

Introduction

No medical treatment is entirely free from risk and infertility treatment is no exception. This document is to inform patients about the possible risks of infertility treatment.

It is important, however, to appreciate that most patients go through IVF and other assisted conception treatments without any problems at all.

The risks associated with infertility treatment can be considered over six categories:

1. The risks associated with the drugs used to stimulate egg production.
2. The surgical risks associated with egg removal.
3. Laboratory issues & risks.
4. The risks associated with pregnancy.
5. The risks of producing an abnormal baby following infertility treatment.
6. Psychological and emotional risks.

Risks associated with drugs used to stimulate egg production

Ovarian Hyperstimulation Syndrome (OHSS)

Over stimulation of the ovaries is a deliberate aspect of IVF treatment as we try to obtain more eggs than would arise in a natural cycle. When the ovaries are stimulated there is a possibility of **OHSS** developing which is an excessive response to the normal drugs used in the IVF cycle.

The majority of cases are a mild to moderate form, occurring in up to 5% of all patients undergoing IVF treatment. This is manifest by abdominal distension, abdominal discomfort and nausea. These cases settle in a few days and require observation, analgesia for discomfort, a good fluid intake and occasionally some blood tests but usually no specialist treatment.

Less commonly a more severe case occurs. This happens in 0.5 - 1 % of all IVF cycles. This is manifest by more marked abdominal distension, nausea and vomiting, decreased output of urine and some difficulty with breathing. This requires admission to hospital for treatment that may include replacement of lost fluids, replacement of protein (albumin), administration of anticoagulants (to thin the blood) and drainage of fluid from the abdominal cavity. This condition normally responds to treatment and resolves completely in 1 - 2 weeks. Rarely OHSS can be life threatening from thrombosis (blood clots in arteries or veins), kidney, liver or heart failure and very rarely fatalities have been reported. To put this in to perspective though, natural pregnancy and childbirth is 10 times more life threatening than a cycle of IVF treatment.

One of the purposes of monitoring the IVF cycle is to detect early signs of OHSS and modify or cancel the treatment if there are indications that this is developing. Treatments may be modified by reducing the strength of stimulation, coasting the stimulation (continuing the treatment but stopping the stimulation for several days) or going ahead with the egg collection but freezing the embryos as we know pregnancy aggravates OHSS and can prolong and worsen its course.

Risk of Under Response

It is also possible for your ovaries to under respond to stimulation. If this happens, your drug dose may need to be increased or the cycle cancelled. If cancellation occurs, a 'cancellation fee' will be charged – see fee schedule for details.

Risk of developing Cancer

Ovarian cancer: it has been suggested that the use of drugs used to stimulate ovaries may increase the risk of developing ovarian cancer. Two studies from North America suggested that the risk of ovarian cancer developing increased in women using the drug Clomifene. Subsequent studies, however, have not confirmed this risk. Follow up data from Scandinavian Registries which have tracked IVF patients' cancer risks from the early days of IVF have also been very reassuring.

Women who have never been pregnant are known to be at a slightly increased risk of developing ovarian cancer. The current position is that if a risk of ovarian cancer exists it is very low and unconfirmed.

Uterine, Breast and Cervical cancer: there is no association between the use of drugs to stimulate ovulation and the development of uterine, breast or cervical cancer.

Surgical risks associated with egg removal for IVF and related procedures

General anaesthetic and intravenous sedation: patients undergoing IVF and related treatments will receive either intravenous sedation, a general anaesthetic or local anaesthesia. These are very safe procedures, but very occasionally there will be an adverse reaction to drugs or other complication. The risk of serious harm is very low, 1 in 10,000, and is similar to that of other elective surgery.

Egg collection and risk of damage to other structures: the ovaries are surrounded by important structures, including bowel, bladder, ureters, the uterus and major blood vessels. It is theoretically possible to puncture one of these structures although the likelihood is very low. The risk of a significant haemorrhage from an internal blood vessel is approximately 1 in 2,500. If significant damage occurs to internal organs or other structures it would require abdominal surgery to rectify the problem.

Pelvic infection: removal of eggs involves passing a needle through the vaginal wall into the ovary and it is possible to introduce infection into the ovary. This possibility is increased if there is an endometriotic cyst in the ovary at the time of treatment. This complication may cause pelvic pain and other signs of infection developing in the weeks after the procedure. It is treated with antibiotics but may very rarely require abdominal surgery to drain an abscess. The risk of serious pelvic infection is likely to be less than 1 in 500.

Embryo transfer: the placement of the embryos into the cavity of the uterus (womb) is usually a relatively simple procedure. There are virtually no risks to the female in carrying this out. Despite taking great care with this procedure the catheter does not always pass through the cervix easily and sometimes the embryos get caught in the mucus. This can usually be recognized with careful checking of the catheter after the transfer procedure is carried out. In these cases a further attempt can be made to replace the embryo(s) in the uterus. Very rarely, one or more of the embryos may be lost in the cervix during the course of placement. In this case, if additional embryos are available, a further replacement attempt may be carried out.

Laboratory issues & risks

Patients' treatment in the laboratory may result in an unexpectedly poor outcome both in the process of fertilization and in embryo development.

No eggs/Immature eggs collected and abnormal eggs: careful monitoring usually ensures that most of the follicles will carry a mature, healthy egg. However there is considerable variability in the number of eggs collected and not every follicle will yield an egg. Occasionally no eggs are collected. Some follicles may contain eggs which are either immature or deteriorating and are thus unlikely to fertilise normally.

No sperm or fewer sperm than expected: sometimes the sperm count is found to have decreased dramatically on the day of egg collection. If IVF was originally planned we may advise a switch to ICSI which requires only one sperm per egg compared to millions. If no sperm can be found in the ejaculate, we may advise an attempt at surgical recovery of sperm or alternatively advise egg freezing.

Problems with Fertilisation: If egg and sperm quality is good, about 70% of mature healthy eggs will fertilise normally following IVF or ICSI. The remainder usually do not fertilise; however, occasionally an egg will fertilise abnormally for example if it has been penetrated by more than one sperm. This occurs in nature too. The percentage of eggs fertilised may be reduced if the egg and/or sperm quality is poor. A complete failure of fertilisation occurs in about 5% of IVF cases and about 1% of ICSI cases, but is more common when only few eggs are collected. In such circumstances, the treatment cycle will be reviewed and discussed with you in a follow up consultation with your consultant.

Problems with cleavage (further development) of the embryo: Most normally fertilised eggs will cleave; however, a small percentage may not. Of those that cleave, not all will be of good quality. A good quality embryo will generally have clearly visible, regularly shaped cells. However, there will usually be some embryos in which a cell(s) has broken into small fragments ("fragmentation"). Minor fragmentation in embryos is quite common and does not appear to affect pregnancy rates. More extensive fragmentation affects the survival of the embryo. We therefore usually try to select only apparently good quality embryos with regular cells or minor fragmentation for replacement, though many healthy pregnancies have developed from embryos with significant fragmentation. Culturing embryos to the blastocyst stage is often undertaken. The embryology team will advise on this.

Incidents and Accidents: as eggs and embryos are very small (just 0.1mm across or seven times smaller than the dot at the end of this!) it is unsurprising that problems may occasionally arise in the laboratory with their manipulation, processing and handling. While accidents and incidents are extremely uncommon, complications such as eggs or embryos sticking in micropipettes or in the cervix during embryo transfer, accidental spillage of culture dishes or equipment malfunction have all been described and may lead to the loss or compromise to eggs, sperm and embryos. CARE's protocols and quality assurance procedures are rigorous, regularly reviewed and designed to minimise problems. In addition, our laboratories are inspected regularly by the regulatory authorities to ensure appropriate procedures are in place.

Where there is an unexpected outcome or event in the laboratory CARE Embryology and Medical staff will be available to discuss the situation. Further investigations to try and gain a better understanding of what occurred may be recommended and you will be offered a follow up consultation with your consultant.

The risks associated with pregnancy resulting from any treatment

Multiple pregnancy: multiple pregnancy can result from any treatment involving the use of drugs to stimulate egg production or when more than one embryo is replaced during IVF / ICSI or egg donation treatment. A twin pregnancy can also establish from a single embryo splitting – this results in identical twins.

The likelihood of a twin pregnancy is approximately 10% following Clomifene treatment, 20-25% following IVF when two embryos are replaced and 10-20% following IUI treatment. CARE is continually looking at strategies to reduce multiple pregnancy risks. The simplest of these is to replace a single embryo, though this does reduce the chance of a pregnancy establishing. CARE are also looking at better embryo selection techniques, such as blastocyst culture, to help us identify embryos with the best implantation potential which we hope will help us to feel more confident about single embryo replacements.

Triplet pregnancy can also result from any of these treatments but is less likely. The risk of triplets following IVF and related treatments is very low if 1 or 2 embryos are replaced although occasionally an embryo can split. If three embryos are replaced the likelihood of triplets increases. After Clomifene therapy the chance of conceiving triplets is less than 0.5% and 1-2 % following IUI treatment.

The complications of multiple pregnancy are:

- increased risk of miscarriage and complications such as haemorrhage and high blood pressure during pregnancy,
- higher rate of premature birth and the problems arising from low birth weight,

- increased risk of Caesarean section,
- higher rate of still birth, or death shortly after birth,
- higher rate of disability and other health problems, which may lead to extended stays in hospital before and after birth,
- increased practical, financial and emotional impact on the family.

For further information about the risks of multiple pregnancy see - www.oneatatime.org.uk.

Ectopic pregnancy (pregnancy occurring outside the womb): IVF and related treatments increase the likelihood of an ectopic pregnancy. The incidence of ectopic pregnancy is 1-3 % of all pregnancies resulting from embryo transfer, about twice the normal rate. Patients who become pregnant following these treatments should have an early scan to establish if the pregnancy is correctly positioned.

Ectopic pregnancy is usually treated surgically either by removing the fallopian tube or removing the ectopic pregnancy from the fallopian tube. If the ectopic pregnancy is very early it may be possible to use a drug called Methotrexate to dissolve the pregnancy tissue.

Patients who have had a previous Caesarian Section delivery are at risk of a subsequent pregnancy establishing at the site of the previous scar in the wall of the uterus. This can usually be recognized by careful ultrasound undertaken in the early stages of pregnancy.

Heterotopic pregnancy: this is a twin pregnancy with one pregnancy in the Fallopian Tube (or other abnormal place) and one correctly situated in the uterine cavity. Although this is a rare condition its incidence increases following IVF and related treatments. This can usually be recognized by careful ultrasound undertaken in the early stages of pregnancy following these treatments.

Miscarriage: early miscarriage is very common in naturally conceived pregnancies. IVF and related treatments neither prevent nor increase the risk of miscarriage.

Risk of a baby with an abnormality following IVF / ICSI and related technologies

IVF and ICSI: to date there have been over a million babies born following IVF and ICSI treatment worldwide. In the UK between 1 and 2% of all babies are conceived following IVF and its related technology.

Concerns have been raised about the possible genetic risk to such children because of the manipulation of the egg and sperm during the process. Many studies have reported the incidence of a baby with an abnormality but most have been too small or of insufficient quality to provide a reliable answer. One recent study has reviewed much of the available data and has concluded that compared to the risk of a baby with an abnormality arising following natural conception of 5.8%, the risk of a baby with an abnormality following assisted conception treatment rises to 8.3%. There is also data to suggest that children born to men who themselves have structural abnormalities of the testes and penis (eg. hypospadias and undescended testes) may, unsurprisingly, inherit a tendency to these conditions. Therefore parental rather than treatment factors seem to play a large part in the increased incidence of abnormality.

There is no conclusive data otherwise to link IVF with any specific abnormality although some recent studies have shown an increase in "imprinting" disorders which can lead to intellectual impairment. These are normally very rare disorders and the recent data indicates that, although they may be increased as a result of IVF, they are still very rare.

At this time we cannot conclusively say whether or not there is a cause and effect relationship between IVF / ICSI and specific abnormalities. It is clear that if such a risk exists it is relatively small and that further monitoring of children resulting from IVF/ICSI, and related technologies, is necessary to conclusively answer this question.

ICSI specific data: Some men with severe sperm abnormalities will have a genetic basis for this, usually an abnormality of the Y chromosome. This is likely to be inherited by male offspring following ICSI. In

addition, men with sperm problems tend to have a larger proportion of sperm that have chromosomal abnormalities (aneuploid) than do men with normal sperm production. It is not surprising therefore that there is some data to suggest that the risk of chromosome abnormalities, including abnormalities of the sex chromosomes, is increased following ICSI. (The overall risk of new chromosome abnormalities is about 3%) Therefore, there may be a risk of passing on infertility problems and any disorder associated with the chromosome abnormality to a future child. Some recent studies have quoted the risk of birth defects in patients requiring ICSI to be 9.9%. When corrected for parental factors the risk of birth defects is lower but still slightly increased. Again, parental factors seem to be contributing heavily to the risk of abnormality and not necessarily the treatment techniques. It must be stressed that not all patients treated with ICSI are in these specifically higher risk categories as this technique is used in a number of different situations.

Extensive data has been reported from large multi-centre studies looking at development of children born after ICSI compared to normally conceived controls. Thus far the data has been very reassuring. Many studies are still on-going and we will continue to monitor these closely.

Miscarriage rates may also be increased following ICSI and there is data to suggest this increases in proportion to the severity of male infertility.

Follow up data is currently limited as ICSI conceived children are still very young. We cannot be fully certain that there will be no problems in older children or the next generation. **In conclusion it is important that the couple is aware of and accepts the potentially increased risk of having a child with a birth defect before undergoing ICSI treatment, the mechanism of which is not entirely clear though parental rather than treatment factors seem to play a large part in this.** Counselling is available to help the couple come to a decision.

Embryo cryopreservation and thawed embryo transfer: this technique has been carried out since 1985. Although the number of babies born after freezing and thawing is considerably less than by IVF, there is no evidence of any increased incidence of abnormalities in babies born following replacement of thawed embryos. Indeed, some recent studies have shown babies born from frozen embryos seem to have a lower rate of birth defects than from fresh cycles embryo replacement. It has been suggested that this may be due to genetically compromised embryos being less likely to survive the thawing process.

Psychological and emotional risks

Treatment for infertility is an emotional "rollercoaster" of expectation, disappointment and success and the marked hormonal changes that occur during the cycle of treatment can create psychological and emotional pressures that can in turn place strain on a relationship. Support is provided by the staff of the clinic during this difficult time and additionally patients may find counselling beneficial.