

DRUGS AFFECTING THE REPRODUCTIVE SYSTEM

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There are drugs that can affect the functioning of many of the endocrine glands. Drugs are used to restore homeostasis of these glands. The glands included are pancreas, gonads, pituitary, thyroid and adrenal cortex. Some of these drugs mimic the hormones produce by the glands are called agonist and those that block them are called antagonist. The chemical structure vary as they can be peptides, steroids and other biogenic amines. Peptide hormones such as those from pituitary and pancreas cannot be given orally since they are degraded by the proteolytic enzyme. Steroids such as those from the gonads and the adrenal cortex are more effective when injected but now these compounds are available synthetically and can be taken orally.

Hormones produce by the anterior pituitary gland

Adrenocorticotrophic hormone: stimulates the secretion of adrenocortical hormones

Follicle stimulating hormone: stimulates the maturation of the ovarian follicle and estrogen production and sperm production in males.

Growth hormone: body growth, development of bones and muscles and mobilizes fat

Luteinizing hormone: ovulation in females, production of gonadal hormone

Prolactin: promotes lactation

Thyroids stimulating hormone: secretion of thyroid hormones

Posterior

Antidiuretic hormone: water retention within the kidneys

Oxytocin: ejection of breast milk, initiates labour, contraction of the myometrium, may be needed for clitoral and penile erection and orgasm in both sexes.

Trophic hormones affecting the gonadal function:

Drugs act on the two major class of hormones to achieve control of the gonad

Two major ones:

Gonadotrophin hormones: LH and FSH (pituitary glands)

Gonadotrophin releasing hormone (GnRH): hypothalamus

These can be available from the human urine or from DNA recombinant technology.

A drug from the human urine is menotrophin containing the LH, FSH and human chorionic gonadotrophin and urofollitrophin. Common side effect is excessive stimulation of the gonadal hormones leading to fluid retention and oedema. May lead to the formation of cysts that are prone to rupture. Mild skin rashes are possible.

GNRH is also known as LH releasing hormone:

These drugs act on the hypothalamus – pituitary axis and lead to stimulate the secretion of the endogenous hormones.

These drugs are analogues of the GnRH and they stimulate the release of LH and FSH. Chronic use of these drugs can lead to dec and inhibited functions of the gonads. Naferelin is used suppress the growth of endometric ectopic tissue. Buserelin used in management of endometriosis and to induce ovulation in women receiveing fertility treatment. Goserelin and leuprorelin used in the management of prostrate cancer.

Adverse effects: are either due to over stimulation or inhibition. Stimulation will lead to ovarian cysts and worsening of the endometriosis. Inhibition will leas to menopause in women, headache, nausea and altered libido.

In men hot flushes, sweating inc bp and chills and impotence may be observed.

This is contraindicated in women of child bearing age, in women who are pregnant and who are breastfeeding.

Partial estrogen agonist: clomiphene : it is an antiestrogenic substance and has affinity for the estrogen receptors. It binds to the receptors and prevents estrogen from binding, hence stimulates the GnRH release by preventing the feedback inhibition of the hypothalamic - pituitary axis by estrogen. Adverse reaction are dose related, abdominal cramps, hot flushes, breast soreness. Liver function needs to be checked. If visual blurring occurs then treatment needs to be stopped

Recombinant fsh: Follitropin : injectable form Subcutaneous or IM.

Two subtypes: alfa and beta: alfa is used to stimulate ovarian function. Beta is used to stimulate spermatogenesis in males with hypogonadotropic hypogonadism and has the same function in females. GI upset, headache rash hyperstimulation of the ovaries and bloating. Contraindicated in ovarian cysts, pituitary or sex hormone dependent tissue have tumor, pregnancy and abnormal uterine or vaginal bleeding.

GnRh antagonist: Cetrorelix and ganirelix: these bind to the GNRH receptors and prevent the release of the gonadotrophins mainly LH and FSH. These are used to prevent premature ovulation with assisted reproduction. Local rxn at the site of injection and also nausea and headache.

Trophic hormone and the adrenal cortex: tetracosactrin: is an ACTH analogue to diagnose the impaired adrenal cortex function and also to treat a range of inflammatory disorders. It stimulated the ac to release corticosteroids.

Hypersensitivity especially allergy and other side effect is elevated levels of gc and mineralcorticoids: fluids retention, hypertension and electrolyte imbalance.

Disorders of the growth hormone:

Hyposecretion: somatotropin used in children with a dec amt of GH and resultant short stature. It stimulates the skeletal and muscular growth, it concert with

other hormones that affect growth. Triggers the release of insulin – like gf from the liver to mediate normal cell growth. It influences nutrient metabolism by the uptake of aa into the cell and induces lipolysis. Adverse rxn: antibody formation, lipoatrophy, local irritation and fluid retention.

Hypersecretion: over secretion of the gh and a condition known as acromegaly. Using synthetic somatostatin agonist called octreotide and lanreotide. Somatostatin inhibits the release of gh as well as some of the gastropancreatic peptide hormones. Irritation and GI discomfort.

Disorders of Prolactin Secretion: are derived from ergot alkaloids. Bromocriptine, lisuride and cabergoline suppress the release of prolactin. Stimulate the dopamine receptors in the pituitary which are involved in the secretion of prolactin.

Clinical use of the posterior pituitary hormones: produces the antidiuretic hormone: vasopressin and oxytocin: both are available in synthetic forms. These are peptides and hence cannot be administered orally.

Vasopressin: synthetic vasopressin called desmopressin is available and is used to treat diabetes insipidus which is characterized by an hyposcretion of ADH. ADH stimulates the reabsorption of water from the collecting ducts back into the bloodstream and plays a role in concentrating the urine. Stimulates vasoconstriction which is helpful during haemorrhage in order to reduce blood loss. Allergic rxn, tachycardia, dec bp.

Oxytocin is a smooth muscle stimulant and is used to initiate labour, promote delivery of the placenta or control a postpartum haemorrhage. Allergic reactions, cardiovascular spasm and hypotension are associated with the use of oxytocin

Drugs affecting the gonads:

Commonly used drugs:

Oestrogen

Clomiphene

Tamoxifen

Testosterone

Flutamide

Progesterone

Mifepristone

The hormones imp for normal sexual development and functioning are the GnRH released from the hypothalamus which stimulates the release of the FSH and LH from the pituitary gland. These in turn stimulate the gonads for the production of sperm and testosterone in males and mature ova and estrogen and progesterone in females. If there is any impairment in the production of the GnRH that in turn will lead to an impaired production of FSH and LH and in turn impaired functioning of the gonads and reduced levels of the sex steroids.

Steroidal hormones are more frequently used since their chemically synthetic forms are easily available as compared to the Gonadotrophins which have to be made from the natural sources and hence are expensive

The steroidal hormones have specific receptors to which they bind on the target tissue.

Steroid hormone : oestradiol : agonist oestrogen and antagonist is tamoxifen and clomiphene.

Steroid hormone : androgen : agonist testosterone and antagonist is Flutamide

Steroid hormone : progesterone: agonist progestogen and antagonist mifepristone.

Androgen agonist are useful in the treatment of hirsutism and masculinising syndromes and has an effect opposite to that of testosterone.

Tamoxifen is an oestradiol antagonist and is used to treat some type of breast cancers.

Oestrogen is produced in the ovary in pre – menopausal women, placenta during pregnancy and in the adrenal glands of both the sexes. It helps in growth and development of the female reproductive organs and hence after menopause there can be some atrophy. They also help in the prevention of osteoporosis by making the tissue less responsive to the PTH.

Orally administered are rapidly removed from the system by the first pass metabolism and hence synthetic or semisynthetic form need to be incorporated.

Since the use of estrogen has been linked to cases of endometrial cancer progesterone is used in conjunction now.

Therapeutic use:

1. Menopause as a Hormone Replacement Therapy
2. Osteoporosis: Ca supplements and vit D are effective but not as much as estrogen in increasing bone density
3. Primary Amenorrhea (Irregular and painful periods): common reason is excessive wt loss or excessive exercise can also be due to pituitary and ovarian failure. They cause the endometrium to proliferate and hence give periods but do not correct the associated infertility.
4. Postpartum lactation: prevents postpartum painful breast engorgement and postpartum lactation.
5. Control of height: estrogen caused the closure of the epiphyseal plates of the long bones and hence limits the growth of height. Hence can be used in treatment for very tall girls.
6. Dermatological problems: acne treatment

Adverse effect: breakthrough bleeding, breast tenderness and GI upset. Another major problem is thromboembolism cerebral embolism and thrombosis and hypertension and also promotes fluid and salt retention.

Anti – estrogen: inhibit the action of estrogen : Clomiphene: fertility drug: stimulates the production of the GnRH. There is a negative feedback mechanism and when estrogen is produced in the body it inhibits the release of GnRH. This is also the basis for the inhibition of ovulation and the function of the estrogen in the COC.

Tamoxifene: used to dec the rate of proliferation of breast cancer cells. Estrogen promote growth and development of the breast hence an antagonist will counter this mechanism.

Progesterone:

Synthesised by the corpus Luteum in the ovary and in the second half of the menstruation cycle. Large amt in the placenta during pregnancy and by the adrenal glands. Absorbed very fast when given orally and has a half life of 5 min it has a high first pass in the liver. Hence synthetic drugs need to be provided.

Use:

1. Contraceptive

2. Menstrual irregularities: control excessive bleeding, painful periods (dysmenorrhoea) and absent or irregular periods (ammenorrhoea).

Reappearance of regular menstrual bleeding does not relate to fertility. Since when there is correct amt of the hormones progesterone and estrogen the endometrium proliferates but when these are withdrawn it stops and withdrawal bleeding occurs.

3. Endometriosis: high dose inhibit growth of the endometrium and lower dose proliferate it.

Adverse effect: wt gain, depression, breast tenderness.

Androgen: anabolic steroids: testosterone is the most potent anabolic steroid and is responsible for the maintenance and development of the male sex organs and secondary sex characteristics. Very high first pass metabolism, hence synthetic forms need to be used.

Therapeutic use:

1. hypogonadism, hypopituitarism and to maintain secondary sex characteristics.
2. Promote anabolism.

Side effects:

Masculinisation in women and their offsprings

Na and water retention: inc bp, excessive sexual stimulation, reduced sperm count and ejaculatory volumes

Prostatic hypertrophy leading to urine retention.

Antiandrogen: Cyproterone: inhibits the action of androgen

Gossypol: prevents spermatogenesis.

Hormonal Contraception

Drugs to know:

COC (Minulet and loette)

POP (minipill) (Femulen)

Depo provera

LNG IUS (Mirena)

Contraception relates to the prevention of unwanted pregnancy. This is obtained by preventing :

1. ovulation
2. fertilization of the ovum
3. implantation of the fertilized egg.

Mode of action of estrogen and progesterone in preventing pregnancy:

1. inhibition of GnRH hence no ovulation
2. inc motility thru the fallopian tube hence the ovum is too immature to be able to implant applies to the effect of estrogen
3. production of cervical mucous hostile to the sperm survival. P effect
4. inhibition of endometrial development p + e proliferation p alone inhibition of proliferation.

COC (Combined oral contraceptives)

Contain synthetic estrogen and progesterone. There is an inc risk of blood clotting with third generation COC as compared to second generation COC.

Three types of COC : Monophasic: amt of p + e remains the same throughout taken daily

Biphasic : amt of e remains the same but + p varies and normally inc from 11 – 25 day calendar pack

Triphasic : amt of p + e vary throughout the cycle and as a result resemble the effect of natural hormonal regulation. Calendar pack.

If the pack is 21 days then there is a 7 day no pill break

If the pack is 28 days then it contains 7 placebo tablets.

Side effects:

E related: nausea, oedema, breast swelling, wt gain. Fluid retention leading to an inc bp.

P Related: inc appetite and fat deposition, wt gain, breast swelling and tenderness, depression , fatigue, dec libido, and vaginal dryness, acne.

Most imp side effect if there is a sudden chest pain since there can be a block in the lungs leading to cough up blood. Severe pain the lower leg also related to blood clots, severe migraine or strokes.

Problems with the use of COC:

1. not suitable to women with a history of blood clots
2. links to some cancer: breast and endometrial
3. inc risk of cardiovascular problems
4. recurrent thrush infection, breakthrough bleeding this can be distressing
5. there can be a tendency of having an e excess or a p exces and hence the effects related to them.
6. headaches.
7. Drug – food interaction.

POP (Minipill or progesterone only pill)

Aware: irregular menstrual bleeding might occur and chances of ectopic pregnancy is there. The dose must be taken continuously and at the same time every day.

Pill Failure:

Occur:

1. forgetting
2. gi upset
3. drug interaction

Recommendation for a missed pill

COC:

One missed pill take as soon as remembered, the next one at the usual time and use the 7 day rule = take active pill and use another form of contraceptive for 7 days.

The 28 day pack contains 7 placebo pills either at the beginning or at the end. If an active pill is missed and an intercourse has occurred then take a morning after pill followed by the 7 day rule.

POP:

Take within 3 hours of the set time since this only affects the cervical mucus.
Advice for a missed pill take as soon as remembered and follow the 2 day rule.
Since ovulation still occurs it is imp to take morning after pill if intercourse has occurred.

Post – coital emergency pill (morning after pill, emergency contraceptive pills)
High dose of combined p + e. 2 tablets asap and 2 tablets after 12 hours. Should be taken within 72 hours of unprotected sex.

Parenteral contraceptive: Depo – provera (injection and 12 weeks)
Contains long acting progestogen. This stops the ovary from releasing an egg.

Disadvantage: periods affected , wt changes, inc risk of breast cancer and withdrawal takes time.

Levonorgestrel – Releasing Intrauterine system (LNG IUS)

Contains 52 mg of progesterone called levenogestrol which is released slowly over a period of 5 years. Used where other contraceptives do not suit. Mirena can also be used for the treatment of menorrhagia. Local effect in the uterus. Endometrial suppression, endometrial cells become resistant to stimulation by the e, sperm migration is affected and ovulation in some women may be inhibited.

Drugs used to delay or promote labour:

Drugs to know:

Salbutamol

Terbutaline

Betamethasone

Syntocinon

Prostin E2 and Dinoprostone

Tocolytics and Myometrial relaxants are used to delay labour

Oxytocics and prostaglandins are used to induce labour.

Key factors:

Corticotrophin Releasing hormone is an early trigger for the onset of labour, women with elevated levels in 24 – 28 weeks are at an chance of having premature labour and this also indicates an intrauterine infection.

The uterus has receptors for oxytocin, and its binding leads to uterine contraction and the number of receptors inc during the full term pregnancy.

Inc pg results in softening of the cervix and inc uterine contractability

The uterus also has adrenergic receptors and hence when stimulated inhibit the uterine contraction.

Drugs used in premature labour: tocolytics and GC

Reasons for pharmacological intervention:

1. Foetal distress may trigger preterm labour since there can be premature placenta separation, placenta insufficiency or chronic foetal stress. The women could have developed an intrauterine infection and in this case it is best to treat the infection and delay the labor.
2. ensuring lung maturity has reached the optimum for the baby else there can be respiratory distress syndrome. This is achived as gc stimulate the release of an surfactant called lecithin.

Myometrial relaxants: terbutaline and salbutamol: they are beta – 2 adrenergic agonist and bind to the adrenergic receptors in the uterus and they mimic the

action of adrenaline and noradrenaline and as a result cause the relaxation of the smooth muscle and delay labour. Side effects: headache, increased heart rate, peripheral vasodilation and an inc in bp. These drugs may be given by IV infusion in saline.

Care should be taken if the women is suffering from hypertension, eclampsia and diabetes.

GC : Betamethasone: in the foetus the surfactant is detectable from weeks 25 - 30 but reach the sufficient levels only in the week 33 – 34 to prevent the RDS. Therefore if there has to be a premature delivery then labour is delayed for 24 – 48 hours and exogenous GC is given as this will lead to the development of the surfactant and prevent the infant from the rds. Side effect: pulmonary oedema. Negative nitrogen and ca balance tends to occur with long term use of gc but since it is only given for a short time there is no problem. It has a tendency to depress the immune system and hence inc the risk of uterine infection.

Drugs used to promote labour: PG and Oxytocics:

Labour requires the softening of the cervix and uterine contraction. The drugs that produce this are pg and syntocinon respectively.

PG: - prostin E2 and Dinoprostone:

These bind to the specific receptors in the uterus and promote the ripening of the cervix and initiate contraction. These are mainly used via application into the vagina and cervix. Topical gel is prostin E2 and an vaginal insert is dinoprostone. Insertion is preferred since if there is hyperstimulation of the fetus then it can be removed.

Syntocinon:

The production of oxytocin an hormonal peptide is a natural factor during labour. It inc the force and frequency of uterine contraction. This pdt mimics the oxytocin and binds to the receptor resulting in uterine contraction. Controlled infusion is the best way to administer it. Once it binds to the receptor it opens the ca channels and this results in the contraction. These receptor inc towards the end of pregnancy. These receptors are affected by the hormones like e+ pg , these can either be produced by the women or may need to be administered. Hence these combinations cause the women to vary in their response to syntocinon. Hence the dose need to be titrated. Excess administration can result in titanic uterine contractions. These can be counteracted by the use of salbutamol which is adrenergic agonist and will bind to its receptor and inhibit the amt of Ca entering as result of which it will cause the relaxation of the smooth muscle. Syntocinon acts even on the mammary glands and helps in the ejaculation of the milk.

Also affects the CV system and hence can lead to hypotension, reflex tachycardia and flushing.