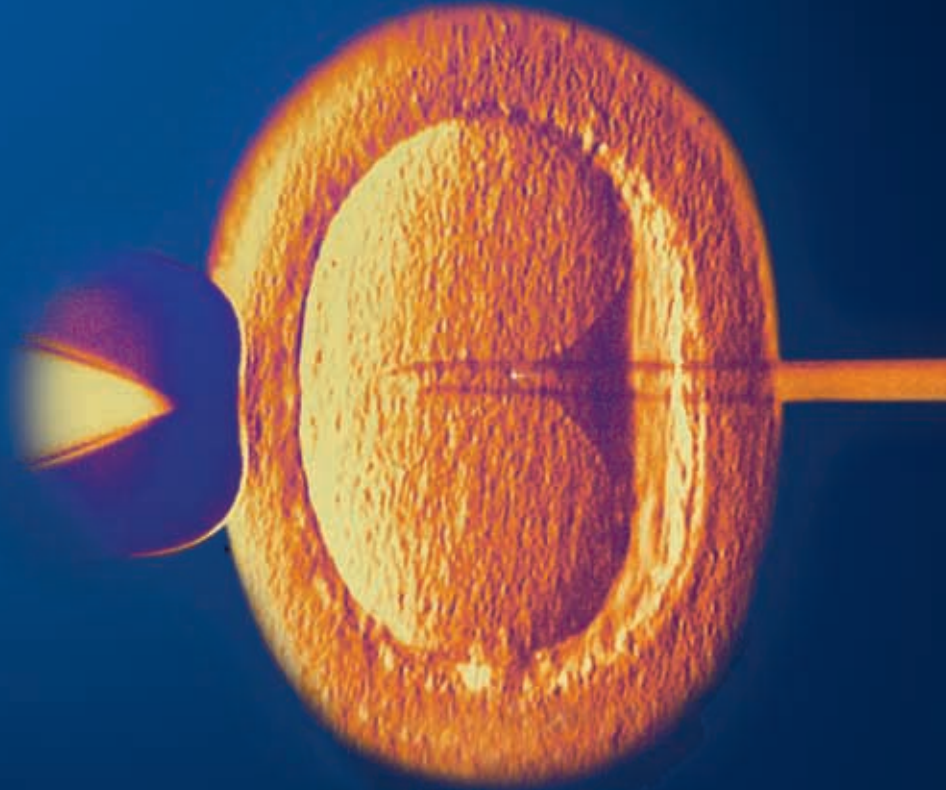




# Midland Fertility Services

ICSI: Intra Cytoplasmic Sperm Injection



'Building futures,  
transforming lives'



## Useful Contacts

Infertility Network UK	0870 118 8088	<a href="http://www.infertilitynetworkuk.com">www.infertilitynetworkuk.com</a>
British Infertility Counselling Association (BICA)	01372 451626	<a href="http://www.bica.net">www.bica.net</a>
Twins and Multiple Births Association (TAMBA)	0800 138 0509	<a href="http://www.tamba.org.uk">www.tamba.org.uk</a>
Miscarriage Association	01924 200799	<a href="http://www.miscarriageassociation.org.uk">www.miscarriageassociation.org.uk</a>
Single Embryo Transfer		<a href="http://www.oneatatime.org.uk">www.oneatatime.org.uk</a>

## What is IVF Using ICSI?

In vitro fertilisation - IVF - literally means fertilisation 'in glass'. Instead of the sperm penetrating the oocyte (egg) within the body (in vivo), it does so within the laboratory in sterile, disposable dishes. Intra cytoplasmic sperm injection - ICSI - means 'the injection of a sperm into the cytoplasm (the jelly type content) of the egg'. IVF using the standard insemination technique requires approximately 150,000 sperm for each egg but ICSI requires just one sperm per egg. This single sperm is injected into each mature egg using a fine glass needle. The injected eggs are placed in an incubator and checked the following morning for signs of fertilisation. The fertilised eggs (embryos) are cultured for a further one to five days before placing one or two of the best quality embryos into the uterus. Any remaining good quality embryos can be frozen and stored for future attempts to conceive.

ICSI resulted from many years of research by teams of scientists around the world, but the team at the Free University of Brussels developed the successful approach which MFS first introduced to the West Midlands in 1994. ICSI has greatly improved the prospects for parenthood for many couples with fertility problems and by December 2008, 1,950 babies had been born after ICSI treatment at MFS.

## How is ICSI Carried Out?

To maximise the chance of pregnancy, MFS will aim to collect several eggs by stimulating the woman's ovaries using fertility drugs which start the growth of several follicles (small fluid filled sacs on the ovaries where the eggs are

produced). Several different drug regimes may be used to achieve this and an MFS fertility nurse or doctor will judge which method best suits the patient. The most common method of stimulation proceeds as follows:

### Preparing the Ovaries

The clinical staff will prepare the woman's ovaries for stimulation and carefully control the rate of growth of the follicles within the ovaries. This is best achieved by first 'switching off' the hormones that control the natural menstrual cycle by the administration of a drug, given either as an injection or via a nasal spray. This drug acts on the pituitary gland and may have temporary side effects similar to the menopause, such as 'hot flushes'. This process is called 'down regulation'.

After two to three weeks of taking this first drug the patient will return to MFS for an ultrasound scan. An MFS nurse or doctor will scan her ovaries and the lining of the uterus to ensure that the drug has worked sufficiently and that she is now 'down regulated', i.e. her own hormones have been successfully, but temporarily, 'switched off'. This scan is therefore often referred to as the 'down regulation scan'.

### Stimulating the Ovaries

The next stage is to stimulate the ovaries with fertility drugs which the patient will self-inject for between seven to 14 days. An MFS fertility nurse will teach the patient to perform her own injections when administering these drugs. If preferred, her partner can be taught to do this instead. Most women find that it is

## ICSI Treatment

not too difficult to learn and it means that they can continue with their daily routine without too much interruption. As all treatment at MFS is 'tailor-made' for each patient sometimes a different drug regime may be advised by the fertility nurse specialist or doctor, including a 'short protocol' which doesn't require 'down regulation'.

It will be necessary to attend the unit for some ultrasound scans during this period, to monitor the number and size of the follicles. When the follicles have grown sufficiently, the date of the egg collection will be confirmed.

### Maturing the Eggs

Before collecting the eggs which have been developing within the follicles, the final stage of their development is initiated with an injection of hCG. This injection needs to be administered at a specific time, 35 hours before the egg recovery is scheduled.

### Producing a Sperm Sample

The sperm sample must be produced at MFS as soon as the patients arrive. A quiet room close to the laboratories is available for this purpose. This means that the patient and her partner can be together both during the egg recovery and afterwards whilst she is recovering.

In exceptional circumstances a sperm sample may be produced at home. Alternatively a sperm sample may be produced at MFS and then frozen and stored before the egg recovery. A charge will be made for this service.

### Egg Collection

The procedure is performed under ultrasound guidance by an MFS fertility specialist. Each follicle is punctured and the follicular fluid drained into sterile tubes via a needle attached to a suction pump. Using a microscope, an embryologist examines the fluid and identifies the eggs within it. These eggs are then washed and placed into labelled culture dishes before being placed into an incubator, which mimics the inside of the body, keeping the eggs warm and at low oxygen concentrations.

During the egg recovery the patient will be given sedation and pain relief; a general anaesthetic is not required. Although awake during the procedure, most women describe it as only 'uncomfortable' and many hardly recollect it subsequently. A nurse monitors the patient constantly throughout the procedure. The patient's partner may choose to attend the egg collection or, alternatively, wait in another room at MFS.

In very rare cases (about 1 in 100) the drugs may fail to properly control the patient's cycle and ovulation may occur before the egg collection. Unfortunately MFS is unable to predict to which women this may happen.

### Sperm Preparation

Around the time of the egg collection a second embryologist prepares the sperm for ICSI. This is usually from a sample produced earlier that day but can also come from a frozen sample or even from a small sample of tissue (a biopsy) taken from the testis (refer to the MFS leaflet

'Surgical Sperm Recovery'). The best quality sperm are isolated using a filtration system and then washed in culture media. The sperm preparation is then placed in the incubator until it is time for the ICSI egg injection procedure.

### Egg Injection

A few hours after the egg collection, the follicular cells are carefully removed from around the egg (referred to as 'denuding' or 'stripping') and the embryologist examines the egg to determine the stage of its development. It is unlikely that all the collected eggs will be at the correct stage of development (referred to as Metaphase II or MII); usually a few are immature and are incapable of being fertilised. Approximately 70-80% of all collected eggs will be mature and therefore suitable for ICSI injection.

The prepared eggs are placed into individual droplets of media in a dish covered with colourless oil which prevents the water within the media evaporating. The prepared sperm

are placed into a droplet in the centre of the dish, within a viscous solution that slows the sperm down, to help the embryologist to 'catch' the sperm. The dish containing the eggs and sperm is placed onto the 'ICSI rig', a high powered microscope with fine glass pipettes attached to micromanipulators and a heated stage which keeps the eggs at the correct temperature throughout the procedure.

A single sperm with the best shape and swimming ability is selected. This sperm is immobilised before it is injected into the egg, by breaking its tail with the fine glass injecting pipette. Once still, the sperm is drawn 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 are able to perform the procedure.



An embryologist at the 'ICSI rig'



A suitable single sperm is identified



The sperm is drawn into a glass pipette



The pipette is positioned ready for insertion into the stabilised egg



The pipette pierces the centre of the egg



The sperm is injected into the centre of the egg

*Sequence of ICSI injection*

### How Many Eggs will Fertilise?

To have a chance of fertilising, the eggs need to be healthy enough to survive the injection procedure. This necessary risk is relatively small and approximately 5% of all injected eggs fail to survive the injection.

The eggs are examined the following morning for signs of successful fertilisation. This procedure is successful for 60-70% of injected eggs, although there is a chance that no eggs may fertilise. The fertilised eggs are now referred to as embryos.

The fertilisation rate can vary between patients and also sometimes between each patient's treatment cycles.

### When and How are Embryos Transferred to the Uterus?

Embryos are usually transferred to the woman two to six days after the egg recovery and the patient will be advised of the most suitable day by the MFS fertility nurse or doctor (see also the MFS booklet '**Blastocyst Transfer**'). This embryo transfer is ordinarily very straightforward and takes approximately twenty minutes to perform; no longer than an average cervical smear. The procedure is performed by a highly trained nurse or doctor under ultrasound guidance, and sedation or pain relief are not normally necessary.

The nurse and embryologist performing the embryo transfer will discuss the quality of the embryos with the patient before the transfer procedure.

The embryos are loaded into a catheter (a fine sterile, plastic tube) which the nurse or doctor threads carefully through the cervix (the neck of the womb) and into the uterus under ultrasound guidance. When it is in the perfect position, the embryos are expelled from the tip of the catheter.

The catheter is passed back to the embryologist, who checks that they have been successfully transferred and that they have not been retained within the catheter.

The patient will be given some hormones, usually in the form of vaginal pessaries, which she will be asked to administer in the days following her embryo transfer. These hormones help to maintain a thick endometrial lining, providing the optimal environment for the embryos to implant. This is described as 'luteal support'.

## What Precautions Should the Patient Take Following Embryo Transfer?

Providing the woman feels well, she should be able to continue with everyday tasks as normal. Some people wish to continue working in order to take their mind off the two week wait for their pregnancy test; others prefer to take things slightly easier. An MFS fertility nurse or doctor will give each patient written advice in the 'Embryo Transfer - What Next?' leaflet.

## What Happens to any Remaining Embryos?

Good quality embryos which are not transferred may be frozen for use at a later



Oocyte (egg)



Fertilised egg (2PN)



2 cell embryo



4 cell embryo



8 cell embryo

*Sequence of fertilisation and embryo development*

## ICSI Treatment

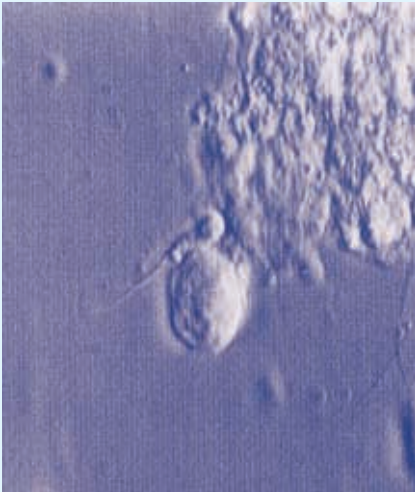
date (refer to the MFS booklet 'Embryo Freezing'). The patient will be asked to contact the embryologists to find out if any embryos were suitable to freeze and will also receive a written summary of the treatment cycle which will include this information. Only good quality embryos can be frozen as strict criteria have to be met if they are to survive the freeze/thaw procedure.

## For Whom is ICSI Suitable?

### Male Factor Infertility

ICSI is a treatment principally used where there are significant sperm problems, although it is not to be regarded as a solution for all fertility problems. ICSI can be used when there are high levels of antibodies in the semen, as these tend to prevent the sperm from swimming actively, which will interfere with the

Immature spermatozoa embedded within their Sertoli cells. Portion of a testicular biopsy sample



normal fertilisation process. ICSI is essential when using sperm which MFS has surgically retrieved from the epididymis or from a biopsy of testicular tissue.

### After Failed Standard IVF

ICSI is also suitable for couples who have failed to achieve good rates of fertilisation following standard IVF techniques or where the quality of sperm is too poor to allow a reasonable chance of success in conventional IVF.

### Frozen Eggs

ICSI is also necessary when fertilising frozen/thawed eggs in order to give a reasonable chance of fertilisation.

## How Safe is ICSI?

ICSI carries all of the normal risks associated with the drugs and procedures used in standard IVF, as well as the natural hazards of pregnancy. The procedures that are performed for IVF, such as the egg recovery and embryo transfer, are all outpatient procedures which do not require a general anaesthetic, only sedation. They are classed as relatively low risk, and each year thousands of women undergo IVF with no problems whatsoever. The following outlines some areas for consideration before consenting to ICSI treatment:

### OHSS

Ovarian Hyperstimulation Syndrome (OHSS) is caused by an over-response by the ovaries to fertility drugs. MFS aims to develop approximately eight – 10 follicles but sometimes many more can grow. This syndrome can have symptoms which range from very minor, such as

feeling slightly bloated, to quite serious side effects, which may require hospitalisation. Some people are more prone to this occurring than others. MFS will try to predict how well a patient's ovaries will respond to the drugs by measuring various hormone levels before she starts treatment and prescribe an appropriate level of fertility drug. The patient will be given ultrasound scans throughout ovarian stimulation so that the rate of follicular development can be monitored and the dose of drug will be adjusted if her ovaries are over-responding. An MFS nurse or doctor will advise the patient of the signs of OHSS, as described in the MFS leaflet entitled 'OHSS'. The symptoms of OHSS can become far worse in pregnancy and so on rare occasions MFS may wish to freeze all of the embryos and delay the patient's embryo transfer until it is suitable to do so.

### Multiple Pregnancy

Approximately 25% of all IVF pregnancies at MFS are multiple, mainly twins (24%) and, much less commonly, triplets (1%). Although the thought of an instant family can be quite appealing, especially after the efforts of fertility treatment, multiple pregnancies bring additional risks both to mother and babies. The HFEA now limits the number of embryos that may be transferred to a maximum of two for women under 40 years old. The HFEA has also recommended reducing the multiple birth rate to 10% and so, for certain patients who are at a high risk of twins or triplets and who meet the criteria for suitable embryo quality, MFS will only transfer a single embryo. A multiple pregnancy carries an increased risk of the babies suffering long-term disabilities or handicaps such as cerebral palsy and they are

also much more likely to suffer from chronic health problems associated with low birth weight. The extra strain on physical, emotional and financial resources when caring for more than one baby at a time cannot be ignored. (Please refer to the MFS leaflet 'Multiple Pregnancies' and visit [www.oneatatime.org.uk](http://www.oneatatime.org.uk))

### Ectopic Pregnancy

There is also a risk that a pregnancy can develop in the Fallopian tubes instead of the uterus. This is known as an ectopic pregnancy which, if left undetected, can have serious consequences. Following a positive pregnancy test, a patient will be asked to return to MFS two weeks later for an early pregnancy scan. At this scan, MFS will check that the pregnancy is a healthy one and that it is inside the uterus. (Please refer to the MFS leaflet entitled 'Ectopic Pregnancy').

### Cystic Fibrosis

Some men who do not have any sperm in their semen (azoospermia) lack the tubes that carry the sperm from the testes to the penis. This condition is *congenital bilateral absence of the vas deferens* (CBAVD). In this situation MFS would need to obtain sperm for ICSI from the testes. Two thirds of men with CBAVD will carry a cystic fibrosis (CF) mutation. If the female partner also carries a similar mutation, any resulting child would have a one in four chance of having CF and a one in two chance of being a CF carrier. (For more details, please read the MFS booklet entitled 'Genetic Screening'). For this reason, MFS tests all azoospermic men for cystic fibrosis. The test is also available to anyone else about to undergo ICSI should they wish; an MFS fertility nurse specialist can provide further information.

## ICSI Treatment



### Second Generation Male Infertility

As ICSI is predominantly a treatment used where there are sperm problems, an additional worry is that the infertility of the father could be passed on to any sons born as a result of ICSI treatment. In a small proportion of men, a tiny section of the male sex chromosome (Y chromosome) is absent, known as a deletion. When this deletion is present it results in a low sperm count. So far, research indicates that when this deletion is present on the Y chromosome of a man undergoing fertility treatment, any sons born will inherit the same deleted Y chromosome. Later in life these sons will most likely suffer the same fertility problems as their fathers.

### Birth Abnormalities and Defects

There has been some concern regarding the incidence of sex chromosome disorders in babies born following ICSI. The sex chromosomes determine whether a baby is male or female and disorders arise when there is an incorrect number of these chromosomes. A male will usually possess one X chromosome and one

Y chromosome (46XY) and a female will usually possess two X chromosomes (46XX). In the general population, an extra Y chromosome will be present in approximately 1 in 1000 male births (47XYY) leading to an increased risk in behavioural problems. An extra X chromosome will occur in approximately 1 in 1000 male births (47XXY) and also in 1 in 1000 female births (47XXX). In males, the extra X chromosome results in Klinefelter syndrome leading to problems including infertility whilst the females tend to be mildly mentally handicapped. Some early studies found an increase in the incidence of these disorders in ICSI babies; however, larger more recent studies have not shown this link. Closer monitoring of IVF/ICSI babies may show up these types of disorders at an earlier age compared with the general population where they may not be detected until they reach adulthood.

To date there have been only a few large studies looking at the incidence of birth defects following ICSI and IVF. The group at the Brussels Free University, responsible for the development of ICSI, found the incidence of major birth defects was 'within normal limits' when compared to the general population. However, there has been some disagreement in the way 'major defect' was classified in this study and when the data was re-analysed it was shown that there were more defects in the ICSI group than originally thought. A further study used data from two units in Göteborg, Sweden and looked at 1139 infants born following ICSI. They found an identified malformation in 87 of these children, 40 being classified as a minor defect (e.g. undescended testicle, unstable or

clicky hip) and 47 a major defect (e.g. cleft lip or palate, hypospadias or Down syndrome). The incidence of any malformation within the ICSI group was therefore 7.3% and in the general population it was 3-4%. However, it has to be remembered that the incidence of multiple births is considerably higher when assisted conception is used. Multiple births carry additional risks to the babies born and they are often born prematurely. When the Swedish group adjusted its data to take the multiple birth influence into consideration, it found that the only abnormality more frequent after ICSI was that of hypospadias. Hypospadias is a developmental abnormality of the tube within the penis. This tube is shortened and therefore the opening can be found anywhere along the underside of the penis instead of at the tip. This abnormality is present in the general population in approximately 2 in 1000 births (0.2%). Hypospadias in IVF males was found in 13/5446 births (0.24%) and in ICSI males was present in 7/1008 births (0.69%). This three-fold increase has been attributed to the use of sperm from otherwise infertile men. MFS clinical staff can provide more details on the implications of this.

The production of eggs and sperm and the subsequent fertilisation process is complex and occasionally the mechanism to ensure that the genetic make-up is correct can go wrong. Any abnormal gametes may not be able to participate in natural fertilisation but there is a concern that when ICSI is used, there is no such selection and could lead to abnormalities in any babies born. Scientists cannot tell by routine microscopic evaluation whether an egg or a sperm is genetically normal, but there is a good association between a normal appearance of the

sperm and normal genetic structure. The incident of these *de novo* (new or unexpected) abnormalities has been reported to occur in up to 3% of ICSI babies compared with around 0.6% in the general population.

### ICSI: Summary of Risks

There are theoretical grounds for concern that there may be additional dangers associated with ICSI pregnancies because it is an invasive technique and the sperm used to create an embryo may otherwise not have had the capacity to fertilise an egg. Since its development in 1990, many thousands of babies have been born worldwide following ICSI treatment. Follow up studies of 'ICSI children' have been carried out in several countries including Australia, Sweden, the UK and USA and the results are reassuring.

The ICSI technique has transformed the outlook for many infertile couples and for some it is the only option should they wish to have their own genetic child. The risks outlined above have to be balanced with the benefits ICSI provides. Even though ICSI has been used throughout the world since the early nineties, it is still defined as a new technique and, until many more studies have been performed, we will not be able to give definitive risks. It has been estimated that until at least '10,000 ICSI' children have been studied in a well-designed, controlled study then many of the risks associated with the technique cannot be confirmed. It is worth remembering that in the studies so far, the biggest risk to any child born is a direct result of being a twin or triplet.

## ICSI Treatment

### How Does a Patient Consent to ICSI?

After the ICSI procedure has been thoroughly discussed with the patient by a member of the clinical or laboratory team at MFS, the patients will be asked to complete various forms, including giving consent to the egg recovery, the mixing of the eggs and sperm and the embryo transfer.

The patient will also be required to complete an ICSI Consent Form to acknowledge that they have been given the information outlined in this booklet and that they are happy for the laboratory staff to perform the procedure.

### How Successful is ICSI at MFS?

MFS started ICSI in June 1994 and was the first unit in the West Midlands to do so. By December 2008 more than 1,950 babies had been born from 5,881 ICSI cycles. Please visit [www.midlandfertility.com](http://www.midlandfertility.com) or see the current MFS Patients' Guide to Services for the success rates for ICSI at MFS. For help understanding the data, please ask a member of staff.

### What Happens if Treatment Fails?

If treatment is not successful, the patient should notify MFS as soon as the result is known, as MFS needs to report the outcome of all treatment cycles to the HFEA.

MFS is often able to learn something from an unsuccessful treatment cycle and will share this knowledge with the patient. MFS staff are able to review the last cycle and give the patient advice on any future treatment options (see the

MFS leaflet: '**Following Unsuccessful Treatment**'). Like all types of fertility treatment, ICSI can be physically, financially and emotionally draining. Staff at MFS, including the team of counsellors, are dedicated to supporting all patients through their treatment (see the MFS leaflet: '**Counselling**').

If a patient decides that they no longer wish to pursue fertility treatment, they may wish to explore other ways of having a family. Discontinuing treatment can be a difficult decision and it may be useful to talk these issues through with a counsellor. Any member of the MFS team can provide telephone numbers for the MFS counselling service, other support groups or adoption agencies, or visit [www.midlandfertility.com](http://www.midlandfertility.com) and view the 'Useful Links' page.

### What Happens after a Positive Pregnancy Test?

As soon as the result of the treatment is known, the patient should contact MFS. Staff will be delighted to know if the treatment has been successful, but equally importantly, MFS has a legal duty to inform the HFEA of the outcome.

A patient should continue to take any hormones MFS has supplied as either injections, tablets or vaginal pessaries, to help maintain a healthy endometrium for the embryo to implant, unless advised to stop by a MFS fertility nurse specialist or doctor. Following a positive pregnancy test a patient may need a further supply of these and may also book an appointment for a pregnancy scan, two weeks later.

At this early stage of development, it is usually possible to see a gestational sac containing the developing fetus with a beating heart. This scan is important to confirm the number of fetuses and to ensure the pregnancy is developing normally within the uterus. Following this early scan, a patient should visit her GP and book antenatal care appointments like any other pregnancy. Of course, patients are always welcome to contact MFS at any time for advice or reassurance.

MFS staff will look forward to news of the birth and to reporting the outcome of the pregnancy to the HFEA.

## Next Steps

For more information on ICSI, contact MFS on 01922 455911 to make an appointment with one of the clinical team. This is the opportunity to discuss the issues in greater detail, to consider how suitable it is for the patient and to talk through the latest ICSI results from MFS. Scientific staff are also available to give further information.







© 2009 Midland Fertility Services Ltd

All rights reserved. No paragraph or other parts of this publication may be reproduced or transmitted in any form or by any means, including photocopying and recording, without the written permission of Midland Fertility Services Ltd.

# List of Services

- In Vitro Fertilisation (IVF)
- Intra Cytoplasmic Sperm Injection (ICSI)
- Surgical Sperm Recovery (PESA/TESA)
- Embryo Freezing
- Blastocyst Culture
- Intrauterine Insemination (IUI)
- Sperm Storage
- Assisted Hatching
- Egg Freezing (including Vitrification)
- Egg Donation
- Egg Sharing
- Tubal Patency Testing
- Fertility Investigation Package
- Phospholipid Auto-antibody Screen
- Sperm Analysis
- Recurrent Miscarriage Investigations
- Genetic Screening
- Ovarian Reserve Testing
- Vasectomy Reversal Back-Up

## How to get to Midland Fertility Services

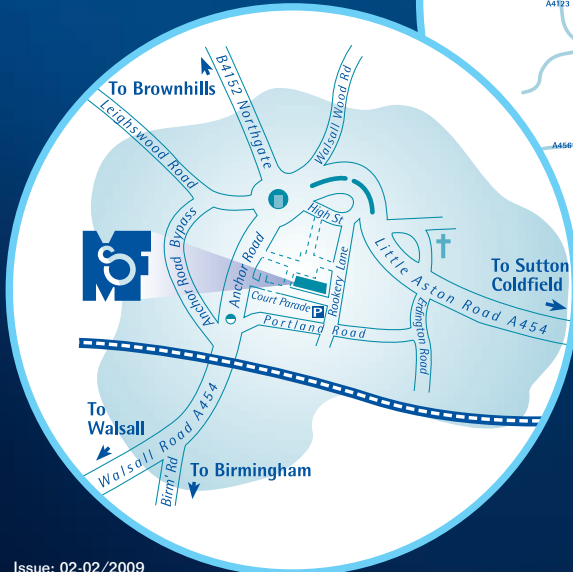
Third Floor, Centre House,  
Court Parade, Aldridge,  
West Midlands WS9 8LT

**t:** 01922 455911

**f:** 01922 459020

**e:** mfs@midlandfertility.com

**w:** www.midlandfertility.com



INVESTOR IN PEOPLE



FS 85979



003