



Drugs Used in Infertility and the Assisted Reproductive Technologies (ART)

Approximately 100,000 couples in Australia marry each year and, typically, one couple in six will have infertility defined as the inability to conceive a pregnancy despite one year or more of unprotected intercourse. General practitioners, specialists, patients and media commentators should all be aware that mother nature is not a perfect midwife. Throughout Australia 1 baby in 40 will have a birth defect. There is no clear evidence that infertility medicines, if properly used, increase this risk. Furthermore, cancers do occur in mothers and babies - breast cancer is newly diagnosed in approximately 150 Queensland women 40 years or younger every year. There is no clear evidence that infertility medicines increase this risk. The advances in the ART procedures have been considerable and greatly assisted by the use of a number of endocrine medicines. This article briefly reviews the use of the common medicines in ART procedures and describes the common side-effects about which a patient may consult a doctor.

Clomiphene Citrate (Clomid: Merrill Dow; Serophene: Serono)

Clomiphene citrate (Clomid: Merrill Dow; Serophene: Serono) is indicated for the treatment of chronic anovulation in carefully selected infertile women who wish to become pregnant. In ART it has also been used in combination with human menopausal gonadotrophin to attempt to stimulate multiple follicular development in order to achieve multiple oocyte collection and therefore increase the patient's chance of pregnancy. In this circumstance, Clomiphene Citrate is used at 100mg (2 tablets) per day from day 2 to day 6 of the ART stimulation cycle, day 1 being the first day of menstruation. The primary action of Clomiphene Citrate is to act as an anti-oestrogen in the human. At the pituitary gland this leads to release of follicle stimulating hormone (FSH) and luteinising hormone (LH), and it is this rise of serum FSH and LH levels which will hopefully help in multiple follicular growth during the ART treatment cycle. Clomiphene Citrate has been used to treat chronic anovulation in carefully selected infertile women for over 30 years in Australia. It has been used in connection with ART treatment for approximately 15 years. As it stimulates the ovaries indirectly via the pituitary, it may cause ovarian enlargement, especially in patients with polycystic ovarian syndrome. Patients with this syndrome are more sensitive to any ovarian stimulant and should be given the smallest possible dose of Clomiphene Citrate. The more common side effects associated with Clomiphene Citrate are hot flushes and hot sweats, related to its anti-oestrogenic action. Ovarian enlargement may be associated with abdominal discomfort and bloating. Patients suffering this should be assessed for ovarian hyperstimulation syndrome (OHSS) (see separate fact sheet) following an ART cycle. Visual symptoms, described usually as blurring, spots or flashes are occasionally reported. Large trials of infants born to mothers who took Clomiphene Citrate have reported no increase in congenital malformations compared with control populations.

Gonadotrophin Releasing Hormone Agonists (GnRH-A) & Follicle Stimulating Hormone (FSH)

A number of GnRH agonists are available in Australia including Nafarelin acetate (Synarel:Searle) and Leuprorelin acetate (Lucrin:Abbott). They all cause an initial stimulation of pituitary FSH and LH release and, with continued usage, have the property of down regulation or switching off pituitary hormone secretion. This has particular advantages in ART as it eliminates the surge of serum LH which leads to ovulation. This has led to the use of GnRH agonists in conjunction with Human Menopausal Gonadotrophins in most Australian ART patients in regimens known as the Flare (short) and Down Regulation (long) protocols.

Flare Stimulation - This short protocol of GnRH agonist treatment makes use of the so called 'flare' effect of gonadotrophins induced by the agonist. This means that prior to eventual pituitary suppression the agonist causes an initial surge of FSH/LH. The folliculogenesis is maintained by exogenous injections of genetically engineered FSH (Gonal-F: Serono; Puregon: Organon). The agonist can be given by intranasal spray (Synarel) or by subcutaneous injection (Lucrin) from day 2 of the cycle. The FSH is given from around day 4 onwards. Doses of FSH depend on ovarian response and are individually adjusted. Serum oestrogen and progesterone levels are measured and follicular growth monitored by ultrasound during stimulation. Once follicular size is adequate, Human Chorionic Gonadotrophin (HCG) (Ovidrel:Serono or Pregnyl:Organon) is administered intramuscularly to achieve final oocyte maturation and ovulation.

Down Regulation Stimulation - This long protocol of GnRH agonist treatment achieves full but temporary suppression of the ovaries, similar to the menopausal state of the ovaries and endometrium. It is achieved after 10-14 days of daily GnRH agonist injections commencing in the luteal phase (approx. day 21) and is followed by a withdrawal bleeding. The agonist injections are continued combined with FSH injections to boost follicular growth, again with monitoring. It differs from Flare largely in duration. The Flare protocol takes around 10 days while Down Regulation takes 22-25 days. They achieve similar results so Flare is usually the treatment of first choice. Down Regulation is used in patients who have responded poorly to Flare, who have significant endometriosis, or whose egg pickups need to be arranged for a particular time.

Contraindications and Precautions

FSH may only be prescribed in Australia by accredited specialists in Obstetrics & Gynaecology or Endocrinology. They are contraindicated where gonadotrophin levels indicate ovarian failure, in severe thyroid or adrenal

dysfunction, with ovarian testicular or pituitary tumours, with unexplained abnormal bleeding, in the presence of ovarian cysts, and in pregnancy. Very high doses of GnRH agonist (Lucrin) in rats and mice have been associated with pituitary hyperplasia and benign pituitary adenomas but doses used in human ART are less than one hundredth of those/kilogram/day. Studies on bacterial and mammalian systems reveal no mutagenic effects but lethal effects on rat and rabbit embryos have been noted. GnRH agonists therefore should not be prescribed in pregnancy. Despite precautions some human pregnancies have been reported during Lucrin use. Although there were no fetal deformities, there was a high rate of spontaneous miscarriage. During down regulation treatment, sexual intercourse should be avoided or condoms used.

Multiple Births

Following stimulation of several ovarian follicles and the transfer of more than one egg or embryo, multiple pregnancies are common. Current policy is to transfer two eggs (at GIFT) or two embryos (at IVF-ET). The incidence of twins is approximately 15% and triplets 2% of all ART pregnancies.

Birth Defects

The incidence of birth defects following ART (2.5%) does not differ significantly from the normal Australian population (3.7%). The Australian and New Zealand Perinatal Statistics Unit detected an increased incidence of spina bifida and great vessel translocation but 1989 world figures for 14,000 ART births showed no increase in any birth defect.

Adverse Effects

The majority of adverse effects caused by ART medicines are mild and well tolerated by patients. The GnRH agonists induce a reversible menopause with the possibility of hot flushes, peripheral oedema, dizziness, headache, nausea and breast tenderness. The growing ovarian follicles can cause lower abdominal pain and bloating. More severe signs of ovarian enlargement may be associated with Ovarian Hyperstimulation Syndrome (OHSS) (see separate fact sheet). Local skin irritation at the injection site may occur with any of the ART drugs.

GnRH antagonists - Cetrorelix, the drug in Cetrotide (Serono) & Ganirelix, the drug in Orgalutran (Organon)

Drugs used in several different injection protocols towards the end of follicle stimulation to stop the natural ovulation of eggs from follicles. They are used when it has been decided not to use GnRH agonists. Once follicular size is optimal, Human Chorionic Gonadotrophin (HCG) (Pregnyl:Organon;Ovidrel:Serono) is administered intramuscularly to achieve final oocyte maturation and ovulation.

Oral Contraceptive Pills

In addition to their designed role of prevention of pregnancy, the contraceptive pill is also used in ART programmes to regulate and modify the timing of cycles during preparation for ART procedures. Their use will have no untoward effect on the chances of achieving a pregnancy from the treatment cycle.

Danazol (Danocrine)

This hormonal drug, used for periods of up to six months or longer, suppresses ovarian function allowing the endometrium of the uterus (and any other endometrial tissue outside the uterus - the endometriosis) to regress. It is often used preceding ART treatment. Side effects include hot flushes, increased weight, acne and increased hair growth.

Human Chorionic Gonadotrophin (HCG)

The hormone HCG (Pregnyl: Organon) which is produced by the placenta during pregnancy, has a similar function to luteinizing hormone (LH). When injected it triggers ovulation in the same manner as the mid-cycle LH surge. It is used for this reason in many ART procedures. It may increase the effects of ovarian hyperstimulation after ART procedures (see separate fact sheet on OHSS). A genetically engineered version (Ovidrel:Serono) is also available.

Luteinising Hormone (Luveris)

A genetically engineered version of the natural hormone LH which triggers ovulation. It may be used for that purpose or given in small doses throughout ovarian stimulation in particular patients.

Progesterone (Prolutin; Pessaries; Crinone)

To support the second half (luteal phase) of the menstrual cycle during which implantation occurs, progesterone may be administered in the form of vaginal pessaries, vaginal gel (Crinone) or intramuscular injections (Prolutin). It is also used to create conditions for implantation for women without ovarian function and in women preparing to receive donated eggs or embryos.

Summary

With modern technologies, ART treatment can be considered safe and performed as day procedures. The most common adverse effects are not considered exceedingly difficult by most patients. Abdominal discomfort is temporary and only moderately more inconvenient than 'normal' cyclic symptoms. The hot flushes can be disturbing but after reassurance as to their reversibility they are tolerated well. Severe OHSS is very rare and is the principal major complication of ART. The risk of severe OHSS can be minimised by careful selection, monitoring and adjustment of ovarian stimulation regimes.