**DIABETES MELLITUS**

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by a high blood concentration of glucose (hyperglycemia)

**Types of D.M:**
- **Type I:** (Immune-mediated D.N, Insulin dependant D.M, Juvenile D.M) ➞ No insulin release (Insulin Dependant) (IDDM)
  - Treatment ➞ mainly Insulin
- **Type II:** (Non-immune mediated, Non-insulin dependant D.M, Adult onset D.M) ➞ There is ↓ insulin release or ↓ peripheral sensitivity to insulin (Non Insulin Dependant) (NIDDM)
  - Treatment ➞ mainly Oral antidiabetic drugs

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**Insulin**

**Chemistry:**
- It is a polypeptide hormone (51 amino a.). Formed of 2 chains:
  - **A** (21 a.a) & **B** (30 a.a) connected together by 2 bisulphide bridges (S-S)

**Secretion:**
- It is secreted from B-cells of the pancreas
- A-cells secrete Glucagone which is the counter insulin hormone & D-cells secrete Somatostatin

**Regulation of secretion:**

<table>
<thead>
<tr>
<th>↑ Secretion by:</th>
<th>↓ Secretion by:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1- Foods:</strong> - Glucose is the strongest</td>
<td><strong>1- Drugs:</strong> Thiazide – Diazoxide – Phenytoin</td>
</tr>
<tr>
<td>- Some amino acids (eg.: Arginin &amp; Leucin)</td>
<td><strong>2- Systemic hormone:</strong> Somatostatin &amp; Adrenaline</td>
</tr>
<tr>
<td><strong>2- Systemic hormones:</strong> Glucagone &amp; Growth h.</td>
<td><strong>3- Local hormone:</strong> PGE₁</td>
</tr>
<tr>
<td><strong>3- GIT hormones:</strong> (eg.: Gastrin – Secretin – Cholecystokinin – Enteroglucagone – Gastrin inhibitory polypeptide)</td>
<td><strong>4- α-agonist</strong></td>
</tr>
<tr>
<td><strong>4- β₂ &amp; Muscarinic agonists</strong></td>
<td></td>
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</tbody>
</table>

**Kinetics:**

1- Not effective orally used SC or IV of soluble insulin in emergency
2- Bound to plasma protein
3- Has extensive hepatic metabolism (50 %) by insulinase enzyme
4- Short t½ after IV injection (5 min.)
Mechanism of action:

1- Insulin binds to (Insulin receptors) which is a (Tyrosine kinase receptor) formed of 2α & 2β subunits
   o this binding → activation of tyrosine kinase → phosphorylation of intracellular protein → insulin action
2- Insulin → ↑PDE & ↓AC → ↓c.AMP induced by counter regulating hormones
   eg: Glucagone

Actions of insulin:

1) ↓Glucose in blood (Hypoglycemia):
   1- Facilitate glucose transfer into cells
   2- ↑Glucose utilization (↑Oxidation, Glycolysis, Glycogenesis & Lipogenesis)
   3- ↓Glucose output (↓Gluconeogenesis & Glycogenolysis)

2) ↓FFA in plasma:
   1- ↑lipogenesis
   2- ↓lipolysis

3) ↓Ketone body formation by the Liver
4) ↓K⁺ - Mg²⁺ & PO₄ in plasma as insulin ↑their uptake by cells
5) Anabolic effect as it ↑amino acid uptake by cells & ↓nitrogen in urine

Indications of insulin:

1) DM:
   1- Type I DM (IDDM)
   2- Type II DM (NIDDM):
      1. Not controlled by diet & oral hypoglycemic drugs
      2. During stress periods: pregnancy – surgery – infections
   3- Emergency Diabetic ketoacidosis (DKA) → soluble
2) Anorexia Nervosa: to ↑Appetite
3) Renal failure: (with glucose) to ↓Hyperkalemia
Side effects of insulin: *Hypoglycemia is the most important

1) Local:
   1. SC lipo-atrophy or lipo-hypertrophy
   2. Allergy & Arthus reaction (Type III hypersensitivity: repeated SC injections \(\Rightarrow\) local vasculitis, necrosis & erythema)
   3. 2ry infection

2) Systemic:
   1. Allergy: (rare) \(\Rightarrow\) Change the source of insulin
   2. Insulin resistance: \(\Rightarrow\) Due to formation of anti-insulin antibodies
   3. Hypoglycemia:
      Causes: 1. Too much insulin 2. Too little food 3. Too much exercise
      Manifestation:
      1. Sympathetic stim. \(\Rightarrow\) sweating – tachycardia – tremors – pallor
      Treatment:
      1. If pt. is conscious \(\Rightarrow\) oral glucose
      2. If pt. is unconscious \(\Rightarrow\) Glucose 50%, 50 ml, IV, + glucagon, 1 mg, IM or SC + adrenaline SC

4- Hypokalemia
5- Weight gain: can be avoided by adding Metformin

**NB.** Somogyi effect (Pseudoresistance): is a rebound hyperglycemia (occurring early in the morning) following insulin induced hypoglycemia (usually occurs at midnight), because of the release of counter-regulatory hormones (as growth hormone & epinephrine). Avoided by ↓ the dose of insulin or ↑ the food intake in the evening

**NB.** Diabetic Ketoacidosis (DKA):

**Causes:** 1. Too little insulin 2. Too much food 3. Stress period

**Manifestations:**
1. Anorexia – nausea – vomiting – abdominal pain
2. Polydipsia – polyuria – dehydration
3. Tachypnea – acetone odour on breath
4. Stupor – coma
5. Laboratory:-Blood \(\Rightarrow\) hyperglycemia & acidosis -Urine \(\Rightarrow\) glucosuria -&acetone

**Treatment:**
1- For hyperglycemia:
   Soluble insulin 20 U IV, then 0.1 U / Kg / h. IV infusion
2- For acidosis: Na lactate – Ringer lactate or Na bicarbonate IV infusion
3- For dehydration:
   - Saline (0.9 % Na Cl) IV infusion till glucose level < 300 mg, then
   - Glucose 5 % IV infusion to avoid hypoglycemia
4- KCl: added to IV fluids to prevent hypokalemia which can develop during insulin therapy
5- Antimicrobials: for infections
Preparations of insulin:

<table>
<thead>
<tr>
<th>Type of Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Ultra-short (Rapid) acting:</td>
<td>5-15 min</td>
<td>1 h.</td>
<td>2-4 h.</td>
</tr>
<tr>
<td>- Insulin lispro (Humalog)</td>
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<tr>
<td>- Insulin aspart (Novolog)</td>
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<tr>
<td>- Insulin glulisine (Apidra)</td>
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<tr>
<td>2- Short acting:</td>
<td>15-30 min</td>
<td>2-4 h.</td>
<td>5-7 h.</td>
</tr>
<tr>
<td>- Soluble (Regular)</td>
<td>30-60 min</td>
<td>4-6 h.</td>
<td>12-16 h.</td>
</tr>
<tr>
<td>- Semilente</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3- Intermediate acting:</td>
<td>2-4 h.</td>
<td>8-10 h.</td>
<td>18-24 h.</td>
</tr>
<tr>
<td>- Lente (insulin zinc suspension)</td>
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<tr>
<td>- Isophane (NPH)</td>
<td></td>
<td></td>
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<tr>
<td>4- Long (Slow) acting:</td>
<td>4-6 h.</td>
<td>14-20 h.</td>
<td>24-36 h.</td>
</tr>
<tr>
<td>- Ultralente (extended insulin zinc suspension)</td>
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<tr>
<td>- Protamine Zinc (PZ)</td>
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</tbody>
</table>

NB:
1. Insulin glargine (Lantus) & insulin detemir (Levemir) are new long acting insulins with no peak value (peakless) ➔ less incidence of hypoglycemia
2. Insulin glargine & insulin detemir can not be mixed with other insulins
3. Soluble insulin can not be mixed with PZ as excess protamine may precipitate soluble insulin

Sources of insulin

1- Bovine: 3 amino acid difference from human ➔ more antigenic
2- Porcine: 1 amino acid difference from human ➔ less antigenic
3- Human: by recombinant DNA technology
Administration of insulin:
1- Routes of administration:
a- SC: usual route  b- IV: of soluble insulin in emergency  c- Inhalation
2- Methods of administration:
   - Disposable plastic syringe or IV set - Portable pen injectors - Insulin pumps - Inhaled insulin

3- Regimens of insulin therapy:
   1- Single daily injection:
      [Intermediate acting + Soluble insulin] 30 min. before breakfast
   2- Twice daily injection:  The commonest regimen
      [Intermediate acting + Soluble insulin] 2/3 dose before breakfast & 1/3 dose before supper
   3- Multiple daily injections:
      [Intermediate acting] before breakfast & supper &  [Soluble insulin] 30 min. before each meal

2- Oral Anti-Diabetics
(Oral Hypoglycemics)
Classifications:
1- Insulin secretagogues:  1. Sulphonylurea
   2. Meglitinides (Repaglinide)
   3. Dipeptidyl peptidase-4 inhibitors (Sitagliptin – Vidagliptin)
2- Insulin sensitizers:  1. Biguanides (Metformin)
   2. Thiazolidenediones (Rosiglitazone & Pioglitazone)
3- Inhibitors of glucose absorption: α-glucosidase inhibitors (Acarbose & Miglitol)

(1) Sulphonylurea

<table>
<thead>
<tr>
<th>1st generation</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Tolbutamide</td>
<td>1/2-2 g</td>
<td>6-12 h.</td>
</tr>
<tr>
<td>2- Acetohexamide</td>
<td>1/4-1.5 g</td>
<td>12-24 h.</td>
</tr>
<tr>
<td>3- Chlorpropamide</td>
<td>0.1-0.5 g single</td>
<td>Up to 60 h.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd generation</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Glibenclamide (Daonil)</td>
<td>2.5-20 mg</td>
<td>10-24 h.</td>
</tr>
<tr>
<td>2- Glipizide</td>
<td>2.5-40 mg</td>
<td>12-24 h.</td>
</tr>
<tr>
<td>3- Gliclazide (Diamicron)</td>
<td>80-240 mg</td>
<td></td>
</tr>
<tr>
<td>4- Glimeperide (Amaryl)</td>
<td>1-8 mg single</td>
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</table>

NB.: Chlorpropamide is effective in both diabetes (DM & DI) as it ↑ADH
**Mechanism of action:**
1- ↑ Release of insulin through block of ATP dependant K⁺-channels
2- ↑ Sensitivity to insulin action
3- ↓ Release of glucagon

**Indications:** *Non IDDM* & *Non*-obese, after failure of diet & exercise

**Contraindications:**
1- Type I DM
2- Type II DM during stress periods (pregnancy – infection – surgery)
3- History of DKA
4- Severe hepatic or renal disease

**Side effects:**
1- Hypoglycemia (the most important & dangerous)
2- Allergy
3- Blood dyscrasia & Bone marrow depression
4- Chlorpropamide may cause: - Water retention ➔ Dilutional hyponatremia - Cholestatic jaundice - Disulfiram like reaction (Alcohol flush phenomenon)
5- Exhaustion of β-cells
6- Failure: either 1ry (from the start) or 2ry (after 1-2 years)
7- GIT disturbance & Weight Gain
8- ↑ incidence of coronary Heart disease (Angina)

**Drug interactions:**

1- **Drugs ↑ hypoglycemic effect of sulphonylurea:**
   - Drugs causing displacement: - Aspirin - Sulphonamides – Oral Anticoagulants - Phenylbutazone
   - HME inhibitors: Allopurinol - Probenicid – MAO.I
   - Drugs causing hypoglycemia: Propranolol (also mask the symptoms of hypoglycemia)

2- **Drugs ↓ hypoglycemic effect of sulphonylurea:**
   - Cortisone – Oral Contraceptives - Thiazide

(2) **Meglitinide** *(Repaglinide & Nateglinide [Starlix]*)
- As Sulphonylurea ➔ ↑ secretion of insulin
- Used instead of Sulphonylurea if the patient is hypersensitive to sulpha
- Side effect: Hypoglycemia
(3) Dipeptidyl peptidase-4 (DPP-4) inhibitors

(Sitagliptin – Vildagliptin)

**Mechanism:** they ↓ DPP-4 enzyme which degrades glucagone like peptide-1 (GLP-1) ➔

↑ GLP-1 ➔ ↑ glucose mediated insulin secretion - ↓ glucagon secretion

Used alone or with metformin

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(4) Biguanide

**Preparations:**
- Metformin (Glucophage): 0.5gm tds.

**Mechanism of action:**
1. ↓ absorption of glucose
2. ↓ gluconeogenesis
3. ↑ glycolysis
4. ↑ glucose uptake
5. ↑ insulin binding to receptors (*No effect on insulin secretion*)
6. ↓ glucagon level

**NB:** Biguanides are not hypoglycemic but Euglycemic

**Indications:** Non IDDM & Obese, After failure of diet & exercise
**NB:** Metformin may be used in ttt of infertility caused by Polycystic ovarian syndrome

**Side effects:**
1. Lactic acidosis (*the most important*)
2. GIT disturbances
3. ↓ absorption of vit.B₁₂ after long use

**Contraindications:**
1. Renal – hepatic – heart disease
2. Advanced age
3. Generalized hypoxia eg.: COPD
4. Alcoholism

**NB:** Metformin & orlistat may be used to ↓ incidence of Type II DM in prediabetics

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(5) Thiazolidinediones "Glitazones"

(Rosiglitazone & Pioglitazone)

- ↑ Peripheral effect of insulin through ↑ PPAR-γ receptor

- **Side effect:**
1. Fluid retention ➔ edema & weight gain
2. Hepatotoxic (marked with *Troglitazone* which is obsolete)
3. Rosiglitazone (Avandia) may ↑ incidence of heart attack
(6) **α-glucosidase inhibitors**  
(Acarbose & Miglitol)

- ↓ glucosidase enz. → ↓ absorption of CHO  
  → ↓ Post-prandial glucose elevation
- **Side effect:**  
  1- Flatulence (Distension)  
  2- Impair oral absorption of Digoxin

### Management of DM

1- **Type I (IDDM)**  
Diet + Exercise + Insulin

2- **Type II (NIDDM)**

1- Start with *Diet + Exercise*

2- If failed → **add oral hypoglycemic:**
   - If obese → Metformine  
   - If non-obese → Sulphonylurea

3- If failed → **Metformine + Sulphonylurea**

4- If failed → **Metformine + Sulphonylurea + Glitazones**

5- If failed → Stop Sulphonylurea & give Insulin

6- **If stress period** → stop temporarily oral hypoglycemic & give soluble insulin till recovery

7- If renal failure → Stop permanently oral hypoglycemic & give Insulin

3- **Management of Hypoglycemia** (see before)

4- **Management of DKA** (see before)

### Diet in DM

* Well balanced diet

**Total caloric intake:**
- Depends on age – weight – physical activities
- About 2000 – 2500 calories / day

**Dietary composition:**
1- CHO: 50 % mainly polysaccharide
2- Fats: 30 % mainly unsaturated fat
3- Proteins: 20 %
4- Fibers: as in bran & vegetables → slow absorption of glucose

**Timing & size of meals:**
1. 3 main meals + 3 snacks in between
2. Breakfast should be taken within 1/2 hour after morning insulin dose

**Sweeteners:** Aspartam (Dietsweet) → 2 amino acids

**Vitamins:** esp. vit. B₁ & B₁₂
**Insulin + oral antidiabetics:**

1- **In type I DM:**
   In severe insulin resistance, *insulin sensitizers* as biguanides may be added to *insulin*

2- **In type II DM:**
   - *Insulin secretagogues* as *sulphonylureas* may be added to *insulin glargine* at bed time:
     - BIDS (Bedtime Insulin, Daytime Sulphonylurea)
   - Also in insulin resistance, *insulin sensitizers* as biguanides may be added to *insulin*

**N.B.: EXENATIDE:**

- **Nature:** It is an analogue of *glucagon like peptide-1* (GLP-1)
- **Actions:** ↑ glucose mediated insulin secretion - ↓ glucagon secretion - ↓ gastric emptying - ↓ appetite
- **Uses:** given by *SC injection* in *type-2 DM* in combination therapy with other antidiabetic drugs

**N.B.: PRAMLIPTIDE:**

- **Nature:** It is an analogue of *amylin* by substitution of proline
- **Actions:** ↓ glucagon secretion - ↓ gastric emptying - ↓ appetite
- **Uses:** given by *SC injection* in *type-1 & type-2 DM* in combination therapy with other antidiabetic drugs

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**Glucagon**

*single chain peptide hormone 29 amino acids secreted from pancreatic A- cells*

**Kinetics:**
- Given parenterally
- Metabolized in: liver, kidney & plasma

**Mechanism:** G-protein linked receptor ➔ ↑ AC ➔ ↑ c.AMP

<table>
<thead>
<tr>
<th>Actions:</th>
<th>Uses:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Metabolism ➔ Hyperglycemia</td>
<td>1- Severe hypoglycemia</td>
</tr>
<tr>
<td>2- Endocrine ➔ ↑ secr. of: Insulin - Catecholamines - Calcitonin</td>
<td>2- Assess pancreatic B-cell secretory reserve (<em>Glucagone test</em>)</td>
</tr>
<tr>
<td>3- Heart ➔ +ve inotropic &amp; chronotropic</td>
<td>3- In β-blocker poisoning</td>
</tr>
<tr>
<td>4- Smooth m. ➔ Relaxation</td>
<td>4- Radiology of the bowel</td>
</tr>
</tbody>
</table>
THYROID GLAND

Thyroid gland secretes:
1- Thyroid hormones: - T₃ (Tri-iodo-thyronine)
   - T₄ (Tetra-iodo-thyronine) (Thyroxin)
2- Calcitonin

Iodine metabolism:
1- Food contain mainly organic iodine (not absorbed)
2- In GIT: organic iodine ➔ Inorganic iodide (well absorbed)
3- 50 % of circulating iodide is trapped & concentrated in thyroid gland & 50% is excreted in urine

Biosynthesis of Thyroid hormones:

1- **Iodide trapping:** Active uptake of iodide by thyroid cell via sodium/iodide symporter (NIS) under the effect of TSH, ATP (source of energy) & Na⁺/K⁺ ATPase enzyme

   **NB:** Trapping is inhibited by:
   1. Monovalent group as "Perchlorate & Thiocyanate"
   2. Cardiac glycosides
   3. Anaerobic conditions

2- **Oxidation:**
   Inorganic iodide ➔ Peroxidase enz. ➔ Elementary iodine
3- **Organification:** Elementary iodine combines with tyrosine residue of colloidal thyroglobulin ➔ Mono-iodo-tyrosine (MIT) & Di-iodo-tyrosine (DIT)

**NB.:** Thyroglobulin is synthesized inside the thyroid cell & stored outside the cell in the colloid

4- **Coupling:** of MIT & DIT catalyzed by peroxidase enz. to form T$_3$ & T$_4$

5- **Storage:** of MIT, DIT, T$_3$ & T$_4$ attached to thyroglobulin extracellularly in the colloid

6- **Endocytosis & Proteolysis:** of thyroglobulin & release of T$_3$ & T$_4$ under control of TSH

### Control of thyroid function:

1) **Thyroid pituitary relationship:**
   1- Cold ➔ Hypothalamus to secrete TRH
   2- TRH ➔ Ant. Pituitary to secrete TSH
   3- TSH ➔ Thyroid gl. Through ➔ of cell membrane receptor ➔ AC ➔ c.AMP ➔ ➔ size & vascularity , ➔ function of thyroid gl. & ➔ release of T$_3$ & T$_4$
   4- T$_3$ & T$_4$ ➔ -ve feedback on TRH & TSH

2) **Autoregulation:** Related to the level of iodine in the blood, eg.: large doses of iodine ➔ ➔ organification

3) **Abnormal thyroid stimulators:**
   In Grave's disease, Lymphocytes secretes TSI (Thyroid stimulating immunoglobulin). This immunoglobulin acts as TSH but with longer action (LATS)

### Kinetics of Thyroid h.:

1- Well absorbed orally
2- Distributed all over the body
3- The Major part are bound to thyroxin binding globulin (TBG)

4- **Fate:**
   1. **Deamination**
   2. **Decarboxylation**
   3. **Deiodination of T4 in tissues:**
      - Of the outer ring ➔ more active T$_3$
      - Of the **inner** ring ➔ reverse T$_3$, which is **inactive**
   4. Conjugation with glucuronic a. & sulphoric a., then excreted in bile ➔ enterohepatic circulation

### Mechanism of action of thyroid hormone:
They enter the cell & bind to intracellular receptor present in the nucleus ➔ affect DNA transcription & synthesis of m.RNA
**Actions of Thyroid h.:**

1- **Caloroginic effect:** ➔ ↑ BMR & O₂ consumption

2- **Metabolism:**
   a. CHO: ↑ glucose absorption
   b. Fat: Lipolysis
   c. Protein: Catabolic effect
   d. Cholesterol: Hypocholestremia
   e. Ca⁺⁺: Mobilization from bones ➔ Hypercalcemia

3- **Growth:** Important for physical, mental & sexual development

4- **CNS:** -ve feedback on TRH & TSH
   - Nervousness & Tremors

5- **ANS:** Supersensitivity of adrenergic receptors & ↑ number of β-receptors

6- **CVS:** Cardiac stimulation & Peripheral VD

7- **GIT:** ↑ appetite & motility ➔ Diarrhea

8- **Kidney:** Diuretic effect

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**Toxicity & side effects:**

1- **Iatrogenic hyperthyroidism**

2- **Cardiotoxic:** Arrhythmia – Angina – Infarction

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**Uses:**

1- **Replacement therapy** in Hypothyroidism
   (Myxoedema – Myxoedema coma – Cretinism)

2- **To ↓ TSH** in:
   - Puberty goiter & Hashimoto thyroiditis
   - TSH dependent tumors

3- **To ↓ Cholesterol** in euthyroid patient by D-thyroxin

4- **Gynecological disorders:** as Amenorrhea & infertility due to hypothyroidism

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**Preparations of Thyroid h.:**

1- **Levothyroxin (L-T4):** delayed onset & long duration

2- **Liothyronin (L-T3):**
   - Rapid onset & short duration
   - Stronger than T4 (3-4 times) ➔ high risk of cardiotoxicity. Used in Myxoedema coma

3- **Liotrix:** T₄ + T₃ in a ratio of 4 : 1

4- **D-thyroxin:** Hypocholestremic in euthyroid patients

5- **Dried extract of animal origin:** Antigenic & obsolete

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**Anti-thyroid Drugs**

Used in cases of Hyperthyroidism

1- **Thioamides (Thiourea)**

2- **Ionic inhibitors**

3- **Iodide**

4- **Radioactive iodine**

5- **B-blockers (Propranolol)**
   ➔ control peripheral effects
(1) **Thioamides** (Thiourea - Thioureylenes)

**Preparations:** 1- Propylthiouracil (PTU) 2- Methimazole 3- Carbimazole

**Kinetics:**
1- Well absorbed orally
2- Passes BBB & Placenta (less with PTU as it is more strongly bound to plasma protein)
3- In the liver: Carbimazole \(\rightarrow\) Methimazole
4- Excreted in urine & milk

**Mechanism of action:**
1- ↓ Synthesis of Thyroid h. through: \(\downarrow\) Peroxidase enz. \(\Rightarrow\) ↓ Oxidation of iodide, ↓ Organification & ↓ Coupling
2- Propylthiouracil \(\Rightarrow\) ↓ peripheral conversion of T\(_4\) into more active T\(_3\)

**NB.:**
1- The effect appears after a latent period 1-2 weeks till depletion of thyroid stores
2- ↓ synthesis \(\Rightarrow\) ↓ release \(\Rightarrow\) ↑ TSH \(\Rightarrow\) ↑ size & vascularity

**Uses:**
1- Mild cases of Hyperthyroidism
2- Adjuvant to radioactive iodine till its effect appears
3- Preparation of the patient for Thyroidectomy (not preferred??)

**Side effect:**
1- Allergy: the most common
2- Agranulocytosis: the most serious
   1. More liable fore infections \(\Rightarrow\) Sore throat
   2. Frequent blood count is needed
3- Depigmentation of hair
4- Exophthalmos
5- ↑ size & vascularity
6- GIT disturbances
7- Liver & Kidney damage
8- Cross the placenta \(\Rightarrow\) Foetal Goiter (more with methimazole than PTU)
9- Joint pain

(2) **Ionic inhibitors**

**Include:** \(K^+\) Perchlorate & Thiocyanate

**Mechanism:** ↓ Synthesis of Thyroid h. through **competitive inhibition of iodine uptake** (so, the effect can be antagonized by excess iodide)

**Side effect:** Fatal aplastic anaemia (so, not used now)

(3) **Iodides**

**Preparations:** 1- Logol's iodine 2- Potassium iodide

**Mechanism of action:**
1- ↓ effect of TSH on Thyroid gland \(\Rightarrow\):
   - ↓ size & vascularity of thyroid gland & become firmer
   - ↓ Organification & iodine binding
2- ↓ Protease enz. \(\Rightarrow\) ↓ Release of T\(_4\) & T\(_3\)
Uses:
1- Hyperthyroidism:
   1. In Thyroid crisis (as it has rapid onset within 24 h.)
   2. Preparation for thyroidectomy (as it ↓ size & vascularity)
   3. Prophylactic to prevent Goiter
2- Saline expectorant

Side effects:
1- Iodism: conjunctivitis, rhinitis, sialadenitis, bronchitis & metallic taste
2- Allergy & skin rash
3- Foetal goiter

NB.: Ipodate sodium: is an iodinated contrast medium which ↓ conversion of T₄ into more active T₃

(4) Radio-active iodine (I¹³¹)

Mechanism of action:
After oral administration, it is concentrated in the gland & emits β particles & γ rays ⇒ destruction of thyroid follicles & the effect appears after 1-2 months

Uses:
1- Treatment of:
   a- Hyperthyroidism:
      i. In old age
      ii. Recurrence after surgery
      iii. Failure of other ttt
   b- Cancer thyroid
2- Diagnosis of thyroid function

Side effects:
1- Hypothyroidism
2- Malignant changes after many years

Contraindications:
1- Young age
2- Pregnancy & lactation

(5) β-blockers (Propranolol)
- Use β-blockers with No intrinsic sympathomimetics activity as Propranolol
- ↓ Peripheral conversion of T₄ into more active T₃

Uses:
1- Control peripheral symptoms until the effect of other anti-thyroid drugs appear
2- In thyroid crisis

NB.: Thyroid crisis (Storm): is treated by:
1- Control of hyperpyrexia
2- IV fluids – Hydrocortisone
3- Propranolol (Life saving) - Propylthiouracil – Sodium iodide
ADRENOCORTICAL STEROIDS (CORTICOSTEROIDS)

- Steroid hormones are secreted from suprarenal cortex
- They include: Glucocorticoids, Mineralocorticoids, & Sex hormones

Cholesterol

Progesterone

Pregnanolone \rightarrow 17-Hydroxypregnanolone

17-Hydroxyprogesterone \rightarrow Dehydroepiandrosterone

[11-\beta-Hydroxylase enz]

Aldosterone

Cortisol

17-Hydroxyprogesterone

Dehydroepiandrosterone

Androsterone

Testosterone

Estradiol

Glucocorticoids (Cortisol)

Physiology:
- Synthesized from cholesterol by the cells of zona fasciculata & reticularis
- Released under the control of ACTH which is secreted from anterior pituitary in a circadian rhythm under the control of CRF secreted from hypothalamus

Kinetics:
1- Well absorbed orally & bound to plasma protein (95 %)
2- In liver: Corisone (inactive) \rightarrow Cortisol (Hydrocortisone) active, then conjugated with glucuronic & sulphoric acid
3- Excreted in urine

Mechanism of action:
- Cortisol enters the cell by passive diffusion & binds with mobile cytoplasmic receptor \rightarrow enter the nucleus & affect DNA transcription, either:
  1- \uparrow DNA transcription \rightarrow \uparrow m.RNA \rightarrow \uparrow protein synthesis \rightarrow anabolic effect esp. in liver & visceral organs
  2- \downarrow DNA transcription \rightarrow catabolic effect esp. in Lymphoid t. – Connective t. – Fibroblast – Sk. m. – Bone
# Actions & Side effects:

<table>
<thead>
<tr>
<th>Actions:</th>
<th>Side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1-CNS:</strong></td>
<td>1- Iatrogenic Cushing (see figure)</td>
</tr>
<tr>
<td>1. -ve feed back: On CRH &amp; ACTH</td>
<td>2- Sudden stop ⇒ Addisonian crisis</td>
</tr>
<tr>
<td>Adrenal atrophy</td>
<td>3- Psychosis &amp; Insomnia</td>
</tr>
<tr>
<td>2. Euphoria &amp; Psychosis</td>
<td>4- Hyperglycemia</td>
</tr>
<tr>
<td>3. Anti-stress</td>
<td>5- Osteoprosis</td>
</tr>
<tr>
<td>2- Metabolic:</td>
<td>6- Myopathy &amp; Sublaxation of joints</td>
</tr>
<tr>
<td><strong>1. CHO:</strong></td>
<td>7- Cataract</td>
</tr>
<tr>
<td>a- ↑ gluconeogenesis</td>
<td>8- Teratogenicity</td>
</tr>
<tr>
<td>b- ↑ glycogenesis</td>
<td>9- Delayed healing of wounds</td>
</tr>
<tr>
<td>c- ↑ glucose leveling blood as it ↓ utilization</td>
<td>10- Lipaemia</td>
</tr>
<tr>
<td>2. Proteins:</td>
<td>11- Moon face &amp; buffalo hump</td>
</tr>
<tr>
<td>a- Catabolic effect on:</td>
<td>12- Oedema</td>
</tr>
<tr>
<td>lymphoid t. – C.T. – sk.m. – bone – fibroblast</td>
<td>13- Weight gain</td>
</tr>
<tr>
<td>b- Anabolic effect on:</td>
<td>14- Hypokalemia (C.I with digitalis)</td>
</tr>
<tr>
<td>liver &amp; visceral organs</td>
<td>15- Hypocalcemia</td>
</tr>
<tr>
<td>3. Fats:</td>
<td>16- Mask infection ↓ inflam. mediators</td>
</tr>
<tr>
<td>a- Lipolysis ⇒ ↑ FFA</td>
<td>17- Contraindicated in TB&amp; viral Infection</td>
</tr>
<tr>
<td>b- Redistribution ⇒ moon face &amp; buffalo hump</td>
<td>18- Contraindicated with live or attenuated vaccines</td>
</tr>
<tr>
<td>4- Electrolytes &amp; salts:</td>
<td></td>
</tr>
<tr>
<td>a- Na⁺ &amp; water retention ⇒ oedema &amp; weight gain</td>
<td></td>
</tr>
<tr>
<td>b- K⁺ depletion ⇒ Hypokalemia</td>
<td>5- Uric a. ⇒ uricosuric effect</td>
</tr>
<tr>
<td>c- Ca++ ⇒ Hypocalcemia as it has anti-vit.D effect &amp; ↓ Ca++ absorption</td>
<td></td>
</tr>
<tr>
<td>d- Uric a. ⇒ uricosuric effect</td>
<td></td>
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<tr>
<td>5. ↑ free water clearance in DCT</td>
<td></td>
</tr>
<tr>
<td>3- Anti-inflammatory:</td>
<td></td>
</tr>
<tr>
<td>1. Synthesis of lipocortin ⇒ ↓ phospholipase A₂ ⇒ arachidonic a. ⇒ ↓ PGs &amp; leukotrien synthesis</td>
<td></td>
</tr>
<tr>
<td>2. ↓ capillary permeability</td>
<td></td>
</tr>
<tr>
<td>3. ↓ migration of Neutrophils</td>
<td></td>
</tr>
<tr>
<td>4. ↓ circulating Eosinophils – Basophils – Lymphocytes – Monocytes</td>
<td></td>
</tr>
<tr>
<td>5. ↓ production of inflammatory mediators</td>
<td></td>
</tr>
<tr>
<td>6. Stabilization of lysosomes</td>
<td></td>
</tr>
<tr>
<td>4- Immunosuppressive:</td>
<td></td>
</tr>
<tr>
<td>1. ↓ T-cell prolif. &amp; activation</td>
<td></td>
</tr>
<tr>
<td>2. ↓ IgG production</td>
<td></td>
</tr>
<tr>
<td>5- Anti-allergic:</td>
<td>↓ Ag/Ab reaction</td>
</tr>
</tbody>
</table>
6- Blood:
1. ↑ Erythropoiesis & RBCs
2. ↑ Coagulability of the blood
3. ↑ Circulating Neutrophils (see before)
4. ↑ Platelets
5. ↓ Eosinophils
6. ↓ Basophils
7. ↓ Lymphocytes
8. ↓ Monocytes

As cortisone redistributes them from blood to lymphoid tissues

7- CVS:
1. Hypervolemia & Hypertension
2. Anti-shock

20- Hypertension

8- Respiration:
↑ Surfactant production in foetal lung at term

9- GIT:
Peptic ulceration due to ↓ mucous & ↑ acidity

21- Peptic ulcer

(Rang & Dale 2003)

Cushing syndrome & Side effects of cortisone
**Uses of cortisol:** Therapeutic & Diagnostic

**A) Therapeutic:**

1- **Physiological dose** as Replacement therapy in Adreno-cortical insufficiency (Addison disease):
   1. Chronic Addison disease: Cortisol or Fludrocortisone
   2. Acute Addison disease: Cortisol IV + Saline + Glucose 5%

2- **Supraphysiological dose in:**
   1. **Adreno-cortical Hyperfunction:** (*Congenital adrenal hyperplasia*):
      In pregnancies at risk of this defect, fetuses can be protected by administration of *Dexamethasone* to the mother (to ↓ ACTH)
   2. **Stimulation of lung maturation:**
      In fetus by giving *Betamethasone* to the mother at term

3- **Suppressive therapy:**
   1. Suppression of immunity in Auto-immune disease as in:
      a. Collagen dis.: Arthritis – Myositis – Systemic lupus erythematosus
      b. Blood dis.: Aplastic anemia – Haemolytic anemia – Agranulocytosis
      c. Ulcerative colitis
   2. Suppression of tissue rejection in transplantation
   3. Suppression of lymphopoiesis in Lymphoma & Leukemia

4- **Anti-inflammatory:**
   1. Encephalitis & *cerebral edema*
   2. Rheumatic carditis
   3. Chronic active Hepatitis
   4. Nephritis & Nephrotic syndrome
   5. Arthritis (Rheumatic – Rheumatoid – Gouty – Osteoartheritis)
   6. Bell’s palsy (unilateral facial paralysis)

5- **Anti-allergic:**
   Skin – Eye – *Bronchial asthma* – anaphylactic shock – contact dermatitis

6- **Anti-shock:**

7- **Antihypervitaminosis D & Hypercalcemia**

**B) Diagnostic:**

**Diagnosis of Cushing syndrome** (*Dexamethasone suppression test*):
   Low dose can suppress normal adrenal but not the tumor (in Cushing)

**Contraindications:** See Side effects
Precautions during long term therapy:

1- Observation of: Body weight – Blood pressure – Blood glucose – Peptic ulcer – Hidden infections
2- Routine X-Ray on spine / 6 months
3- Diet: Rich in proteins – K⁺ - Ca²⁺ – Low NaCl – Give anabolic steroids
4- ↑ dose in stress
5- Gradual withdrawal

Preparations:

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Glucocorticoid activity (Anti-inflammatory effect)</th>
<th>Mineralocorticoid activity (Salt retaining effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cortisol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>- Cortisone</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>- Prednisone</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>- Prednisolone</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Intermediate acting:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tramcinolone</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>- Paramethasone</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Long acting:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Betamethasone</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>- Dexamethasone</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mineralocorticoids:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fludrocortisone</td>
<td>10</td>
<td>150</td>
</tr>
<tr>
<td>- Desoxycorticosterone acetate (DOCA)</td>
<td>0</td>
<td>50</td>
</tr>
</tbody>
</table>

NB.: Cortisone & Prednisone are activated in the liver
2- Prednisone is given orally only
3- Structure activity relationship:
   1. ↑ Anti-inflammatory effect by:
      a- Double bond between C₁ & C₂
      as in: Prednisolone
      b- Fluorine atom at 9 position
      as in: Tramcinolone – Paramethasone
      – Betamethasone - Dexamethsone
   2. ↓ Salt-retaining activity by
      16-α hydroxylation or methylation as in:
      Tramcinolone – Paramethasone – Betamethasone - Dexamethsone
Mineralocorticoids

(1) Aldosterone:
- **Synthesis:** from Cholesterol in zona glomeruloza
- **Control of release:**
  1. Renin-angiotensin system (mainly):
     Angiotensin-II $\uparrow$ both synthesis & release
  2. $\downarrow$ Na$^+$ or $\uparrow$ K$^+$ in blood $\Rightarrow$ $\uparrow$ only the release
- **Actions:**
  - On DCT: - Na$^+$ & H$_2$O retention
  - K$^+$ & H$^+$ depletion
- **Not used clinically**

(2) Desoxycorticosterone (DOC)
- It is a precursor of aldosterone
- **No** glucocorticoid activity
- Used with cortisol in Addison: Used **SL or IM not orally**

**NB.:**
- **Desoxycorticosterone acetate (DOCA):** given **SL, IM or SC**
- **Desoxycorticosterone trimethyl acetate (DOCTA):** **IM** once monthly

(3) Fludrocortisone:
- **Both** glucocorticoid & Mineralocorticoid activity
- Used **orally** alone in Addison dis.

Glucocorticoid Antagonists
(Adrenostatics)

1) Metyrapone (Metopyrone):
   - $\downarrow$ 11-$\beta$ Hydroxylase enz. $\Rightarrow$ $\downarrow$ Both Cortisone & Aldosterone
   - Used in (metyrapone test) to assess ant.pituitary & adrenal function

2) Mitotane:
   - Causes **atrophy** of adrenal gland
   - Used in **Adrenal carcinoma**

3) Aminoglutithemide:
   - $\downarrow$ conversion of Cholesterol into Pregnanolone $\Rightarrow$ $\downarrow$ Steroid synthesis
   - Used in **Adrenal carcinoma** after failure of Mitotane

4) Ketokonazole in high doses:
   - It is antifungal & in high doses $\Rightarrow$ $\downarrow$ Steroid synthesis

**NB.:** Mineralocorticoid antagonists (Aldosteron antagonists):
Spironolactone & Eplerenone $\Rightarrow$ see kidney
SEX HORMONES

1) Progestins
Synthesized & Released from corpus luteum, placenta, adrenal cortex & testes

Preparation:
1. Natural: Progesterone I.M
2. Synthetic:
   - IM: Hydroxyprogesterone & Medroxyprogesterone
   - Oral: Medroxyprogesterone, Norethindrone, L-Norgestrel

Mechanism of action: As cortisone

Actions:
2. Endometrium:
   - Secretory changes after ovulation
   - Maintain pregnancy as it:
     - ↓ Sensitivity to oxytocin
     - Suppress T lymphocytes ➔ ↓ rejection
3. CNS:
   - Thermogenic action & ↓ LH
4. Androgenic & Virilising effect.
5. Antagonize aldosterone

Uses:
1. Hormone replacement therapy
2. Suppress ovulation in cases of: Contraception – Dysmenorrhea – Endometriosis

Side effects:
1. Teratogenic
2. Breakthrough bleeding
3. Breast cancer
**Anti – progesterone**

1- **Mifepristone (Mifebrix):**
   1. **Mechanism of action:** competitive antagonist at progesterone & glucocorticoid receptors
   2. **Uses:** as an emergency postcoital contraception & abortifacient to terminate pregnancy in the 1st 7 weeks after conception.

2- **Danazol:**
   1. **Mechanism of action:**
      - Partial agonist at progesterone & Androgen receptors
      - Midcycle surge of L.H. & F.S.H \(\Rightarrow\) ↓ ovulation & spermatogenesis
   2. **Uses:**
      - Endometriosis
      - Fibrocystic disease of the breast.
   3. **Side effects:**
      - Virilization (deepening of voice - acne - hirsutism - weight gain - ↓ breast size)
      - Hepatic dysfunction.

2) **Estrogens**

- Synthesized & released from ovary, placenta, adrenal cortex & testes
- Under control of FSH

**Preparations:**

1. **Natural steroidal:** [not effective orally]
   - *Estradiol, Estrone, Estriol*
   - Estradiol is the most potent & it is metabolized in liver & peripheral tissues into Estrone & Estriol

2. **Synthetic:**
   1. **Steroidal:**
      - Orally: *Ethynyl estradiol & Mestranol*
      - Parenterally: *Estradiol monobenzoate & Estradiol valerate*
   2. **Non–Steroidal:**
      - *Diethylstilbestrol, Dienestrol & Chtorotrinisene*

**Mechanism of action:** \(\Rightarrow\) as cortisone through stimulation of estrogen receptors

**Actions:**

1. **Female maturation:**
   - Development of 2ry sex characters
   - Development of the vagina, uterus & uterine tubes.

2. **Endometrium**
   - Responsible for proliferative phase
   - Continuous exposure to estrogen \(\Rightarrow\) Endometrial hyperplasia & bleeding

3. **Endocrine:**
   - Pituitary: - In females: - ↓ Prolactin - ↓ F.S.H \(\Rightarrow\) ↓ ovulation
     - In males: ↓ F.S.H & LH \(\Rightarrow\) infertility & atrophy of prostate & ↓ androgen secretion
• Thyroid: ↑ Globulin level ⇔ ↑ binding of T₃ & T₄ ⇔ ↓ Free form ⇔ ↑ TSH ⇔
  Physiological goiter.
• Parathyroid: antagonize the osteoclastogenic effect of PTH ⇔ ↓ bone resorption

4. Metabolism:
• Na & H₂O retention ⇔ edema
• Lipid profile: ↑ HDL, ↓ LDL & ↓ Cholesterol BUT ↑ triglycerides
• Hyperglycemia

5. Blood coagulation:
• ↑ Coagulability as they ↑ synthesis of coagulation factors

6. Others:
• ↑ libido & mood
• ↑ Synthesis of progesterone receptors & ↑ Sensitivity to oxytocin

Uses:

1. Replacement therapy:
   a. Primary hypogonadism:
      It’s used as replacement therapy to develop 2ry sex characters at age of 13 years
   b. Post menopausal therapy:
      • Benefits:
        1. Improves ⇔ hot flushes, sweating & atrophic vaginitis
        2. ↓ Rate of bone loss & osteoporosis
        3. ↓ Incidence of cardiovascular disease as they ↓ LDL & cholesterol.

2. Suppressive therapy:
   1. Suppress temporarily excessive uterine bleeding
   2. Suppress ovulation in: dysmenorrhea - contraceptive pills & Endometriosis
   3. Suppress Lactation
   4. Suppress (ovarian function associated with ↑ secr. of androgens) in cases of
      Amenorrhea & Hirsutism
   5. Suppress androgen in Androgen dependent prostatic tumours.

Side effects:

1. Nausea & rarely vomiting
2. Na⁺ & water retention ⇔ 1- Migraine headache
   2- Breast tenderness (Mastalgia)
   3- Edema- Weight gain
   4- Hypertension
3. Hyperpigmentation
4. Thromboembolic disease
5. Cholestasis & gall bladder stones
6. Post–menopausal bleeding which may mask bleeding due to endometrial cancer
   2 - ↑ risk of adenocarcinoma of the vagina in young women whose
    mother were treated during pregnancy with diethylstilbestrol
Anti-estrogens

1- Selective estrogen receptor downregulators (SERDs)

**Examples:** Clomiphene - Tamoxifen - Fulvestrant

**Mechanism of action:** competitive pure antagonist at estrogen receptors

**Uses:**
- Clomiphene ➔ induction of ovulation is cases of infertility (as they ↓ estrogen ➔ ↓ –ve feedback ➔ ↑ F.S.H & L.H ➔ ↑ ovulation)
- Tamoxifen & Fulvestrant ➔ Estrogen dependent breast cancer

**Side effects of clomiphene:**
- Ovarian cyst
- Multiple pregnancy
- Hot flushes
- Alopecia.

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2- Selective estrogen receptor modulators (SERMs)

**Examples:** Raloxifen

**Mechanism of action:** estrogen receptor agonist at bone, brain & liver
But antagonist at breast & endometrium

**Uses:**
- Raloxifen ➔ Estrogenic effect on bone ➔ ↓ osteoporosis
  - Anti-estrogenic effect on breast ➔ ↓ breast cancer

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3- Selective aromatase enzyme inhibitors (SAEIs)

- **Examples:** Anastrazole & Letrazole
- **Mechanism:** potent inhibitors of aromatase enzyme, which is responsible for conversion of androgens to estrogens
- **Uses:** to ttt advanced breast cancer

**NB.: Hormone replacement therapy in menopause**

- Estrogen is given to replace its decreased level
- Progestin may be added to counter the estrogenic effect on uterus (uterine hyperplasia)
- **Tibolone:** is a synthetic molecule with combined weak estrogenic, progestogenic & androgenic effects

**Benefits:** ➔ see estrogen

**Side effects:** ➔ Side effects of estrogen

**NB.:**
1- ↑ risk of uterine cancer if estrogen is used alone
2- ↑ risk of breast cancer if estrogen is used with progestin

**Contraindications:** ➔ See side effects of estrogen.
Hormonal contraceptives

Preparations:

1. **Injectable contraceptives:**
   1. Medroxyprogesterone acetate 150 mg I.M every 3 months.
   2. Side effects: - Irregular bleeding
      - Suppression of ovulation may persist up to 18 months after last injection.

2. **S.C Implants:**
   1. L-Norgesterel is implanted under the skin giving contraception for 5 years.
   2. Side effects: Irregular bleeding

3. **Oral contraceptive pills:**
   1. **Combined method:**
      - Estrogen + Progesterone:
        started on the 5th day of the cycle for 3 ws & rest for 1w.
      A – Ordinary dose pills:
        - Estrogen (Ethinyl estradiol or mestranol) + Progesterone
        - High content of Estrogen  ➔ nauseae, vomiting & thromboembolic dis.
      B - Low dose pills: Low dose  ➔ Break through bleeding.
      C - Triphasic pills
        - 0.03 mg Estrogen + 0.050 mg progestogen for 6 d.
        - 0.03 mg Estrogen + 0.075 mg progestogen for 5 d.
        - 0.03 mg Estrogen + 0.125 mg progestogen for 10 d.
      Advantages: - ↓Thrombo–embolic dis & vomiting
      - ↓Break through bleeding
   2. **Sequential method:**
      - Start by estrogen alone for 14-16 d.
      - Then Estrogen + Progestogen for 5 – 6 d
   3. **Progesterin only or Minipill:**
      - Low dose of progestogen is given daily.
      - Advantages:  ➔ Can be given to lactating women.
   4. **Post-coital contraceptives (Emergency contraception):**
      - Start pills within 72 hour after coitus.
      - Types:
        ▪ Estrogen alone
        ▪ L-Norgestrel (Plan-B)
        ▪ Mifebristone + Misoprostol (abortifacient)
      - Side effects: - Nausea & vomiting
        - Cancer vagina of female offspring if pregnancy has occurred.
Mechanism of action:

1) **The combination of Estrogen & progestogen:**
   - ↓ Pituitary gonadotropins (F.S.H & L.H) ➔ ↓ ovulation
   - Change the cervical mucous, Endometrium, motility & secretion of uterine tubes ➔ ↓ conception & implantation.

2) **Progestin alone:**
   Doesn’t always ↓ ovulation & the contraception is largely due other mechanisms

Uses:
1. Contraception
2. Severe Dysmenorrhea
3. Dysfunctional uterine bleeding.
4. Endometriosis

Side effects:

1- **Mild:**
1. CNS: Headache & Migraine headache
2. Skin: Pigmentation, Acne, Hirsutism
3. Edema ➔ Weight gain - Mastalgia
4. GIT: Nausea
5. Blood: Change in serum proteins: ↑TBG, ↑SHBG, ↑CBG
6. Gynecological:
   1- Failure of withdrawal bleeding ➔ confusion with pregnancy.
   2- Breakthrough bleeding: the most common with progestational agents
   3- Vaginal infection
   4- Amenorrhea & Galactorrhea may occur for several years following cessation of oral contraceptives.

2- **Severe:**
1. C.V.S: a- Thromboembolic disease, Hypertension & Myocardial infarction
   b- Cerebrovascular stroke
2. C.N.S: Depression
3. G.I.T: a- Cholestatic Jaundice
   b- Cholecystitis
   c- Ischemic bowel disease

**Contraindications:**
1. Adolescents & women > 35 years esp. obese & smokers
2. Breast & uterine tumors as uterine fibroid
   (both are Estrogen sensitive tumors)
3. C.N.S: Migraine – Convulsions – Depression
4. C.V.S: Hypertension – Thromboembolic disease – CHF
5. D.M
6. Liver disease
7. Vaginal bleeding with unknown cause
**Drug interactions:**

1) **Drugs ↓ effect of pills:**
   1. Enzyme inducers: eg: Phenobarbiton, phenytion, smoking
   2. Liquid paraffin: ↓ absorption

2) **Drugs ↑ side effect of pills:**
   1. Smoking
   2. Antifibrinolytic

3) **Pills ↓ effect of other drugs:**
   1. Anti hypertensives
   2. Anti hypercholesteremic (Clofibrate) through ↑ glucuronide conjugation
   3. Anti coagulant
   4. Anti diabetic

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**3) Androgens & Anabolic steroids**

**Preparations:**

1) **Natural**
   1. Testosterone (mainly) & Dihydrotestosterone (More potent) secreted mainly from testis under the control of L.H
   2. Androstenedione & Dehydroepiandrosterone secreted mainly from adrenals under the control of A.C.T.H

2) **Synthetic:**
   1. Testosterone esters: Testosterone Propionate
   2. 17 – alkyl testosterone derivatives: - Methyl testosterone - Oxandrolone - Nandrolone

*N.B.* Oxandrolone & Nandrolone are anabolics used in:
- Osteoporosis
- General wasting
- Acute renal failure
- Aplastic anaemia

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**Mechanism of action:**

With mobile cytoplasmic receptor

1) In most tissue: testosterone $\xrightarrow{5-\alpha \text{ reductase}}$ dihydrotestosterone

2) In sk.m. It’s active by itself.

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**Actions:**

1) Androgenic:
   1. Stimulate development of male 2ry sex characters
   2. With F.S.H $\Rightarrow$ stimulate spermatogenesis

2) Anabolic: effect on sk.m – bone & blood

3) Metabolic: salt & $\text{H}_2\text{O}$ retention
Uses:
1. Replacement therapy in hypogonadism in male – whether 1ry or 2ry
2. Delayed Puberty in boys
3. Gynecological disorders:
   - Metastatic cancer breast
   - With estrogen in post-menopausal syndrome
4. Osteoporosis

Side effects:
1. Hepatic dysfunction & Jaundice esp with 17– alkyl derivatives
2. Verilization & Muscularization of women & female fetus of pregnant women.
3. ↓ Testicular size & function with azospermia
4. Gynecomastia & oedema

Anti – androgens

1) Cyproterone & Flutamide:
1. Competitive androgen receptor antagonists.
2. Used in:
   - To decrease sexual desire in men
   - To treat cancer prostate
   - To treat hirsutism in women & can be combined with estrogen.

2) Finasteride: [Proscar]
1. Steroid like inhibitor of 5-α reductase enz. ➔ reducing the production of the more potent androgenic; dihydrotestosterone at peripheral tissues
2. Used in: Benign prostatic hypertrophy (B.P.H) as it ↓ prostatic volume & ↑ urine flow.

3) Danazol: see before

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NB.: Drugs used to treat benign prostatic hypertrophy (BPH):
1- $\alpha_1$ -adrenoceptor antagonist:
   as Terazosin & Tamsulosin
2- 5-α reductase enz. Inhibitor:
   as Finasteride
3- Saw palmeto plant extract:
   may reduce the synthesis of testosterone
**CALCIUM HAEMOSTASIS**

*1ry agents affecting Ca++ haemostasis:*
1. Parathyroid hormone
2. Calcitonin
3. Vit. D

*2ry agents affecting Ca++ Haemostasis:*
1. Biphosphonates
2. Plicamycin
3. Calcimemetics: *Cinacalcet*
4. Glucocorticoid
5. Estrogen
6. Thiazide diuretic
7. Loop diuretic
8. Calcium supplements
9. Fluoride

<table>
<thead>
<tr>
<th>Structure &amp; secretion</th>
<th>1- Parathyroid hormone (P.T.H)</th>
<th>2 – Calcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action:</strong></td>
<td>Peptide hormone secreted from parathyroid in response to: ↓ Ca++ or β agonists.</td>
<td>Membrane bound receptor ➔ A.C ➔ c.A.M.P</td>
</tr>
<tr>
<td><strong>Actions:</strong></td>
<td>↑ Ca++ &amp; ↓ P</td>
<td>As PTH</td>
</tr>
<tr>
<td></td>
<td>- ↓ reabsorption of phosphate</td>
<td>↓ reabsorption of Ca &amp; P</td>
</tr>
<tr>
<td></td>
<td>- ↑ formation of 1,25 (OH)₂ D₃</td>
<td>2. <em>Bone</em>:</td>
</tr>
<tr>
<td>2. <em>Bone</em>:</td>
<td>↑ activity of osteoclast ➔</td>
<td>↓ activity of osteoclast ➔</td>
</tr>
<tr>
<td></td>
<td>↓ Bone resorption</td>
<td>↓ Bone resorption</td>
</tr>
<tr>
<td>3. <em>G.I.T</em>:</td>
<td>↑ absorption of Ca++ indirectly via ↑ 1,25 (OH)₂D₃</td>
<td></td>
</tr>
<tr>
<td><strong>N.B:</strong> PTH, paradoxically stimulate osteoblast activity if given therapeutically in low intermittent dose (<em>Teriparatide</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uses:</strong></td>
<td>in severe hypocalcemia &amp; Acute tetany</td>
<td>1. Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Osteoporosis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Paget’s disease**</td>
</tr>
<tr>
<td><strong>Preparations:</strong></td>
<td>Parathyroid hormone</td>
<td>1. Human calcitonin: IM- S.C</td>
</tr>
<tr>
<td></td>
<td>IM (not effective orally)</td>
<td>2. Synthetic salmon calcitonin: IM- S.C &amp; Nasal spray</td>
</tr>
</tbody>
</table>

*Osteoporosis:* there is decrease in the bony mass predisposing to fracture, while in *Osteomalacia* there is no decrease in bony mass, but there is defect in mineralization (*Rickets* is a juvenile form of osteomalacia)

**Paget’s disease:** is a localized bone disease characterized by uncontrolled osteoclastic bone resorption with 2ry increase in poorly organized bone
3 – Vitamin D.

* **Synthesis & preparations**

1. **vit. D₃**: cholesterol → Skin UV → *Cholecalciferol* (vit D₃) → Liver

   25 (OH) D₃ (*Calcifediol*) → Kidney PTH → 1,25 (OH)₂ D₃ (*Calcitriol*)

   (The most active metabolite)

2. **Vit. D₂**: Ergosterol → Plant Metab. → *Ergocaliferol* (vit D₂)

    2. **Calcipotriene**: 1,24 hydroxylated vit D₃ for topical administration & has reduced effect on Ca Haemostasis

3. **Alfacalcidol**: 1 (OH) cholecalciferol By passing the kidney

* **Mechanism of Actions**: through binding with intracellular receptor

* **Actions**: ↑ Ca & ↑ P

   1. Kidney: ↑ Reabsorption of Ca & P
   2. G. I. T: ↑ Absorption of Ca & P
   3. Bone: regulate Ca & P resorption & bone formation

   vit D is needed for maturation & calcification of epiphyseal cartilage

* **Uses**:

   1. *To ↑ serum Ca in cases of Hypocalcemia due to*:


   2. *To ↓ cellular proliferation*

      1. *Calcitriol* may be used in leukaemia
      2. Topical *calcipotriene* may be used in psoriasis

* **Side effects**: Hypervitaminosis which lead to:

   1. Hypercalcemia
   2. Osteoporosis
   3. Soft tissue calcification & renal calculi

---

**2ry agents affecting Ca⁺⁺ haemostasis**

1) **Biphosphonates**:

   - Etidronate – Pamidronate – Alendronate

   * **Action**: ↓ plasma Ca⁺⁺ as they ↓ bone resorption


2) **Calcinemetics (Cinacalcet)**:

   * **Action**: antagonise the effect of PTH through ↑ of Ca sensing receptor (CaSR)

   * **Uses**: in ttt of hyperparathyroidism & parathyroid carcinoma

3) **Plicamycin (Mithramycin)**:

   * **Action**: Cytotoxic antibiotic ↓ plasma Ca⁺⁺ via ↓ bone resorption

   * **Uses**: Paget’s disease & Hypercalcemia [small dose]

4) **Loop diuretic**:

   ↑ Renal excretion of Ca → ↓ plasma Ca⁺⁺ → used in Hypercalcemia.
5) Thiazide diuretic:
   ↓ Renal excretion of Ca^{++}  ⇒ ↑ plasma Ca^{++}  ⇒ used in osteoporosis & hypercalceuria

6) Glucocorticoids:
   - ↓ Intestinal absorption of Ca^{++} by interfering with 1,25 (OH) D_{3}  ⇒ hypocalcemia
   - ↓ Osteoblastic activity  ⇒ ↓ bone formation.

7) Estrogens:
   - They inhibit the action of PTH on bone & kidney  - Used in osteoporosis

8) Calcium supplements:
   Ca carbonate (40% Ca), Ca lactate (18%) & Ca gluconate (9%)

9) Fluoride:
   - Effective in preventing dental caries
   - When combined with Ca^{++}  ⇒ ↓ frequency of fracture

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**N.B.: Treatment of osteoporosis:**

1) Antiresorptive drugs: Drugs that ↓ osteoclastic activity & bone resorption
   1- Biphosphonates
   2- Calcitonin
   3- Estrogen
   4- Selective estrogen receptor modulators (SERMs): Raloxifen

2) Anabolic drugs: Drugs that ↑ osteoblastic activity & bone formation
   - Teriparatide: recombinant PTH, given once daily SC injection

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**THYROID GLAND**

1) Hypoparathyroidism:
   - Due to damage after thyroidectomy or idiopathic
   - Hypoparathyroidism  ⇒ ↓ Ca^{++} & ↑ PO_{4} & manifested by Tetany
   - **ttt of Tetanic convulsions:**
     1- Calcium gluconate, 20 %, 10 ml, slow IV
     2- PTH
     3- Vit D_{3}
     4- Vit. D_{2} analogue [Dihydrotachysterol (AT10)] which has weak anti-rachitic actions but more active in ↑ blood calcium

---

2) Hyperparathyroidism:
   1- 1st: due to adenoma treated by X-ray or surgical
   2- 2nd: to hypocalcaemia due to:
      1. Renal Dysfunction:
         a) Renal failure where hyperphosphatemia interfere with bone resorption  ⇒ ↓ blood calcium  ⇒ hyperparathyroidism
            - ttt: by correction of Ca^{++} level as in hypoparathyroidism
         b) ↓ of hydroxylase enz. In kidney  ⇒ ↓ formation of 1, (OH) vit.D_{3}
            ⇒ inadequate Ca^{++} absorption
            - ttt: by Vit. D (active forms)
      2. Dietary deficiency: as Vit. D deficiency or low Ca^{++} intake
         - ttt: by correcting the deficient factor
HYPOTHALAMIC & ANT. PITUITARY HORMONES

1) Hypothalamic hormones:
   1. Growth hormone releasing factor (GHRF): Sermorelin is an analogue
   2. Growth hormone inhibitory factor (GHIF): Somatostatin
   3. Prolactin releasing factor (PRF)
   4. Prolactin inhibitory factor (PIF): Dopamine
   5. Thyrotropin releasing hormone (TRH)
   6. Corticotropin releasing hormone (CRH)
   7. Gonadotropin releasing hormone (GnRH)

2) Anterior Pituitary hormones:
   1. Growth h.
   2. Prolactin
   3. Thyroid stimulating h. (TSH)
   4. Adrenocorticotrophic h.
   5. FSH
   6. LH

1) GHIF (Somatostatin):
   - Peptide hormone secreted from: Hypothalamus – D cells of pancreas – Gut
   - **Actions:** ↓ release of: Growth h. – Glucagons – Insulin – Some gut peptides
   - **Uses:** ttt of Acromegally

   **NB.:** Octreotide: Somatostatin analogue

2) Gn.RH:
   - Peptide hormone released from hypothalamus
   - **Actions & Uses:**
     1. **Acute or pulsatile administration:** ↑ LH & FSH. Used as:
        - Diagnostic: to diagnose pituitary function in hypogonadism
        - Therapeutic: to induce ovulation in females & spermatogenesis in males (Gonadorelin – Leuprolin – Histrelin – Nafarelin)
     2. **Chronic administration:** ↓ LH & FSH

1) Growth hormone:
   - **Preparations:**
     1. Somatotropin: natural peptide from anterior pituitary
     2. Somatren: Synthetic by recombinant DNA
   - **Actions:**
     1. ↑ longitudinal growth via stimulating the synthesis of somatomedins (insulin like growth factors [IGFS]) mainly IGF-1
     2. ↑ protein synthesis & lipolysis
   - **Uses:** Replacement therapy in GH deficiency before epiphyseal closure
2) **Prolactin:**
- Peptide hormone released from anterior Pituitary & it ↑ milk production
- No available preparation

3) **TSH:**
- ↑ secr. Of T\textsubscript{3} & T\textsubscript{4} from thyroid gland & ↑ size & vascularity through stimulation of membrane bound receptor ➔ ↑ AC ➔ ↑ c.AMP

4) **ACTH:**
- Polypeptide hormone secreted from ant. pituitary & secretion is controlled by:
  1. Plasma cortisol conc. (feedback mechanism)
  2. Stress where it is ↑ by fever & surgery
  3. CRH ➔ ↑ ACTH secr.

- **Actions:**
  1. Act on membrane bound receptor ➔ ↑ steroidogenesis from cholesterol & ↑ adrenal cortex to secrete steroid h. with little effect on aldosterone
  2. Suppress growth less than exogenous steroids

- **Uses:** IM not effective orally
  1. Diagnosis of adr. Function by estimation of 17-ketosteroids in urine or by esinopenia
  2. Therapeutic as cortisone esp. in children & elderly but not in adrenal insufficiency

* Difference between ACTH & Exogenous cortisone:*
  1. No adrenocortical atrophy
  2. ↓ incidence of muscle wasting & osteoporosis
  3. ↑ incidence of acne & hypertension
  4. Given by injection

- **Preparations of ACTH:**
  1. Corticotropin
  2. Synthetic Tetracosactrin (less immunogenic)

5) **Gonadotrophins: (LH & FSH):**
- They are glycoproteins secreted from ant. Pituitary

- **Actions:**

<table>
<thead>
<tr>
<th></th>
<th>FSH</th>
<th>LH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1- Maturation of ovarian follicles 2- ↑ estrogen release</td>
<td>↑ secretion of estrogen &amp; progesterone from CL</td>
</tr>
<tr>
<td>Male</td>
<td>↑ Spermatogenesis</td>
<td>↑ release of testosterone from interstitial cells of Lyding</td>
</tr>
</tbody>
</table>

- **hMG & hCG:**
  - Human postmenopausal gonadotropins (hMG) (Menotropins) have FSH & LH activity ➔ used to ↑ ovulation
  - Human chorionic gonadotropins (hCG) have LH activity ➔ used to ↑ gonadal steroidogenesis
**NB.: Drugs that stimulate ovulation & used to treat infertility:**

1. GnRH…..Gonadorelin
2. Gonadotrophins (hMG) & (hCG)…..[Menotropins]
3. **Clomiphene** (Antiestrogen)
4. Progestin: in patients with defective secretory phase
5. Bromocryptin: in patients with hyperprolactinemia
6. Metformin may be used in Polycystic ovarian syndrome

**POSTERIOR PITUITARY HORMONES**

They are synthesized in hypothalamus but stored & released from posterior Pituitary

<table>
<thead>
<tr>
<th></th>
<th><strong>1) Oxytocin</strong></th>
<th><strong>2) Vasopressin (ADH)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nature:</strong></td>
<td>- Polypeptide hormone</td>
<td>- Polypeptide hormone:</td>
</tr>
<tr>
<td><strong>Release:</strong></td>
<td>- released in response to suckling &amp; cervical dilatation</td>
<td>- ‪↑ release by ‪↑ osmotic pressure &amp; nicotine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ↓ release by ↓ osmotic pressure &amp; alcohol</td>
</tr>
<tr>
<td><strong>Mechanism:</strong></td>
<td>membrane receptor ‪↑ AC ‪↑ c.AMP</td>
<td>2 types of receptors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1- ‪V₁ in vascular smooth m. ‪↑ PLC ‪↑ IP₃ &amp; DAG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2- ‪V₂ in renal tubules ‪↑ AC ‪↑ cAMP</td>
</tr>
<tr>
<td><strong>Actions:</strong></td>
<td>1- Contraction of myometrium ‪→ labour</td>
<td>1- Antidiuretic ‪→ salt &amp; water retention (V₂)</td>
</tr>
<tr>
<td></td>
<td>2- Contraction of myoepithelium of mammary alveoli ‪→ milk ejection</td>
<td>2- Vasopressor &amp; colics in large dose (V₁)</td>
</tr>
<tr>
<td><strong>Uses:</strong></td>
<td>1- Induction of labour – abortion &amp; milk production</td>
<td>1- Diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>2- Control post-partum hemorrhage</td>
<td>2- Bleeding esophageal varices</td>
</tr>
<tr>
<td><strong>Preparations:</strong></td>
<td>1- Natural: IM &amp; IV</td>
<td>1- Vasopressin parentally</td>
</tr>
<tr>
<td></td>
<td>2- Synthetic (Syntocinon): IM, IV &amp; intranasaly</td>
<td>2- Lypressin intranasally</td>
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<td></td>
<td></td>
<td>3- Desmopressin intranasally (V₂ activity 200 times &gt; V₁ activity)</td>
</tr>
<tr>
<td><strong>Side effects:</strong></td>
<td>1- Dose related hypotension (it has VD effect)</td>
<td>1- Nasal spray may cause ulcer</td>
</tr>
<tr>
<td></td>
<td>2- Water retention (it has weak ADH like effect) with consequent relative</td>
<td>2- IV may cause anginal attack</td>
</tr>
<tr>
<td></td>
<td>hyponatraemia</td>
<td></td>
</tr>
</tbody>
</table>
Drugs affecting uterine contractility:

1- Oxytocics:
- **Definition:** Drugs that stimulate uterine contraction
- **Uses:**
  1- Induce labour & abortion
  2- Control post-partum hemorrhage
- **Examples:**
  1- Oxytocin
  2- Ergometrine
  3- Prostaglandins: - Dinoprostone (PGE₂), - Carboprost (PGF₂α), - Gemeprost or Misoprostol (PGE₁)

2- Tocolytics
- **Definition:** Drugs that relax the uterus
- **Uses:**
  1- Dysmenorrhoea.
  2- To delay labour in threatened Abortion & premature labour.
  3- Contraction ring of the uterus during labour.
- **Examples:**
  1- β₂ agonist: eg.: Ritodrine & Isoxsuprine
  2- Antiprostaglandins (NSAIDs)
  3- Antioxytocin (Atosiban)

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**NB.: Other drugs used in Diabetes Insipidus (DI):**

1- **Nephrogenic DI:** Thiazide
2- **Pituitary DI:** Chlorpropamide – Clofibrate – Carbamazepine – Metformine

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**NB.: Mechanism of actions of hormones:**

1- Steroidal hormones ➔ intracellular receptor (Cytoplasmic)............
2- Thyroid hormone ➔ intracellular receptor (Nuclear).......................
3- Insulin ➔ Tyrosine kinase receptor......................
4- Other hormones ➔ Membrane bound receptors ......................