

IN VITRO FERTILISATION – IVF and ICSI

WHAT ARE IVF and ICSI?

IVF is short for '*in vitro fertilisation*' which means fertilisation outside of the body. It usually involves the stimulation of the ovaries with fertility drugs to produce a number of eggs, which are collected in a short operation. With IVF the eggs are mixed with prepared sperm and fertilisation takes place over the next few hours. With ICSI a single selected sperm is injected into the egg to fertilize it.

The resulting fertilised eggs are allowed to develop for 2-3 days. The best embryos are selected for transfer in to the woman's uterus (womb). Following the embryo transfer, any other suitable embryos are cryopreserved (frozen) to be replaced at a later stage.

Normal reproduction

Each month a number of eggs start to grow, but only one develops to full maturity. This egg is released from the ovary and passes down the Fallopian tube to the uterus. For pregnancy to occur, sperm released into the vagina during intercourse, meets the egg at the right time to fertilise it. This leads to the development of an embryo. After about 5 days the developing embryo embeds in the thickened lining of the womb (implantation) and progresses to normal pregnancy.

WHO CAN BENEFIT FROM IVF?

Couples with the following:

- Blocked, damaged or no Fallopian tubes
- Endometriosis
- Ovulatory problem
- Unexplained infertility
- Modest sperm problems

WHO CAN BENEFIT FROM ICSI?

ICSI is a treatment used in male infertility and may be advised when:

- The sperm count is very low
- The sperm have a problem with motility (i.e. they cannot swim properly)
- An attempt at IVF has resulted in failure of fertilisation
- Sperm are removed directly from the testis using a surgical technique.

ASSESSMENT AND TESTS

Many couples referred for IVF/ICSI may have been diagnosed with a particular condition. Any condition and need for IVF/ ICSI will be discussed with them at their initial consultation, and a number of further tests may be required.

Prior to commencing IVF the following recent test results will be required:

- Ovarian assessment (anti-Mullerian hormone; AMH) and semen analysis
- Rubella (German measles)
- A recent cervical smear test (within the last 3 years)
- Hepatitis B and Hepatitis C and HIV (both partners) Within 2 years.

With ICSI, some men may require test for inheritable conditions:

- Chromosome analysis
- cystic fibrosis

These tests are carried out in accordance with guidelines and obligations under the Human Fertilisation & Embryology Act. The act also dictates that the clinic considers the potential impact of treatment upon any child within the family group, and also the welfare of any child born as a result of treatment.

Please read the leaflet on Folic Acid & General Health

COUNSELLING

Infertility is one of the biggest challenges ever to enter your life and can be more stressful than you imagine, and independent counselling is offered to couples undergoing treatment at GCRM. You can arrange counselling for either Glasgow or Edinburgh by telephoning Glasgow on 0141 891 8749.

WHAT IS INVOLVED IN THE TREATMENT OF IVF / ICSI

There are usually 6 main stages of the IVF/ICSI procedure:

1. Screening (assessments and tests, above) and consents for treatment
2. Stimulation of the ovaries using fertility hormones to produce a number of eggs.
3. A minor procedure with conscious sedation to remove eggs from the ovaries.
4. Preparation of the sperm for combining with the eggs in the laboratory, leading to fertilisation. For ICSI, individual sperm are isolated and injected into each mature egg.
5. Replacement of embryos into the womb.
6. Luteal support to assist implantation.

Stage 1. - Screening and consents

Prior to starting treatment it is necessary to have the appropriate results of your tests outlined above, including your ovarian assessment to enable us to select the best drug regime for you. With this combination of information an appointment will be made with a nurse to discuss details of the treatment and complete the appropriate consent forms. Provisional dates and the ordering and payment of the drugs will be discussed with you. Payment for the treatment would be expected at this stage.

Stage 2. -Stimulation of the ovaries.

In IVF we use fertility drugs to produce a number of eggs to increase the chance of success, and the responses to these drugs can vary from 'low' to 'excessive'. In all cases we need to avoid the spontaneous release of these eggs prior to the operation using drugs called "GnRH-analogs".

There are 3 ways to use these -

- a. Down-regulation – Agonist protocol** – this is achieved by taking a drug given as an injection (or as a nasal spray) starting around day 21 of a menstrual cycle
- b. Down-regulation – Flare Agonist protocol** – this method uses the same drug as the down-regulation protocol, but FSH injections are started in the same menstrual cycle.
- c. Antagonist** – this is where you take a daily injection during your fertility drug treatment.

All methods allow us to time the release of the eggs at precisely the right time.

a. Down-regulation – Agonist. Following the down-regulation injection you will have a menstrual period, and we aim to start the fertility drug (FSH; follicle stimulating hormone) injections a couple of days later, following a blood test and a transvaginal ultrasound scan.

You will be taught how to give yourself these daily injections.

b. Down-regulation – Flare Agonist protocol. The treatment starts 5 days after stopping the programming with Norethisterone tablets. The daily FSH injections start on the 2nd day after down regulation drug is administered.

c. Antagonist. In the antagonist protocol, you attend for a baseline scan and blood test on day 2 – 4 of your menstrual period. You will start your daily injections of FSH at this stage. The start of your antagonist injections will be advised. Depending on your ovarian responses this protocol may be programmed with Norethisterone, or supplemented with Metformin.

All protocols

To monitor the response of the ovaries to the fertility drug treatment, we require occasional blood samples and scans. The average number of days to be on injections is 8 -14 days.

HCG injection - Once the monitoring indicates that an adequate number of maturing follicles are present, a final injection is self-administered at the **specified time, 36- 40 hours before the planned egg-collection**. This is to prepare the eggs for fertilization.

Stage 3. - retrieval of eggs from the ovaries under sedation

Report to the GCRM at the specified time, 2 days later. **Do not eat or drink** anything after 12 midnight on the day before surgery, as you are required to fast before the procedure. You are advised to have a small glass of water 2 hours prior to admission.

Sedation: The procedure is performed under conscious sedation. The consultant anaesthetist will review your health and relevant matters with you. An intravenous cannula will be placed in your arm through which your sedation will be given. You will feel yourself drifting to sleep, although you may still be aware of noise and touch. The anaesthetist controls your sedation and monitors your wellbeing throughout.

The Procedure. The ovaries are visualised on the ultrasound as in the monitoring scans. A fine needle is passed into the ovary to aspirate the contents of the follicles. The fluid is examined by the embryologist to identify the eggs. After egg collection, you will be transferred to your room and allowed to rest until fit for discharge. Tea and toast is provided prior to discharge.

Stage 4 sperm collection and fertilisation

On the day of egg retrieval, a fresh sample of sperm is required. Specific details will be given to you at the start of treatment. For IVE, the sample is prepared in a special way so that the most motile sperm are selected. Usually around 50,000 - 100,000 sperm are added to each egg, to enable one of them to penetrate through the 'shell' of the egg.

For ICSI, a single sperm is taken up in a fine glass needle and injected directly into the egg. Sometimes sperm has been stored following surgical sperm retrieval, and this will be thawed and prepared in time for the ICSI procedure.

Not all eggs collected will be of a high enough quality, or mature enough, to be suitable for injection. It should be advised that some eggs may not survive the injection process.

Fertilisation

The eggs are checked at specific intervals to see whether fertilisation has taken place. Not all eggs will fertilise and in a small number of cases there may be no fertilisation.

Stage 5. – Embryo transfer

The embryos will be placed in to the womb two, three or five days after egg collection. It is a very simple procedure similar to having a smear taken, and does not require any sedation or anaesthetic.

Please do **not** empty your bladder before the procedure as this assists the transfer of embryos into the womb using a fine catheter (tube).

GCRM aims to minimise the risks associated with multiple pregnancy, and have constructed a policy for embryo transfer numbers, following the guidelines from the HFEA. *Please see below.*

Stage 6 - Luteal Support and outcome

After embryo transfer, you will require hormone support until the outcome date. This will be discussed with you at embryo transfer.

Arrangements will be made for a pregnancy test to confirm your outcome.

After the treatment cycle, the whole team reviews your results, and a follow up appointment is offered to discuss the implications.

As a licensed centre we are required to record the outcome of all pregnancies resulting from assisted conception. We will appreciate your assistance in this matter.

IF YOU HAVE A PROBLEM

Staff from the GCRM are available from 08.30h until 16.15h Monday - Friday, and 09.00h - 11.00h Saturday.

If you have any uncertainty about your treatment - please contact the GCRM on 0141-891-8749. A member of staff will be available to discuss any such worries with you.

Outwith the above hours and only in an emergency situation, you can contact medical staff on – 07590756672. Alternatively, you or your doctor can contact the Southern General Hospital and ask for the on call Gynaecology Registrar (0141-201-1100, page 2519) who will direct the patient either to Gyn. Emergency Dept. or to be admitted directly to Ward 50.

POSSIBLE SIDE EFFECTS

Common side effects of down-regulation drugs are hot flushes, headaches and mood swings. These symptoms are due to low oestrogen levels. Oestrogen is the hormone normally produced by the ovary in the early phase of the menstrual cycle and symptoms are short-lived and subside when the injections start.

Ovarian Hyperstimulation Syndrome - Despite careful monitoring, a small number of women may over respond. This can result in a condition known as Ovarian Hyperstimulation Syndrome (OHSS) which can vary in severity.

In a mild form - the ovaries are slightly enlarged and you may feel abdominal 'cramps'. If so, please notify nursing staff when attending the unit.

In the severest form - the ovaries are very enlarged and fluid can gather in the abdominal cavity causing discomfort or pain. On rare occasions vomiting, diarrhoea, abdominal swelling and breathlessness may occur, and you may feel weak and faint, and notice a reduction in urine output. Admission to hospital may be required for observation and appropriate treatment.

This rare complication requires the attention of trained staff. If you feel these symptoms occurring, it is important that you are assessed by an appropriate doctor or nurse.

GENERAL INFORMATION

The potential risks specific to ICSI treatment

ICSI is an invasive technique and may also use sperm that would not otherwise be able to fertilise an egg.

For these reasons, concerns about the potential risks to children born as a result of ICSI have been raised, and several follow-up studies have been published. These studies include relatively small numbers of children, and do not cover effects that may be seen in later life.

More studies are needed, but in general, the use of ICSI appears to have a similar safety record to IVF, with a few exceptions. ICSI has been linked with certain genetic and developmental defects and these are explained below.

Possible inheritance of genetic and chromosomal abnormalities:

Sex chromosome defects and the inheritance of subfertility

The Y chromosome is the "male" chromosome, so men have one and women do not, and certain genes on the Y chromosome are involved in the production of sperm.

A small proportion of subfertile men have parts of the Y chromosome missing (deletions) and this may be the cause of a poor sperm assessment in some men. Using sperm with such deletions to create an embryo may result in the same problem 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. However, it is estimated that up to 2.4% of the wider 'normal' population have a chromosomal abnormality.

New chromosomal abnormalities

The process of egg and sperm production is complex, and even if an individual possesses a normal number of chromosomes, their eggs / sperm could be abnormal. It is not possible to detect beforehand which eggs or sperm have chromosomal abnormalities, and eggs or sperm that might not have been able to participate in natural fertilisation could be used in ICSI.

Babies born after ICSI have been reported to have new chromosomal abnormalities in up to 3% of cases. The rate in the general population is around 0.6%.

Inheritance of cystic fibrosis gene mutations

Some men who have no sperm in their semen are found to have *congenital bilateral absence of the vas deferens* (CBAVD). In this condition, the tubes that carry sperm from the testes to the penis are missing. Two thirds of men with CBAVD are also carriers of certain cystic fibrosis (CF) mutations. As such, when indicated, we recommend that some couples undergo testing for CF genes and, if found to be positive, genetic counselling about the implications.

Possible developmental and birth defects

Birth defects

There is not yet any clear evidence whether ICSI results in higher rates of birth defects. The number of babies reported to have major birth defects, such as cleft palate, is between 1 and 5% in both the general population and in babies born following ICSI. Early studies suggested that minor abnormalities occur in up to 20% of ICSI babies, compared with up to 15% of the general population. More studies of this subject are being reported every year, and more are needed. The summary data are mostly re-assuring.

The Chances of Success

The chances of successful conception vary greatly depending upon many factors, although the single most important element is that of female age. As women get older, both the number of eggs and their viability decrease, and after 38 years of age, a dramatic decline in treatment success is seen universally. You will be provided with indications of your chances of successful treatment outcome following your consultation and ovarian assessment.

The pitfalls of a treatment cycle

Although most cycles proceed according to plan, whether a pregnancy results or not, there are stages along the way, where treatment cycles can be discontinued, and everyone should be aware of these critical points. Cycles can be stopped during monitoring due to either insufficient ovarian response or abnormal hormone profiles. A patient can go to theatre for egg pick-up, but no eggs may be collected, eggs that are collected may fail to fertilise. There is also, very rarely, the case where the embryos cannot be transferred because of obstruction in the cervix.

The table below shows the approximate incidence of these events;

Event	Category	Incidence per hundred cycles
Stopped during stimulation	AMH \geq 7.0 pmol/L	4
	AMH $<$ 7.0 pmol/L	14
No eggs at egg collection	AMH $>$ 7.0 pmol/L	$<$ 0.5
	AMH $<$ 7.0 pmol/L	5
Failure of fertilisation	IVF	6
	ICSI	5
Failure of embryo transfer		$<$ 0.5

Pregnancy

Women conceiving a singleton pregnancy following IVF or ICSI probably show similar degrees of problems to a matched population conceiving without medical intervention. However, miscarriage or abnormalities do occur, as with natural conception. Statistics show that women conceiving over the age of 35 have increased problems.

Probably the greatest source of problems in pregnancy is multiple conception – see below.

Embryo transfer policy

IVF is now associated with a high risk of twin pregnancies. Multiple pregnancies have a higher risk of obstetric complications leading to premature delivery. These are associated with an increased risk of handicap after birth.

The social, psychological and financial pressures of twin pregnancies can be great, and we therefore have a policy for the number of embryos transferred on each occasion. The aim of treatment is to try and maximise the pregnancy rate while minimising the multiple pregnancy rates. This policy depends upon the number and quality of embryos resulting from treatment as well as other criteria. Some patients will be advised that a **single embryo transfer** will be in their best interests, because of the risks of twin pregnancies. In contrast, older women (more than 39 years of age) may be advised that a three embryo transfer may be preferable.

Depending on the quality and quantity, extra embryos may be stored in a special freezer and replaced in a later cycle. However, there is no guarantee that these frozen embryos will survive the thawing process.

ONGOING RESEARCH PROGRAMMES

Infertility treatment is continually advancing and improving, due to continued research. In this unit we undertake research projects which we hope will benefit future treatments and outcomes.

You may be asked to participate in research at any stage of your infertility treatment, but you are never under any obligation to do so.

SUGGESTIONS AND COMPLAINTS PROCEDURE

At the GCRM our aim is to develop, improve and maintain the quality of the service. We value any suggestion that you have which would contribute to the wellbeing of all we care for.

If you have any questions or difficulties, please discuss them with any member of the GCRM team. It is our professional role to help and support you throughout your treatments.

If you have any cause for complaint, please speak to Pat Ambrose or the complaints officer, who will discuss the matter with you.

If you are not satisfied with any aspect of your care, and wish to make a written complaint you should write to:

**Mrs. Dorothy Lucas, Complaints Officer,
GCRM Ltd, 21 Fifty Pitches Way,
Cardonald Business Park
Glasgow, G51 4FD**