ASSISTED CONCEPTION

What is Assisted Conception?

- Assisted conception is a term used to describe the methods available to help couples get pregnant when they have difficulty conceiving. It is also referred to as fertility treatment.
- Approximately 1 in 6 couples find it hard to fall pregnant in the UK.
- IVF (In Vitro Fertilisation)/ICSI (Intra Cytoplasmic Injection Technique) is the most advanced and effective treatment for infertility available today.
- This booklet aims to give you an overall idea of what to expect in a nutshell, but we make every effort to give each patient, an individualized plan of treatment cycle to maximize her chances of pregnancy.

What is IVF?

- IVF, a Latin word literally means ‘fertilisation in a glass’. It is one of the most popular fertility treatments, giving hope to thousands of couples with infertility.
- In the UK alone, approximately one baby in every 80 is born as a result of IVF treatment.
- In a nutshell, this treatment entails stimulating your ovaries with hormone drugs in order to produce more than one egg, taking out eggs from the stimulated ovaries and fertilising these eggs with sperm in a laboratory dish.
- Not every egg will fertilise when mixed with the sperm so, to increase your chances of success, we use hormones to stimulate the ovaries to produce multiple eggs.
- The resulting embryos (fertilised egg) are then placed in the woman’s womb.

What are the common reasons you may need IVF?

- The female partner has blocked or damaged fallopian tubes – it may not be possible for the egg and sperm to meet or the fertilised egg can not make its way into the womb.
- Male partner has low sperm count or the sperm do not move forward well (low motility) or there are high numbers of abnormal sperm. More severe sperm problems may need ICSI treatment.
- Unexplained Infertility - No cause can be found for not being able to conceive for a length of time (usually over 3 years)
- Older age group (over 35yrs.) women.
- The female partner has ovulatory (egg releasing) problems such as polycystic ovaries
- The female partner has significant degree of endometriosis
- If you have been unsuccessful with other techniques such as ovulation induction or IUI
What are the steps involved in an IVF cycle?

Scan performed in IVF treatment are internal scans and need an empty bladder. The steps depend on whether you have Long Protocol, Short Cetrotide Protocol or Short Flare Protocol.

**Long Protocol IVF cycle (about 6-7 weeks duration)**

1. **Down Regulation** – The female partner’s normal cycle (production of hormones from the ovary) is temporarily suppressed. This is achieved using hormonal medication which suppresses the pituitary gland. This turn suppress the ovarian hormone production. This helps us to have a control over the egg production and release. This may last for 2-3 weeks.

2. **Controlled Ovarian Stimulation (COS)** – The female partner’s ovaries are stimulated with hormone injections to produce many eggs. The hormone injections usually last between 7 to 14 days, with an average of 10 days.

3. **Ovulation Trigger** – This achieved with a hormone injection which controls the timing of egg release and final egg ripening.

4. **Egg Collection** – The female partner’s eggs are collected from her ovaries with an ultrasound guided needle aspiration under sedation and local anesthesia. This procedure is planned about 35-37 hours following the ovulation trigger injection.

5. **Sperm Sample** – The male partner produces a sperm sample on the morning of egg collection day in the fertility unit.

6. **Insemination** – The eggs and sperm are placed together in a laboratory dish to allow fertilisation to occur and early embryo growth.

7. **Fertilisation** – Fertilisation occurs in the laboratory when the sperm cell enters the egg, usually within hours after insemination.

8. **Embryo Transfer** – The embryos are placed in the female partner’s womb, usually on the second, third or fifth day after egg collection when the fertilised egg has divided and contains two to eight cells or if on the fifth day – a blastocyst.
Step 1. Down Regulation

In a standard IVF cycle, the woman’s normal cycle needs to be suppressed first. This process is clinically referred to as ‘down regulation’.

- This is achieved using hormonal medications – Buserelin (Suprefact®/Suprecur®) or Nafarelin (Synarel®). This is the first medication you will be given, either as a nasal spray or by an injection given under the skin on the thigh or tummy.
- On the standard regime, you will start the first injection/spray on Day 21 of your cycle and this continues for 2-3 weeks. All patients will be given a written schedule to follow.

Down Regulation helps
- Make the ovaries temporarily inactive
- Make sure the ovaries respond better to the hormone injections; and
- Prevent you from releasing all the eggs before we collect them.

- Side effects such as hot flushes, night sweats, head aches, or mood swings may be experienced.

- These side effects can occur because the oestrogen hormone level in your blood drops. You may not experience all or any of these symptoms but, if you do, they will improve once you start your ovarian stimulating injections, which will increase the oestrogen levels in your blood. These are usually minor.

- It is also normal to have a period like bleed during this phase.

- After two to three weeks of down regulation, a scan is performed to check that the ovaries are inactive and do not contain any large follicles or cysts and that the lining of the womb (endometrium) is thin. This indicates a satisfactory down regulation.

- You may be asked to double the dose and continue the medication for another week or two (maximum up to 5 weeks from the start of injections) and have a scan to confirm satisfactory down regulation.

- If there is a persistent ovarian cyst after down regulation we may drain this under ultrasound guidance (procedure similar to egg collection).

- If satisfactory down regulation is not achieved, the treatment may be stopped and restarted a later date after further consultation. This is essential to maintain a good end result.

- There are variations and alternative ways to this standard regime. The reason for variation is that the patients are treated with different dosages and schedules of medication, depending on their ovarian reserve testing or prior response.

Step 2. Controlled Ovarian Stimulation (COS)

- During IVF the goal is to produce multiple mature eggs because some may not fertilise at all while others may fail to develop normally after they have fertilised. Rarely will all the eggs collected fertilise and go on to develop normally (Usually about 60% do fertilise)
• The (FSH) injections (Gonal F® or Menopur®) are given to the female partner as daily injection, on an average over 10 days depending on how your body responds to the medications, to stimulate egg development in the ovaries. These injections are given just under the skin on the thigh or tummy.

• The initial dose of the FSH injection is decided depending on your age, your blood AMH hormone levels, your baseline day 2-3 FSH hormone level, scan findings and any previous response. If you are on the Long Protocol, you will be instructed to halve the dose of Buserelin or Nafarelin, with the start of FSH injections.

• We will need to monitor your response to the FSH injections. This is done using internal scans and if necessary a blood test to measure the level of oestrogen hormone.

• Normally, oestrogen levels start increasing as the follicles develop. (Follicle - a fluid-filled structure in the ovary containing an egg and the surrounding cells that produce hormones. Follicles are visible on internal scans but Egg itself being very tiny can only be seen under a microscope.) The internal scans measure the number and size of the follicles within the ovaries.

• We may need to adjust the dose of medication either to improve follicular development or to prevent you from over stimulating. The amount of medication prescribed depends upon the results of the blood tests and ultrasound findings.

• The first scan along with a blood test (if necessary) to measure oestrogen level is usually done 5-7 days after starting the FSH injections.

• Thereafter you may need scans and/or blood tests every alternate day to monitor follicular growth and determining when the follicles are mature and ready for egg collection. On an average you will need about 3 scans and blood tests as required, after starting the FSH injections.

• We are aiming to get at least a minimum of three follicles which measure about 18 to 20 millimeters of diameter. The average number of mature follicles is between 8 and 12.

• You may be under stimulating if ovaries have less than 3 follicles.

• You may be over stimulating if you have more than 15 follicles developing.

• The cycle might be cancelled before egg collection if you under or over stimulate.

• The FSH injection causes the oestrogen hormone level in your blood to rise. This might make you feel bloated, nauseated, feel increasingly emotional and have tender breasts.
• Once we are happy that you have good number of follicles on scan measuring over 18 millimeters, we then plan the timing for triggering ovulation and egg collection.

Step 3. Ovulation Trigger

• Once the follicles are ready as determined by a scan, the next step is to trigger ovulation and help egg maturation. Ovulation is triggered by giving a hormone injection (Pregnyl® or Ovitrelle®).

• This is a ‘one off’ injection, which is given exactly the same way as FSH injection. This injection helps the final stages of egg ripening to take place and control the timing of egg release to coincide with timing of egg collection.

• The timing of this particular injection is crucial and needs to be taken exactly 35-37 hours before the scheduled time of egg collection. This is very important and you will be given clear verbal and written instructions explaining the timing.

• This is because if you get this timing wrong, either you will ovulate and release all the eggs before we have had a chance to collect them if the injection is taken more than 36 hours before the egg collection or we will not be able to collect any eggs during the egg collection procedure if the injection is taken less than 34-35 hours before egg collection.

• Once you have had the trigger injection, you do not need to take any more FSH or Buserelin injections.

• You will be given clear verbal and written instructions about the timing of your egg collection and also about producing a semen sample on the morning of egg collection.

• Occasionally, if you are at a high risk of hyperstimulation (over stimulation), we may ask you to take Buserelin injection for ovulation trigger instead of the standard trigger injection, as this may help reduce the risk of severe OHSS. (Ovarian Hyper Stimulation Syndrome)

Step 4. Egg Collection

• This is scheduled about 35-37 hours after the trigger injection. This procedure is performed in the Day Stay Unit (DSU) under intravenous sedation (drugs that make you drowsy, so that you do not feel the intensity of pain) and local anaesthetic.

• The procedure takes about 30 minutes from start till end on an average. You will be instructed not to have anything to eat or drink from the midnight before your egg collection. This is to prevent any anaesthetic complications.

• You will be asked to arrive between 0800-0830 am on the day of your egg collection to the DSU where you will be seen by the nurses to go through a checklist. Your partner will need to produce a fresh sample of sperm in the morning on the day of egg collection (unless a frozen sample is being used).

• Once you are in the egg collection room in the theatre, we will confirm your name and date of birth as part of our strict witnessing procedure. We check these details against your medical records and confirm the storage tubes for your eggs are correctly labelled.
• It is best for you to pass urine just before the procedure. An empty bladder makes the procedure technically safer and easier for us.

• A small cannula (plastic tube) is inserted into a vein in your arm and used to give you medication during the procedure. You will be monitored continuously throughout the procedure with pulse, blood pressure and oxygen levels. You will be given extra oxygen to breathe.

• Once you have had the medication for sedation, we start the procedure of egg collection. In vast majority of cases, this a very straightforward procedure performed through vaginal route under ultrasound guidance.

• Once you are comfortable and relaxed, the vagina is cleaned with simple water using a speculum (an instrument used for smear test). Local anaesthetic (1% Lignocaine diluted) is then injected into the vaginal wall on either side through which the needle is inserted for collecting eggs.

• Then a vaginal ultrasound probe is introduced into the vagina to identify the follicles. If we find that your bladder is full on the scan, we may have to empty your bladder with a catheter.

• A fine needle is passed alongside the probe, with a protective cover. This needle is attached to a suction machine and a glass tube. The needle is gently passed through the vaginal wall into the nearest follicle. The fluid from each follicle is sucked gently through the needle into the connected glass tube.

• As each tube fills up with follicular fluid, the embryologist examines the follicular fluid, identifies the egg, and then transfers each egg to a special culture medium.

• The needle is passed from one follicle to the next until we have emptied all the follicles in one ovary. The needle is then removed and the procedure is repeated on the other ovary. Sometimes we may need to flush the follicles using a special fluid in order to obtain eggs.

• Once the procedure is completed, the vagina is again cleaned and we make sure there is no excessive bleeding. At the end of this procedure, we normally give you a pain killer and an antibiotic through your back passage (rectum). This is to prevent any slightest
chance of infection. After the procedure you will rest in the recovery area for about one to two hours before going home.

- Not every follicle will contain an egg and very rarely, no eggs may be found during egg collection. This may be the case where we have a very less number of follicles. Sometimes there are ovarian cysts that contain no eggs but appear identical to follicles that do contain eggs. Also, follicles of smaller size may not yield eggs. The number of follicles seen with ultrasound, therefore, may not correspond to the number of eggs obtained. Ultrasound provides only an approximation of the number of oocytes that one can expect to recover.

- Very rarely we may need to perform this procedure either abdominally under ultrasound guidance or in extreme situation, laparoscopically. These procedures may be needed for a very small proportion of women, whose ovaries are not easily accessible through vaginal route; the ovaries are situated very high in the abdominal cavity (this can happen after any surgery due to formation of adhesions/fibrous tissue)

- It is not unusual to experience some lower tummy or pelvic pain after the procedure. It is perfectly safe to take paracetamol for this. You might have some blood stained vaginal discharge, which will stop after a couple of days. This is from the site where the needle has passed through the vaginal wall and is not the lining of the womb breaking down.

- Following this procedure you will be prescribed the hormone, progesterone to help the lining of the womb be as receptive as possible to the embryos. Progesterone is usually given as a pessary through vagina or rectum. This will need to be continued at least till the result of pregnancy test.

Step 5. Sperm Sample

The male partner will have to produce a fresh sperm sample on the morning of egg collection day (unless a frozen sample is being used). This sample will be washed and prepared by spinning at a high speed, so that the healthiest and most active sperm can be selected. This process is called sperm preparation.

Human Sperm

Step 6. Insemination
In this step, the prepared sperm sample containing the best quality, motile sperm is placed together with eggs in a carefully labelled dish. This dish containing the eggs and sperm in special culture medium is placed into an incubator overnight, to allow fertilization to take place. This process of placing the sperm together with egg is called insemination.

In some cases, especially where the sperm count is very low, we may need to inject a single best quality sperm into each mature egg, to maximize the chances of fertilization. This is called Intra Cytoplasmic Sperm Injection (ICSI). This particular topic is dealt in detail in the next section.

**Step 7. Fertilisation and Embryo development**

- Fertilisation occurs in the laboratory when the sperm cell penetrates the egg, usually within hours after insemination. The embryologist carefully examines each egg to check for fertilisation, usually the next morning, 16 to 20 hours after insemination.

- Visualisation of two pronuclei the following day confirms fertilisation of the egg. One pronucleus is derived from the egg and the other from sperm. Approximately 40% to 70% of the mature eggs will fertilise after insemination. Lower rates may occur if the sperm and/or egg quality is poor.

- The embryologist will call you the next day morning, after egg collection to inform you how many eggs have fertilised and when the embryo transfer is planned (provisionally).
• Very rarely in about 1 in 100 cases, none of the eggs fertilise and there are no embryos to be replaced. This obviously is very distressing and disappointing. You will be offered the earliest possible appointment to see a senior doctor to discuss the cycle and your future treatment options. You will also be offered an appointment to see the counsellor.

• Eggs that have fertilised are called embryos. As embryos develop, their cells divide. Two days after the egg collection, the fertilised egg would have divided to become a 2 to 4 cell embryo. By the third day, the embryo will contain approximately 6 to 8 cells. By the fifth day, a fluid cavity forms in the embryo, and the placenta and foetal tissues begin to develop. An embryo at this stage is called a Blastocyst.

• We transfer the embryos into the womb two, three or five days after the egg collection. If successful development continues in the womb, the embryo hatches and implants into the lining of the womb approximately six to ten days after the egg collection.

Step 8. Embryo Transfer

• This is an important step where the best quality embryos are transferred into female partner’s womb. This is a much simpler procedure than egg collection and there is no need for sedation or anaesthetic. But however this is a very delicate procedure where gentle handling is critical and the procedure itself needs to be as ‘smooth’ as possible.

• In order to make this procedure as smooth as possible, it will be preferable, if you can have a full bladder for this procedure.

• This helps us in two ways – firstly a full bladder makes the procedure technically easier. This is because in four out of five women, the womb naturally bends forwards. Since the bladder lies in front of the womb, filling up the bladder will ‘straighten out’ the womb and make it easier to direct a soft catheter, which contains the embryos, into the cavity of the womb. On the other hand this may not be useful if the womb is tilted backwards. Secondly, if we need to perform this procedure under ultrasound guidance (in most cases), it will be easier to see the womb with a full bladder, on an abdominal ultrasound.
• The other important point, although difficult at times, is to ‘relax’ as much as possible during the procedure.

• The embryologist will select the best embryos for transfer and the doctor will discuss this decision with you along with the number of embryos to be transferred. If there are any spare embryos of good quality suitable for freezing, you will be offered the option of freezing these embryos for future use.

• Once you are in the embryo transfer room, we will confirm your name and date of birth before the transfer. The doctor and embryologist will check that the dishes containing your embryos are labeled with your name and date of birth, once again, just before the transfer of embryos.

• A speculum is introduced in the vagina to clearly see the cervix (neck of the womb). The cervix is cleaned thoroughly with water several times. Any mucus from inside the cervical canal is removed. It is important to clear the mucus as this might prevent the embryos from getting deposited in the right place (embryos can get stuck to the mucus).

• The embryologist again confirms your name and date of birth just before loading the embryos into a soft catheter. The embryos, suspended in a drop of culture medium, are drawn into a soft transfer catheter (a long, thin sterile tube with a syringe on one end).

• The doctor gently guides the tip of the transfer catheter through the cervix and injects the fluid containing the embryos into the cavity of the womb very gently. The catheter is then removed and checked to make sure all the embryo(s) have been replaced.

• You may be asked to lie down for a few minutes (less than 5 minutes), but if you are desperate to empty your bladder you can do so soon after the transfer without any risk of losing the embryos as resting does not seem to enhance the implantation of embryos.

• A nurse will speak to you before you leave the fertility unit and give you a sheet of written instructions to follow for the next two weeks until the pregnancy test is arranged.

**Alternative Regimes**

**Short Cetrotide Protocol (4-5 weeks)**

• This differs from the Long protocol- you are not on the hormone medication for a long period of time to suppress the normal menstrual cycle.

• Instead in this protocol, you are usually but not always, pretreated with the ‘pill’ starting day 1-3 of your periods, for a few days (between 5-20 days). Following this, you will be asked come for a scan to check that the ovaries are inactive.

• If you are advised not to start on the pill, then you will come in for a scan on day 1-3 of your periods for a scan to ensure that your ovaries are inactive.

• Once this is confirmed, you may start with the ovarian stimulating hormone injections called Follicle Stimulating Hormone (FSH) (Gonal F® or Menopur®), to stimulate the ovaries to produce more than one egg. Five to Six days after starting the hormone...
injections, patients on this protocol will be commenced on a hormone medication called Cetrorelix (Cetrotide®), to prevent premature ovulation. This injection will need to be taken daily, given just under the skin on tummy or thigh. You will have to continue taking the FSH injections alongside these Cetrotide injections

- Rest of the instructions remains the same as above with the Long Protocol until the day of pregnancy test.
- Live birth rates remain comparable to the conventional Long protocol and patient satisfaction is better, though it remains more expensive financially.

**Short Flare Protocol (4-5 weeks)**

- The other alternative regimen that can be used is the Short flare which basically varies in the dose and timing of hormone medication Buserelin (Suprefact®/Suprecur®). A very small selective group of patients may benefit with this stimulation protocol.
- You will start the Buserelin injections along with the FSH injections between Day 1-3 of periods after having a scan to ensure that ovaries are inactive. Buserelin injections usually stop after taking them for about 5-6 days but the FSH injections continue.
- Rest of the steps is similar to short cetrotide protocol as above.

**Estrogen Priming Protocol**

- Estrogen priming protocol can be used along side the short cetrotide and flare protocols to improve the egg production in women with very low ovarian reserve.
- Estrogen Valerate tablets orally (dosage may vary from a patient to patient but usually about 4-6mg/day) are used for 1 month, preceding the actual IVF cycle, starting on Day 1-3 of periods. Once the tablets are finished, the period is awaited and the ovarian stimulation using FSH injections, as mentioned above, is commenced between Day 1-3 of the periods as per the chosen protocol.
- Benefits are limited using this protocol and further research is awaited to see whether this improves pregnancy rates.

**What are the reasons one may need alternative regimens?**

These regimens are usually reserved for a specific group of patients, such as:

- Patients with decreased ovarian reserve (decreased ovarian reserve is associated with depletion in the number of eggs and worsening of egg quality. Both quality and quantity of eggs are affected).
- Poor response to ovarian stimulation in previous cycles.
- Older women usually over 40 years of age.
- Short protocol is also used for women who are at risk of severe hyperstimulation (over stimulation to the drugs).
Patients with moderate or severe endometriosis

- This subset of patients pose specific challenges to the clinician and need careful planning and individually tailored regimes for IVF. There is good scientific evidence to suggest that prolonged suppression of ovarian activity with hormone injections for at least three to four months prior to starting IVF treatment in this group of patients, improves pregnancy rates. The current ESHRE (European Society for Human Reproduction and Endocrinology) guidelines support this view.

- This prolonged suppression of ovarian activity is achieved by having monthly hormone injection called Goserelin (Zoladex® / Gonapeptyl). This injection is given by a doctor just under the skin on the tummy. This injection is repeated every month at least for three months before starting IVF.

- Patients may experience hot flushes; night sweats; head aches; or mood swings while on these injections. This is because of the prolonged ovarian suppression giving rise to very low oestrogen levels in your body.

- Usual protocol here is Long Protocol IVF.

Number of embryos to be transferred- how to decide?

- Current HFEA (Human Fertilisation and Embryology Authority) guidelines allow us to transfer a maximum of two embryos (or a maximum of three if the woman is older than 40 years of age). The number of embryos is restricted because of the risks associated with multiple births.

- Also for the same reasons, we have guidelines policy of performing elective Single Embryo Transfer (eSET) in a targeted group of patients, as per HFEA recommendations. Of course, we also respect patient choice when it comes to performing eSET.

What happens to any remaining embryos?

- Good quality embryos at blastocyst stage, that are not transferred, may be frozen for use at a later date.

- This will be discussed with you when you see the doctor before your embryo transfer.

- You will also receive a written confirmation from the embryologist of how many embryos have been frozen and for how long they can be frozen and when you will need to contact them.

- Only suitable embryos will be frozen as they have to meet strict criteria if they are to survive the procedure. The remaining embryos not suitable for freezing will be discarded.

- You will also be made aware at this stage if any costs are involved and the amount that will cost prior to the freezing. This becomes a legally binding agreement and if the costs are not met, the embryos can be discarded after further communication.
What happens after embryo transfer?

- You will be instructed to continue taking the progesterone pessary and any other medication you will need to be on till we know the result of your pregnancy test. You will have a urine pregnancy test and also a blood test checking for pregnancy hormone approximately 14 days after the embryo transfer.

A Positive Pregnancy Test

- This means that one or more embryos have implanted. This is very early stage to scan as we will not be able to visualize the pregnancy sac and a heart beat until you are about six weeks pregnant (four weeks after embryo transfer).

- We will usually arrange your first pregnancy scan about three weeks after a positive pregnancy test. A second scan will be about two weeks after the first scan which may happen at the early pregnancy assessment unit (EPAU). These scans are to make sure the pregnancy is in the right place, determine the number of fetuses (single or multiple pregnancies), look for the baby’s heart beat and that the pregnancy is progressing well. Patients find this reassuring.

- Sadly we sometimes diagnose miscarriages and ectopic pregnancies at this stage.

- After the second scan if you have an ongoing pregnancy, we will refer you back to your GP to arrange further antenatal care. Unfortunately, a small number of pregnancies can still miscarry even if the early scans have been reassuring and encouraging.

A Negative Pregnancy Test

- Sadly this means that the treatment was unsuccessful. You may already have started bleeding but, if not, you will have a period in the next few days after stopping all the relevant medications.

- This might be heavier than normal because of the medications, which make the lining of the womb thicker than normal. We appreciate that this can be very disappointing and distressing for you.

- We will arrange an appointment as soon as possible for you with one of our senior doctors to discuss the treatment cycle and options for future treatment. You might also find it useful to see the counselor.

What are the reasons an IVF cycle can be cancelled/abandoned?

- Treatment may have to be cancelled before the eggs are collected or before the embryos are put back in to the womb.

- Around 10% of IVF cycles might be cancelled prior to eggs collection. IVF cycles may be cancelled for a variety of reasons as follows.
1. Most common reason being poor response where the ovaries do not respond to the drugs used to stimulate egg production and therefore not enough follicles have developed.

2. Less commonly a cycle may be cancelled to reduce the risk of severe ovarian hyperstimulation syndrome (OHSS), where the ovaries over-respond to the drugs and produce too many follicles.

3. Very rarely ovulation occurs spontaneously in a small percentage of IVF cycles, despite the use of medications to prevent ovulation. When this occurs, no eggs are found during egg collection - the follicles are found to be empty (the eggs may be lost in the pelvic cavity), and the cycle is usually cancelled.

- When cycles are cancelled due to a poor response, alternate drug strategies may be helpful to promote a better response in a future attempt. If your fallopian tubes are open, we might ask you to take the ovulation trigger injection (for release of egg) and arrange for insemination of prepared semen (IUI), if appropriate or advise you to have intercourse at a certain time.

- When cycles are cancelled due the risk of hyperstimulation, we might ask you to stop the FSH injections (Gonal F® or Menopur®), but to continue with the hormone suppressing injections Buserelin (Suprefact®/Suprecur®) which help to inactivate the ovaries which have been over stimulated, for the next three weeks. This strategy of preventing the risk of OHSS is sometimes referred to as ‘Roll Over’.

- After three weeks of continuing with Buserelin (Suprefact®/Suprecur®), you will have a scan to make sure that the ovaries are inactive and then restart the FSH injections (Gonal F® or Menopur®), with a smaller dose.

- But sometimes we might cancel the cycle altogether, where you stop all your medication. You will be advised to use contraception (condoms) to prevent any chance of multiple pregnancy. This is because if a large number of eggs are released at once, a triplet or higher order multiple pregnancy could result. The more number of babies you are carrying, the greater the chance of miscarriage and other serious problems.

- On very rare occasions, the treatment cycles can be cancelled before the embryos are put back in to the womb. The reasons may be:
  1. The collected eggs do not fertilise so there are no embryos to be transferred to the womb. Failed fertilisation occurs in about 5%-10% of cases.
  2. The embryos fail to develop further after fertilisation (failure to cleave as per medical term) in the laboratory, so cannot be transferred to the womb.
  3. Occasionally we may have to freeze all the embryos and not transfer any embryos at this stage, in patients who are at high risk of severe hyperstimulation, as usually a pregnancy worsens this condition. However in this situation, we replace the embryos at a later date in about 6-8 weeks when the ovaries have calmed down. Usually we would advise these patients on an individual basis the way forward.
What happens if your treatment cycle is cancelled/abandoned?

- If your cycle has to be cancelled, we will ask you to stop taking all of the medication. We will arrange a follow up appointment with a doctor, as soon as possible.

- At this appointment we will reassess your treatment and plan a further attempt, if appropriate. We realise that it is disappointing to have a cycle cancelled and you may find it helpful to speak with our counsellor.

- Having your cycle cancelled does not mean you will never respond appropriately. We may be able to adjust your stimulation regime to achieve a better response. This will be a very individualized approach and will vary from a patient to patient.

- Self funding/Private patients may be eligible for refund if the treatment has stopped before the egg collection. Once the eggs are collected, there is no financial refund.

- NHS patients will usually loose a cycle if it is abandoned or cancelled but different PCT have different policies and we will inform you accordingly.

Success Rates with IVF at our centre

Please look at our updated success rates under success rates heading on the website.

Risks involved with IVF treatment

1. Risks associated with hormone injections:

   Possible side effects of the drugs include:
   - Mild bruising and soreness at the injection site. Using different sites for the injections can help.
   - Allergic reaction - rare, gastrointestinal distress, headache, or mood changes.

Specific side effects of each different drug have been covered in sections on Down Regulation and Controlled Ovarian stimulation.

Serious untoward complications from the medications and procedures required for IVF are rare. However, as with all medical treatments and procedures, there are some risks such as increased risk of blood clot formation.

2. Ovarian hyper-stimulation syndrome (OHSS)

   - This is a potentially serious complication of fertility treatment, particularly of in vitro fertilisation (IVF) treatment, in which the ovaries produce many follicles (fluid filled sacs each containing an egg) and become much larger than usual. Almost any fertility drug can lead to this complication.

   - Usually, in the vast majority of cases, it is mild and improves without treatment. However, in severe cases, OHSS can result in much enlarged ovaries, dehydration, fatigue, and the collection of large amounts of fluid in the abdomen and lungs. Very rarely (less than 1% of women undergoing egg retrieval for IVF/ICSI), OHSS can lead to blood clots and kidney failure and such patients would be then treated under critical or intensive care wards.
What causes it?

- Fertility drugs stimulate the ovaries to produce many egg sacs (follicles). Sometimes there is an excessive response to fertility drugs and this causes OHSS. The human chorionic gonadotrophin (hCG) used to trigger ovulation is also the main trigger for OHSS in these patients.
- Over stimulated ovaries enlarge and release chemicals into the bloodstream that make blood vessels leak fluid into the body. Fluid leaks into your abdomen and, in severe cases, into the space around the heart and lungs. OHSS can affect the kidneys, liver and lungs. A serious, but rare, complication is a blood clot (thrombosis).

Who is at risk of OHSS?

- As many as one in three (33%) women develop mild OHSS. About one in 20 (5%) women develop moderate OHSS and less than 25% of women may develop severe OHSS needing critical or intensive care.

The risk of OHSS is increased in women who:

- have polycystic ovaries
- are under 30 years
- have had OHSS previously
- are pregnant as a result of fertility treatment, particularly if this is a multiple pregnancy (twins or more).

What are the symptoms of OHSS?

The most common symptoms are abdominal swelling or bloating because of enlarged ovaries, nausea and, as the condition gets worse, vomiting.

- **Mild OHSS** – mild abdominal swelling or bloating, abdominal discomfort and nausea.
- **Moderate OHSS** – symptoms of mild OHSS but the swelling and bloating is worse because fluid is building up in the abdomen. There is abdominal pain and vomiting.
- **Severe OHSS** – symptoms of moderate OHSS plus extreme thirst and dehydration because so much fluid is building up in the abdomen, passing very small amounts of urine which is very dark in colour (concentrated), difficulty breathing because of build-up of fluid in the chest and a red, hot, swollen and tender leg due to a clot in the leg or lungs (thrombosis). If you develop any of the symptoms, seek medical help immediately.

Can the risks of OHSS be reduced or prevented?

The risk of severe OHSS can be reduced to a lower level by the following strategies:

1. **Lowering the dosage** of fertility drugs to reduce the ovarian response.
2. **Coasting** – This is a process whereby the FSH injections are discontinued for usually about 2 days, till the estradiol levels fall to a safer level at which time the egg collection procedure is planned. However if the egg collection procedure does not seem imminent after two days of discontinuing the FSH injections, it is very likely that the we may have to abandon the cycle,
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as the outcome tends to be very unfavourable after more than two days of discontinuation of FSH injections, as some follicles start to disintegrate.

3. Proceeding with the egg retrieval, but **freezing all embryos or eggs** for a later frozen embryo replacement cycle, as pregnancy can worsen the condition.

4. Using **short cetrotide protocol** seems to reduce the OHSS along with the ovulation **trigger with Buserelin**.

5. Using cabergoline oral tablets, starting a day before the ovulation trigger and discontinuing before embryo transfer, seems to work in some group of patients.

6. **Roll over cycle** – If a patient is at high risk of moderate to severe OHSS (based on the increased number of follicles and very high estradiol levels), the FSH injections are stopped altogether and only the suprefact injections (or nasal spray) continued for at least three weeks in order to suppress the enlarged ovaries. Alternatively a long acting GnRH analog (Injection Zoladex/Gonapeptyl) can also be used to suppress the ovaries, the advantage being it is a single injection given under the skin and lasts for four weeks.

7. After approximately three weeks of ovarian suppression, a scan is performed to check that the ovaries have come back to normal size and if so, then the FSH injections are restarted all over again, but with a much lower dose than before.

8. Withholding the human chorionic gonadotropin (hCG) used to trigger ovulation and cancelling the cycle. Usually suprefact (injection or nasal spray) is continued for 2-3 weeks or alternatively a single dose of long acting GnRH analog (injection Zoladex/gonapeptyl) is given to suppress the enlarged ovaries and also to prevent ovulation. A fresh cycle can be started after a couple of months.

- The decision to opt for any one of these strategies to reduce the risk or prevent OHSS depends upon the individual risk of OHSS assessed by the age of the patient, presence or absence of polycystic ovaries, previous cancelled cycle for OHSS, number and size of developing follicles and the estradiol levels. But safety always comes first.

**Treatment of OHSS**

- Mild OHSS is usually self limiting and can be looked after at home.

- Most of all cases of moderate to severe OHSS will need admission to the hospital for careful observation and monitoring, as this can lead to serious complications.

- OHSS will get better with time, so treatment is mainly aimed to help symptoms and prevent problems. This includes:
  - pain relief such as paracetamol or codeine
  - anti-sickness drugs to help reduce nausea and vomiting
  - an intravenous drip to rehydrate you
  - support stockings and heparin injections to prevent a clot in the leg or lungs (thrombosis)
  - a procedure known as a paracentesis may be offered if your abdomen is tense and swollen because of fluid build-up. This is when a thin needle or tube is inserted into the abdomen to remove fluid.
There is no evidence of problems in the baby as a result of OHSS but it may increase the risk of miscarriages in the first 8-12 weeks of pregnancy.

How long does OHSS last?

Most of the symptoms should usually resolve in a few days. But sometimes it can take longer depending on the severity of OHSS, up to 2-4 weeks.

- If your fertility treatment does not result in a pregnancy, OHSS will get better by the time your period comes.
- If your fertility treatment results in a pregnancy, OHSS can get worse and last up to a few weeks or longer.

3. Multiple Pregnancy

- This is a well recognized risk of IVF/ICSI, as in vast majority of cases, two embryos get transferred. The current guidelines allow two embryos to be transferred to increase the chances of pregnancy, but this may lead to multiple pregnancies in about one in four cases (25%).
- After natural conception, about one in 80 births in the UK are multiple births compared with one in four after IVF.
- Identical twins carry higher rate of complications than the non-identical twins.
- More the number of babies, higher the chances of problems.

Why are multiple pregnancies considered to be a risk?

- For some it may seem ideal to become pregnant with more than one baby after treatment, having waited for a long time to have a baby.
- However there are some significant risks associated with multiple pregnancies which need to be considered and addressed before treatment. All the risks of pregnancy and birth are significantly increased for women who are pregnant with more than one baby. These include:

Risks to the mother

- Miscarriage
- Premature labour/birth
- Hypertension/pre-eclampsia (high blood pressure with subsequent risks of kidney, Liver and clotting problems). Up to 25% of multiple pregnancies are complicated by pregnancy-induced high blood pressure and the risk of pre-eclampsia increases almost three times for twin pregnancies and is nine times higher for women pregnant with triplets.
- Incidence of diabetes during pregnancy is two to three times more than in singleton pregnancies.
- Caesarean section or delivery with forceps/ventouse.
- Haemorrhage (bleeding)
- Anemia (iron deficiency)
- Although the risk of mortality is still very small, it is doubled for women expecting twins compared to women who are pregnant with a single baby.
Risks to the babies

The chances of illness, disability and death are highly increased for multiple pregnancies, because the babies most often tend to be premature. A baby’s lungs, brain, circulatory system, intestinal system, and eyes may be too immature. Survivors of premature birth may have lifelong handicaps.

- 50% of twins are born prematurely (before 37 weeks of pregnancy) and have a low birth weight (less than 2500 gms or 5.5 lbs).
- Triplets have a 90% chance of being born before 37 weeks of pregnancy and of having a low birth weight.
- The risk of death for premature babies around the week of birth is five times higher for twins and nine times higher for triplets compared to singletons. Some effects of prematurity can affect a child well into their childhood.
- Twins are four times more likely to have cerebral palsy than singleton babies and triplets are 18 times more likely to have this condition.
- Identical twins have a significantly increased risk of congenital abnormalities (birth defects) and prone to Twin to Twin transfusion syndrome, a life threatening condition. This occurs when blood flows from one fetus to the other. Poor growth occurs in the “donor” twin, and excessive blood passes to the “recipient” twin.

4. What about Ovarian Cancer?

Despite some older reports suggesting a link with ovarian cancer, more recent studies fail to provide any convincing evidence that supports any association between fertility drugs and ovarian cancer.

5. Is there an increased risk of fetal abnormalities with IVF?

- The risk of an abnormality in a natural conception is about 3%.
- There is evidence that IVF babies are more likely to be born early (prematurely) and weigh less than naturally conceived babies born at the same age.
- All the published evidence suggested there is no increased risk of fetal abnormalities in children born as a result of IVF treatment.
- Children born after ICSI treatment show increase risk of birth defects such as hypospadias compared to natural conceptions. This is still an on going research and a debate.

6. Egg Retrieval

- During egg retrieval, we use a vaginal ultrasound to guide the insertion of a long, thin needle through your vagina into the ovary and then into each follicle to retrieve the egg. This procedure is usually done under sedation or anesthesia.
- Specific possible risks include:
  - Mild to moderate discomfort (during or after the procedure) which varies according to individual pain threshold.
  - Rarely injury (less than 1%) to organs near the ovaries, such as the bladder, bowel, or blood vessels.
• Bleeding from the ovary or pelvic vessels (less than 1%). Any bleeding is usually mild, rarely requiring transfusion or surgery.
• Pelvic infection (mild to severe). Such infections are very rare (less than 1%). However, if they do occur, they may be severe and typically are treated with intravenous antibiotics. Rarely, surgical intervention may be required.

7. Risk of Miscarriage
• This is similar to natural conception.

8. Ectopic Pregnancy
• The incidence of ectopic pregnancies is slightly higher after IVF in patients who have damaged tubes as compared to spontaneous pregnancies-about 5%.
• Patients with significant tubal damage may be advised to have their tubes clipped or removed prior to IVF if necessary.
• In spite of removal of tubes, ectopic pregnancy can still occur in other parts of womb.

ICSI (Intra-cytoplasmic sperm injection)
• Intra-cytoplasmic sperm injection (ICSI) is a laboratory procedure developed to help infertile couples undergoing in vitro fertilization (IVF) due to severe male factor infertility.
• ICSI involves the injection of a single sperm directly into the cytoplasm or centre of a mature egg using a glass needle (pipette) in an attempt to achieve fertilisation.
• ICSI revolutionised the treatment of severe male infertility and gave hope for those couples whose only option used to be donor sperm. This has also given these couples a chance to have their own genetic child.
• ICSI is generally unsuccessful when used to treat fertilization failures that are primarily due to poor egg quality.

Common reasons for performing ICSI?
• The male partner has very low numbers of motile sperm or increased number of sperm with an abnormal appearance.
• The male partner has no sperm in his ejaculate, but sperm can be obtained from the testicles, with a minor operation using microsurgical techniques.
• Prior or repeated fertilization failure with standard IVF methods where no apparent reason can be found.
• Frozen sperm limited in number and quality – for example, before cancer treatment.
• The male partner has retrograde ejaculation – the sperm passes backwards into the bladder and can be found in the urine.
• Sometimes if the female partner has responded poorly to ovarian stimulation, producing only few eggs, we may consider ICSI in order to boost the chances of fertilisation.

What happens in an ICSI cycle?
Stimulation and egg collection steps and protocols are the same as in an IVF cycle. The difference between the two is that, in an ICSI cycle, mature eggs are directly injected with sperm instead of being placed together in a laboratory dish, as in IVF.

**How is ICSI performed?**

- A few hours after the egg collection, the cells surrounding the egg are carefully removed from around each egg (referred to as ‘denuding’ or ‘stripping’) and the embryologist examines the eggs to determine the stage of development.

- It is unlikely that all the eggs collected will be at the correct stage of development for sperm to be injected (referred to as Metaphase II or MII), usually a few are immature and these are not suitable for injection. Approximately 70-80% of all eggs collected will be mature and therefore injected. The prepared eggs are placed into individual droplets of media within a dish.

- The prepared sperm (as in IVF) are placed into a droplet in the centre of the dish, within a viscous solution that slows the sperm down, thereby aiding the embryologist to catch the sperm.

- The dish containing the eggs and sperm is placed onto the specialised ICSI equipment. This ‘ICSI rig’ consists of a high powered microscope, micromanipulators attached with fine glass pipettes and a heated stage which keeps the oocytes at the correct temperature throughout the procedure.

- A single best quality sperm is selected with the best shape and moving ability. This sperm has to be immobilised before it is injected into the egg, and this is done by breaking the tail of the sperm with the fine glass injecting pipette.

- Once still, the sperm is aspirated into the end of the pipette and taken to the egg. A rounded pipette holds the egg still by gentle suction and the sperm can then be injected into the centre of the egg.

- The ICSI technique requires great skill and only embryologists who have undergone extensive training and gained a licence from the HFEA are able to perform the procedure.

- The embryos thus formed are replaced in your womb in exactly the same way as for conventional IVF. Any suitable embryos not used at this stage can be frozen for future use. Rest of the treatment steps are the same as with IVF cycle.

**How many eggs will fertilise and how successful is this procedure?**

- Although we are helping by injecting the sperm directly into the egg, this does not always guarantee fertilisation. Fertilisation occurs in about 60-70% of injected eggs.

- The process of ICSI may damage a small percentage of eggs. 5% to 10% of the eggs can be damaged and lost during the ICSI procedure. The fertilized egg may fail to divide, or the embryo may arrest at an early stage of development.
• Approximately 30% of all ICSI cycles performed result in a live birth, which is comparable to rates seen with traditional IVF. Younger patients may achieve even more favorable results. Factors such as poor egg quality, poor sperm quality and advanced maternal age may result in lower rates of success.

• ICSI does not improve live birth rate if performed as a substitute for IVF but only improves outcome in male factor sub fertility mainly.

What are the risks specific to ICSI treatment?

• Because ICSI involves injecting a sperm directly into an egg, therefore allowing the use of sperm that may not otherwise be able to fertilise an egg, concerns have been raised about the potential risks to children born as a result of ICSI.

• Since ICSI is a relatively new technique, first performed in 1992, children conceived using ICSI are still very young and therefore long-term data concerning future health and fertility of children conceived with ICSI is not available. Clearly, more studies are needed, but the use of ICSI has been potentially linked with certain genetic and developmental defects.

• A small proportion of sub-fertile men have parts of their Y chromosome missing (deleted). Certain genes on the Y chromosome have been shown to be involved in the production of sperm, and deletion of these genes may be responsible for some men having few or no sperm in their semen. Therefore using sperm with such deletions to create an embryo may result in the same type of sub-fertility being passed from father to son.

• Abnormal numbers or structures of chromosomes, particularly the sex chromosomes (X and Y), may be associated with infertility in both men and women, and babies born from ICSI treatment may have a slightly increased risk of inheriting these abnormalities. Studies have found that up to 3.3% of fathers of ICSI babies have abnormal chromosomes. It is estimated that up to 2.4% of the wider population have a chromosomal abnormality.

• Some men who have no sperm in their semen may have absent tubes that carry sperm from the testis to the penis; this is called Congenital Bilateral Absence of the Vas Deferens (CBAVD). Two thirds of men with CBAVD may also be carriers of certain cystic fibrosis mutations which can be passed on to any baby born from ICSI treatment.

• Before the start of treatment, a blood test can be done to look at the male chromosomes and check if there is a detectable chromosome abnormality. We can also screen both you and your partner to see if either or both of you carry the gene for cystic fibrosis. You will be offered genetic counselling if there is any abnormality.

• There is not yet any clear evidence whether ICSI results in higher rates of birth defects. Some studies report that the incidence of a congenital malformation called hypospadias (urethra opening on underside of penis) is increased in babies conceived through ICSI. This is an area of ongoing investigation.
Possible risks during pregnancy:

- With ICSI, it is possible that abnormal gametes, which would not usually be able to produce a viable embryo, could be used. This may increase the chance of an abnormal embryo being formed. However, most abnormal embryos will not implant into the womb and grow, but some might, leading to a possible higher risk of miscarriage. It has been reported that the risk of miscarriage increases in proportion to the severity of male infertility.

- Despite these concerns, ICSI is a major advance in the treatment of severe infertility.

Other risks mentioned in IVF section also apply to any ICSI treatment cycles in addition to the above mentioned risks specific to ICSI.

**Success Rates with ICSI at our centre**

Please look at the section of success rate