Risks and complications of assisted conception

Introduction
No medical treatment is entirely free from risk and infertility treatment is no exception. 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:

- The risks associated with the drugs used to stimulate ovaries
- The surgical risks associated with egg collection
- Laboratory issues and risks
- The risks associated with pregnancy
- The risks of an abnormal pregnancy
- Psychological and emotional risks

RISKS ASSOCIATED WITH DRUGS USED TO STIMULATE OVARIES
Ovarian Hyperstimulation Syndrome (OHSS)
Stimulation of the ovaries is a deliberate aspect of IVF treatment as we try to obtain more eggs than the one that would usually be produced in a normal menstrual cycle. When the ovaries are stimulated there is a possibility of **OHSS** developing which is an excessive response to the stimulatory drugs used to encourage multiple follicles to form.

Preventing OHSS
As part of your fertility investigations, we will review information from your medical history, past treatments, ultrasound scans and blood test results to try and assess your risk of OHSS before you commence treatment. There are several strategies that we can use to minimise the risks of you developing OHSS

- using an antagonist protocol for ovarian stimulation for high risk patients
- using lower dose stimulation
- monitoring your response carefully with serial ultrasound scans and sometimes estradiol levels
- using a GnRH trigger injection such as buserelin
- freezing all embryos and allowing ovaries to settle before preparing for transfer
- more rarely we may suggest cancelling your cycle before egg collection and reviewing any further attempts at treatment

The majority of cases are a mild to moderate form, occurring in up to 5% of all patients undergoing IVF treatment.

Mild OHSS

- mild abdominal distension and discomfort
- nausea

These cases settle in a few days and require observation, painkillers for discomfort, a good fluid intake and occasionally some blood tests but usually no specialist treatment.

Moderate OHSS

- more marked abdominal distension and pain
- nausea or vomiting

Severe OHSS

- dehydration and extreme thirst
- more marked abdominal distension and pain
- nausea and vomiting,
- passing smaller amounts of urine
- difficulty with breathing

What causes OHSS?
Fertility drugs, usually gonadotrophins, are used to stimulate the ovaries during IVF treatment to make follicles grow.

Eggs are then collected from these follicles. Sometimes there is an excessive response to these drugs, leading to OHSS. Overstimulated ovaries enlarge and release chemicals into the bloodstream. Fluid from the blood vessels leaks into your abdomen and in severe cases into the space around the heart and lungs. OHSS can affect the kidneys, liver and lungs. A very small number of deaths due to OHSS have been reported.

Who gets OHSS?

Mild OHSS is common in women having IVF treatment affecting as many as 33 in 100 women (33%). However, just over 1 in 100 women (1%) will develop moderate or severe OHSS.

The risk is higher in women who:

- have polycystic ovaries
- are under 30 years old
- have had OHSS previously
- get pregnant in the same IVF cycle as they get their symptoms, particularly if this is a multiple
- pregnancy (more than one baby).

How long does it last?

Most of your symptoms should resolve in 7–10 days. If your fertility treatment does not result in a pregnancy, OHSS usually gets better by the time your next period starts. If you become pregnant, OHSS can get worse and last up to a few weeks or longer.

What should I do if I have mild OHSS?

If you have mild OHSS, you can be looked after at home. Ensure that you drink fluids at regular intervals depending on how thirsty you feel. If you have pain, take paracetamol or codeine (no more than the maximum dose). You should avoid anti-inflammatory drugs (aspirin or aspirin-like drugs such as ibuprofen), which can affect your kidneys. It is advisable to remain moderately active to reduce the risk of clots forming in the legs or lungs.

When should I call LCRH for help?

If you start to vomit, have urinary problems, shortness of breath or chest pain then we advise you go to your local A&E department at your local hospital

If you have increasing abdominal pain or swelling, nausea or vomiting please contact the clinic directly. We may then ask you to come to clinic for some further tests.

We may do the following:

- ask about how much urine you are passing and whether it is darker than normal (concentrated)
- measure your blood pressure, pulse rate and breathing rate
- take an initial measurement of your waistline and check your weight to see whether the fluid is building
- arrange an ultrasound scan to measure the size of your ovaries and to check whether there is any fluid build-up in your abdomen
- take blood tests to measure how concentrated your blood is and how well your kidneys are working.

A diagnosis is made on the basis of your symptoms, the examination findings and the results of your tests. If you are well enough to stay at home, you may be advised to attend for regular check-ups.

When will I need to stay in hospital?

Many women can be managed as outpatients but you may need admission if:

- your pain is not helped by pain-relieving medications
- you have severe nausea and vomiting
- your condition is not getting better
- you will be unable to attend LCRH easily for monitoring and follow-up.

If you are vomiting, you may need a drip to replace the fluids you have lost. The fluid will help to keep you hydrated. The team looking after you in hospital may want to speak to us at LCRH regarding your condition, particularly if they are not experienced in looking after OHSS patients.

What is the treatment for OHSS?

Although there is no treatment that can reverse OHSS, it will usually get better with time. Treatment is to help symptoms and prevent complications.

This includes:

- pain relief such as paracetamol or codeine
- anti-sickness drugs to help reduce nausea and vomiting
- an intravenous drip to replace fluids
- support stockings and heparin injections to prevent thrombosis (a blood clot in the leg or lungs).

Heparin injections for blood thinning should be continued for 7 days from cure of your symptoms if you are not pregnant or until the end of the 12th week of your pregnancy.

If your abdomen is tense and swollen because of fluid build-up, you may be offered a procedure known as a paracentesis. This is when a thin needle or tube is inserted under ultrasound guidance into your abdomen to remove fluid. You may be offered a local anaesthetic for this procedure. This treatment helps relieve discomfort and improve kidney function and your breathing. Rarely, advice may be sought from a more specialist team which may involve anaesthetists and/or intensive care doctors.

Are there any ongoing concerns if I have had OHSS and become pregnant?
To lower the risk of developing a blood clot in your legs or lungs, you will be advised to continue wearing support stockings and taking heparin (blood-thinning) injections until 12 weeks of your pregnancy. You may be at increased risk of developing pre-eclampsia or giving birth to your baby prematurely. However, there are no known risks to your baby's development as a result of OHSS.

Is there anything else I should know?

- If you develop OHSS, your ovaries will be enlarged and painful. You should avoid having sex or doing strenuous exercise to avoid injury to the ovaries.
- A few women develop OHSS as an after-effect of other fertility treatment

Key points

- OHSS is a potentially serious complication of fertility treatment, particularly of IVF.
- It can range from mild to severe. Mild OHSS is common and usually gets better with time. More severe cases require specialist care and hospital admission.
- It is important to make contact with your fertility unit if you develop symptoms suggestive of more than mild OHSS.

Risk of thrombosis (forming blood clots)
There is an increased risk of thrombosis in naturally conceived pregnancies. For assisted conception treatment the risk is thought to be approximately 3 times higher, most of this risk occurring in the first 12 weeks of pregnancy. Most of these pregnancies affected by thrombosis are where OHSS and subsequent pregnancy has occurred. There does not appear to be an increased risk of clot formation with frozen embryo replacement cycles shown in some studies although using estrogen in the form of tablets and patches does increase the risk of thrombosis with long term use. Currently the only indication for blood thinning medications is where OHSS has occurred in which case injections such as clexane are indicated up until 12 weeks of pregnancy.

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
Women who have never been pregnant are known to be at a slightly increased risk of developing 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. Therefore 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 that we know of between the use of drugs to stimulate ovulation and the development of uterine, breast or cervical cancer.

SURGICAL RISKS ASSOCIATED WITH EGG COLLECTION

Intravenous sedation
Patients undergoing IVF and related treatments will generally receive intravenous drugs through their veins to make them drowsy and make egg collection comfortable. This is generally a 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 surgery.

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 then usually a laparoscopy is required to look inside the pelvis to assess any potential damage. This means a telescope needs to be passed through the abdominal wall to see inside the pelvis. A general anaesthetic is needed for a laparoscopy.

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 1000**.

Embryo transfer
The placement of embryos into the cavity of the uterus (womb) is usually a relatively simple procedure. There are virtually no risks to the female. 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.

Laboratory issues and 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
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 a sperm sample 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 egg freezing.

Problems with Fertilisation
If egg and sperm quality is good, about 70% of mature healthy eggs would normally be expected to 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.

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 aim to culture embryos to the blastocyst stage. The embryology team will advise on this.

Incidents and Accidents:
As eggs and embryos are very small (just 0.1mm across). 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. Our 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 the 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.

THE RISKS ASSOCAITED WITH PREGNANCY

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. By culturing embryos to blastocyst this gives us better embryo selection. This helps us identify embryos with the best implantation potential so we 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.

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: https://www.hfea.gov.uk/about-us/our-campaign-to-reduce-multiple-births/

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. The risk with IVF pregnancies is about twice the normal rate 4-5%. 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. If methotrexate is used you will need to wait six months before attempting further treatment.

Patients who have had a previous Caesarean 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 sometimes be recognized by careful ultrasound undertaken in the early stages of pregnancy following these treatments. A common symptom is continued bleeding in the presence of a normally developing intrauterine pregnancy with pelvic pain.

Miscarriage

Early miscarriage is very common in naturally conceived pregnancies. IVF and related treatments neither prevent nor increase the risk of miscarriage. PGT-A does help to reduce the risk. Please see for more information: https://www.hfea.gov.uk/treatments/treatment-add-ons/pre-implantation-genetic-testing-for-aneuploidy-pgt-a/

RISKS OF AN ABNORMAL PREGNANCY

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 related cycles.

Concerns have been raised about the possible risk to children born as a result of these treatments because of the preparation of eggs 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:

- the risk of a baby with an abnormality arising following natural conception is 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 where the opening of the penis is on the underside or at the base of the penis and undescended testes) may, unsurprisingly, be more likely to have these conditions themselves. Therefore, parental rather than treatment factors seem to play a part in some of the increased risk of abnormality with assisted conception treatments.

There is no conclusive data otherwise to link IVF with any specific abnormality although some recent studies have shown an increase in “imprinting” disorders. Imprinting disorders are a rare group of disorders which can affect growth, development and metabolism with a lifelong impact on quality of life. Examples of these disorders are Angelman and Prader-Willi syndromes. We have two complete sets of chromosomes, one from each parent with equal expression from genes from each parent. Imprinting is when expression is from one parent only.

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 risks exist it is relatively small and that further monitoring of children resulting from IVF/ICSI, and related technologies, is necessary to really answer this question.

Risks of ICSI

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.

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.

Embryo cryopreservation and frozen 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.