



Assisted Fertilisation in IVF (ICSI)

fertility
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About 30% of infertility is caused by poor quality sperm. "Poor quality" can mean the number of sperm is reduced, the proportion of sperm moving (motile) is reduced, the patterns of movement are abnormal, or the average shape of the sperm is abnormal. Sometimes sperm have defects in their function that are not reflected in their number, the way they move, or the way they look.

In conventional IVF, sperm and oocytes are mixed in vitro (usually in a Petri dish), a sperm fertilises the egg to form an embryo, and the embryos are placed into the woman's uterus, in the hope that one (or more!) may implant. Although IVF was developed as a treatment for overcoming tubal disease, it can also be used to treat male infertility. However, there are limits to the use of conventional IVF for male infertility - many men have sperm that are unable to fertilise eggs, or the fertilisation rates would be very low. Also, some men have no sperm in their ejaculate but produce sperm that can be retrieved from the testis and used to fertilise oocytes.

What is Assisted Fertilisation?

Assisted Fertilisation is used to describe techniques which help a sperm fertilise an oocyte by bypassing some of the steps that normally occur.

Normally, fertilisation involves a complex sequence of events. Of the various techniques tried, the one that has been universally adopted is Intra-cytoplasmic Sperm insemination (ICSI). This uses sophisticated equipment to inject a single sperm into the middle of each mature oocyte. The sperm does not have to do any work itself.

Men with Azoospermia (no sperm in the ejaculate)

Sperm are produced in the seminiferous tubules and pass into the testis and on into the epididymis. If a man has a blockage to the outflow tract - from infection, vasectomy or even congenital absence of the vas, this will give rise to "obstructive azoospermia". Sperm production continues but the sperm are absorbed as they move down the epididymis. Other men have sperm production in the testis but the number produced is too few for them to appear in the ejaculate. This is called "non

obstructive azoospermia". Occasionally in these men, there may be a few sperm in the ejaculate one month but one the next.

It is important to be able to differentiate between the two types of azoospermia since with obstructive azoospermia it is always possible to retrieve sperm from the testis for ICSI whereas with non-obstructive azoospermia, retrieval of sperm for ICSI is only possible in 50% of men. The differentiation can usually be made on physical examination and a blood test. Occasionally a testicular biopsy will be necessary to be sure.

Therefore, in men with non-obstructive azoospermia, a biopsy is really only helpful to those people who want to be certain it is possible to retrieve sperm from the testis. Since a testicular biopsy is not without risk, (see below), whether or not to have a testicular biopsy before proceeding to IVF, needs careful discussion.

Sperm for ICSI can be obtained from directly the testis in a variety of ways.

MESA (Micro-epididymal sperm aspiration) refers to an operation under general anaesthetic, in which the surgeon collects fluid from the epididymis with the help of an operating microscope. The operation is expensive, so this technique is usually only done if the man is having a vasectomy reversal (or a similar operation) at the same time. The sperm from MESA is frozen for later use. The advantage of MESA is that a couple knows that there is definitely sperm before starting their ICSI cycle.

PESA (Percutaneous epididymal sperm aspiration) refers to passing a fine needle 'blindly' through the skin into the epididymis. Local anaesthetic is usually sufficient. PESA usually gives enough sperm for ICSI treatment, but often not enough to freeze. It is commonly done the day before the egg collection in the ICSI cycle.

TESA (Testicular sperm aspiration) or TESE (Testicular sperm extraction) can be used if there are no sperm on PESA, and for men whose testes make very few sperm. For TESA, a fine needle is used to take tissue from the testes, while in TESE a larger sample of tissue is taken through a cut in the skin.

Both techniques are usually done under local anaesthesia, the day before or the day of the egg collection in the ICSI cycle.

Chances of Success

The chance of pregnancy per embryo seems to be at least as high with assisted fertilisation as with conventional IVF. This is probably because the women seldom have any infertility factors themselves, and the oocytes are not exposed to the metabolic by-products of many sperm (typically 50,000 sperm are used per oocyte in conventional IVF). A consequence of the probably higher pregnancy rate per embryo is that many clinics advise a maximum of two embryos be replaced, whereas three is more common with conventional IVF. Extra embryos arising from assisted fertilisation that are of good quality can be frozen for later use.

Combination of ICSI with Conventional IVF

Sometimes when many oocytes are obtained and when the sperm quality is relatively good, there may be a place for performing assisted fertilisation on some oocytes and conventional IVF on the others. If reasonable fertilisation rates were obtained with conventional fertilisation, then you would not have to use assisted fertilisation in subsequent treatment cycles. This option maximises the amount of information gained about sperm-oocyte function while still giving a good chance of having embryos for transfer.

Miscarriage and Abnormality

Miscarriage rates for couples with male infertility, pregnant after conventional IVF, may be slightly higher than for IVF pregnancies from other types of infertility, although the difference is slight.

The rate of major foetal or neonatal abnormalities in IVF pregnancies is similar to that in 'normal' pregnancies (at around 25 per 1000 births), although there is some suggestion that some types of abnormalities, such as neural tube defects (eg. spina bifida) may be more common than usual. With ICSI, the incidence of major abnormalities appears to be no higher than that following IVF, or 'normal' pregnancies.



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There may be an extra risk of abnormalities in the number of sex chromosomes in children conceived by ICSI, which usually can only be detected by CVS or amniocentesis. Evidence from the leading ICSI clinic in Belgium suggests 1% of pregnancies may be affected. Some of these abnormalities (in the number of X and Y chromosomes) seem to have little or no effect; others can be associated with infertility and/or some degree of mental retardation. They can be detected by CVS or amniocentesis between 11-16 weeks of pregnancy. It is almost certain these abnormalities are caused by abnormalities in the sperm used, and are not due to the technique itself.

At present assisted fertilisation seems to work equally well for all types of severe male infertility; ICSI can be used when there are very few sperm (even fewer than one million/ml), very low motility (1-20%) and very poor morphology (1-10% normal). There have even been ongoing pregnancies when no sperm were moving and when no sperm were considered normal in shape. This is possible because the process of packaging the genetic material in the head of the sperm and the process of forming the shape of the sperm (head, tail, etc) are quite separate. The genetic quality of sperm is true to the adage that 'you can not tell a book from its cover'. At the moment one can not use the appearance of the sperm to estimate the chance of congenital abnormality or miscarriage. However, fertilisation and hence pregnancy rates are much lower when non-moving sperm are used.

Genetic causes of male infertility are thought to involve the Y (or male) chromosome. Up to 15% of men with zero or very low sperm counts have small pieces of the Y chromosome missing. The loss of this genetic information (called a deletion) leads to poor sperm production. There is no known reason

for the loss of this genetic material. As expected, boys conceived of fathers who have a Y deletion inherit the Y deletion, and will themselves be infertile when they grow up.

Analysis of the man's chromosomes (karyotype) is advised unless the poor semen quality or azoospermia is due to an obstruction. A blood test to determine whether there are deletions on the Y chromosome will soon be available in New Zealand.

Decisions to Make

Assisted fertilisation adds an extra option for couples with severe male infertility, whose only treatment option had previously been donor insemination (DI). The chance of having a child genetically one's own has to be balanced with the very different chances of pregnancy between the two techniques, and the very different costs. Counselling can be helpful in exploring the issues before making decisions.

For couples choosing assisted fertilisation, the scientific team also has to make decisions - which sperm preparation technique or techniques to use and whether to try conventional IVF with some oocytes. Many couples find it useful to talk with an embryologist, as well as the doctors, nurses and counsellors, before treatment.

Sperm Assessment

For some couples, the laboratory will ask for a semen sample at least several days before the anticipated day of oocyte collection. There are several ways of preparing sperm for ICSI, depending on sperm numbers and quality - this sample is an opportunity for the laboratory staff to test the method they are going to use.

Other Differences

The only difference between assisted

fertilisation and conventional IVF is in the handling of sperm and oocytes in the laboratory - the management of drugs to stimulate the ovaries, oocyte collection, and embryo transfer are the same.

Emotional Impact

The major emotional impact of assisted fertilisation is that for about 5-10% of couples, the check the day after oocyte collection will reveal that fertilisation has not occurred. This can be a traumatic and sorrowful time; hopes are dashed and fears realised. In conventional IVF for other types of infertility, most people expect fertilisation to occur; of all the disappointments that can accompany IVF, failed fertilisation seems to be one of the hardest to bear, perhaps because it comes so quickly and so soon after oocyte collection.

Conclusions

Assisted fertilisation gives couples with severe male infertility the chance of pregnancy, and may be used as an alternative option to donor insemination. In a well established programme, over 90% of couples will have at least one oocyte fertilised, and the chance of pregnancy, per embryo, is at least as high as with conventional IVF for other types of infertility. The chance of abnormality may be higher in pregnancies arising from assisted fertilisation, probably due to genetic defects in sperm or oocytes, rather than due to the technique. IVF with assisted fertilisation carries all the risks, side effects and issues of IVF itself.

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