Drugs Acting on Endocrine System

1- Pituitary Hormones

Pituitary gland

The pituitary gland is situated in sella turcica or hypophyseal fossa of the sphenoid bone attached to the brain by a stalk which is continuous with the part of brain i.e. hypothalamus and there is a communication between the hypothalamus and the pituitary gland by means of nerve fibres and a complex of blood vessels. Pituitary gland consists of three parts – **anterior lobe** or adenohypophysis, **posterior lobe** or neurohypophysis and **middle lobe** or pars intermedia. The anterior lobe secretes various trophic hormones, the posterior lobe is responsible for the secretion of **oxytocin** and **antidiuretic** hormone (vasopressin) and middle lobe secretes **melanocyte-stimulating** hormone (MSH) which may affect the synthesis of melanin.

ANTERIOR PITUITARY HORMONES

Anterior lobe of pituitary is the master gland of the endocrine system as a whole because it produces peptide trophic hormones which affect the other ductless/endocrine glands. **The anterior lobe secretes the following hormones**:

1- Growth hormone or somatotrophic hormone (GH & STH):

It stimulates growth directly and in conjunction with other hormones. It stimulates the multiplication of the cells of epiphyseal cartilage and thus increases the length of the cartilage bone. After administration, there is an increased body growth due to its direct effect on the tissues. It stimulates the growth of muscles. It also increases the secretion of milk during lactation.

- **Hyposecretion of pituitary during childhood** leads to '**dwarfism'** which is of two type, **Lorain** type and **Frohlich's** type and is characterized by stunted growth of the skeleton with resultant 'dwarfism.'
- **Hyposecretion during adult** life leads to 'Simmond's disease' and is characterized by dry and wrinkled skin, grey hair and there is a atrophy of the sexual organs and cessation of menstrual cycle in the female.
- **Hypersecretion during childhood** leads to 'gigantism' and is characterized by excessive skeletal growth.
- **Hypersecretion during adult life** leads to '**acromegaly'** and is characterized by excessive growth of facial bones, hands become large and spade like, thickening of facial and hand's skin etc.

Clinical Preparations

The preparation available are:

1- **Sometrem (PROTROPIN)** : 5 mg (13 IU) inj.

2- **Somatropin (GENOTROPIN)**: (12 & 16 IU per vial inj. and 1 mg contains 2.6 IU)

The main use of growth hormone is in the treatment of dwarfism.

Side effects

1- Include allergic reaction.
2- pain at the site of injection.
3- Hypothyroidism.
4- glucose intolerance.
5- Water retention may also occur.

3- **SOMATOSTATIN**

It is a peptide containing 14 amino acids and inhibits the release of growth hormone, TSH and prolactin from the pituitary and insulin and glucagon in pancreas. It has a very short plasma half-life. Because of its shorter duration of action and lack of specificity in inhibiting only GH secretion, its use in the treatment of acromegaly is limited.

4- Another newer synthetic compound, **octerotride** is a longer acting analogue of somatostatin and is used in acromegaly.

2- Thyroid stimulating hormone (TSH) or thyrotrophic hormone:

This hormone controls the growth and activity of the thyroid gland. It influences the uptake of iodine, synthesis of **thyroxine (T4)** and **triiodothyronine (T3)** by the thyroid gland and their release into the blood stream.

3- Adrenocorticotrophic hormone (ACTH):

It is secreted by basophil cells under the control of CRF (corticotropin releasing factor) from the hypothalamus. ACTH controls the growth of adrenal cortex and the synthesis of corticosteroids and is essential to life. The action of ACTH on adrenal cortex is mediated through cyclic AMP. This hormone stimulates the cortex of adrenal gland to produce its hormones. The amount of ACTH secreted depends upon the concentration in the blood of the hormones from the adrenal cortex and on stimulation by hypothalamus.

The cortex of adrenal gland produces three types of hormones:

A- **Glucocorticoids**: The secretion is stimulated by ACTH from the anterior lobe of pituitary gland. **Cortisone** and **hydrocortisone** are the main glucocorticoids and their main function is to regulate carbohydrate metabolism.

B- **Mineralocorticoids**: It is associated with the maintenance of the electrolyte balance in the body. **Aldosterone** is the main mineralocorticoid which stimulates the reabsorption of sodium by the renal tubules and when the amount of sodium reabsorbed is increased the amount of potassium excreted is increased. Angiotensin (vasopressor agent) produced by the renin (from kidneys) stimulates the secretion of aldosterone.

C- **Sex Hormones**: The secretion of **estrogens** in females and **androgens** in males by the adrenal cortex is controlled by ACTH. They are responsible for the development and maintenance of secondary sexual characters in both males and females. They also increase the deposition of protein in muscles and reduce the excretion of nitrogen in males.

- **Hyposecretion** of hormones from the adrenal cortex leads to development of '**Addison's disease'** which is characterized by loss of appetite, muscular weakness, loss of weight due to loss of water, hypoglycemia, subnormal body temperature, decreased basal metabolic rate, increased blood potassium, decreased blood sodium and inability to maintain the normal protein deposition in the muscles.
- **Hypersecretion** from the adrenal cortex leads to condition known as '**Cushing's syndrome'** which leads to 'feminism' in males, which is the tendency to develop female sex characters and in females 'virilism' develops, which is the tendency to develop male sex characters such as excess growth of hair on chest and pubic region, increase and darkening of facial hair, atrophy of mammary glands (breasts) and cessation of menstrual cycle (amenorrhoea).
- ACTH is available as lyophilized powder which on reconstitution gives 40 IU/ml solution and is used mainly for the diagnosis of pituitary adrenal axis disorders.

4- GONADOTROPHIC HORMONES (GTH) OR GONADOTROPHINS:

The basophil cells secrete gonadotrophins which control the growth and ac tivity of the gonads and indirectly other processes connected with it. There are two gonadotrophins:

• Follicle stimulating hormone (FSH).

• Luteinising hormone (LH) or interstitial cell stimulating hormone (ICSH).

FSH

In females, the target organs are the ovaries where it increases the number and size (maturation, development and ripening) of Graafian follicles and prepare them for ovulation. During its development, the ovarian follicles secrete its own hormone estrogen. In males, it stimulates spermatogenesis. Under the influence of this hormone, seminiferous tubules produce spermatozoa.

LH

In **females**, it is responsible for:

- Complete development of the ovarian follicles to secretory stage and secretion of estrogen.
- Promotes the final maturation of ova rian follicles and ovulation and the for mation of corpus luteum which se cretes progesterone.

In males, the same hormone under the name of ICSH stimulates the development and functional activity of interstitial cells and ultimately the production of testicular androgen, testosterone.

- Gonadotrophin secretion is under the control of hypothalamus and sex hormones. The hypothalamic nuclei secrete a specific releasing factor for the release of both FSH & LH.
- Gonadal hormones from ovary and testis regulate the FSH and LH secretion by direct action on pituitary as well as through hypothalamus.
- Gonadotrophins are used in the treatment of amenorrhoea, infertility, cryptorchidism and hypogonadotrophic hypogonadism in males. It is also useful in in vitro fertilization.

There are two types of gonadotrophins available:

- Obtained from urine of pregnant women, chorionic **gonadotrophin** as 1,000-10,000 IU (powder form, can be used after reconstitution by parenteral route).
- Obtained from urine of menopausal women, **menotrophin** (combination of FSH 75 to 150 IU and LH 75 to 150 IU).

Preparations of gonadotrophins have been used to treat infertility for the last several years.

MENOTROPHIN

Purified extract of human postmenopausal urine containing follicle stimulating hormone (FSH) and luteinising hormone (LH) is known as human menopausal gonadotrophin. The relative in vivo activity is designated as a ratio, the 1:1 ratio is also known as menotrophin.

Adverse effects: include polycystic ovary, edema, pain in lower abdomen and allergic reactions.

Used: in amenorrhoea and infertility, hypogonadism in males and females, follicle stimulation in IVH and cryptorchidism.

NAFARELIN ACETATE

It is potent analogue (200 times more potent) of gonadotrophin releasing hormones (GnRH). It is rapidly absorbed into the systemic circulation following intranasal delivery. It stimulates the release of LH and FSH from the anterior pituitary resulting in a temporary increase of ovarian steroidogenesis. After 2 to 3 days of daily

administration, the pituitary becomes refractory to further stimulation. LH/ FSH release is inhibited within 10 days and is followed by a decrease in secretion of gonadal steroids within 2 to 6 weeks. After intranasal administration maximum serum concentration are achieved within 10 to 45 minutes. It is 80% bound to plasma proteins.

Adverse effects include hot flushes, change in libido, vaginal dryness, headache. Incidents of emotional lability and depression are higher in infertile patients. Nasal mucosal irritation, migraine may also occur. Naferelin therapy for six to nine months may lead to three to five percent bone loss.

Used in endometriosis, precocious puberty. In infertile women choosing in vitro fertilization, naferelin in combination with gonadotrophins can be used for stimulating ovulation. It is also useful in management of uterine leiomyoma, benign prostatic hypertrophy, hirsutism and polycystic ovarian syndrome.

5- Luteinising hormone (LH) or interstitial cell stimulating hormone (ICSH):

It is a single chain peptide hormone, isolated in pure form and contains **tyrosine**, **tryptophan**, **cystine**, **arginine**, **methionine** of approximately 25,000 molecular weight. It has a direct effect upon the breasts immediately after the delivery of baby and in conjunction with other hormones, it stimulates the breast to secrete milk. It also stimulates the proliferation of the glandular elements of the mammary glands during pregnancy and helps in complete development of breasts. Prolactin secretion is under the inhibitory control of hypothalamus through prolactin inhibiting hormone (PRIH) which is a dopamine and acts on pituitary lactotrope D2 receptor.

A- BROMOCRIPTINE (Bromoergocriptine)

It is a semisynthetic ergot alkaloid and dopamine receptor agonist. It acts on pituitary lactotrophic cells to inhibit the synthesis and release of prolactin by agonist action on dopaminergic receptors.

Adverse effects are nausea, vomiting, postural hypotension, behavioral alterations, mental confusion, psychosis.

Used in hyperprolactinemia and for suppression of lactation and breast engorgement. It is also useful in parkinsonism because it has levodopa like actions and in the treatment of acromegaly.

Dose: PROCTINAL 1.25 mg BD.

6- POSTERIOR LOBE OF PITUITARY GLAND:

The posterior lobe secretes two hormone namely **oxytocin** and **antidiuretic hormone** (ADH or vasopressin).

UTERINE STIMULANTS (OXYTOCICS, ABORTIFACIENTS)

OXYTOCIN

Oxytocin is an octapeptide synthesized in hypothalamus and transported down the axons into the posterior lobe of pituitary.

Used: It promotes contraction of the uterine muscle. It also causes contraction of the myoepithelial cells of the lactating breast and squeezing milk into the large ducts situated behind the nipple of the mammary gland.

Oxytocin takes part in the onset of parturition, expulsion of the foetus and placenta. It also facilitates the transport of sperm in the female genital tract.

Oxytocin is Used in induction of labour, in postpartum haemorrhage, abortion and in breast engorgement. It is used by IM/IV route (PITOCIN, 2-5 IU/ml inj).

ERGOMETRINE

It increase force, frequency and duration of uterine contractions. It is used to control and prevent postpartum haemorrhage. It is also used to prevent uterine atony after cesarean or instrumental delivery.

PROSTAGLANDINS

PGE2 , PGF2α and 15-methyl PGF2α are potent uterine stimulant.

2- Antidiabetic Agent

1- INSULIN

Insulin (MW 5,800) a polypeptide hormone secreted from β-cells of islets of Langerhans in pancreas was discovered by Banting and Best in 1921. It was purified and crystallized by Abel and it's amino acid sequence was established by Sanger in 1960. It's formed from proteolysis of proinsulin to give rise to two peptide chains (A with 21 amino acid residues and B with 30) which are interconnected by disulphide bond.

Mechanism of Insulin Action

Insulin acts by binding to insulin receptors on cell membrane. The insulin receptor complex is internalized. By phosphorylation and dephosphorylation reactions there is stimulation or inhibition of enzymes involved in metabolic actions of insulin. Second messengers like phosphatidyl inositol glycan and DAG also mediate the action of insulin on metabolic enzymes. Normally, insulin stimulates storage of glucose in liver as glycogen and in adipose tissues as triglycerides and storage of amino acids in muscle as protein. It also promotes utilization of glucose in muscle for energy. Insulin inhibits the breakdown of triglycerides, glycogen, and protein and conversion of amino acids to glucose (gluconeogenesis). Conversion of amino acids to glucose and glucose to fatty acids occur mainly in liver.

In diabetes mellitus, there is either insulin deficiency or insulin resistance in peripheral tissues which lead to hyperglycemia and glycosuria. Insulin corrects the various abnormalities of carbohydrate metabolism by its action on various tissues.

Pharmacokinetics

Insulin is not given orally. After IV or SC injection, it circulates as free, monomer in blood and has a short plasma half life. Insulin is degraded mainly in liver, muscle and kidney.

Adverse effects

The most frequent and serious adverse reaction is hypoglycemia. It can occur in any diabetic patient due to heavy dose of insulin, failure to eat or missing a meal, performing extensive exercise or by consuming alcohol.

The hypoglycemia caused by insulin is characterized by neuroglucopenic symptoms that include confusion, dizziness, behavioural changes, visual disturbances, fatigue, muscle incoordination and may be fall in blood pressure.

The other side effects include insulin allergy which consists of local itching, swelling, redness at the site of injection. Urticaria and anaphylactic reactions are rarely seen.

Other rare side effects include insulin lipodystrophy (atrophy at the site of injection), insulin neuropathy and weight gain (obesity).

Therapeutic Uses

Insulin is used in:

- Insulin dependent diabetes mellitus (IDDM).
- Diabetic ketoacidosis or diabetic coma.

2- HUMINSULIN

Huminsulin 30/70 [biphasic isophane insulin injection (30% soluble insulin and 70% isophane insulin)] is a mixture of soluble human insulin injection, a short acting blood glucose lowering agent and isophane insulin human suspension, an intermediate acting blood glucose lowering agent.

Adverse Effects

Local allergy: Patients occasionally experience redness, swelling, and itching at the site of injection of insulin.

Systemic allergy: Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases may be life threatening.

3- ORAL ANTIDIABETIC AGENTS

A- Sulfonylureas

These drugs stimulate insulin secretion from pancreatic β ββ-cells (so called ‘sulfonylurea receptors’) which cause depolarisation by reducing conductance of ATP sensitive K+ channels. They lower down the blood sugar level in type II diabetics and non-diabetic individuals. They also decrease the elevated plasma free fatty acid levels. They also sensitize the target tissues to action of insulin by increasing the number of insulin

receptors. Sulfonylureas inhibit neoglucogenesis and glycogenolysis. Sulfonylureas are rapidly absorbed from the gastrointestinal tract after oral administration and are more than 90 percent bound to plasma proteins and excreted unchanged in urine.

1- Chlorpropamide (COPAMIDE)

After oral administration, it is rapidly absorbed and has long plasma half life and excreted by kidney slowly.

Adverse effects include nausea, vomiting, cholestatic jaundice, skin rash, anaemia, leucopenia, hypoglycemia and intolerance to alcohol (disulfiram like reaction).

It is indicated in the treatment of maturity onset non ketotic diabetes mellitus unresponsive to diet and neurogenic diabetes insipidus.

2- Tolbutamide (RASTINON)

It is a short acting, less potent oral hypoglycemic agent and after administration it is readily metabolized in liver.

Adverse effects include, nausea, vomiting, skin rash and epigastric distress.

It is mainly used in maturity onset diabetes mellitus.

3- Glibenclamide (BETANASE)

Glibenclamide is a second generation sulfonylurea. There are two mechanisms of action for the lowering of the blood glucose:

1. The pancreatic effect, in the case of failure of β-cell function together with an existing but inadequate insulin secretion, gives rise to an intensified insulin secretion as a result of a greater response of the β-cells to glucose.
2. The extrapancreatic effect, in the case of resistance to insulin due to a reduced sensitivity of the peripheral tissue to insulin.

Adverse reactions include visual dis turbances (transient, at the beginning of therapy), nausea and epigastric bloating (rare) and diarrhoea. Hypersensitivity in cluding allergic skin reactions, thrombocy topenia, leucopenia, agranulocytosis, haemolytic anaemia, vasculitis, cholestatic jaundice and hepatitis.

It is indicated in non-insulin dependent diabetes mellitus (type II, maturityonset diabetes) whenever treatment by diet alone proves to be inadequate.

4- Glipizide (DIBIZIDE)

It is an oral blood glucose lowering drug of sulfonylurea class. It is fast acting and post prandial insulinemic action persists even after prolonged use. Glipizide is completely and rapidly absorbed ensuring prompt and constant activity.

It is indicated in management of type II diabetes where diet control alone is not effective in controlling the hyperglycemia.

Adverse effects include hypoglycemia, GIT disturbances, allergic reactions include urticaria and erythema.

5- Gliclazide (GLIZID)

Gliclazide reduces blood glucose levels by correcting both defective insulin secretion and peripheral insulin resistance. Gliclazide also has been reported to reduce plasma cholesterol and triglyceride levels after repeated administration.

Adverse effects include nausea, diarrhoea, gastric pain, vomiting, skin rash, pruritus, flushing, erythema, headache and dizziness with low incidence of hypoglycemia.

It is indicated in non-insulin dependent diabetes mellitus, diabetes with or without obesity in adults, diabetes in the elderly and diabetes with vascular complications.

6- Glimepiride (GLIMER)

It is a very potent sulfonylurea with long duration of action **indicated** in non-insulin dependent (type II) diabetes, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise or reduction in body weight.

Adverse effects include hypoglycemia, temporary visual impairment, gastrointestinal disturbances. Rarely leucopenia, haemolytic anaemia. Occasionally allergic or pseudoallergic reactions like itching, urticaria or rashes. In isolated cases allergic vasculitis, photosensitivity or a decrease in serum sodium may occur.

B- Biguanides

They lower the blood sugar levels in all types of diabetes mellitus but like sulfonylureas they do not lower the blood sugar level in normal individuals. They act by increasing peripheral anaerobic glycolysis (stimulate peripheral utilization of glucose), inhibit absorption of carbohydrates in gut and sup presses hepatic gluconeogenesis.

1- Metformin (GLYCOMET)

Metformin improves glucose tolerance in NIDDM subjects by lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). They are rapidly absorbed from gastro intestinal tract and show adequate plasma levels and excreted unchanged in urine.

Adverse effects include anorexia, nausea, bitter or metallic taste in mouth, abdominal discomfort, tolerance and lactic acidosis which is the most serious complication and more common with phenformin.

They are indicated in maturity onset non-insulin dependent diabetes mellitus and diabetes mellitus not responding adequately with dietary restrictions or with sulfonylureas.

Biguanides are **contraindicated** in hypotension, alcoholics (can precipitate lactic acidosis), respiratory, hepatic, cardiovascular and renal diseases.

C- Meglitinides

1- Repaglinide (RAPILIN)

Repaglinide is a novel insulin secretagogue. It lowers postprandial blood glucose as well as fasting blood glucose in patients with type II diabetes mellitus by acting on the beta cells of pancreas. It stimulates insulin release only during meal time. It is taken with or just before each meal, thus introducing the concept of 'one meal one dose, no meal no dose' and flexibility of meal times.

Adverse effects include mild or moderate hypoglycemia. Other adverse effects are nausea, vomiting, arthralgia, back pain, and headache.

It is indicated in the management of type II diabetes mellitus in patients who are not responding to diet and exercise.

2- Nateglinide (GLINATE)

Nateglinide is a novel drug designed for the management of postprandial hyperglycemia in type II diabetes. Nateglinide belongs to the meglitinide class of oral hypoglycemic agents. It restores the first phase of insulin secretion in type II diabetes. It is well tolerated and appears to have a significantly lower likelihood of inducing hypoglycemia than sulfonylureas.

Adverse reactions include dizziness, URTI, back pain, flu-like symptoms, bronchitis, cough and hypoglycemia.

It is mainly indicated in the management of postprandial hyperglycemia in type II diabetes mellitus.

D- Thiazolidinediones

1- Rosiglitazone (ENSELIN)

Rosiglitazone, a member of the thiazolidinedione class of antidiabetic agents, improves glycemic control by improving insulin sensitivity. The oral bioavailability of rosiglitazone is 99%. Peak plasma concentrations are observed about one hour after dosing. Rosiglitazone plasma concentration increases in a dose-proportional manner over the therapeutic dose range.

Adverse reactions include weight gain, edema, increase of total cholesterol and reduction in haemoglobin content.

It is indicated in the management of type II diabetes mellitus as monotherapy or in combination.

2- Pioglitazone (GLIZONE)

Pioglitazone hydrochloride, a thiazo lidinedione, acts primarily by decreasing insulin resistance. It improves sensitivity to insulin in muscle and adipose tissue

and inhibits hepatic gluconeogenesis. It also im proves glycemic control while reducing cir culating insulin levels.

E- α-Glucosidase inhibitors

Acarbose (GLUBOSE)

It is a pseudo-tetrasaccharide derived from the fermentation process of the fungus Actinoplanes utahensis. It acts by competitively inhibiting pancreatic alphaamylase and intestinal alpha glucosidase hydrolase enzymes. Thus, it delays carbohydrate digestion, prolongs digestion time and reduces the rate of glucose absorption thereby lowering postprandial hyperglycemia. Given orally less than 2% is absorbed as the oral drug. It is metabolised in the GI tract primarily by intestinal bacteria and to a lesser degree by digestive enzymes.

Adverse effects include flatulence, soft stools, diarrhoea, abdominal distention and pain, rarely abnormal liver function tests and skin reactions.

It is used as first line therapy in NIDDM inadequately controlled by diet and as adjunct to existing conventional oral hypoglycemic agents where hypoglycemic control is inadequate.

3- Glucocorticoids & Sex Hormones Glucocorticoids

Secretion of adrenocortical steroids is controlled by the pituitary release of corticotrophin (ACTH).

The adrenal gland has two main parts:

1- **Adrenal medulla**: which is responsible for the release of catecholamines.
2- **Adrenal cortex**: which secretes glucocorticoids, mineralocorticoids and sex hormones.

The **glucocorticoids** and mineralocorticoids are twenty one carbon compounds having a cyclopentanoperhydro-phenanthrene nucleus. Both these hormones are synthesised in the adrenal cortex from cholesterol (see Fig. 8.3.1).

The important glucocorticoid secreted in human being is **hydrocortisone** (10 mg/ day). They are listed in table 8.3.1.

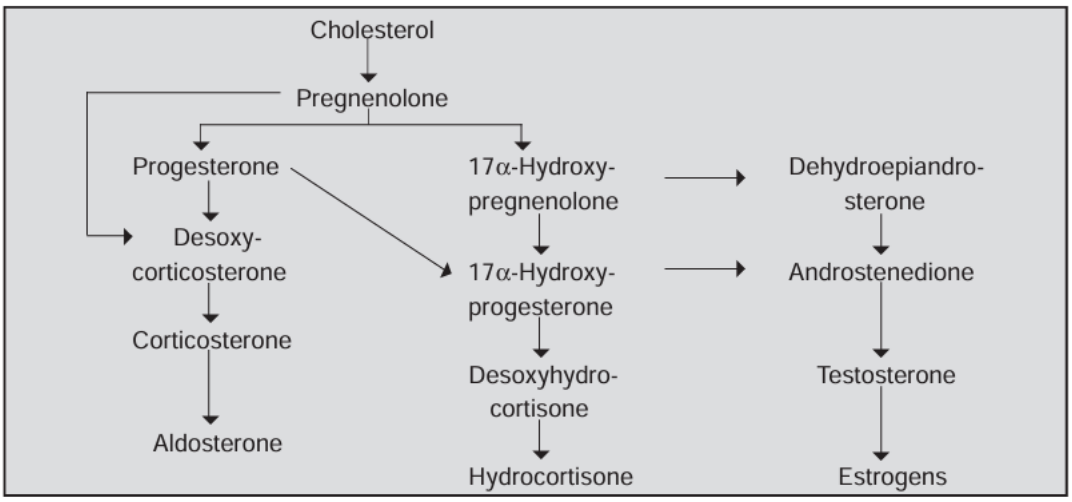

Fig. 8.3.1: Biosynthesis of various steroid hormones.

1- Hydrocortisone (Cortisol; HYCOSON)

Pharmacological Actions

Corticosteroids are synthesized in the adrenal cortex under the influence of ACTH. Glucocorticoids affect the metabolism of carbohydrates, proteins, fats, calcium and electrolytes.

Metabolic effects: Glucocorticoids promote glycogen deposition in liver by stimulating glycogen synthetase activity and increasing glucose production from protein. They also inhibit peripheral utilization of glucose and increase glucose release from liver. It produces resistance to insulin. Glucocorticoids also cause breakdown of protein and amino acid mobilization from peripheral tissues. They stimulate the conversion into glucose (neoglucogenesis) in the liver. Glucocorticoids inhibit the uptake of glucose by fat cells, resulting in increased lipolysis. The increased insulin secretion in response to hyperglycaemia also stimulates lipogenesis and ultimately increase in fat deposition. The catabolic effect on bone can cause osteoporosis in Cushing's syndrome. Glucocorticoids maintain normal glomerular filtration rate. The adrenalectomized animal cannot excrete a water load and tend to develop water intoxication and this can be treated by glucocorticoids. Glucocorticoids also inhibit calcium absorption from intestine and enhance renal excretion of Ca^{2+}.

Mechanism of Action

Most of the established pharmacological effects of glucocorticoids are mediated by cytoplasmic glucocorticoid receptors. After binding to the receptor, the steroid-receptor complex binds to chromatin and stimulate the formation of mRNA. The mRNA stimulates the synthesis of enzymes which produce various pharmacological actions.

Pharmacokinetics

They are given by oral, parenteral and topical route. Oral bioavailability of synthetic cortico-steroids is high. Hydrocortisone after oral administration undergoes extensive first pass

metabolism in liver. They are metabolized in liver and after conjugation are excreted in urine. The synthetic derivatives are metabolized slowly and have longer duration of action.

Adverse Reactions

GIT: Acute erosive gastritis and haemorrhage. Peptic ulcer risk is increased.

Endocrine system: Cushing's habitus, hirsutism, retardation of growth, suppression of hypothalamopituitary-adrenal axis.

Metabolic disorders: Hyperglycemia, glycosuria and diabetes mellitus may be precipitated, osteoporosis.

Eye: Glaucoma, cataract may develop.

CNS: Psychiatric disturbances, euphoria. Other side effects include muscular weakness, delayed healing of wounds, alopecia, hyperglycemia, susceptibility to infections etc.

Therapeutic Uses of Glucocorticoids

Glucocorticoids are used in the following physiological and clinical conditions:

1- Adrenocortical insufficiency:
   - Acute: Hydrocortisone/dexametha sone IV inj.
   - Chronic: Addison's disease; congen ital adrenal hyperplasia (genetic disorder due to deficiency of ste roidogenic enzymes).

2- Rheumatology:
   a. Intraarticular injection: Rheuma toid arthritis, osteoarthritis, gouty arthritis, joint sequelae of fractures and dislocations.
   b. Periarticular/soft tissue injection: Scapulohumeral periarthritis, peri arthritis of hip, bursitis, tendinitis, synovitis, tenosynovitis, tarsalgia, metatarsalgia, epicondylitis, Du puytren's contracture, Peyronie's disease, cystic tumors of aponeuro sis or tendon (ganglia).

3- Severe allergic reactions such as urticaria, serum sickness, anaphylaxis.

4- Bronchial asthma, in acute and severe chronic asthma, aspiration pneumonia and pulmonary edema.

5- Autoimmune haemolytic anaemia, thrombocytopenia etc.

6- Ear disorders:
   a. Allergic rhinitis, nasal polyposis.
   b. Allergic sinusitis.
   c. Cicatrizing lesions of the middle ear.

7- Dermatology: Topical steroids are useful in keloids, hypertrophic scars, other localised hypertrophic, infiltrated, inflammatory lesions of lichen planus,

psoriatic plaques, granuloma annulare and lichen simplex chronicus; discoid lupus erythematosus, necrobiosis lipoidica diabeticorum and alopecia areata.

7- Neurology: Lumbago, sciatica, cervicobrachial neuralgia and other painful radiculopathies; selected cases of inflammatory disorders such as tuberculous meningitis and multiple sclerosis.

8- GIT: Ulcerative colitis, Crohn's disease etc.

9- Malignant diseases: Corticoids are used in combination with other therapy in the treatment of Hodgkin's disease, acute lymphatic leukemia and other lymphomas.

10- Miscellaneous uses: Corticoids in higher dose can be given along with other immunosuppressants in certain organ transplantation cases to prevent rejection reaction.

3- Prednisolone (EMSOLONE)

It is more potent (4 times) than hydrocortisone. It has intermediate duration of action. **Adverse effects** include peptic ulceration, myopathy, steroid psychosis. On prolonged use posterior subcapsular cataract, glaucoma, osteoporosis, hyperglycemia, increased susceptibility to infection, delayed wound healing and Cushing habitus.

It is indicated in suppression of inflammatory and allergic disorders, inflammatory bowel disease, asthma, immunosuppression and rheumatic disease.

4- Triamcinolone (TRICORT)

It is a highly, selective glucocorticoid used in asthma, allergic disorders, rheuma toid arthritis and dermatoses.

5- Dexamethasone (DEXONA)

It is a selective and very potent long act ing glucocorticoid. It causes suppression of pituitary adrenal axis. Used in shock due to trauma, allergic emergencies, rheumatoid arthritis, asthma, nephrotic syndrome and suppression of inflammation in eye and skin disorders.

6- Betamethasone (BETNESOL)

It is a glucocorticoid similar to dexamethasone. **Used** in status asthmaticus, acute allergic reactions, anaphylactic allergic reactions, anaphylactic reaction to drugs, severe shock arising from surgical or accidental trauma or overwhelming infection; Addison's disease, Simmond's disease, hypopituitarism following adrenalectomy, tennis elbow, tenosynovitis and bursitis; rheumatological disease, ulcerative colitis, regional enteritis, TB meningitis and subarachnoid bleed.

SEX HORMONES

A- ESTROGENS

Estrogens are produced mainly by the ovary and the placenta and the synthesis of estrogens takes place from cholesterol (as discussed in section on 'glucocorticoids'). Estrogens are classified into two main groups (see table 8.3.2).

1- Estradiol (as benzoate/cypionate/ enanthate/valerate; ESTRADERM)

is the major secretory product of ovary. Estrogens are required for normal maturation of the female. They stimulate the development of secondary sexual characters e.g. stimulate stromal development, ductal growth in the breast, growth of axillary and pubic hair and alter the distribution of body fat to produce typical female body contours. It also stimulates the development of skin pigmentation particularly in the region of the nipples and areolae and in the genital regions. Estrogens also play a role in stimulation of the proliferative or preovulatory phase of endometrium and vasodilatation of endometrial capillaries. Estrogens are anabolic but weaker than testosterone. Estrogens also cause retention of nitrogen, sodium and fluid in tissues. Estrogens also protect from osteoporosis in postmenopausal women, which occur as a result of estrogen deficiency.

Table 8.3.2: *Classification of estrogens and antiestrogens.*

I. **Natural**	
Estradiol (as benzoate/cypionate/ enanthate/valerate; ESTRADERM)	2.5-10 mg IM
II. **Synthetic**	
Ethinyl estradiol (EVALON)	0.1-1 mg/day
Mestranol	0.1-0.2 mg/day
Diethylstilbestrol	0.5-5 mg/day, oral/IM
Tibolone (LIVIAL)	2.5 mg/day
III. **Antiestrogens**	
Clomiphene citrate (CLOMID)	50 mg/day × 5 days
Tamoxifen citrate (TAMODEX)	20-40 mg/day

Pharmacological Actions

Estrogens act by interacting with the specific estradiol receptors in the cytoplasm of the target cells and mediate the transcription of the relevant mRNA by attaching itself to the appropriate gene. Estrogens produce proliferative changes in the endometrium. On chronic administration, estrogen suppresses the secretion of FSH and somewhat LH resulting in inhibition of ovulation. In testes it may reduce the secretion of androgens and inhibit spermatogenesis. Estrogens suppress lactation without affecting the prolactin level in plasma. On chronic administration it may inhibit the growth of epiphyseal cartilage.

Pharmacokinetics

Natural estrogens are inactive orally due to rapid metabolism in liver. Synthetic estrogens are well absorbed after oral administration as well as by transdermal application. Estradiol is metabolized to estrone and estriol. All these are conjugated and excreted in urine and bile. Synthetic estrogen are metabolized very slowly and are more potent.

Adverse effects include breast discomfort, pruritus, exanthema, thrombophlebitis and local skin irritation, increased risk of gall stones.

Therapeutic Uses

The most common use of estrogen are as oral/parenteral contraceptive and for hormone replacement therapy.

- **Primary hypogonadism**: Estrogens have been used for replacement therapy in estrogen deficient patients (treatment of amenorrhoea).
- **In post-menopausal hormonal therapy**: Estrogen have been used in prevention and treatment of osteoporosis. Improve the general physical, mental and also sexual activity. Maintain calcium balance. Decreases the risk of cardiovascular (coronary artery) disease.

Transdermal estradiol is equally effective:

- In atrophic vaginitis.
- In atrophic urethritis.
- For the treatment of vaginal complaints such as dyspareunia, dryness and itching.
- Pre and postoperative therapy in postmenopausal women undergoing vaginal surgery.
- Infertility due to cervical hostility.
- As a diagnostic aid in case of doubtful atrophic cervical smear.

1- TIBOLONE(LIVIAL)

It is a synthetic steroid which combines oestrogenic and progestogenic activity with weak androgenic activity. It needs to be given continuously without cyclical progestogen. It restores plasma endorphin level in postmenopausal women and act centrally to affect the thermoregulatory system.

Adverse effects include weight changes, ankle edema, dizziness, headache, abdominal pain, GI disturbances, vaginal bleeding, arthralgia, myalgia, migraine, visual disturbances, liver function changes, increased facial hair, depression, skin rash and pruritus.

It is indicated in vasomotor symptoms in estrogen deficiency and osteoporosis prophylaxis.

B- ANTIESTROGENS

Also known as estrogen antagonists or ovulation inducing agents. They act by binding to estrogen receptors.

1- Clomiphene citrate (CLOMID)

It is a triphenyl ethylene compound and a competitive partial agonist inhibitor of endogenous estrogen. It can produce regression of estrogen induced proliferative endometrium. It can also prolong the luteal phase in normal menstruating women. Due to its probable direct effect on ovaries, it may increase the gonadotrophin secretion. It also exerts a weak estrogenic action on endometrium. It is well absorbed after oral administration, metabolized and excreted in bile.

Side effects include hot flushes, ovarian enlargement and cyst formation which may be due to overstimulation and can also lead to rupture and bleeding. Clomiphene is mainly used in the treatment of female infertility due to ovulatory failure and is also found useful to aid in vitro fertilization. It is also used to promote spermatogenesis in male due to oligospermia and asthenosper mia.

2- Tamoxifen citrate (TAMODEX)

It is a competitive partial agonist inhibitor of estradiol at the estrogen receptor and is **used** mainly in the treatment of advanced breast cancer in postmenopausal women. It is also used in male infertility due to its weaker estrogen effect and lesser side effects. It is effective on oral administration and is excreted in bile.

Adverse effects include hot flushes, vaginal bleeding, menstrual irregularities, anorexia, depression and dermatitis.

C- PROGESTERONE

1- Progesterone (MICROGEST)

The physiological functions of progesterone include:

- Induction of secretory phase of the menstrual cycle.
- Development of alveolar system of breasts.
- Preparation of endometrium for the implantation of fertilized ovum for further pregnancy.
- Induction of certain changes in the vaginal epithelium and secretion.
- Increases the basal body temperature and inhibit uterine contractions by decreasing sensitivity of myometrium to oxytocin.

Table 8.3.3: *Classification of progestins and antiprogestin.*

I.	**Progesterone derivatives**	
	Progesterone (MICROGEST)	10-50 mg OD/wk IM
	Medroxyprogesterone (PROVERA)	5-20 mg oral, 50-400 mg IM
II.	**19-Nortestosterone derivatives**	
	Norethisterone (NORGEST)	5-10 mg OD
	Lynoestrenol (Ethinylestrenol)	5-10 mg OD
	Allylestrenol (NIDAGEST)	10-40 mg/day
	Levonorgestrel (OVRAL-G)	0.5-1 mg OD
III.	**Antiprogestin**	
	Mifepristone	600 mg single dose

Pharmacological Actions

Progesterone prolongs the luteal phase and induce decidual changes in the endometrial stroma. It prevents the cornification of the vaginal epithelium and brings about increased glycogen deposition. It changes the watery cervical secretion to viscid, thick and scanty secretion for sperm penetration. Progesterone causes proliferation of acini in the breasts and with the help of estrogen, prepare them for lactation. It causes slight rise in body temperature and this is seen during the luteal phase. Administration during follicular phase suppresses the preovulation LH and prevents ovulation. After reaching cell nucleus it binds to progesterone receptors and influences the transcription of a limited set of genes. After oral administration progesterone undergoes extensive first-pass metabolism in excreted in urine. It has a short plasma half life.

Adverse effects include acne, urticaria, fluid retention, weight changes, GI disturbances, change in libido, breast discomfort, premenstrual symptoms, irregular menstrual cycles, chloasma, depression, pyrexia, insomnia, somnolence, alopecia, hirsutism and rarely jaundice. Injection may be painful.

It is indicated as contraceptive, in hormone replacement therapy, primary and secondary amenorrhoea, dysfunctional uterine bleeding, endometriosis, post ponement of menstruation, premenstrual syndrome, uterine hypoplasia, threatened or habitual abortion and premenstrual ten sion. It is also useful in endometrial carcinoma.

2- Medroxyprogesterone (PROVERA)

Medroxyprogesterone It is a synthetic progestogen structurally related to progesterone given orally or by IM injection.

Adverse effects include skin rash, urticaria, pruritus, depression, nausea, alopecia, acne, hirsutism, galactorrhoea, anaphylaxis, thromboembolic disorders, insomnia, fatigue, dizziness, headache, tenderness of breast and somnolence.

It is used in dysfunctional uterine bleeding, secondary amenorrhoea and endometriosis.

3- Norethisterone (NORGEST)

Norethisterone and its acetate and enanthate esters are synthetic progestogens given orally in the treatment of abnormal uterine bleeding and endometriosis.

Adverse effects include breakthrough bleeding, amenorrhoea, spotting, exacerbation of epilepsy and migraine.

It is indicated in primary and secondary amenorrhoea of long duration, metropathia haemorrhagica, menorrhagia, dysmenorrhoea, polymenorrhoea and premenstrual syndrome.

4- Lynoestrenol (Ethinylestrenol)

It is an oral synthetic progestogen.

Adverse effects include nausea, vomit ing and epigastric discomfort, breakthrough bleeding or spotting, headache, nervousness, migraine, dizziness, edema and breast pain.

It is indicated in dysfunctional uterine bleeding, amenorrhoea, dysmenorrhoea, hypo and hypermenorrhoea, delay of menstrual period, oligo and polymenorrhoea, benign breast disease, endometriosis, metrorrhagia and endometrial carcinoma.

5- Allylestrenol (NIDAGEST)

It stimulates placental progesterone synthesis and increases the secretion of placental hormones.

Adverse effects include nausea, vomiting and epigastric discomfort.

It is indicated in habitual abortion, failure of nidation, threatened abortion, premenstrual tension, metrorrhagia and threatened premature labour.

D-Antiprogestin

Mifepristone

It is 19-norsteroid partial agonist that binds to the progesterone receptor and inhibits the activity of progesterone. If given during the follicular phase it slows down the follicular development and failure of ovulation. It also stimulates uterine contraction and induces menstruation. Oral bioavailability is 25%. It is metabolized in liver and excreted in bile. Its major use is to terminate pregnancy.

It can be used alone or in combination with vaginal pessary of prostaglandin E1 (1 mg) or oral misoprostol to terminate the pregnancy. It is also used as contragestational agent and for induction of labour.

E- ANDROGENS AND ANABOLIC STEROIDS

Androgens are substances which cause development of secondary sex characters in males. The most important androgen secreted by testes is testosterone. Testosterone is synthesized from the cholesterol in testes mainly, under the influence of LH from pituitary. In peripheral

tissues testosterone is partly converted into more active dihydrotestosterone. Adrenal cortex also produces small quantities of weak androgens (androstenedione and dehydroepiandrosterone) which are partially converted to testosterone in peripheral tissues. In females, ovaries also secrete small quantities of testosterone. Follicle stimulating hormone is responsible for the growth of testes. It promotes spermatogenesis. Along with LH, FSH plays an essential role in maintaining the normal testicular functions such as development of male sex organs e.g. penis, scrotum; development of secondary sexual characters e.g. growth of facial, axilla, chest and pubic hair and change in voice; development of accessory sexual organs e.g. seminal vesicles, prostate and epididymis and development of male skeletal musculature. Androgens and anabolic steroids are classified as in table 8.3.4.

Table 8.3.4: *Classification of androgens, anabolic steroids and antiandrogens.*

I. **Natural**	
Testosterone (as propionate, cypionate undecanoate, enanthate; NUVIR)	Propionate 25-200 mg IM per day to bimonthly; undecanoate 40 mg OD-TDS
II. **Synthetic**	
Methyltestosterone	25 mg/day SL
III. ***Anabolic steroids***	
Nandrolone (as decanoate, phenyl propionate; DURABOLIN)	10-100 mg IM once a wk to every 3 wks
Stanozolol (NEURABOL)	2-6 mg/day
Mesterolone (PROVIRONUM)	25-50 mg/day
IV. ***Antiandrogens***	
Danazol (DANOGEN)	200-800 mg/day
Cyproterone acetate	
Flutamide (PROSTAMID)	250 mg TDS

1- Testosterone (as propionate, cypionate undecanoate, enanthate; NUVIR)

It is a natural androgen secreted by testis. The secretion is regulated by LH hormone secreted by pituitary gland. It is responsible for development of sex organs and secondary sex characters in males at puberty. It leads to growth of genitals, growth of hair (pubic, axillary, beard, moustache, body hair), thickening of skin, larynx grows and voice deepens and also behavioural changes. It is also needed for normal spermatogenesis and maturation of spermatozoa. It is also responsible for pubertal spurt of growth in boys leading to increased bony and skeletal muscles growth.

Pharmacokinetics

Testosterone is not given orally as it is extensively metabolised in liver and the bioavailability is low. Testosterone is converted by 5a-reductase in target tissues to more potent dihydrotestosterone. It is metabolized in liver to glucuronic acid and sulfate conjugates and excreted in urine.

Adverse effects include menstrual irregularities, deepening of voice in women, edema, cholestatic jaundice, virilization, priapism, increased libido, acne, precocious puberty, premature epiphyseal closure, gynaecomastia and hepatic

carcinoma and reduction in spermatogenesis. The capacity of androgens to enhance the epiphyseal closure in children may persist for as long as several months after discontinuation of the drug. In children androgens should be used with great caution.

It is indicated in replacement therapy to maintain sex characteristics in adults with testicular failure, accidental castration; in hereditary angioneurotic edema, infertility due to defective spermatogenesis, osteoporosis, refractory anaemia, breast car cinoma, menopausal syndrome, en dometriosis; to improve nitrogen balance in catabolic states; certain types of infertility due to disorders of spermatogenesis.

2- Nandrolone (as decanoate, phenyl propionate; DURABOLIN)

It is closely related to androgen testosterone having both lower androgenic and higher anabolic properties.

Adverse effects include virilism, edema and hypercalcaemia.

It is used in debilitating illness, postmeno pausal osteoporosis, burn or major illness, postmenopausal metastatic mammary carci noma, haemolytic, hypoplastic or malignancy associated anaemias.

3- Stanozolol (NEURABOL)

It is a synthetic steroid with anabolic and androgenic properties.

Used in prophylactic treatment of hereditary angioedema, vascular manifestations of Behcet's syndrome.

Adverse effects include liver damage, virilism, nausea, skin rash, headache and epigastric discomfort.

4- Mesterolone (PROVIRONUM)

It provides oral therapy and does not cause liver damage.

It is indicated in hypogonadism and male infertility.

Adverse effects include frequent erection of penis and priapism.

F- ANTIANDROGENS

1- Danazol (DANOGEN)

It is an isoxazole derivative of ethisterone (17α-ethinyl testosterone) with weak progestational and androgenic activities used to inhibit ovarian and testicular function. It inhibits gonadotrophin secretion from pituitary in both men and women thus inhibiting both testicular/ovarian function.

It is used in menorrhagia, gynaecomastia, fibrocystic breast disease, treatment of visually proven endometriosis or symptomatic control when surgery is contraindicated. It is also used in infertility in women and precocious puberty in boys.

Adverse effects include skin rash, nausea, flushing, headache, weight gain, acne, hirsutism, loss of libido and amenorrhoea.

2- Cyproterone acetate

It has a potent antiandrogen and mild progestional activity. It can also inhibit gonadotropin secretion in larger dose and also suppresses spermatogenesis and Leydig cell function.

It is used in precocious puberty in males, acne, carcinoma prostate and hirsutism and virilization in women.

3- Flutamide (PROSTAMID)

Non-steroidal drug having specific antiandrogen activity. Active metabolite, 2-hydroxyflutamide competitively blocks androgen action on accessory sex organs and pituitary. It leads to increased LH secretion by blocking feedback inhibition.

It is used in advanced carcinoma prostate, female hirsutism.

Bicalutamide is a congener of flutamide, causing less hepatotoxicity and can be given once daily.

4- Thyroid Hormone & Antithyroid Agents

Thyroid gland secretes two important hormones, thyroxine (T_4) and triiodothyronine (T_3). The third hormone, calcitonin secreted from interstitial cells is physiologically different and is responsible for the regulation of calcium metabolism. Thyroid hormones exert their effect by binding to nuclear receptors in target organs. Both the thyroid hormones are well absorbed after oral administration. They are conjugated with sulfuric acid in liver and excreted in bile.

The various preparation used are:

Thyroxine (l-thyroxine sodium) (ELTROXIN)	50-300 µg/day
Liothyronine sodium (TETROXIN)	20-60 µg/day
Thyroglobulin (PROLOID)	32.5-195 mg/day

Therapeutic Uses of Thyroid Hormones:

- Infant hypothyroidism (cretinism).
- Adult hypothyroidism (myxoedema).
- Myxoedema coma: It is an emergency. Liothyronine 100 µg IV can be used and maintained by thyroxine 500 µg IV.
- In the treatment of non-toxic goitre.
- Papillary thyroid carcinoma: It is often responsive to TSH.

Adverse reactions include palpitation, angina, tremors, thyrotoxicosis, allergic reactions, headache, tachycardia, diarrhoea, sweating, restlessness, loss of weight and muscle weakness.

ANTITHYROID AGENTS

These are used to inhibit the functional activity of hypersecretive thyroid gland. The hypersecretion leads to the development of thyrotoxicosis. The antithyroid agents acts by interfering with the synthesis and release of thyroid hormones. They are classified as in table 8.4.1.

Table 8.4.1: *Classification of antithyroid agents.*

I. **Agents which inhibit hormone synthesis**	
Propyl thiouracil	50-100 mg/day (initial) and maintained at 20-30 mg/day
Carbimazole (THYROZOLE)	5-15 mg/day (initial) and maintained at 2.5-20 mg/day
Methimazole	5-10 mg/day (initial) maintained at 2.5-15 mg/day
II. **Agents which inhibit iodide trapping**	
Thiocyanates, perchlorates and nitrates	
III. **Agents which inhibit hormone release**	
Iodine (Lugol's solution: 5% iodine in 10% KI; Colloid iodine: 10% solution)	
Sodium and potassium iodide	
Organic iodide	
IV. **Agents which destroy thyroid gland tissue**	
Radioactive iodine (^{131}I)	3-5 mcurie.

I- Drugs Inhibiting Hormone Synthesis:

The thioamides which include propyl thiouracil and methimazole are the major drugs for the treatment of thyrotoxicosis. In India carbimazole is most commonly used drug. They bind to thyroid peroxidase and prevent the oxidation of iodide and iodotyrosyl residue which subsequently inhibits the formation of tyrosine residue in thyroglobulin and coupling of iodotyrosine residues to T_3 and T_4 .

1- Carbimazole (THYROZOLE)

It inhibits oxidation of iodide, inhibits iodination of tyrosine residue and inhibits the coupling of iodotyrosine residue. After oral administration, it is rapidly absorbed and metabolized to methimazole which is active form and crosses the placental barrier.

Adverse reactions include agranulocytosis, transient leucopenia, arthralgia, nausea, fever, loss of hair and hepatic damage.

It is used in hyperthyroidism due to Graves' disease, prior to surgical treatment of hyperthyroidism i.e., thyroidectomy. It is also used in the treatment of paroxysmal tachycardia and intractable congestive cardiac failure.

II-Agents Which Inhibit Iodide Trapping:

Monovalent anions such as **thiocyanates**, **perchlorates** and **pertechnetate** can block the uptake of iodide by the gland through competitive inhibition of iodide transport mechanism. But it requires higher dose which can cause aplastic anaemia and due to this major drawback they are not used clinically.

III- Agents Which Inhibit Hormone Release:

Iodine inhibits hormone release. They inhibit organification and hormone release and also decrease the size and vascularity of hyperplastic gland on regular administration. Peak antithyroid affect is seen in two weeks after which thyrotoxicosis may reoccur. It is well absorbed orally and crosses the placental barrier.

Adverse effects include angioedema, fever, thrombocytopenia, arthralgia, lymphadenopathy, salivation, sneezing and swelling of lips and eyelids.

Iodine is used in thyroid storm, hyperthyroidism, preoperatively before thyroidectomy and prophylaxis of endemic goitre. Iodine is also useful as antiseptic and in expectorants.

The iodinated contrast agents, ipodate and iopanic acid are used in the treatment of hyperthyroidism. These drugs rapidly inhibit the conversion of T4 to T3 in the liver, kidney, brain and pituitary gland.

IV- Agents Which Destroy Thyroid Gland Tissue:

^{131}I is the only radioisotope of iodine used in the treatment of thyrotoxicosis. The other isotopes ^{123}I and ^{125}I are used only in diagnosis. ^{131}I emits gamma and beta radiations. It is available as sodium solution. When taken orally, it is rapidly absorbed, concentrated by the thyroid and incorporated into the storage follicles. Beta radiation penetrates up to 3 to 5 mm into the soft tissue, they destroy some of the thyroid follicles and produce fibrosis.

Adverse reactions include hypothyroid ism, thyroid carcinoma, damage to foetal thyroid and possibility of genetic damage, so contraindicated during pregnancy.

Radioactive iodine is indicated in hyperthyroidism due to Graves' disease or toxic nodular goitre and also used as palliative therapy after thyroidectomy for papillary carcinoma of thyroid.

5- Hormonal Contraceptives

Hormonal contraceptive are the most effective spacing methods of contraception. They are used for reversible suppression of fertility.

A- ORAL CONTRACEPTIVES

The oral hormonal contraceptive can be classified as in table 8.5.1.

Table 8.5.1: *Classification of oral contraceptives.*

Estrogen		Progestins
Ethinyl estradiol (20, 50 µg)	+	Norethindrone (1, 3 and 4 mg) (ANOVLAR)
Ethinyl estradiol (50 µg)	+	Norgestrel (0.5 mg) (OVRAL-G)
Ethinyl estradiol (30 µg)	+	Norgestrel (0.5 mg) (PRIMOVLAR-30)
Ethinyl estradiol (30 µg)	+	L-Norgestrel (0.3 mg) (OVRAL-L)
Mestranol (100 µg)	+	Ethynodiol diacetate (1 mg) (OVULEN)
Mestranol (50 µg)	+	Ethynodiol diacetate (1 mg) (OVULEN-50)
Ethinyl estradiol (50 µg)	+	Lynestrenol (1 mg) (LYNDIOL)

1- COMBINED PILLS

It is a combination of estrogen and progestin given together for remarkable efficacy, safety and ease in administration. It has total 21 pills, each pill is given orally for 21 consecutive days beginning on the 5th day of menstrual cycle (when the bleeding occurs this is considered the first day of cycle). The pill is to be taken everyday at a fixed time, preferably before going to bed at night.

2- PHASED PILLS

This is a combined pill but biphasic or triphasic in nature e.g. the estrogen level is kept constant but the progestin amount is low in early phase and increasing in subsequent phases of menstrual cycle. Fifth day to tenth day menstrual cycle (ethinyl estradiol 30 µg + levonorgestrel 50 µg), eleventh to fifteenth day (ethinyl estradiol 30 µg + levonorgestrel 75 µg), sixteenth to twenty fifth day (ethinyl estradiol 30 µg + levonorgestrel 125 µg). They are supplied in one pack of different coloured pills starting from fifth day of menstrual cycle to twenty-fifth day and next pack can be started after a gap of seven days as in case of combined pills.

3- MINIPILL

It is also known as progestin only pill (POP). It contains only progestins, which is given in small amount throughout the men strual cycle (without interruption) but because of lower efficacy rate, it is not much popular.

Norgestrel (OVRETTE)	0.075 mg
Norethindrone (MICRONOR)	0.35 mg

4- POSTCOITAL CONTRACEPTION

The postcoital (morning after) contraception is recommended within 48 hours after an unprotected intercourse, rape or contraceptive failure.

Diethylstilbestrol 5 mg per day is given for five days.

Other regimens used are combination of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 to 1 mg. Two tablets are taken 12 hours apart within three days of intercourse. Levonorgestrel 0.75 mg (1 tablet) is also used and is taken as early as possible (within 72 hrs) and second tablet after 12-24 hours of first tablet. Withdrawal bleeding occur within 3-7 days.

B- INJECTABLE FORMULATIONS:

They are usually given by IM route. They lead to higher incidence of menstrual irregularities and amenorrhoea.

- Norethindrone enanthate (NORISTERAT) 200 mg given once in two months.
- Depot medroxyprogesterone acetate (DEPOT PROVERA) 150 mg given once in 3 month and 400 mg given once in 6 month. Some subcutaneous and intrauterine implants of progesterone have also been used which are prepared in biodegradable polymeric matrices.

Mechanism of Action of Oral Contraceptives

The oral contraceptives act by the dif ferent mechanisms.

- Inhibiting ovulation by blocking the release of follicle stimulating hormone and luteinising hormone from the anterior lobe of pituitary gland.
- Increasing the thickness of cervical mucus due to progestins and producing an unfavourable environment for pen etration of sperm and further conception.
- Inducing other changes in the uterine mucosa which may be unfavourable for the implantation of fertilized ovum. This action is important in minipills and postcoital pills.

Adverse Effects

The most common side effects are nausea, vomiting, headache, dizziness, fatigue, weight gain and breast fullness. The other side effects which appear after sometime of therapy are acne, increased body hair, pigmentation of cheeks, nose and forehead (chloasma).

The other serious side effects include high blood pressure, increased risk of myo cardial infarction, thromboembolic diseas es like thrombophlebitis, venous thrombo sis, cerebral thrombosis.

They were suspected to lead to increased risk of cancer of breast and carcinoma of cervix and endometrium.

CENTCHROMAN

Its a nonsteroidal estrogen antagonist, which acts by preventing implantation due to embryouterine asynchrony, accelerated tubal transport and suppression of decidualization. It has no effect on pituitary or ovarian functions. It is taken 30 mg twice weekly for 12 weeks followed by once a week as long as fertility is to be suppressed.

C- MALE CONTRACEPTIVE

The main research focus is different approaches e.g. agent which prevent spermatogenesis, interfering with sperm storage and maturation and preventing sperm transport in vas deferens. But the hormones which suppress sperm production tend to lower testosterone and affect the potency and libido. The one product obtained from cotton seed oil, Gossypol which is categorized as non-hormonal selective spermatogenesis suppressant, is effective in producing azoospermia or severe oligospermia but it is not widely used as male contraceptive. Mechanism of action is not known. Adverse effects are edema, diarrhoea, hypokalemia, neuritis.

Reference:

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