

RISKS AND SIDE EFFECTS WITH DRUG TREATMENTS AND SURGERY ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

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

You must now understand the risks and side effects that may occur with drugs we might suggest you take, and the surgical treatment possibly required for ART ie. IVF, GIFT 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 (the method of choice)

The following complications of surgery have been described:

General

- **Bleeding** ie. 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:** Some Concept patients take antibiotics before and during treatment to help prevent this occurring but the possibility still exists.
- **Anaesthesia:** Risks include allergic rashes, temporary paralysis, vomiting and even, in more extreme cases, death. With young, fit, healthy women these risks are lower than for general surgery patients.

Laparoscopy.

Laparoscopy requires deeper anaesthesia than for Transvaginal Aspiration which may be carried out under sedation with local anaesthesia.

- **"Accidental" bowel injury.** Patients who have had previous surgery (and this applies to many requiring ART) may have bowel adhesions. This increases the risk of injury to the bowel. Any injury must be repaired immediately to avoid peritonitis (infection of the abdomen).
- **"Superficial" haemorrhage.** Some bruising around the puncture marks or abdominal wall is common.
- **"Retained "gas.** The carbon dioxide gas which is placed into the abdomen during laparoscopy may not all be expelled at the end of the operation; again this is more usual in patients with adhesions. This may provide some discomfort under the ribs or in the shoulder. It does not usually last longer than twenty four hours.

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Trans-vaginal Ultrasound Aspiration

- **“Unrecognised bleeding”.** Symptoms should be noted within four hours and this is the basis of our requirement that nursing observation be carried out for this period of time.

In general, the risks of surgery are higher where the patient is obese, smoke excessively or is in a state of poor nutrition.

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 (eg. 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 (eg. Pethidine produces relief of pain but commonly "queasiness" or light headed feelings).

The specific medications which are used in ART are as follows:

1) LUCRIN/SYNAREL

This medication is used to suppress the natural menstrual cycle to allow greater control over the response by the ovaries to gonadotrophins eg. Puregon and Gonal F.

It will produce similar effects to the menopause. It does not produce an early menopause. The main side effects are hot flushes and mood swings.

Stopping the drug will allow the pituitary to recover (similar to the effect of oral contraceptives). Hence the normal menstrual cycle may be delayed.

2) CETROTIDE / ORGALUTRAN

Cetrotide & Orgalutran are pituitary analogues used to inhibit ovulation. They are both subcutaneous injections given when the dominant follicle is approximately 11 to 14 mm in diameter.

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3) GONADOTROPHIN (PUREGON/GONAL F)

These are the injectable drugs which directly stimulate the ovaries to produce more oocytes (eggs). The side effects are very similar to the menopause since these medications are exactly the same hormones as menopausal women have in their own bodies. Patients may notice weariness, mood changes, hot flushes, nausea and headaches. These are temporary and cease as soon as the medications are stopped.

As the ovaries will swell to accommodate the follicles, some patients may notice an increased pelvic pressure. If the ovaries are bound down by adhesions the pressure may be felt as pain. This pressure may continue into the second half of the cycle (luteal phase) and if pregnant, for up to three (3) months.

Very rarely, the ovary may rotate and twist or may bleed. These may produce severe pelvic pain and lead to a requirement for further surgery.

4) HUMAN CHORIONIC GONADOTROPHIN (HCG/PROFASI/PREGNYL)

This medication causes the final maturing of the oocyte before aspiration and is referred to the "trigger" injection.

It may be a slightly more uncomfortable injection than the others.

Sometimes this medication may be used to assist in the "thickening / building-up" of the endometrium on the uterus. This would be given after ovulation as support in the luteal phase of the menstrual cycle.

5) CLOMIPHENE (CLOMID/SEROPHENE)

This oral drug is used to stimulate the pituitary to stimulate the production of extra oocytes.

Occasionally side effects like headache, weariness, occasional visual disturbance and hot flushes may be noticed after a few days on this drug. These cease as soon as patients stop taking it.

Some patients who have used Clomid have suffered breast and ovarian cancers in later life but there is no proven association between the use of Clomid and cancer. (*NOTE: women who delay child bearing until later in life or those who do not have children also have a higher incidence of breast and ovarian cancer in later life and Clomid users are in these groups).

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6) FOLIC ACID

A deficiency of this vitamin may be responsible for neural tube defects (eg. spina bifida). All Concept patients are advised to supplement their diet with folic acid before ART treatment.

7) DOXYCYCLINE

Concept believes that the use of the tetracycline drug, doxycycline will be of benefit in the following situations:

- a) In reducing the chance of pelvic infection during oocyte aspiration.
- b) Protecting the embryo from cervical or vaginal bacteria after embryo transfer.
- c) Protecting the embryo from bacteria in the semen sample during fertilisation.

The side effects of doxycycline may occasionally be:

- a) nausea, vomiting or diarrhoea
- b) skin rashes, including photo sensitivity to sunlight, ie. making some areas of skin more sensitive to sunlight.
- c) Increased chances of vaginal thrush

Women who are susceptible to thrush should use anti-thrush medication at the same time. Patients with side effects should stop the drug and contact the Co-ordinator and their doctor.

8) PROGESTERONE PESSARIES / PROGESTERONE GEL (CRINONE)

The medication progesterone which helps to build & maintain the lining of the uterus (endometrium) can be given in the form of pessaries or a vaginal gel. The pessaries can be used either vaginally or rectally depending on your doctor's orders. The vaginal gel (Crinone) is supplied in single dose applicators.

Some people feel drowsy when using these medications so be careful driving or operating machinery until you know how it affects you.

Common Side effects: (See product insert for more information)

- Perineal pain
- Headache
- Breast enlargement or breast pain
- Sleepiness, feeling emotional
- Constipation, nausea

9) PROLUTON

Proluton is an injectable form of progesterone & can be given instead of the progesterone pessaries or in conjunction with, to assist in the maintenance of the endometrium.

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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 Assisted Reproductive Technology treatments commence.

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 (as described on page 6) 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.

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.

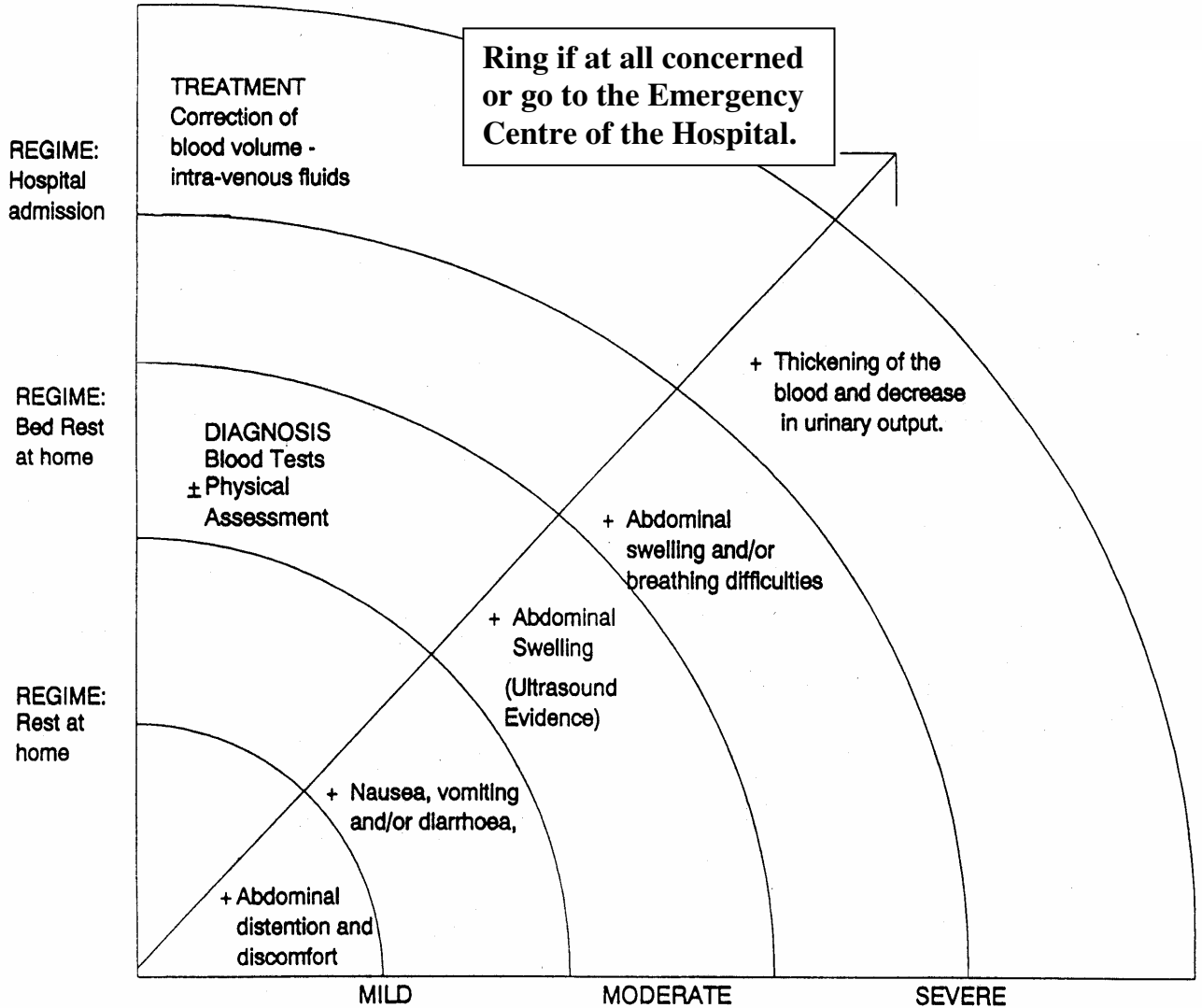
Patients are generally monitored daily and those who have oestradiol (E2) levels approaching 12,000pm/L are considered to be getting close to the risk level. If this occurs, the options are as follows:

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

These will be discussed with you should this situation arise.

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OVARIAN HYPERSTIMULATION SYNDROME



ohsa.bmp

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C) MISCELLANEOUS

1. 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.

2. MULTIPLE PREGNANCY

There is an increased pregnancy rate with an increase in the number of oocytes or 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 but, very occasionally, depending upon age, cause of infertility and previous outcomes three may be replaced. This will be discussed with you before the oocytes or embryos are replaced. With two embryos replaced the chances of twins are about one in five.

There are some possible disadvantages in multiple pregnancies.

- *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.

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3. ECTOPIC PREGNANCY

(i.e. implanting, and growing in the Fallopian tube and not in the uterus.)

It is easy to understand that this can happen in GIFT procedures but it may not be realised that placing embryos into the uterine cavity can also result in this situation. The embryo may frequently transfer to the Fallopian tubes: in 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.

- A patient diagnosed as pregnant following IVF or GIFT 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.

D) 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. Both 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 Percoll, Nycodens and Isolate.

These agents have been in use routinely, to improve the fertilizing capacity of sperm, for a number of years.

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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 Dr.Bellinge or your doctor.

2. CULTURE MEDIUM

The Quinn's Advantage and HTF culture fluids for A.R.T. 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, PVP, hyaluronidase puresperm and D.M.S.O may also be used in the culture and in the 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 seventeen 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 the media such as the Quinn's Advantage Media for use in Australia even though it is not a listed or registered product.

If you have any concerns over the use of any of these agents please discuss these with Dr. Peter Burton or your doctor.

E) BIRTH OUTCOMES FOLLOWING ART

At present it is not known whether ART procedures such as ICSI or IVF increase the risk of a child being born with a congenital abnormality. Many research studies have examined this issue but conflicting results have been presented. In a study of nearly 6000 children born after IVF or ICSI, researchers in Belgium did not observe any increased risk of major malformations or neonatal complications. In a smaller study from Western Australia the researchers reported an observed increase in abnormalities in children born after ICSI and IVF.

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Whether the observed increase in this study is due to the treatment procedures or parental fertility related issues is not known, although recent reports suggest that parental factors might be involved. In early 2003, separate reports from Britain and the Netherlands have suggested that children born after ART procedures have an increased risk of the very rare genetic disorder known as Beckwith – Wiedemann Syndrome and the childhood cancer retinoblastoma. Beckwith – Wiedemann Syndrome normally occurs at a rate of 1 in 30,000 children. The researchers studied 149 children with the syndrome and found that 6 were conceived by ART, representing a calculated frequency of around 4 in 30,000. In studying a population of children with retinoblastoma, researchers from the Netherlands 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 in late 2002 were free of disease.

Among studies from around the world on birth outcomes after ART, the consistent finding is that over 95% of children born after ART procedures are free from congenital abnormalities. Follow-up studies on the birth outcomes of ART children are ongoing.