparation, the wait to get started and the intensity of the treatment, if a period starts it can be devastating.

The complex nature of treatments like IVF and ICSI means that the process can fail at any of the stages described previously. Thus eggs may not be produced, fertilisation may not be achieved and so on. Failure of any of these stages can be upsetting.

All who work in the Centre will do their best to keep you informed at all times about how treatment is progressing and, if things are not working out as planned, provide you with answers. If treatment fails, you will be provided with a written report and given the opportunity to come back and discuss the reasons for failure with the medical team and the prospects for further treatment.
If all goes well and you do not start a period, a pregnancy test will be carried out on a urine specimen. If there is any doubt about the pregnancy test result a further urine pregnancy test will be carried out a week later.

If the pregnancy test is positive, a scan will be arranged three weeks later to assess the viability of the pregnancy, how many sacs (developing embryos) are present and to excude an ectopic pregnancy. If the first scan is not satisfactory, a second scan will be carried out.

Key point: It is most important to have a pregnancy test carried out, even though you may have started bleeding.

Cancellation or failure of treatment

It will be clear from all that has been written that there are many stages in the cycle of IVF or related treatments, where failure can occur. Treatment may fail or be cancelled because of:

- **Under response to the Gonadotrophin drugs**
- **Over response to the Gonadotrophin drugs**
- **Failure to collect eggs**
- **Insufficient sperm or no sperm sample produced**
- **Failure of fertilisation**
- **Failure of early development of the embryos (failed cleavage)**
- **Difficulty with replacement of the embryos**
- **Unable to carry out embryo transfer due to problems with your uterus**
- **Failure of implantation of the embryos**
- **Pregnancy fails due to early miscarriage or ectopic pregnancy**

There may be other unforeseen circumstances in which a treatment cycle has to be cancelled. Detailed information will be provided and advice given regarding the possibility of further treatment and its likely outcome. There may be costs involved in cancellation of treatment, this will depend on at which stage your treatment is cancelled – please see the price list for further details or speak to any member of staff.

We welcome patient's views and comments about our service and the information we provide. If you have any comments, particularly about this information sheet, please let us have them either by post or dropped into the suggestion box.

Cryopreservation of spare embryos

Treatments such as IVF, ICSI and Egg donation sometimes generate embryos which are surplus to the immediate requirements of the treatment. If these "spare" embryos are sufficiently good quality they can be placed in storage for your future use.

Why are surplus embryos created? IVF and related treatments involve stimulation of the ovaries to produce a number of eggs. We aim to fertilise all of the eggs removed in order to have a selection of embryos to grow as not all embryos have the potential to develop. As they are growing we are able to select the best for replacement. In about 20% of cases more embryos than the one or two necessary for replacement are of good quality and have the potential to survive storage and be viable once they are thawed. If we place these embryos in storage this provides the possibility of another pregnancy without having to go through the process of ovarian stimulation.

Further details of embryo cryopreservation and the replacement of thawed embryos are provided on a separate information sheet.

If you have any queries please contact us on one of the numbers

Office hours tel no. 024 76 96 8879; Emergency contact no. 024 76 96 7000
Nurses Line: 024 76 96 8856

The Trust has access to interpreting and translation services. If you need this information in another language, please contact the Quality Manager on (024) 76968864, and we will do our best to accommodate your needs. The Trust operates a smoke free policy.

Document History

Author:	S Keaveney/S Keay
Department:	CRM
Contact Tel No:	(024) 76968889
Doc. Location:	QM computer, I drive (patient information)
Version:	GEN-PI-000016V14
Reference No:	Quality/information sheets/IVF
Review Date:	March 2024
Revision History:	February 2020 (amends), February 2022 (amends), March 2023 (amends)