

# Drugs and Infertility Treatment

Fact Sheet

09

updated June 2015

The successful regulation of the female menstrual cycle, including ovulation, to achieve fertility depends on the correct interaction of the hypothalamus and pituitary gland in the brain, the ovaries and the uterus. The hypothalamus secretes gonadotrophin releasing hormone (GnRH) in a pulsatile fashion that acts locally on the pituitary gland to stimulate secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH). FSH and LH in turn stimulate the ovaries and are important for the normal growth of ovarian follicles, oestrogen secretion, maturation of the egg, ovulation and later progesterone production. Hypothalamic function can be affected by stress, exercise, weight loss and drugs such as narcotics and antidepressants. Implantation of the embryo can be affected by infection and possibly by endometriosis.

Many drugs can affect the normal controlling mechanisms of ovulation by either suppressing ovulation or inducing ovulation.

## Oral Contraceptive Pills

Many types of the Pill are now available and are obviously more commonly used to prevent unwanted pregnancies. They may also be used to regulate and time cycles in preparation for planned stimulation for egg collection. For women who have endometriosis (a condition where the lining of the uterus is outside the uterus) the pill can be useful in treating pelvic pain.

## Bromocryptine (Parlodel)

Unusually high prolactin levels can prevent regular ovulation and cause milk production in the breasts. A CT or MRI

scan is usually requested to examine the pituitary gland. If no abnormality is present then bromocryptine is prescribed to reduce prolactin secretion by the pituitary gland and is usually taken as a tablet at night. Side effects include nausea and low blood pressure.

## Danazol (Danocrine)

This is a synthetic hormone used as one therapy for the treatment of endometriosis. It acts by suppressing ovarian function causing a regression of the endometrium in the uterus (i.e. stops menstruation) and hopefully also the extra patches of endometrium outside the uterus (endometriosis). This oral therapy usually lasts six to nine months. Side effects include hot flushes, weight gain, acne and hirsutism (increased hair growth). Danazol due to its side effects is not prescribed as often these days.

## GnRH Antagonists (Orgalutran, Cetrotide)

In contrast to the GnRH agonists these compounds block the receptors on the pituitary to prevent the release of gonadotrophins. This results in a rapid, profound and rapidly reversible suppression of the ovaries. Both agents are administered daily as a subcutaneous injection. Orgalutran comes as a solution in a pre-filled syringe. Cetrotide comes as a powder and solution that is mixed immediately prior to administration. GnRH antagonists are used in two ways: (i) to suppress conditions that may be hormonally controlled such as uterine fibroids and endometriosis. (ii) to suppress the pituitary FSH & LH production in cycles of IVF. This prevents the midcycle LH surge and unplanned ovulation. When used in combination with injected gonadotrophins this allows for more reliable timing of the

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egg collection and usually an increased number of eggs being available for IVF. Treatment is commenced approximately five days after commencement of the FSH and continued throughout the duration of the FSH administration.

## GnRH Agonists (Lucrin, Synarel)

These synthetically produced compounds are exceptionally active forms of GNRH that paradoxically “overstimulate” the pituitary to the extent that FSH and LH secretion is completely suppressed. This quickly results in suppression of the ovaries. Lucrin is administered daily by subcutaneous (just under the skin) injection or intramuscularly as a monthly depot (long lasting) injection. Synarel has similar effects and is administered by nasal spray twice a day. GNRH agonists are used in two ways: (i) to suppress conditions that may be hormonally controlled such as uterine fibroids and endometriosis. (ii) to suppress the pituitary FSH & LH production in cycles of IVF. This prevents the midcycle LH surge and unplanned ovulation. When used in combination with injected gonadotrophins (see below) this allows for more reliable timing of the egg collection and usually an increased number of eggs being available for IVF.

## Antibiotics

Broad spectrum antibiotics may be prescribed for infections of the female reproductive tract such as pelvic inflammatory disease. Sites of infection may include the tubes, the uterus or the cervix. Chlamydia should be specifically excluded.

## Drugs used in female infertility treatments

### Clomiphene (Clomid, Serophene)

This is the most commonly used fertility drug for women with irregular cycles or anovulatory cycles (where no ovulation

occurs). Its exact mode of action is unknown but it results in increased production of FSH by the pituitary gland. The dose is usually 50-100mg daily for five days early in the cycle. Seventy per cent of women taking Clomid will ovulate and half of those who ovulate will conceive by six months. Side effects include nausea, hot flushes, gastrointestinal upset, bloating, headache, dizziness, visual disturbances, mood swings and thickening of cervical mucus. Multiple pregnancy occurs in ten per cent of conceptions. Clomid is not usually tried for more than 12 cycles.

### Letrozole

This is a newer drug that can be used to initiate ovulation like clomiphene. It is not covered on the PBS and is therefore more expensive, it may be more effective and its biggest advantage is its lower risk of multiple pregnancy compared to clomiphene.

### Recombinant FSH (Putegon, Gonaf)

Recombinant FSH is manufactured synthetically by recombinant DNA technology. Unlike the urinary compounds Gonaf and Puregon contain pure FSH. Both these compounds are administered daily as a subcutaneous injection. Gonaf comes as a powder and solution in either single use ampoules or a multi-dose vial for reconstitution and administration. Puregon comes as a premixed solution in either vials or a cartridge to be used in the Puregon Pen device. These FSH injections may be used (i) in low doses for women who are unsuccessful using Clomid but still trying to conceive at home or (ii) in higher doses for women undergoing IVF as they act directly on the ovary to stimulate multiple follicular growth. Treatment is usually started a few days after the start of a period and dosage is adjusted according to the ovarian response. The risk of multiple pregnancy is higher with FSH treatment and so frequent monitoring of cycles by ultra-

sound and measuring hormone levels is usual. Side effects include local irritation at the site of injection, bloatedness, mood swings, ovarian hyperstimulation (see below) and multiple pregnancy.

### Human Menopausal Gonadotrophin (Menopur)

The substrate for production of HMG is extracted from the urine of post-menopausal women. Extensive processes of extraction and purification result in derivation of the medicinal compound. HMG contains a 1:1 ratio of FSH activity and LH activity, with the majority of the LH activity being derived from hCG secreted from the post-menopausal pituitary. There is evidence to suggest that for some women, additional LH activity in the form of hCG may improve pregnancy rates after IVF, possibly due to an effect on endometrial receptivity or oocyte quality. HMG is administered by daily subcutaneous injection. HMG may be used (i) in low doses for ovulation induction for both WHO type I hypogonadal hypogonadism or (ii) WHO type II anovulation associated with polycystic ovary syndrome, with or without intrauterine insemination or (iii) in higher doses for women undergoing IVF to stimulate multiple follicular growth. The dose of HMG must be determined according to the predicted ovarian response. This should be assessed using serum AMH (anti-Mullerian Hormone) and/ or ultrasound measurement of antral follicle count. Underdosing results in absence of response while overdosing may result in ovarian hyperstimulation syndrome, a potentially lethal condition. Ovarian stimulation with any FSH containing preparation carries risk of multiple ovulation and hence multiple pregnancy, so frequent monitoring with ultrasound and/or measurement of serum estradiol is mandatory. Side effects include local irritation at the site of injection, bloatedness, mood swings, ovarian hyperstimulation (see below) and multiple pregnancy.

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## Human Chorionic Gonadotrophin (HCG – Profasi, Pregnyl)

HCG is a hormone made by the placenta in pregnancy and is biologically similar to LH. When injected intramuscularly, HCG triggers ovulation by mimicking the natural midcycle LH surge. After ovulation HCG may be given to boost the ovary's production of progesterone to aid implantation. HCG may worsen the side effects of ovarian hyperstimulation in an IVF cycle (see below).

## Progesterone (Crinone, Pessaries)

To support the second half of the cycle (the luteal phase) and implantation progesterone may be administered in the form of intramuscular injections (not readily available in Australia) or vaginal pessaries. This type of hormonal support may also be combined with oestrogen replacement for women who have no ovarian function and require artificial preparation of the uterus ready to receive donated eggs.

## Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a complication of ovulation induction. It is characterised by ovarian enlargement, bloating, abdominal pain and if severe may cause a difficulty in breathing and reduced urine output. OHSS is more common in younger women and in conception cycles. It is particularly related to high oestrogen levels before ovulation and HCG administration in the luteal phase. The best approach to OHSS is to prevent it! When a woman is considered at risk of developing OHSS in a treatment cycle, the cycle is likely to be cancelled and the HCG trigger withheld. Alternatively, in IVF, egg collection can be performed and all embryos frozen in order to avoid transfer and the need for further hormone support. If embryo transfer is performed then progesterone may be substituted for HCG as a means of luteal support. If the woman has un-

dergone an antagonist cycle an agonist trigger can be given dramatically reducing the risk of OHSS. The freezing of embryos is also recommended.

Treatment may involve admission to hospital if severe, otherwise rest, adequate pain relief and conservative observation will usually be sufficient to allow the condition to resolve slowly and naturally over seven to ten days. In the event of a pregnancy the hyperstimulation may continue for several weeks (see specific AccessA factsheet on OHSS)

## Drugs and medications that affect male infertility

Many drugs potentially affect male fertility and the underlying illness could also interfere with sperm production and sexual performance.

Drugs including cancer chemotherapy agents, methotrexate, salazopyrin and some antibacterial agents usually reduce sperm production, sometimes irreversibly. Anabolic steroids, testosterone, narcotics, alcohol and frequent use of marijuana may affect sperm production. These and tranquillisers, anti-depressants and anti-hypertensives may also interfere with erections and ability to ejaculate, and may be associated with retrograde ejaculation in which the bladder neck fails to close so the semen passes into the bladder.

## How is a drug effect detected?

The possible involvement of drugs in male infertility or sexual disorders is usually detected by questioning the patient. Semen analysis may show specific abnormalities. Stopping the use of recreational drugs or, for medications, reducing the dose or changing to another form will reverse the effects of some of the agents over several weeks.

## Drugs used in male infertility treatments

Medically treatable causes of male infertility are rare. Sperm autoimmunity is the commonest, followed by gonadotrophin deficiency, genital tract inflammation and some forms of sexual disorders.

### Prednisolone

This or other glucocorticoids can be given for sperm autoimmunity. Sperm antibody levels fall and sperm number, motility and mucus penetration increase in about 50 per cent of men treated with high doses over several months. About 25 per cent of female partners conceive during the treatment. Side effects may be severe, especially aseptic necrosis of the hip.

### FSH or HCG

Rarely a male can have a pituitary problem resulting in a deficiency in the secretion of FSH and LH. This can arise from either genetic causes or pituitary damage and can be treated with FSH and HCG injections. Treatment often takes many months to develop sperm production in the testes but it is frequently successful in producing pregnancies.

### GnRH

This is delivered by pulsatile injection can also be used as an alternative treatment to FSH and HCG for some forms of deficiency of production of FSH and LH by the pituitary gland. Pulsatile injection requires carrying a pump 24/7 which can be cumbersome but is effective.

### Bromocryptine

As in the woman, this can be used to lower pathologically elevated levels of prolactin.

### Antibiotics

These can be given for infections in the reproductive tract of the male. Specific antibiotics are used where possible, otherwise doxycycline, erythromycin, norfloxacin or trimethoprim are used.

## Vasodilator injections

These drugs are injected directly into the penis to increase blood flow. This can be used to treat some infertile men with inadequate sexual performance. Occasionally retrograde ejaculation can be treated with antihistamine and antidepressant tablets.

## Empirical treatments

Many approaches have been used in the past in the attempt to treat defects of sperm production or function, other than those already described. These include the hormones and other agents mentioned above and also testosterone, anti-oestrogens, vitamins, minerals and other nutritional supplements. None of these have proved to be effective by adequately controlled clinical research.

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