PROGESTINS

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PROGESTINS

- **Progestin =** Favouring Pregnancy
- **1929 =** Progesterone was isolated à not effective orally à extensive 1st pass metabolism à short duration of action (5-7 min).
- **1950 =** Synthetic progestins were developed.

  Micronised progesterone formulation developed à orally effective à slow 1st pass metabolism à longer duration of action (1-3 days)

Progestins - Classification

- **I) Progesterone analogues :-**
- (a) Hydroxy progesterone acetate (HPA– I.M.)
- (b) Medroxy progesterone acetate (MPA– I.M., Oral))
- (c) Megesterol acetate (oral)
- (d) Nomegesterol
- **Properties :-**
- Pure progestins
- Weak androgenic & antiovulatory action
- **Used as an adjuvant to estrogens in :-**

1)HRT in postmenopausal women(PMW)

2)Threatened abortion

3)Endometriosis (Nomegestrol à Strong effect on endometrium à has anti-androgenic & weak antiovulatory action)

Progestins - Classification

- **II) 19- Nortestosterone derivatives :**
- **(a) Norethindrone (Norethisterone—oral)**
- **(b) Lynestrenol (Ethinyl estrenol - oral)**
- **(c) Allylestrenol (oral)**
- **(d) Norgesterol (Oral)**
- **(e) Levonorgestrel (Oral)**
- **Properties :-**
- **Are 19- nortestosterone derivate**
- **Devoid of 19–CH group in testosterone molecule**
- **Addition of Ethinyl (-=C=CH) at C-17 à ↑ Bioavailability**
- **Addition of Ethyl (C2H5) group at C-13 à ↑ Potency**
- **Have potent progestogenic activity, but weak estrogenic and androgenic action.**
- **Used for contraception with estrogen**

Progestins - Classification

- **III) Newer 19- Nortesterone Derivatives** :-
- (a) Desogestrel (oral)
- (b) Norgestimate (oral)
- (c) Gestodone (oral)
- **Properties :-**
- Very potent pure progestins
- Strong antiovulatory action
- No antiandrogenic effect
- Does not antagonize beneficial effect of estrogens on Lipid profile
- **Used :-**
- i) As contraceptives with estrogens
- Ii) suitable for women with Hyper-androgenemia

Progestins - Actions

1) Uterus :-

- (a) Non-pregnant uterus :-
- Brings secretory changes in endometrium
- Loss of progestational supportà shedding of mucosa during menstruation

(b) Pregnant uterus :-

- Decidual changes in endometrium
- Enlargement of stromaà becomes spongy
- Glands atrophised
- Decrease sensitivity of myometrium to oxytocin

Progestins - Actions

2) Cervix :-

- Makes cervix viscid, scanty à hostile to sperm penetration

3) Vagina :-

- Induces pregnancy like changes in vaginal mucosa

4) Breast :-

- Proliferation of acini in mammary gland à prepares for lactation after delivery.

5)Metabolism :-

↑LDL, ↓HDL à reduces beneficial effect of estrogens

(More common with 19-noetestosterone derivatives & less with micronized natural progestins)

Progestins - USES

1)Hormone Replaement Therapy (HRT) in PMW

2) As oral contraceptive

3) Dysfunctional Uterine Bleeding (DUB)

associated with anovulatory cycles à occurs without progestational support but continuous exposure to estrogens

(MPA/Norethindrone 10-20mg/day followed by 3-6 months cyclic small dosesà regularizes & control bleeding)

Progestins - USES

4) Endometriosis :-

- Continuous administration of progestins for 6 months corrects endometriosis.
- Alternative treatment are combined OC pills;
- GnRH agonists, Danazol & Aromatose inhibitors in refractory cases.

5) Threatened Abortion :-

- A pure progestin without androgenic activity prevents premature delivery in high risk pregnancy with progestin deficiency.

6) Premenstrual syndrome/Tension :- High dose of Progestin in combination with estrogen preferred

Progestins – Adverse Effects

- Breast engorgement
- Rise in Body Temperature
- Weight gain
- Breakthrough bleeding
- Thromboembolosm (19-testosterone derivative)

HORMONE REPLACEMENT THERAPY IN POST MENOPAUSAL WOMEN

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HRT - PMW

- Menopause : Cessation of Ovarian functions
  ↓ in Plasma Estrogen Levels

Clinical Manifestations :-

1) Vasomotor Disturbances
2) Psychological Disturbances
3) Urogenital atrophy
4) Dermatological
5) Osteoporosis
6) Cardiovascular risk

HRT - PMW

- Different Treatment Modalities:-
- 1) HRT regimens :-
- a) Estrogen + Progestin combination therapy
- b) Estrogen alone therapy
- 2) Tibolone
- 3) Treatment to prevent osteoporosis :-
- i) Bisphosphonates (Alendronate sodium)
- Ii) Selective Estrogen Receptors Modulators (Raloxifene)
- Ii) Calcium and Vitamin D3 supplements
- Iii) Strontium renolate
- Iv) Blend oils
- V) Evening Primerose oil
- Vi) Phyto - soya

HRT-PMW

HRT – regimens :-

(I) Estrogen + Progestin Combinations HRT:

- **Conjugated estrogen (0.625 mg/0.3-0.45mg)** 3 weeks continuously **+ Medroxy Progesterone Acetate (MPA) 10 mg /Norethisterone (2.5mg/day)** to be given last 10 days in postmenopausal women with intact uterus.
- (Estrogen provides à Metabolic & CVS benefits; whereas, Progesterone blocks increase risks of DUB & Endometrial CA).

HRT-PMW

- **II) Estrogen alone regimen** as transdermal patches or oral conjugated estrogen given uninterrupted cyclically monthly :-

i) Recommended in Hysterectomized women

ii) When Progesterone is contraindicated or not tolerated.

EHT does not poses risk of Endometrial cancer in menopausal women who has undergone hysterectomy.

HRT-PMW

- **II) TIBOLONE :-**
- 19-Nonsteroidal estrogen
- Metabolized to 3 metabolitesà which exerts estrogenic, progestational and weak androgenic actions
- **Advantages :-**
- i) Suppresses menopausal symptoms
- Ii) Lowers raised Gn levels
- Iii) Improves à Urogenital, Vasomotor, Psychological symptoms, libido & osteoporosis.

Tibolone (Contd…

- 2.5 mg per day orally without interruption
- Start therapy only after women has been menopausal for atleast 12 months.
- Side effects of Tibolone :-
- Weight gain
- Increase facial hair growth
- Vaginal spotting

Benefits of HRT in PMW

- Early and complete abatement of vasomotor symptoms
- **Improvement in general, physical, mental and sexual well being**
- **Resolves uro-genital problems by arresting genital dermal changes**
- **Effective in arresting and improving menopausal vasomotor symptoms and atrophic changes**

Benefits of HRT in PMW (contd..

- Prevents Bone Calcium loss
- **Restores calcium balance**
- **Increases Bone Mineral Density (↑BMD)**
- **Prevents development of osteoporosis**
- **Decreases risk of Fractures of vertebrae, Hip, Femur, Radius à** therefore, supplement HRT before significant bone loss à osteoporosis once established is not reversible

Benefits of HRT in PMW (contd..

- **In addition to HRT,** supplemention of Ca 2+ and Vit-D3 as an adjuvant increases effective ness of HRT.
- **Bisphosphonates are DOC in all types of osteoporosis**
- **Strontium racelate, oil blends, phyto- soya supplementation** can also be used as an adjuvant in PMW to prevent osteoporosis

Risks/Limitations of HRT in PMW

- Increases risk of CVS diseases, MI, Stroke if HRT combination regimen is given continuously beyond 10 yrs; in older women with pre-existing CVS diseases
- Increases risk of dementia and cognitive functions in older PMW
- Increases risk of breast cancer & endometrial cancer in elderly PMW & PMW with intact uterus with HRT combination regimen (due to MPA pro-carcinogenic effect)

Risks/Limitations of HRT in PMW

- ü Less or no risk of Endometrial cancer if Estrogen alone HRT is given to PMW with Hysterectomy
- ü **Increases risk of development of Gall stones (Estrogens) and Migraine(Progesterone)**

Thank You.