

TRANSPORT IVF

INFORMATION FOR PATIENTS

KINGSTON HOSPITAL

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Introduction:

In-vitro fertilisation (IVF) literally means the fertilisation of eggs by sperm outside the body. IVF is used as a treatment for infertility caused by blocked fallopian tubes, endometriosis, impaired sperm function (low count or motility), sometimes when there are problems with ovulation and in some cases of 'Unexplained' subfertility when no obvious cause for infertility is found.

In a natural cycle, it is usual for a woman to produce only one egg which is released from the developing follicle (fluid filled structures in the ovary that contain the egg) two weeks before the next period starts. The follicle grows to about 17 - 22mm before releasing its egg (ovulation). Each follicle will usually contain one egg only.

In standard IVF treatment the aim is to achieve the growth and development of several follicles in order to maximise the chance of collecting several eggs. This is done by daily injections of a hormone called follicle stimulating hormone (FSH) which stimulates the ovaries and facilitate the development of several follicles. The growth of the follicles is monitored by ultrasound scan and egg retrieval is scheduled when the follicles / eggs are mature. The number of follicles that develop and the number of eggs retrieved from each woman will depend on the woman's egg count (ovarian reserve). Women with good egg count usually respond better and produce more eggs and women who have low egg counts may not respond well to the stimulating hormones and so we may harvest only few or sometimes no eggs.

The Drugs:

IVF involves the use of various medications depending on the treatment protocol. We have listed below some of the medications that we commonly use. Their functions and possible side effects are also outlined below.

The medications used for each case will depend on the protocol prescribed by the doctors and may not include all the drugs listed below:

- **The Oral Contraceptive Pill**

The oral contraceptive pill is known by the generic name of **levonorgestrel_ethinylestradiol 150_30**

Using the pill before starting IVF helps in 3 main ways:

A) it prevents the formation of simple ovarian cysts which sometimes may delay starting your IVF ,

B) it helps in down regulation, (a process that must be achieved before stimulation can start)

C) it allows for cycle control and enables us to help you plan when your treatment will commence.

- **Buserelin (Suprecur)** Two sniffs, three times daily or 0.5ml injected daily. These drugs have the effect of “switching off” the pituitary gland’s natural production of FSH and LH, in order to prevent interference with stimulated development of eggs and to prevent premature release of eggs.
- **Cetrorelix (Cetrotide)** is used to prevent premature release of the eggs (premature ovulation) before the eggs are retrieved. This drug which is called gonadotropin released hormone antagonist, is used only in certain protocols.
- **Menopur and Merional** contain FSH and are used at doses between 75 and 450 units daily to stimulate development of eggs and are given by daily injection. These drugs are collectively known as gonadotrophins .
- **Human Chorionic Gonadotrophin:** HCG (Ovitrelle) is given in the evening two days before egg collection to facilitate final egg maturation. It has the effect of causing the eggs within the follicles to mature so that the eggs would be suitable for fertilisation.
- **Cyclogest** (progesterone) is given in the form of suppositories placed in the rectum or pessaries in vagina. This drug prepares the endometrium for implantation of the embryo and supports the early pregnancy. This support is given for two weeks starting from the day of the egg retrieval.

It is NOT necessary to use progesterone beyond two weeks, irrespective of the result of the pregnancy test.

These preparations may delay the onset of the next period even if you are not pregnant. A urine pregnancy test should always be performed two weeks after the embryo transfer even if you have started to bleed.

Possible side effects of the drugs:

The Pill

Nausea, fluid retention, headache, breast tenderness / enlargement, contact lenses may irritate eyes, leg cramps, photosensitivity and absence of withdrawal bleed.

You should not take the pill if you suffer from severe migraine, if you or a close family member has had a blood clot, thrombosis or pulmonary embolism, if you have heart disease, liver disease, gallstones, history of itching or cholestasis / jaundice in pregnancy, history of breast cancer, or if you have had treatment for varicose veins. The Pill is suitable for most women to use during IVF especially as the duration is only for a short time.

Buserelin/Nafarelin/Gonadotrophins

Discomfort at injection site
Headaches.(you may take paracetamol)
Tiredness
Allergy
Mood swings
Hot flushes
Pelvic discomfort
Nausea (very occasionally)
Vaginal bleeding
Nasal irritation
Ovarian hyperstimulation (see below)

Cyclogest/HCG

Breast tenderness
Can delay the onset of a period by a few days
Constipation

Cetrotide:

Nausea, headache, injection site reaction, rarely hypersensitivity reaction

We hope that you do not experience significant side effects from your medications, but if you do experience any side effects which are persistent whilst on the fertility drugs and you are concerned, **please contact us for advice.**

Arranging Treatment:

Initial Consultation:

If this is your first IVF cycle, an appointment will be arranged for you to meet with one of our doctors to review your history and test results, discuss the process of IVF and to discuss your chances of a pregnancy. This consultation may involve an internal examination and/or a trans-vaginal ultrasound scan to assess your pelvis, womb and ovaries to help plan your IVF treatment. The doctor will discuss your treatment protocol with you and prescribe the appropriate medications.

This consultation will be followed by a meeting with one of our IVF nurses who will check that your blood results are up to date and go through some paper work with you. At this stage we should know if you are immune to rubella. If you are not you will need to have a rubella vaccination and your treatment will be delayed by a couple of months. If everything is normal, the nurse will advise you when you would start taking your medications and arrange for you to receive detailed and specific information regarding your treatment cycle. This initial consultation / appointment may last up to 2 hours.

In order to comply with Human Fertilisation and Embryology Authority (HFEA) regulations we will also require the following to be completed -

1. You and your partner will both need to be screened for HIV, Hepatitis B, Hepatitis B Core and Hepatitis C. This blood test needs to be completed every two years and you must complete your first treatment cycle within three months of this test.
2. You and your partner will need to complete a "Welfare of the Child" assessment form which the nurse will provide.
3. You will need to complete a "Consent to Disclose" HFEA approved form.
4. We will need to see photographic proof of identity for both of you. This will be in the form of your passports
5. You will need to consider whether you wish to consent for research. We would encourage you to participate in research as this is an essential part of improving assisted conception processes. It is strictly controlled by the HFEA and no identifiable information is disclosed when publishing results.

The nurse will provide you with the relevant forms and assist you with any queries that you may have during completion of the forms.

A semen analysis may also be required and we will request one if need be.

When a patient is being treated for the second or third time these tests do not usually need to be repeated unless they have become out of date.

We would advise patients to start folic acid 0.4mg once a day 3 months prior to treatment. This can be purchased directly from the chemist. This will need to be continued until you are 3 months pregnant.

Starting the treatment:

The type of ovarian stimulation Protocol (process) and the combination of medications used for ovarian stimulation during IVF may vary from woman to woman depending on individual requirements. Your doctor will discuss the protocol that is prescribed for you during your consultation. Whatever protocol is used you will receive detailed specific instructions and you are always able to contact the ACU for advice.

The long (Agonist) Protocol:

Down Regulation: If your doctor prescribes this protocol for you, you will usually start taking the Pill (Microgynon) from day 2-5 of your menstrual cycle (the first full day of bleeding being day 1). If your cycles are irregular or if you do not have periods then you will commence the Pill once you have had a negative pregnancy test. You will take one tablet daily for between 15 and 42 days. The nurse will advise you how long you will take the Pill for. If there is a need to continue the Pill for longer than three weeks, you should do so without stopping. We will advise you when to stop taking the Pill and to start sniffing the nasal spray on the same day that you stopped the Pill. You should expect to have a bleed within 7 days of stopping the Pill. You should continue to sniff the nasal spray as usual. We will arrange a scan to assess your ovaries and womb after you have been sniffing for about 2 weeks. This is to ensure that we have successfully 'switched off' your own hormones (down regulation) before we can start ovarian stimulation. The scan is performed transvaginally using a thin ultrasound scan probe passed into the vagina. This method provides a clearer picture of your pelvis. An empty bladder is required for the transvaginal scan and so we would ask that you empty your bladder when you arrive the department and before your scan.

Occasionally the scan may show that the nasal spray has not caused the desired down-regulation effect and if this is the case we may ask you to sniff for a little longer. Sometimes we may have to stop the treatment and start again using a different medication. This would cause a delay of a month or two before you can start your IVF treatment again.

Please note that treatment cycle ultrasound scans are always performed in the mornings of Monday, Wednesday and Friday only. We are not open on Bank Holidays.

It is important that you DO NOT stop the nasal spray until you are told to do so by the clinic. You are expected to continue sniffing the nasal spray until usually just prior to egg collection. The clinic will advise you when to stop sniffing.

Starting stimulation:

When your scan confirms that the nasal sprays have switched off your own hormones (down regulation has been achieved), we would start the ovarian stimulation injections. In most cases the follicle stimulating hormone (FSH) injections are commenced on a

Monday, Wednesday or Friday. These injections are given on a daily basis. We will show you and your partner how to give these injections. These are given manually. After 7 days of injections you will be scanned on alternate days to monitor response to the stimulation and growth of the follicles. Occasionally an earlier scan is required. We would inform you if this is the case.

When your follicles are big enough / mature, you will be instructed to take an injection of another hormone called HCG (Ovitrelle). This important trigger hormone causes final ripening of the eggs before they are ready for harvesting. **The timing of the administration of the HCG injection is very important** and the nurse will advise what time that you should take the HCG injection. It is important that you take this injection at the correct time that you were advised to administer. Administering the HCG injection on the wrong day or at the wrong time may mean that the eggs fail to mature properly or may cause the follicles to rupture / release the eggs prematurely before the eggs are harvested. The HCG trigger injection will usually be given within 34-36hours before the eggs are collected. The HCG drug (Ovitrelle) will be handed to you at your final scan appointment and will **need to be stored in a refrigerator until it is administered at the time that you were advised to administer it.** This is usually to be administered during the late evening. Egg collection (see below) will be scheduled for between 34-36hours after the HCG injection.

Short Agonist Protocol:

This is a shorter treatment protocol which the doctor may recommend for you if appropriate in your case. You will be advised to call the department on day one of your period (being the first day of full menstrual bleeding). A scan appointment will be arranged for you on day 2, 3 or 4 of your cycle and if the scan is normal, you will start taking the nasal spray and start the stimulation injections on the same day. Further scan appointments will be arranged after 7days of injections and on alternate days thereafter to monitor development of the follicles which usually contain eggs.

When your follicles reach the correct size, you will have an injection of HCG (Ovitrelle) to ripen the eggs before they are collected. The timing of the administration of the HCG injection is very important and the nurse will advise what time you should take the HCG injection. If the injection is given at the wrong time it may cause the follicles to rupture with premature release of the eggs before the eggs are collected. The HCG trigger injection will usually be given within 34-36hours before the eggs are retrieved. You will be advised of the exact time by the unit and this is usually to be administered during the late evening

The HCG drug (Ovitrelle) will be handed to you at your final scan appointment and will **need to be stored in a refrigerator until it is administered.**

Short (Antagonist) Protocol:

Your doctor may recommend this protocol for you if appropriate in your case. You will not need to take the Pill.

You will be asked to contact the department on day 1 of your menstrual bleed (being the first day of full menstrual bleeding). An appointment for a scan will be made for you for day 2, 3 or 4 of your cycle to assess your pelvis, womb and ovaries. If the scan is normal you would start the stimulation injections (gonadotrophins) on the same day. A further scan will be arranged for you after 6 days of injections to assess the response to stimulation and growth of the follicles. You will be advised to commence taking a second type of hormone injection called Cetrotide daily when appropriate. This injection (Cetrotide) is used to prevent premature release of the eggs (premature ovulation) until the eggs are ready for harvesting. You will continue taking your stimulation injections and the Cetrotide injection daily until you are advised by the unit to stop.

When your follicles are big enough / mature, you will be instructed to take an injection of another hormone called HCG (Ovitrelle). This important trigger hormone causes final ripening of the eggs before they are ready for harvesting. **The timing of the administration of the HCG injection is very important** and the nurse will advise what time that you should take the HCG injection. Administering the HCG injection on the wrong day or at the wrong time may mean that the eggs fail to mature properly or may cause the follicles to rupture / release the eggs prematurely before the eggs are harvested. The HCG trigger injection will usually be given within 34-36hours before the eggs are retrieved. The HCG drug (Ovitrelle) will be handed to you at your final scan appointment and will **need to be stored in a refrigerator until it is administered**. This will usually be during the late evening. Egg collection (see below) will be scheduled for between 34-36hours after the HCG injection

The egg collection:

Irrespective of the treatment protocol that you were prescribed, you will be given a date and a time for egg collection at your last scan appointment when the follicles are judged to be mature. Egg collections are almost always performed in the Assisted Conception Unit at Kingston Hospital. Occasionally these will take place at King's College Hospital, although this is unusual. You will be informed if this is the case.

In preparation for the procedure, you should have nothing to eat or drink for at least six hours before the egg collection apart from a glass of water which you may have up to two hours before your procedure. The egg collections are performed after you have been given a sedative by the anaesthetist. The procedure usually takes about 20-30 minutes and should not be painful. We will ask your partner to remain in the recovery area or waiting room while the procedure is taking place.

Egg retrieval is performed trans-vaginally. The scan probe has a fine needle attached to it, which is passed into the ovaries through the vagina and the fluid from the follicles is aspirated. We expect to obtain an egg from about 70% of mature follicles. The number of follicles seen on scanning therefore does not always correspond to the number of eggs present. On very rare occasions (usually when the ovarian response has been poor) we may not find any eggs..

After the egg collection the follicular fluid, in which the eggs are contained, will be taken by your partner (or if you have no partner, another person whom you may elect), in a specially designed portable incubator to the IVF Unit at King's College Hospital . Please note that the incubator, although not large is fairly heavy at 9.5kilo. King's College Hospital is a very well respected NHS assisted conception unit situated very close to Denmark Hill Station. They provide embryology services for us and other transport centres as well as for their own patients.

If your partner's sperm is being used to fertilise the eggs, he will need to produce a sperm sample at King's College Hospital when he takes the incubator to the laboratory.. **If he is likely to have difficulty in producing a sample by masturbation on the day please discuss this with us beforehand.** It is possible for sperm to be frozen at King's College Hospital in advance and prior to commencing treatment. There may be a charge for this service if you are a self-funding patient. We have had cases where the partner has been unable to provide his sample on the day and these cycles have not been able to continue.

What are the risks of egg collection?

Complications of transvaginal egg collection are uncommon. However, like every operative procedure there could be associated small risks, including infection (0.5%) and bleeding, and an even smaller risk of damage to other organs inside the abdomen such as bowels (your guts) or blood vessels. These are very uncommon.

After the egg collection

After the egg collection you may feel drowsy for the rest of the day. You should be ready to go home approximately three hours after the procedure. **It is important to have somebody to accompany you.** You should not drive a car or operate machinery for at least 24 hours following the procedure

It is common to feel some lower abdominal discomfort, for which you may take paracetamol tablets, two tablets every four hours. The discomfort and bloating may last for a couple of days. If you feel sick, avoid eating substantial meals and stick to fluids for the rest of the day.

A small amount of vaginal bleeding is not unusual. It is best to use sanitary towels rather than tampons.

You will be asked to use Progesterone suppositories (Cyclogest 400 mg twice daily) to prepare the lining for implantation and to support the embryo(s). You should start taking these progesterone pessaries on the evening of the egg collection and continue for two weeks after the embryo transfer. We will ensure that you have written information regarding this.

It is wise to take things easy after the egg collection and perhaps have a day off work the following day.

If you have any concerns, please ring the ACU and speak to one of our staff on 020 8934 3155 or email us on khn-tr.kingstonacu@nhs.net

In an EMERGENCY ONLY when the centre is closed, the unit may be contacted through the above number

The embryo transfer:

Staff at King's College Hospital IVF unit will contact you the day following egg collection to inform you of the number of eggs that have fertilised and how the embryos are developing. Unfortunately not all the eggs will fertilise and even when the eggs fertilise to form embryos, not all of the embryos may develop and grow. The embryologists at Kings Hospital will advise you how your embryos are developing. We will obviously only want to replace healthy and normal looking embryos into the uterus.

The embryo(s) will be transferred into your uterus at King's College Hospital, usually between two and five days after egg collection. If you have several embryos that appear to be good quality, King's may recommend culturing them for a longer time in the laboratory to help selection of the best embryo (this is known as blastocyst culture – see information at the end of this document).

The embryo(s) are transferred into your uterus during a procedure that resembles a cervical smear test. You would normally not require any pain relief as the procedure is usually quick and normally not painful.

Very occasionally however, you may experience period like cramps. This is not unusual.

You should do an early morning urine pregnancy test 2 weeks after transfer of the embryo(s). It is important not to take the pregnancy test until two weeks after the embryo transfer as taking it early may give a false result.

Please contact us with the result of this test even if it is negative.

Please see appendix 2 at the end of this document for more information supplied by King's regarding embryo transfer.

Number of embryos / Multiple Pregnancy

The law allows for the transfer of three embryos only in exceptional circumstances when women are over 40 years old. Our policy is to transfer one (or two embryos in some cases) in order to minimise the chances of multiple pregnancy. Multiple pregnancies are associated with an increased risk of miscarriage and complications during pregnancy. These include premature birth of very small babies, which may be handicapped or may not survive. In addition to these risks, a multiple birth can create enormous strains for the parents, including financial difficulties, emotional and physical exhaustion. Currently 11% of our ongoing pregnancies or births are twins and less than 0.2% triplet.

For the majority of couples, having 3 embryos replaced does NOT increase the chances of a live birth. The most successful treatments are those in which one or two embryos are selected from 3 or more embryos available.

The HFEA is currently recommending single embryo transfer in selected patients to reduce the risk of multiple pregnancies. Spare embryos can then be frozen and replaced if necessary at a later date. Large studies have shown that the pregnancy rates are the same for a 2 embryo transfer when compared to a single embryo transfer plus subsequent frozen embryo transfer and multiple pregnancy rates are significantly reduced. We would strongly recommend that you consider this approach.

After embryo transfer:

You can go back to 'normal routine' after the embryos have been transferred. The embryos are quite safe within the womb and you can walk about, bathe, shower and undertake normal daily activities. It is best to avoid strenuous activity and heavy lifting until your abdomen is less tender and back to normal. Sexual intercourse can be resumed whenever you feel like it.

Abdominal distension and a bloated feeling is common, and this may be associated with feeling sick. Sometimes these symptoms occur after a few days. It is important to drink plenty of fluids and paracetamol may be taken for pain relief if necessary. Please ring the clinic if you have any concerns..

If pregnancy occurs

Again, there is nothing special that you need to do. We will monitor your early pregnancy with a scan at 6-8 weeks gestation, which is about 3-4 weeks after a positive test. At this stage, we can confirm the position and number of foetuses and confirm that the foetal heart is beating. We will then send a letter to your GP and they will refer you for antenatal care. You will be discharged from the Assisted conception unit at this stage.

The risk of miscarriage following IVF is comparable to that in the general population. Approximately 12-15% of pregnancies will miscarry; this is higher with multiple pregnancies.

If you conceive following IVF the risk of an ectopic pregnancy (pregnancy growing outside the uterus, usually in the fallopian tube) is about 3%. In the event of this happening, an operation may be necessary as ectopic pregnancies do not develop normally, and may have to be removed. The ultrasound scan will indicate if this has occurred. However, if you have any pain or bleeding in early pregnancy, you should report your symptoms to us or your GP. The risk of ectopic pregnancy is higher in those with known tubal damage and if this is the case you will be offered a scan a week earlier than usual.

Freezing embryos:

After a treatment cycle of IVF, surplus embryos may be frozen for your future use. In accordance with the HFEA guidelines, we are allowed to store the embryos for up to 10 years in normal circumstances. This storage period may be extended to 55 years in total if the conditions of the extended storage regulations are met (premature infertility) and after the appropriate consent forms have been signed. It is your choice to decide how long to store the embryos but if your treatment is NHS funded you may need to pay for any additional years of storage yourself.

It is important to be aware that if you or your partner die or become mentally incapacitated your sperm, eggs or embryos cannot be used in treatment unless the consent for posthumous use has been provided and your partner named.

Only good quality embryos will be proposed for freezing. Of these, approximately 50-80% will survive the freezing and thawing process according to the stage of embryonic development on the day of freezing.

There is a risk of possible deterioration or loss of viability of embryos as a result of storage, and the potential risk of cross-contamination between stored samples of embryos, although this is very small. There is no current evidence of an increased risk of adverse consequences in children born following frozen embryo transfer.

You and your partner will need to sign a written consent form for freezing of embryos. You will need to specify the duration of time you wish them to be stored for. You will also need to consider whether you would like any surplus embryos (which are not suitable for freezing) to be used for research or training purposes.

King's College Hospital will give you advance notice when the end of the storage period is approaching if you wish to extend this. You should inform the Centre or us of any change of contact details.

If you are considering replacing frozen-thawed embryos, you will need to see one of the clinicians to discuss your options. Please refer to a separate document (Replacement of Frozen Thawed Embryos) for more details.

If your treatment is NHS funded there will usually not be any charge for the storage of excess embryos for the first year. If you are self funding your treatment you will have received a Costed Treatment Plan with the costs of embryo storage set out. Self Funded patients will be charged by Kingston Hospital for the initial freezing and storage once freezing has taken place. If embryos remain in storage after the initial storage time (usually one year) then King's will charge you directly for any subsequent storage

Please see appendix 1 at the end of this document for information, which has been supplied by King's, regarding embryo freezing

Use of gametes (eggs or sperm) or embryos for research and training:

You will need to consider if you wish to consent for use of any surplus eggs or sperms (gametes) or embryos created during the treatment, which are not suitable for your treatment, for research or training purposes.

The research will be conducted by a licensed laboratory and is regulated by the Human Fertilization and Embryology Authority. The principal purposes for conducting research are to increase knowledge or developing treatments about serious diseases or medical conditions, promoting advances in treatment of infertility, increasing knowledge about the development of embryos and detecting abnormalities in embryos before transfer etc. You will be provided with information regarding the research project, its benefits and funding. The principal purposes of training are to train laboratory staff in embryo biopsy, embryo storage or other embryological techniques, and only gametes or embryos not suitable for your treatment would be used.

Your decision to donate will not affect your treatment in any way. You can vary or withdraw the terms of your consent until the point the embryos are used in the research or training. Both you and your partner will need to provide this consent prior to starting treatment.

Counselling:

We appreciate that this is an emotionally stressful time for you and your partner and it sometimes helps to alleviate stress to talk to someone. Our counsellor is very experienced in the field of infertility. Anything you discuss with her will be in strict confidence. If you would like to arrange an appointment with her please contact us.

Complaints procedure:

Mr Nick Pulsford is the manager of the Kingston Hospital Assisted Conception Unit. If you have any queries, suggestions, compliments or complaints, he would be pleased to hear from you. We are very keen to monitor patients' satisfaction on a regular basis. Your feedback would help us to continue to improve our service. Alternatively you may wish to contact the Kingston Hospital Patient advice and Liaison Service (PALS)

Further information:

Further information about the assisted conception unit is available on our website www.kingstonacu.org.uk.

Treatment funding:

In order to be eligible for NHS funded IVF treatment you will need to fulfil the criteria set by your funding body and an assessment will be made before you are seen within the ACU.

We provide NHS and self funded treatments and you will be aware of which option you are undergoing prior to the start of the cycle. If you are an NHS patient you will not pay for any part of the treatment cycle and in most instances this will include the freezing of spare embryos. If you are a self funding patient you will be required to pay for the treatment at the time of the commencement of the gonadotrophin injections. Please see our separate funding documents for these details

Contact information:

Assisted Conception Unit
Level 5 Roehampton Wing
Kingston Hospital
Galsworthy Road
Kingston upon Thames
Surrey
KT2 7QB
Tel: 020 8934 3155

Assisted Conception Unit
1st floor Unit 6
KCH Business Park (off Bessemer
Road)
King's College Hospital NHS
Foundation Trust
Denmark Hill, London SE5 9RS
Tel: 020 3299 5390/ 5391

www.kingstonacu.org.uk
email: khn-tr.kingstonacu@nhs.net

Blastocyst transfer:

We offer blastocyst transfer to patients undergoing IVF. This technique enables us to select the best embryo(s) to transfer and so can increase, our IVF success rates whilst decreasing the risk of multiple pregnancy (twins or triplets). It also enables us to select the best embryos to freeze if there are any surplus embryos.

Introduction

During IVF the embryo transfer can be carried out on day 2 or 3 following the egg collection. At this time the embryos are at the 4 to 8 cell (cleavage) stage of development. It is sometimes difficult for the embryologists to accurately select which embryos have the best chance of forming a pregnancy at such an early stage of their development. Because of this difficulty in selecting the best embryo at this early stage of embryo development, sometimes two or occasionally three embryos are transferred in the hope that at least one will implant and result in a live birth.

Sometimes all the embryos implant and the result is a multiple (twin or triplet) pregnancy. Multiple pregnancies are associated with an increased risk of complications, such as pre-term delivery, abnormalities in the babies and complications in the mothers during pregnancy and childbirth. It would be preferable therefore to transfer only one (and in some women two) good embryos so as to minimize the chances of having twins.

How does a blastocyst differ from a cleavage stage embryo?

A blastocyst is a highly developed embryo. The embryo usually reaches this advanced stage of development on day five or six following the egg collection. This means the embryo has divided many times into a large number of cells whilst in the laboratory. At this stage it is nearly ready to attach to the walls of the uterus (implantation).

During its development, the embryo is contained inside a protective shell called the zona pellucida. This is similar to a hen's egg inside its shell. However, unlike hen's eggs, human embryos do not remain inside their shells. Instead, the embryo hatches (breaks out of the shell) on the fifth or sixth day so it can attach to the uterine wall. Just prior to hatching, an embryo becomes a blastocyst.

Blastocysts look very different compared to embryos at earlier stages of development. At the blastocyst stage the embryo is now made up of two very different types of cells and a central fluid filled cavity. The surface cells lining the inside of the shell, called the trophectoderm, will become the placenta, and the inner cells, called the inner cell mass, will become the foetus (baby). A healthy blastocyst should hatch from its shell, by the end of the sixth day. Within about 24 hours after hatching, it should begin to implant.

What are the advantages of blastocyst transfer?

Whilst the majority of fertilised eggs will develop into a 4-cell embryo, only about half of these embryos will develop into the important blastocyst stage. Therefore, blastocysts are considered to be a more “select” group of embryos with a higher chance of implantation. Because they are more likely to form a pregnancy we can transfer fewer without reducing the chance of pregnancy.

Also Blastocysts enable us to select the best embryos to freeze for future use when there are surplus embryos.

What are the disadvantages of blastocyst transfer?

On average only half of all embryos developed on day 2 will form blastocysts. Therefore, there is a possibility that an IVF cycle will not result in a transfer of any embryos if none of the 2-day-old embryos develop into blastocysts. In this situation the IVF cycle will be abandoned before the transfer stage and this will be tremendously disappointing. This can be viewed, however, as a possible advantage of blastocyst transfer. If blastocyst development does not occur, it is extremely unlikely that a pregnancy would have developed if the embryo had been transferred at the 4-cell stage. This means that the patient does not have to wait for two weeks to find out that a pregnancy has not occurred.

Which patients will benefit from blastocyst transfer?

Deciding which patients will benefit from blastocyst transfer is a rapidly developing area. Blastocyst transfer will be offered to those patients who develop (more than 2 or more good quality embryos and who would have a high risk of a multiple pregnancy if more than 1 or 2 embryos were transferred.

Who will not benefit from blastocyst transfer?

Blastocyst transfer will probably not benefit patients who only develop a few embryos of relatively poor quality.. However, these patients may wish to use

extended culture to the blastocyst stage as a diagnostic tool to see if their embryos are of good enough quality to reach the blastocyst stage, particularly if they have had multiple failed attempts at IVF and embryo transfer.

How many blastocysts can I expect to get?

IVF units performing blastocyst transfer report that about half of all embryos developed during IVF go on to develop into blastocysts. However, this can mean that for some patients nearly all of their embryos develop into blastocysts whilst for others only one or two out of a large number of embryos will do so. However, an individual blastocyst's chance of forming a pregnancy is not related to how many other blastocysts developed with it. This means that someone has as much chance of pregnancy if only one good blastocyst developed and is transferred, as someone who has one blastocyst transferred out of a group of ten developed.

What are my chances of having a blastocyst to transfer?

It is possible that no blastocysts will develop during an IVF cycle. However, for the groups of patients with good numbers of embryos who are offered blastocyst transfer at King's College Hospital the chances of having transfer are similar to those having routine day 2-3 embryo transfer. We expect that 98% of patients will have at least one blastocyst and 93% will have two.

On which day following the egg collection will I have my blastocyst transfer?

Embryos can develop into blastocysts on day five or six following the egg collection. The embryologists will monitor the development of the embryos whilst they are in the laboratory. The embryos will be graded during this time and this will give an indication of which day the transfer will take place on. You will be given a provisional time for a blastocyst transfer on day 5. If blastocysts have not developed fully on day 5 this will be changed to an appointment on day 6.

Blastocyst Transfer

Blastocysts are transferred in the same way that embryos are transferred. Your pregnancy test will be due 14 days following the blastocyst transfer. We will advise you of the date at the time of the transfer.

Can excess blastocysts be frozen?

Good quality blastocysts tend to have a very good survival rate after cryopreservation (freezing). Since blastocysts are a selected group of embryos the pregnancy rates after a thawed blastocyst cycle should be higher than with frozen

embryos. Any good quality blastocysts available following your blastocyst transfer can be frozen for your future use.

Human Fertilisation and Embryology Authority (HFEA) information:

The HFEA keeps a confidential register of information about donors, patients and treatments. This register was set up on 1st August 1991 and therefore contains information concerning children conceived from licensed treatments from that date onwards.

As from the October 2009, any person born between 1st August 1991 and the 1st May 2005 and aged 18+, who ask the HFEA, will be told whether or not they were born as a result of licensed assisted conception treatment. If so, they will be able to make contact with genetically related donor siblings (provided both parties consent) and obtain non identifying information about their donor. For individuals born after 1st May 2005 identifying information about donors can be obtained.

Donor conceived persons over 16 years old are able to access anonymous information about their donor and find out whether they have any genetically related siblings.

The HFEA have a legal obligation to contact and forewarn donors if a donor-conceived offspring has made a request for identifiable information.

Until April 2005 no information about patients, their children and donors could be given out by the Authority, under any circumstances other than those outlined above. The current law does not allow people who apply for information from the register to know the identity of donors prior to April 2005*, or of patients and their children unless the donor re-registers as an identifiable donor. It is a criminal offence to disclose that information.

**An exception would be if the child were born with a disability as a result of a donor's failure to disclose inherited disease. If they were to sue a clinic for damages, a court might require the HFEA to disclose the donor's identify under the Congenital Disabilities (Civil Liabilities) Act 1976.*

A license fee has been brought in by the Government to help finance the HFEA. This is currently £75.00 for each IVF cycle. You will only need to pay this if you are a self funding patient

The HFEA website is www.hfea.gov.uk. The website has useful information regarding clinics, treatment and regulations.

Why should I consider having my embryos frozen?

- 1.) Frozen embryo replacement offers a further chance of conceiving without the associated risks of ovarian stimulation and egg collection.
- 2.) If you have been told that you are at risk of OHSS (Ovarian Hyper-stimulation Syndrome) following egg collection, you may be given the option to freeze all of your embryos. Even if you then develop early OHSS you will not be at risk of the later version (because no embryos will be transferred), thus reducing your overall risk from the syndrome. Frozen embryos can then be thawed and replaced in a future cycle.
- 3.) The overall cost of embryo freezing and frozen embryo replacement is significantly less than that of a fresh cycle. Some PCTs will pay for embryo freezing and replacement. There is more information about this in our information sheet "Embryo freezing at King's".

What are the pregnancy rates for Frozen Embryo Transfer at King's?

Cryopreservation results for embryos thawed January 2013 – December 2013

| | |
|--|--------------|
| Thaw Cycles | 71 |
| Embryos Thawed | 131 |
| Number Survived (% survival rate) | 106 (81%) |
| Embryo Transfers (% of Thaws) | 70 (99%) |
| Ongoing Pregnancies (% of Embryo Transfers) | 20 (29%) |

When will I find out if I have embryos suitable for freezing?

On the day after the egg collection an embryologist will telephone you to let you know how many fertilised eggs you have and to arrange the day and the time of the embryo transfer. If you have 2 or fewer fertilised eggs and are planning to have all available embryos transferred there will not be enough embryos left over to freeze after embryo transfer.

On the morning of transfer if you do have enough embryos to freeze an embryologist will telephone you to ask you if you wish to have your spare embryos frozen. If you decide you would like this to be done or you would like to discuss any aspect of the process with someone in person before you make your decision you will **both** have

to attend the Assisted Conception unit before the scheduled time for embryo transfer.

What criteria are used when deciding whether to freeze embryos?

We only freeze if there is **1** spare embryo of **good quality** remaining after fresh embryo transfer – this occurs in about 20% of patients.

I have decided that I would like to have my embryos frozen if possible, what do I need to do next?

- **Prior to egg collection you will need to have completed the appropriate consent forms**
HFEA consent forms WT and MT should be completed by both partners, along with King's consent to embryo cryopreservation before freezing can take place.

If you do have embryos frozen.

Please make sure that you keep your signed copy of Consent to embryo cryopreservation as it contains some important information you may wish to refer to in the future. In particular;

- It is your responsibility to inform the Unit each year, whether or not you want your embryo(s) retained and to send the annual storage fee. If you neglect to do this, your embryos will be discarded
- It is your responsibility to keep the Unit informed of any change of address.
- Finally, please remember that unless the embryos are used beforehand they will have to be allowed to perish at the end of the storage period that you specified in section 4 of HFEA consent form WT/MT. This is unless you are interested in considering embryo donation. If this is something you think you might like to explore further please discuss this with a member of staff.

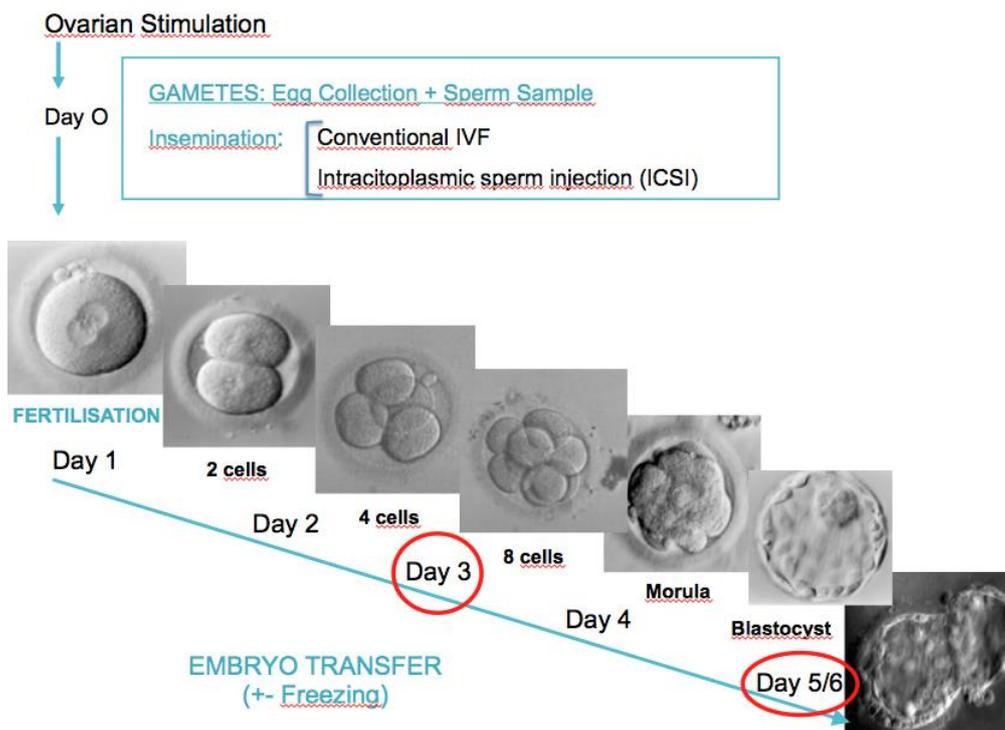
Appendix 2

Embryo development, selection and Embryo Transfer

Embryo Grading

This document is designed to help you understand how embryos develop during the first days of life. It also describes how we assess embryo quality and select the most suitable embryo(s) for your embryo transfer. The traditional and most frequently used method of embryo selection is based on morphological assessment (looking at the way the embryos are shaped) under the microscope. It is a non-invasive method through which we assess how the embryos develop daily, at specific times.

Embryo development during the first 5 to 6 days is summarised in the following am:

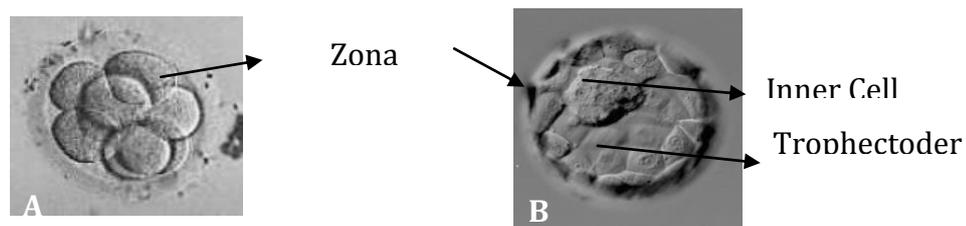


Based on scientific publications, we grade the embryos differently depending on the day of the assessment.

For **embryos at cleavage stage**, between **day 2 or 3** after the egg collection, we mainly check the number of cells, size and symmetry and the level of cell fragmentation. Fragments are pieces of cell that have broken away during cell division. It is completely normal to see embryos with fragmentation, but depending on the level (amount), it may impair the embryo's development. We also score the presence of the nucleus in each of the cells if they can be visualised. Ideally only one nucleus should be seen in each of the cells. Based on these parameters,

embryos receive a grade from 1 to 4, 1 being a top quality embryo. Usually, two embryos are transferred into the uterus after only 2-3 days of culture.

However, sometimes we transfer embryos at blastocyst stage, 5 days after egg collection. At this point, the embryo has two different cell types and a central cavity (cell free space). The surface cells, called the trophoblast (TE), will become the placenta, that supports the baby's growth, and the inner part, called the inner cell mass (ICM), will become the baby. We grade the blastocyst depending on the expansion or size of the cavity from 0 to 6, 4 or 5 being the ideal grade. Also, we grade the TE and ICM on a scale from A to C/D, A being the top quality grade.



A human embryo in cleavage stage (A) and blastocyst stage (B)

Although morphological assessment based on the appearance of the embryo is the best non-invasive strategy for embryo selection, it has its limitations. The main question is: are the embryos that look the best (i.e. the embryos we have given the highest grades) the ones more likely to be genetically normal? This is a very controversial subject, and after several studies, a link was found to exist, although this is not always the case. Therefore, normally, the higher the embryo grade is, the more likely the embryo is to implant in the uterus and result in a pregnancy. However, it should be stressed that transferring lower grade embryos can also result in a normal pregnancy. Importantly, there is no relationship between the quality of embryos transferred and the chance of a baby being born with an abnormality.

When should we transfer your embryos: at cleavage or blastocyst stage?

In a natural pregnancy, embryos at the cleavage stage (day 2/3 after egg collection) would normally still be moving down the Fallopian tubes, and would not yet have arrived in the uterus. The implantation process begins about three days later, when the cleavage stage embryo has become a blastocyst and hatches from its outer shell, (which is called the zona pellucida), by the end of the sixth day. Within about 24 hours after hatching, it should begin to implant into the lining of the woman's uterus.

By transferring embryos at the blastocyst stage, the process occurs at a more "natural" time, and shortly before implantation should occur. The fact that these embryos have reached the blastocyst stage in the laboratory implies they are better at developing than the embryos that fail to reach this stage, and therefore, the chances of pregnancy are higher. Transferring blastocysts also enables us to select

one embryo for transfer and obtain high pregnancy rates while reducing the risk of multiple pregnancy.

While Blastocyst culture allows better embryo selection there is a risk of embryo arrest (stopping of development) during those extra days in the laboratory. Therefore, the decision on when we should do your embryo transfer will depend on the number of embryos available, their quality on day 3 and your previous cycles, in order to maximise your chances of pregnancy without compromising the chance of having an embryo transfer. Our criteria to proceed to blastocyst culture is the presence of at least 3 good quality embryos on day 3. For example, patients who have a low number of oocytes retrieved, fertilised or dividing embryos by day 3 in culture, have no advantage using blastocyst culture, since little is to be gained in further embryo "self-selection".

If you continue with extended culture and the embryos show slower development and don't reach the blastocyst stage by day 5, we will still perform an embryo transfer, as pregnancies do occur with this sort of embryos. However, the pregnancy rates for slower embryos are reduced compared to the ones obtained by transferring blastocysts. There is therefore a very small possibility that an IVF or ICSI cycle will not result in a transfer of any embryos if they stop developing and none progresses past the cleavage stage.

If after the embryo transfer, there are remaining good quality blastocysts available they may be frozen for future use. If the embryo transfer is performed at cleavage stage and there are spare dividing embryos, we can culture them for two further days and if they meet the criteria we can freeze at the blastocyst stage. Survival following freezing and thawing processes mean that pregnancy rates for frozen/thawed blastocysts are lower than for fresh blastocysts. This is the main reason why we only freeze good quality blastocysts

Embryo Transfer

You should attend the appointment for embryo transfer with a full bladder, unless instructed differently. Immediately before your procedure, you will be able to discuss with a scientist and a doctor the number and quality of embryo/s to be transferred or frozen.

The procedure usually only takes a few minutes, is quick and painless and is similar to having a smear test. You can go home immediately after the transfer.

However, the procedure is not always straightforward. First, there may be unexpected difficulty in passing the catheter into the uterus. The doctor may have to give the catheter containing the embryo/s back to the embryologist while he or she passes an "introducer" into the womb to make passing the catheter easier.

Second, after all embryo transfer procedures the catheter is checked to confirm that the embryos have not been retained in the catheter. Occasionally, one or more have

stuck inside the catheter and the procedure has to be repeated. This does not reduce your chances of getting pregnant.

Third, very rarely, the embryos may be lost or damaged during a difficult transfer. This probably happens if mucus gets into the end of the catheter when the embryos, which are close to the tip, may be sucked out as the catheter is withdrawn down the neck of the womb. If there are more embryos available they will be transferred in lieu of the lost embryos - but they may not be of such good quality. There may be no alternative embryos available.