



INFERTILITY THERAPY

Over the past few years the world of infertility treatment has exploded, particularly in the area of assisted reproduction techniques (ART). As a result, an increasing number of medications are prescribed as components of ART treatments. Fertility therapies may include medications for ovulation induction, spermatogenesis induction and adjuvant ART medications prescribed for use in in-vitro fertilization (IVF) and intrauterine insemination (IUI). Consequently, it is important that pharmacists are aware of these treatment regimens in order to understand why these medications are prescribed and counsel accordingly.

Commonly Prescribed Medications - Female Treatments ^{1,2,3,4}

A. Treatment of underlying cause(s) of infertility

Treatment type	Drug name	Action	Dose
Hormonal treatments	Bromocriptine (Parlodel®), generics), cabergoline (Dostinex®)	Long-acting dopaminergic agonists used to inhibit prolactin production in the pituitary gland. Excess prolactin interferes with ovulation.	Individualized doses until prolactin levels have normalized.
	Methimazole (Tapazole®), levothyroxine (Synthroid®, Eltroxin®)	Thyroid hormone imbalances interfere with pituitary sex hormone production.	Individualized doses to normalize thyroid stimulating hormone (TSH).
Polycystic Ovary Syndrome Treatments (PCOS) ⁵	Metformin (Glucophage®, generics)	Increases the sensitivity of body tissue to insulin effects, decreases high levels of testosterone. Facilitates ovulatory cycles. May reduce 1 st trimester pregnancy loss in women with PCOS.	1500-2000mg daily in divided doses starting prior to conception and continuing throughout pregnancy.
Endometriosis treatments ⁶ (A recent review concluded that the evidence of improved fertility is NOT sufficient to justify the risk of adverse effects when these agents are used for this purpose,) ⁷	Gonadotropin Releasing Hormone (GnRH) agonists	Ovarian suppression due to slowing of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) production and/or release. Also decreases production of estradiol.	Individualized doses.
	Danazole (Cyclomen®, generics)	A synthetic steroid analog. Inhibits midcycle LH and FSH surge from pituitary gland thereby suppressing ovarian hormone production	Individualized doses.
	Medroxy-progesterone (Provera®, generics)	To treat abnormal uterine bleeding and endometriosis.	Taken for 5-13 days near the end of the menstrual cycle.

B. Treatment of Infertility ^{1,2,3,4}

Treatment type	Drug name	Action	Dose
Synthetic ovulation stimulants; used with or without assisted reproduction techniques (ART).	Clomiphene citrate (Clomid®, Serophene®)	Mixed estrogen agonist-antagonist. Binds to estrogen receptors → increased secretion of GnRH → increased LH and FSH → ovarian follicle maturation and the LH surge which triggers ovulation.	50 mg daily for 5 days starting on day 4 or 5 of menstrual cycle (if no bleed, can start anytime). The dose can be increased to 100 mg daily if ovulation fails.
	Tamoxifen (Tamofen®, Novaldex D®, generics)	As above	20 mg daily for 5 days starting on day 4 or 5 of cycle as above.
	Letrozole (Femara®)	Aromatase inhibitor. Inhibits estradiol production in liver → increased FSH	2.5 – 5 mg days 3 – 7 of cycle.
	Gonadorelin (Lutrepulse PWS®)	Short-acting analog of Gonadotropin Releasing Hormone (GnRH).	5 ug given IV or SC every 60-90 min (using programmable pulsatile pump) for 10-20 days.
Gonadotropins (sex hormones) All are indicated for anovulation, hypogonadotropism and failure to ovulate/ conceive with synthetic stimulant. Also used in ART to produce several viable follicles.	Human Chorionic Gonadotropin (hCG) (Profasi®, Pregnyl®)	A natural hormone produced by the placenta with an action identical to LH. Usually used in combination with other gonadotropins to trigger ovulation.	A single hCG injection (5,000 IU – 10,000 IU) usually follows a regimen of hMG or urofollitropin injections. Doses are variable, depending on patient characteristics.
	Choriogonadotropin alfa (Ovidrel®)	Recombinant hCG	As above.
	Human Menopausal gonadotropin (hMG) (Pergonal®, Humegon®, Repronex®)	An LH/FSH combination extracted from the urine of postmenopausal women. Usually given along with hCG to stimulate a natural LH surge and ovulation.	Dose depends on patient characteristics, generally 75 IU – 150 IU IM daily for 7-12 days.
	Urofollitropin (Fertinorm®, Metrodin®)	Purified FSH. Usually given in patients with low FSH and high LH levels. Given along with hCG to stimulate LH surge and ovulation.	Injected for 7-12 days to prompt ovaries to produce multiple follicles. Doses vary.
	Follitropin (Gonal-F®, Puregon®)	Recombinant FSH. As above, to stimulate formation of multiple follicles.	As above.
	GnRH agonist (Lupron®, Suprefact®)	Used at the beginning of an IVF treatment to allow for a controlled stimulation cycle by reducing LH and FSH production and release prior to IVF.	SC injections daily.
Oral contraceptives	Ethinyl estradiol / progestin	May be used in IVF cycle to suppress a woman's natural cycle, preventing ovulation in preparation for ovarian stimulation and cycle synchronization.	Various types available.

***Caution patients – women receiving hCG injections will report false positives with home pregnancy tests since these detect hCG in urine. Do not recommend home pregnancy tests for use with these patients.**

Commonly Prescribed Medications - Male Treatments ^{1,8,9,10}

Treatment Type	Drug name	Action	Dose
Underlying causes / contributors	Bromocriptine (Parlodel®, generics), Cabergoline®	Hyperprolactinemia may decrease sperm production and impede erection and ejaculation functions.	Individualized doses
	Levothyroxine (Synthroid®, Eltroxin ®)	Hypothyroidism is associated with abnormalities in spermatogenesis.	Individualized doses
Increase sperm quantity / quality	Gonadotropins or GnRH analogs (Gonal-F ®)	Hypogonadotropic hypogonadism treatment. Induces production of sperm, provided the cause of low counts is not due to primary testicular failure.	Dose is individualized, usually given in conjunction with hCG injections three times a week.
	Clomiphene citrate (Clomid®, Serophene®)	Increase hypothalamic secretion of GnRH, therefore increase LH, FSH and testosterone. Unfortunately, mainly only uncontrolled studies report a higher percentage of patients with improved semen quality and subsequent pregnancies	12.5-50 mg daily or with 5 day rest each month. Discontinue if no response in sperm after 6 months.
	Tamoxifen citrate (Tamofen®, Novaldex D®, generics)	As above. Only one study; tamoxifen in combination with testosterone resulted in improved sperm quality and an increased incidence of pregnancy.	10 mg BID with testosterone undecanoate 40 mg TID
	Testosterone – androgenic anabolic steroid	Large doses of exogenous testosterone have been given parenterally to suppress pituitary gland action. Once stopped, the system will rebound and improved spermatogenesis will result.	Individualized doses
	Growth Hormone or its releasing factor	Recent evidence suggests that growth hormone induced insulin like growth factor-1 may be important for spermatogenesis.	Ongoing studies

Other Drugs Associated With Infertility Treatment

1. **Progesterone** – used to help prepare the lining of the uterus for the arrival of the embryo. It may be needed for full maturation of endometrium. Can be given as capsules, vaginal suppository 25 mg once or twice a day commencing immediately post ovulation, or daily IM injections of progesterone in oil. ¹
2. **Estrogens** – used to maintain follicular and endometrial development for a frozen embryo transplant. Administered orally, vaginally or topically. If pregnancy occurs, estrogen may be continued for 10 weeks to ensure the placenta is fully developed. ³
3. **Sildenafil** – may be used to increase blood flow in uterus and stimulate the development of endometrium in order to increase the chance of pregnancy. ³

4. **Dexamethasone, methylprednisolone** – Dexamethasone may be taken with ovulation stimulation drugs to help the ovaries be more receptive to treatment by decreasing androgen production.¹¹ It is taken daily starting on day 2 of the menstrual cycle continuing until ovulation. Methylprednisolone may also be used for anti-inflammatory treatment after IVF oocyte retrieval. It is usually taken daily beginning on the day of retrieval and ending on day of embryo transfer.¹²
5. **Antibiotics** – Doxycycline or tetracycline are the empiric treatments of choice for patient and partner when cervical mucus appears to be affected by cervicitis and inflammatory changes. These antibiotics may also be prescribed to each partner during an IVF cycle to control bacteria that may affect implantation in the female and sperm quality of the male.¹⁰
6. **Aspirin 81mg** – Taken before and during IVF cycles to improve blood circulation to the endometrial lining. (Evidence is anecdotal.)¹³

Over-The-Counter Products

Supplies:

- Syringes, needles, alcohol swabs, sharps containers
- Ovulation predictor kits, basal body thermometers may both be used to determine ovulation time for the exact timing in ART therapies.

Medications:

- Guaifenesin, 200mg TID from day 5 to day of ovulation may improve cervical mucus quality. (Evidence is limited.)¹⁴

Supplements:

- Folic acid 0.4 mg – 1.0 mg daily for women to reduce risk of neural tube defects in fetus.³ Start before pregnancy is attempted.
- Trace amounts of zinc and selenium are required for optimal sperm production and function; however there is no evidence that supplementation improves fertility.
- Infertile men may have increased levels of reactive oxygen in their reproductive tract, which can cause lipid peroxidation damage to sperm membranes.¹⁵ Various antioxidants including glutathione 600mg/day, vitamin E 400-1200 IU/day and vitamin C 500 mg/day have been studied but the results to date are inconclusive.¹⁵

Herbal:^{1,16}

- Dong Quai, Wild Yam, Black Cohosh, Chasteberry Tree, Evening Primrose Oil - All purported to aid in enhancing female fertility although not supported by scientific evidence.
- CoQ10, Ginseng and Yohimbe bark – all purported to aid in enhancing male fertility although not supported by scientific evidence.

Suggested Reading

1. Roedler R & Nystrom M. *Infertility: a review of its treatment*. Pharmacy Practice 2004;20 (December): Continuing Education Lesson.
2. Berry M. *Infertility: an update*. CCCEP Home Study Program 2003 Lesson 4. Available on request from the CPDP office – t: (306) 966-6350; f: (306) 966-6377.
3. National Guideline Clearinghouse. www.guideline.gov . (Search words “female infertility” and “male infertility”).
4. E-Medicine CME. *Infertility* www.emedicine.com/med/topic3535.htm . (Registration is free)

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References are posted with the newsletter on the Saskatchewan Drug Information Service website,

www.usask.ca/druginfo .

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3. Roedler R, Nystrom M. Infertility: a review of its treatment. *Pharmacy Practice Continuing Education Lesson* 2004; December.
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12. Lainas T, Petsas G et al. Administration of methylprednisolone to prevent severe ovarian hyperstimulation syndrome in patients undergoing *in vitro* fertilization. *Fert Steril* 2002;78:529-33.
13. Victoria Fertility Centre. www.victoriafertility.com/services/in-vitro-fertilization.htm. (Last accessed 15 March 2005.)
14. Check JH, Adelson HG, Wu CH. Improvement of cervical factor with guaifensin. *Fertil Steril*. 1982;37(5):707-708.
15. Agarwal A. Role of antioxidants in treatment of male infertility: an overview of the literature. *Reproductive BioMedicine Online*. 2004;8:616-27.
16. Natural Medicines Comprehensive Database. Various monographs. www.naturalmedicines.com (Accessed March 10, 2005)