

Risks and Side Effects of Assisted Reproductive Technology (ART)



Concept
Fertility
Centre

12.1.10

There are risks associated with everyday living and all of us unconsciously calculate these in undertaking daily activities (e.g. car accident, falling down stairs). We also suffer side effects as a result of daily exposure to most things we come into contact with (e.g. hay fever, sunburn).

You must now understand the risks and side effects that may occur with drugs we might suggest you take, and the treatments possibly required for ART (IVF, ICSI etc). You must decide whether these risks are worth taking and whether the side effects are worth tolerating.

A) SURGERY

Oocyte (eggs) collection is undertaken using either:

- Laparoscopy (now rarely performed)
- Trans-vaginal ultrasound guided aspiration (the method of choice)

The following complications of surgery have been described:

Bleeding

From the ovary or from adjacent pelvic structures. Bleeding usually settles by itself but very rarely the "bleeding point" must be tied off requiring surgery.

Pelvic Infection

This may lead to a pelvic abscess, permanent damage to the fallopian tubes and require further surgery and hospitalisation. Most patients take antibiotics before and during treatment to help prevent this occurring, but the possibility still exists.

Accidental Bowel Injury

Can occur, even in patients with no previous surgery. Peritonitis may occur which may lead to further surgery and/or drainage of abscesses. Bowel injury is more likely to occur with laparoscopy, rather than with a transvaginal egg retrieval, although this risk does still exist.

Bruising

Around the ovaries from the needle puncture may cause pelvic discomfort for a few days, but no special treatment is required.

Anaesthesia

Risks of a full general anaesthetic include allergic rashes, temporary paralysis, vomiting and in more extreme cases, death. However, a full general anaesthetic is rarely used. Nowadays, basal sedation is used to just make a patient pleasantly drowsy and relaxed, so the risks are very minimal.

In general, the risks of surgery are higher when the patient smokes excessively and where there has been previous surgery.

Obesity is also an anaesthetic risk. As such Concept Day Hospital cannot admit patients for surgery who have a BMI over 38 kg/m².

B) MEDICATIONS

It is neither possible nor useful to list all the possible reactions to medication.

All drugs produce some side effects. These can be one or more of the following;

Allergic reactions: These are bizarre responses peculiar to some individuals and not to others. For example Penicillin can produce lumpy rashes or sudden fluid retention and, if this occurs within the larynx, some obstruction to breathing is possible.

Exaggerated side effects: These are the effects of medication which in some degree are common to many patients taking drugs but some people have an exaggerated reaction. For example Pethidine produces relief of pain but commonly "queasiness" or light headed feelings.

ART Medications

For information on the specific medications used in ART and their side effects see document 12.1.5 "Medications used in Infertility".

C) OVARIAN HYPERSTIMULATION SYNDROME (OHSS)

What is it?

This is a specific problem that occurs in about 1% - 2% of patients who undergo super-ovulation induction. It is impossible to predict which patients may suffer from it before ART treatments commence. See figure on page 4.

During the treatment it is more likely to occur in those producing large numbers of follicles and high hormone levels. It does NOT occur if the final HCG injection is not given.

Essentially, fluid from the blood stream leaks into the abdominal cavity causing it to swell noticeably and leaving the blood more concentrated and more viscous. Mild cases of OHSS may pass unnoticed.

It is extremely important that women experiencing symptoms of OHSS discuss this with the patient co-ordinator so that their clinician can be notified and further monitoring organised if necessary.

The consequences of severe OHSS can be breathing difficulties, temporary kidney "shut-down", and some arterial and venous thrombosis. Rarely, extensive thrombosis could cause interference with blood supply to parts of the brain or to other organs. Death due to OHSS whilst very rare, is possible.

Patients who suffer severe OHSS must be hospitalised and treated. This treatment would involve the infusion of intravenous fluids and the fluid in the abdomen may need draining off.

OHSS always disappears in a few days unless a pregnancy occurs. In early pregnancy the problem may last weeks and require prolonged hospitalisation.

Ring Concept Fertility if at all concerned.

Alternatively, go to the emergency center at King Edward Memorial Hospital or your nearest emergency center.

Ovarian Hyperstimulation Syndrome (OHSS)

In most cases OHSS can be prevented by careful monitoring with blood tests and ultrasound scans.

Symptoms of OHSS

Mild

Abdominal distention and discomfort, nausea, vomiting and or diarrhea

Moderate

Mild symptoms plus – abdominal swelling

Severe

Moderate symptoms plus decrease in urinary output and or breathing difficulties

PREVENTION OF OHSS

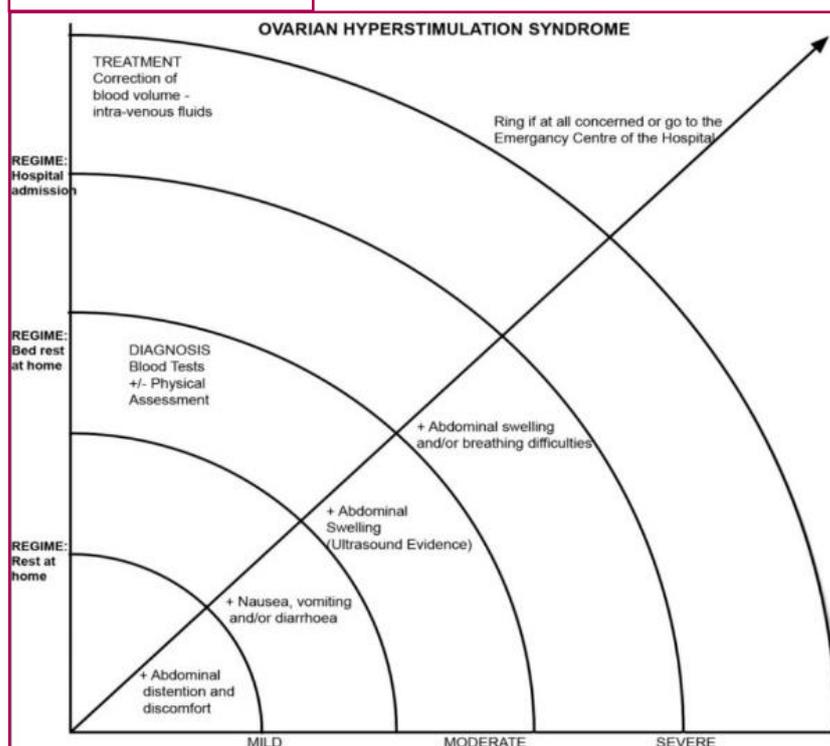
All patients using Gonal-F or Puregon will require close monitoring using blood tests and ultrasound scanning of the ovaries to ensure the ovaries do not over- respond to the drugs.

Patients are generally monitored daily and for those who have oestradiol (E2) levels considered by their doctor to be getting close to the risk level, the following options can be considered:

- To cancel the cycle
- To collect and fertilise the oocytes and then freeze the embryos (ie. avoiding pregnancy in that cycle)
- To use a techniques known as "coasting"

These will be discussed with you should this situation arise.

Symptoms of OHS



D) DISAPPOINTMENT

Infertility itself creates a feeling of intense hurt and disappointment. The opportunity of an ART treatment and thus the possibility of a pregnancy offers hope. However, the intensity of effort put in undergoing ART procedures is more than likely to be unrewarded in each cycle (otherwise the pregnancy rate would be more than 50%). Success is achievable for most couples, as long as a number of attempts are tried.

It is also likely that your parents, relations or friends will not appreciate what you have been through. They cannot really know. You may feel lonely yet become irritated by sympathy; angry, but not sure who or what with or why. Do not be afraid or ashamed to ask for help. The Concept Counsellor is available for everyone to talk to.

E) VENOUS THROMBOSIS

Venous thrombosis refers to blood clots occurring in the veins, usually deep veins in the legs (DVT) but can occur elsewhere including the lungs (pulmonary embolism or PE). Symptoms may range from tenderness and swelling in the affected area, e.g. the calf muscle, to chest pain, shortness of breath and stress on the heart if occurring in the lungs

Current research shows that there is an increased risk of thrombosis with OHSS (see earlier section) but there is also some evidence to suggest that there may be a small increased risk in early pregnancy for women who have become pregnant directly from an IVF or ICSI cycle.

If you have additional health factors that increase your risk of developing blood clots then you may be offered blood thinning agents (anticoagulant therapy)

during pregnancy. However these treatments are not routinely offered to all patients as they also carry significant side effects.

It is important to be aware of potential risk for venous thrombosis (DVT or PE) and report any symptoms to your doctor. Early detection and treatment can prevent serious consequences of these events.

F) MULTIPLE PREGNANCY

Multiple pregnancy after ART is directly related to the number of embryos replaced into the uterus and can increase the risk of many pregnancy complications and poor birth outcomes. Concept has one of the lowest multiple pregnancy rates in Australia.

There is an increased pregnancy rate with an increase in the number of embryos replaced but there is also an increased risk of multiple pregnancies. However, the cumulative chances of pregnancy with two single embryo transfers are comparable.

Mostly, one sometimes two embryos are currently replaced. This will be discussed with you before the embryos are replaced. With two embryos replaced the chances of twins are about one in five.

There are some possible disadvantages in multiple pregnancies. These are:

Medical (Maternal)

Obstetrically, carrying two babies places greater pressures on the pregnant women. There is an increased risk of miscarriage, obstetrical complications, premature deliveries and birth

complications. Please discuss these with your Gynaecologist.

Medical (Babies)

Babies born as one of multiple birth have a greater risk of prematurity which may or may not then require neonatal intensive care. These babies are also at greater risk of cerebral palsy. Please discuss this further with your obstetrician.

Social (Babies)

Babies born as one of a multiple need to compete for the attention and care provided by the parents. This may cause greater social problems in due course. Please discuss this with your Gynaecologist

G) ECTOPIC PREGNANCY

An ectopic pregnancy occurs when the baby is growing outside of the uterus. (i.e. implanting, and growing in the Fallopian tube and not in the uterus.) Concept's monitoring procedures are designed to reduce the risk of ectopic pregnancies remaining untreated.

It may not be realised that placing embryos into the uterine cavity can also result in an ectopic pregnancy. The embryo may move to the Fallopian tubes: the great majority returning normally to the uterus. Some embryos, however, may stay and implant "ectopically".

A tubal pregnancy can grow, rupture and lead to a surgical emergency. If recognized early measures can be taken to avoid such emergency situations. It is important that Concept's screening procedures be followed to minimise the risk of an unrecognized ectopic pregnancy.

These screening procedures include;

- A patient diagnosed as pregnant following ART should have an ultrasound carried out at such time that an intra-uterine pregnancy can be identified. This is possible from three weeks after ovulation or when the QHCG level reaches 3000 units or more.
- That patients assumed "not pregnant" have this confirmed by a negative QHCG at two weeks (14 days) after ovulation. A "period" can occur with an ectopic pregnancy and is not sufficient reassurance.

These precautions are most important for "country" patients, i.e. outside metropolitan Perth, as an ectopic pregnancy far from medical help could be disastrous.

H) LABORATORY MATERIALS

1. Sperm Treatments

In some cases where reduced sperm motility or numbers indicate that normal fertilisation rates might not be attainable, the use of a stimulant on the sperm will be recommended.

This stimulant will be Pentoxifylline. These agents act by removing some of the excess oxygen compounds from the sperm and eliminating some of the damaging effects of these compounds. The result is that sperm are more capable of swimming faster and have an increased fertilizing potential. Some other chemical agents are used to improve the sperm recruitment procedures. These include "puresperm" and "sperm slow".

These agents have been in use routinely, to improve the fertilizing

capacity of sperm, for a number of years.

While there has been no evidence, to date, that these agents have any damaging effect on the developing embryo or baby, there is no proof that this cannot occur. None of these agents were developed or registered for these specific uses but have been used in these ART treatments since the early 1980's.

If you have any concerns over the use of any of these agents please discuss these with Scientific Director or your doctor.

2. Culture Medium

The Sage and Vitrolife culture fluids for ART procedures utilise inert salt solutions, non-essential amino acids and an antibiotic (gentamycin). All media are supplemented with 5% Human Serum Albumin (HSA).

A number of other materials including but not limited to such products as Propylene Glycol, Hepes, hyaluronidase, puresperm and D.M.S.O may also be used in the culture and freezing of sperm and embryos. None of these agents were developed or registered for the specific uses but have been used in ART culture treatments since the early 1980's. Penicillin and Streptomycin may also be included in the culture medium but in such minute quantities that even women who have penicillin allergies have not noticed any effects at Concept in the past twenty years.

Human Serum Albumin (HSA) is made from plasma which has been screened or tested for known transmissible agents (virus or prions) such as HIV (AIDS), hepatitis B and hepatitis C and Creutzfeldt-Jakob Disease, there

may be possible contamination with these or other unknown agents. Chemical processing and virus inactivation stages included in the manufacture of these products are believed to render them safe from the risk of infection. Nevertheless the possibility of transmitting these agents must always be considered.

All products are subjected to strict quality control testing by the manufacturers. The Therapeutic Goods Administration has approved these culture media for use in Australia.

If you have any concerns over the use of any of these agents please discuss these with the Scientific Director or your doctor.

I) BIRTH OUTCOMES FOLLOWING ART

Many research studies have examined the abnormality rate in children born after ART but conflicting results have been presented. A review in 2008 has established that there is likely to be an increased risk of abnormalities from 4% -5% in natural conception to 6%-7% after ART. Whether the observed increase in this study is due to the treatment procedures or parental fertility related issues is not known and is currently under investigation.

It has also been suggested that children born after ART procedures may have an increased risk of the very rare genetic disorder known as Beckwith – Wiedemann Syndrome and the childhood cancer retinoblastoma although this has yet to be established.

Beckwith – Wiedemann Syndrome normally occurs at a rate of 1 in 30,000 children. The researchers calculated a frequency of around 4 in 30,000 after IVF/ICSI.

In studying a population of children with retinoblastoma, researchers found that 5 of the children were from ART procedures and from this "estimated" that an increased risk might be apparent. Retinoblastoma normally occurs at a rate of 1 in 17,000. All 5 children were successfully treated and are free of disease.

The research on birth outcomes after ART, suggest that over 93% of children born after ART procedures are free from congenital abnormalities. Follow-up studies on the birth outcomes of ART children are ongoing.



OTHER CONSIDERATIONS

1. No eggs collected at Ovum pick-up.

This rarely happens, due to no access to the follicles, or ovulation has unexpectedly occurred, but is more likely to occur when only 1 or 2 eggs are developed. Although ultrasound and blood test findings may give some indication that follicles contain an egg this is not always the case and no eggs may be found in the fluid collected from the follicles at ovum pick-up.

2. No fertilization.

In some cases it is possible that no eggs will fertilize. There are many causes of failed fertilization. ICSI can be tried after no fertilization using IVF.

3. No embryo development.

Some embryos fail to develop at the required rate and others might arrest in the early stages of development. Many factors are thought to be responsible for poor embryo development.

4. No Implantation.

It is possible that some couples may need many ART attempts before becoming pregnant. Unfortunately some couples will decide to discontinue treatment without becoming pregnant.

5. No Fetal Heart found on pregnancy ultrasound.

Unfortunately a rising pregnancy hormone (HCG) does not always mean that a pregnancy with implantation of an embryo is occurring. A blighted Ovum is a mass of cells that produce HCG and mimics the rising HCG seen in a pregnancy. At ultrasound no fetal heart is found

FURTHER INFORMATION

For further information please contact the your Concept doctor, the Director of Nursing or the Scientific Director.

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