EXOGENOUS HORMONE ADMINISTRATION

Hormones administered for medical purposes or as performance enhancers, with potentially negative effect on fertility.

⚠️ Risk factor ♂ Male & Female

About Exogenous hormone administration

Exogenous hormone administration is the use of various hormones or their analogues (substances working similarly) either in medical treatment, or as performance-enhancing drugs. The term exogenous refers to any hormones entering the organism that are not produced by the patient’s own endocrine glands. The many uses of hormones in medical treatment are summarily called hormone therapy or hormonal therapy. Some hormones or analogues, most notably anabolic steroids, are also frequently used as performance enhancers, and are associated with significant risks for the user’s future health and fertility.

Uses of hormones and their analogues in medical therapy include:

- hormonal replacement therapy
- menopausal hormone therapy, for women suffering from menopausal symptoms
- androgen replacement therapy, for men with low testosterone levels
- growth hormone in growth hormone deficiency
- thyroid hormones in hypothyroidism (decreased function of the thyroid gland)
- glucocorticoids as immunosuppressant, anti-edematous and anti-inflammatory drugs
- progesterone and progestins in gynaecological disorders
- human chorionic gonadotropin in fertility treatment

Out of these, the hormones affecting fertility the most or being prescribed for fertility-related reasons include human chorionic gonadotropin, estrogen, progesterone (Pic. 1) and progestins, and various combinations of estrogen and progestins in hormonal contraception. Both natural and synthetic androgens (male sex hormones, such as testosterone) are used as hormonal replacement therapy in men with testosterone deficiency or for their anabolic (promoting tissue growth and regeneration) effects. However, they are also widely used as performance-enhancing drugs (Pic. 2), which can lead to severe complications in future life.

**Estrogen**

Estrogen is the primary female sex hormone. Estrogen is primarily used in combination with progesterone or progestins in hormonal contraception and in hormonal replacement therapy. Hormonal replacement therapy utilizes administration of a combination of estrogen and progestins to postmenopausal women, who experience various symptoms of menopause (Pic. 3) caused by a decline in circulating estrogen. The therapy prevents postmenopausal osteoporosis (loss of bone density, leading to frequent fractures) and also treats the symptoms, such as hot flashes, vaginal dryness due to vaginal atrophy, night sweats and irritability.

The administration of estrogen, however, can lead to several adverse effects, depending on the dosage. Common side effects include breast tenderness, headache, retention of fluids and subsequent edemas. Exogenous estrogen administration can also lead to the state of hyperestrogenism (elevated estrogen levels in the body) with its consequences. If estrogens are used in males (such as in the treatment of certain types of cancer) the may cause gynecomastia (enlarged breasts), sexual dysfunction, testicular atrophy and even infertility.
Progesterone and progestins

Progesterone is a hormone that is normally found in women and it reaches particularly high levels during pregnancy. Progestins are synthetic drugs that mimic the biological actions of progesterone and they have been widely prescribed to women.

Progestins are used either alone in the progestin-only type of hormonal contraception (also known as mini-pill), or in combination with estrogen in combined hormonal contraception and in hormonal replacement therapy. The administration of progestins together with estrogens lowers the risk of some adverse effects of estrogen, such as blood clots or endometrial hypertrophy (excessive growth of the uterine lining) and endometrial tumors.

Furthermore, progesterone and progestins are used to treat many gynaecological disorders, such as secondary amenorrhea (cessation of menstrual cycle in a woman who has menstruated before), dysfunctional uterine bleeding (uterine bleeding caused by hormonal imbalance) or endometriosis (presence of endometrial tissue in abnormal locations). Progestins are also used in fertility treatment as a part of IVF (in vitro fertilization) protocols, to increase the chances of implantation and support the early stages of embryo development.

Human chorionic gonadotropin

In females, human chorionic gonadotropin (hCG) is extensively used parenterally for final oocyte maturation (the final stages of oocyte development and its release from ovary) induction in lieu of luteinizing hormone (LH). In the presence of one or more mature ovarian follicles, ovulation can be triggered by the administration of hCG. As ovulation will happen between 38 and 40 hours after a single hCG injection, procedures can be scheduled to take advantage of this time sequence, such as intrauterine insemination (IUI) or sexual intercourse. Also, patients that undergo IVF, in general, receive hCG to trigger the ovulation process, but have an oocyte retrieval performed at about 34 to 36 hours after injection by, a few hours before the eggs actually would be released from the ovary. As hCG supports the corpus luteum, administration of hCG is used in certain circumstances to enhance the production of progesterone.

In males, hCG injections are used to stimulate the Leydig cells (cells of the testes, producing testosterone) to synthesize testosterone. The intratesticular (within-the-testicle) testosterone is necessary for spermatogenesis (production of sperm) from the Sertoli cells (testicular cells that support and protect the sperm cells during their maturation). Typical uses for hCG in men include hypogonadism (insufficient sex hormone production in the sex glands) and fertility treatment.

Androgens

The natural androgenic hormone, testosterone, and its synthetic analogues (also known as anabolic steroids) are primarily used in androgen replacement therapy. It includes administration of androgens through injections, creams or patches, and it has been the traditional treatment of male hypogonadism. Furthermore, the use of androgen replacement therapy in various other conditions, such as diabetes, heart failure, osteoporosis and erectile dysfunction (inability to develop or maintain an erection during sexual activity) is being researched. Potential adverse effects of exogenous androgens administration include heart attack, worsening of pre-existing prostate cancer, prostatic hyperplasia, and also reduction in spermiogenesis (sperm production) and even infertility.

Androgens have also been used for its anabolic effects in sports and bodybuilding. Long-term use or high doses of exogenous anabolic androgens can produce many health risks, such as liver damage, high blood pressure and changes of the left heart ventricle. Anabolic steroids can also cause hormonal imbalances and lead to decreased fertility due to reduction of the man’s own testosterone, and even to non-obstructive azoospermia (Pic. 4).

Symptoms

Symptoms associated with exogenous hormone intake vary depending on the type of hormone, and are usually associated with its adverse effects.

Common symptoms associated with estrogen administration include breast tenderness, headache, edemas, nausea and breast enlargement. When they cause hormonal imbalance, there may be menstrual irregularities and abnormal vaginal bleeding. In males, administration of estrogens can cause gynecomastia and sexual dysfunction.
Symptoms of progestin use are relatively similar to estrogenic symptoms, including nausea, headache, menstrual irregularities, acne, breast tenderness and mood changes.

Androgen administration may cause acne and oily skin, loss of hair, increase of body weight and growth of muscle tissue, atrophy of testicles and eventually event infertility.

**Associated diseases**

**Menopause**

Menopause refers to the time of cessation of a woman's reproductive ability. Menopause can also be described as the permanent cessation of the primary functions of the ovaries: the ripening and release of ova and the release of hormones that cause both the creation of the uterine lining, and the subsequent shedding of the uterine lining. At the physiological level, menopause happens because of a decrease in the ovaries' production of the hormones estrogen and progesterone. This decrease in estrogen and progesterone levels can lead to various symptoms such as hot flashes and night sweats, vaginal dryness and dyspareunia (painful sexual intercourse), anxiety, nervousness, lack of concentration, irritability, and poor memory. Decrease of estrogen also increases the risk of postmenopausal osteoporosis. To prevent the osteoporosis and relieve the symptoms, hormonal replacement therapy is commonly used in postmenopausal women.

**Male hypogonadism**

In males, hypogonadism represents the failure of testicular function, the production of testosterone and spermiogenesis. This can be either due to diminished hormonal stimulation of the testes, also known as hypogonadotropic hypogonadism, or due to primary disorder of the testes, known as hypergonadotropic hypogonadism. Apart from reduced fertility, hypogonadism causes impaired muscle development and poor beard growth, gynecomastia and sexual dysfunction. To treat these symptoms, androgen administration in androgen replacement therapy is used.

**Complications**

**Hyperestrogenism**

The consumption of exogenous estrogen can lead to hyperestrogenism, a condition of excessive amount of estrogenic activity in the body. This can lead to hyperplasia (excessive growth) of estrogen-dependent tissues, such as the endometrium (the lining of uterine cavity), which in turn may produce dysfunctional uterine bleeding, or may progress into certain types of uterine cancer. Similarly, hyperestrogenism is associated with an increased risk of breast cancer. The elevated levels of estrogen, via the negative feedback mechanism, suppress the secretion of gonadotropins (the follicle-stimulating hormone and luteinizing hormone) and may therefore lead to menstrual irregularities or even amenorrhea (cessation of menstrual cycle).

**Non-obstructive azoospermia**

Because of the same negative feedback mechanism, the administration of exogenous androgens in males may suppress the hormonal stimulation of the testes and their own testosterone production. This results in lower sperm counts (oligozoospermia) or even non-obstructive azoospermia (no sperm in the ejaculate due to testicular failure) and, over the course of time, in testicular atrophy (loss of testicular tissue). Azoospermia is a direct cause of male infertility, and when the androgen administration is discontinued, testicular atrophy leads to symptoms of hypogonadism.

**Risk factors**

In the following conditions, exogenous hormones are commonly administered:

- menopause
- hypogonadism
- use of anabolic steroids for performance enhancement
- oral contraception
- gynaecological disorders

**Prevention**
Prevention is possible mainly in cases where the hormone administration is eligible. Anabolic steroid use is generally discouraged because of its many health risks in the future. Hormonal contraception is not advised in women who have other identified risk factors of thromboembolism (blood clot formation), such as family history or certain genetic mutations, as the estrogen in combined hormonal contraception increases the risk of blood clots.

### How it can affect fertility

**Estrogens**

Estrogens are most commonly used in combined hormonal contraception and hormonal replacement therapy in postmenopausal women. Therefore, in hormonal contraception, they are used to directly impair the woman's fertility at the moment, and in hormonal replacement therapy are used in patients that have already completed their fertile period. However, hyperestrogenism resulting from estrogen administration may cause menstrual irregularities, amenorrhea and subsequent infertility in otherwise healthy women.

In men, estrogens can be administered in the treatment of some hormone-sensitive cancers, most notably prostate cancer. Estrogens act as anti-androgens, disrupting the growth stimulation of the tumour by androgens. However, the side effects of estrogen therapy in men can reduce both fertility and life quality of the patient. Due to suppressed testosterone activity, the patients may experience feminization (development of female physical characteristics), gynecomastia, sexual dysfunction due to combined reduced sex drive and erectile dysfunction, hypogonadism (decreased function of the testes) and infertility.

**Progestosterone and progestins**

Progestins can be used to reduce the adverse effects on fertility caused by estrogen excess, such as anovulation and endometrial hyperplasia. Progesterone and progestins are also used during the luteal phase of the menstrual cycle to increase the chances of success of IVF procedure – a practice known as luteal support. They prepare the uterine lining for implantation and support early pregnancy.

Progestins are also used in combined or progestin-only hormonal contraception. They mimic the effects of progesterone and suppress the release of gonadotropin from the pituitary, creating a state of reversible infertility (fertility is restored if their administration is discontinued).

In men, administration of progestins can similarly lead to gonadotropin suppression, reduced testosterone secretion, and therefore, reduced fertility.

**Androgens**

Exogenous androgens mimic the functions of testosterone in the body, and therefore lead to an increase in muscle mass and sex drive. However, they inhibit the release of gonadotropins through the negative feedback mechanism, and thus impair the hormonal stimulation necessary for the function of the testes. The testes then produce less testosterone, which is needed directly in the testicular fluid for healthy spermiogenesis. Without testicular testosterone production, the spermiogenesis is ineffective and may cease completely. This eventually leads to failure of the testes to produce sperm, called non-obstructive azoospermia, which is a direct cause of male infertility.

Androgen administration in women disrupts gonadotropin and female sex hormone secretion, leading to menstrual irregularities, amenorrhea, breast atrophy, hypogonadism and infertility. Anabolic androgens are also teratogenic during pregnancy (may cause damage to the fetus).

### Prognosis

In most cases, hormones are administered due to medical reasons and do not lead to severe adverse effects affecting the patient’s fertility. However, unnecessary hormone consumption should be avoided to prevent irreversible changes to the organs of the genital tract and fertility issues later in life.
**Pic**
A summary of hormones produced by organs of the reproductive system.

**Pic**
A photograph of an injectable testosterone preparation, used as an anabolic-androgenic drug.

**Pic**
An overview of the symptoms of menopause.

**Symptoms of Menopause**

- Headache
- Palpitations
- Hot flashes
- Dryness
- Itching
- Thinning
- Tingling
- Joints
- Soreness
- Stiffness
- Urinary
- Incontinence
- Urgency
- Vaginal
- Dryness
- Painful intercourse
- sistemaic
  - Weight gain
  - Heavy night sweats
- Breasts
  - Enlargement
- Pain
- Skin
  - Hot flashes
  - Dryness
  - Itching
  - Thinning
  - Tingling
- Joints
  - Soreness
  - Stiffness
- Back pain
- Transisitional menstruations
- Shorter or longer cycles
- Bleeding between periods
- Psychological
  - Dizziness
  - Interrupted sleeping patterns
  - Anxiety
  - Poor memory
  - Inability to concentrate
  - Depressive mood
  - Irritability
  - Mood swings
  - Less interested in sexual activity

**Sources**

"Anabolic steroid" [https://en.wikipedia.org/wiki/Anabolic_steroid#Adverse_effects]" — sourced from Wikipedia licensed under **CC BY-SA 3.0**

"Management of Poor Responders in IVF: Is There Anything New?" [https://www.hindawi.com/journals/bmri/2014/352098/]
—by Ubaldi et al. licensed under **CC BY 3.0**

"The Association between Endometriomas and Ovarian Cancer: Preventive Effect of Inhibiting Ovulation and Menstruation during Reproductive Life" [https://www.hindawi.com/journals/bmri/2015/751571/]
—by Grandi et al. licensed under **CC BY 3.0**