Indian Menopause Society-Goals

- Forum for discussion on all aspects of Menopause and Hormone Therapy
- To promote Public Awareness
- Multi disciplinary body
- Research
- Promote comprehensive health care for Adult women
- Membership open to Medical and Non Medical professionals
Team 2016-2017

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Riding high on the waves of menopause
Prescription Writing - Teaching Module

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Menopause Hormone Therapy (MHT) Prescription Writing
Module 1A
Basic: Module 1

Basics Physiology And Sex Steroids
Agenda

Module 1A:

- Overview of reproductive physiology
- Reproductive steroids
  Estrogens
Agenda

Module 1B:

Reproductive steroids

• Progestogens
• Androgen
• Tibolone
• SERMs
Overview: Endocrine Physiology

- TSH (Thyroid Stimulating Hormone)
  - Thyroid hormone
  - Growth & differentiation
  - Energy balance

- ACTH (Adrenocorticotropic Hormone)
  - Cortisol, aldosterone, androgens
  - H2O & Na balance
  - Inflammation & metabolism

- LH & FSH (Luteinizing Hormone & Follicle-Stimulating Hormone)
  - Estrogen, progesterone, & testosterone
  - Reproductive function & behaviour

- GH (Growth Hormone)
  - Insulin-like growth factor
  - Growth & differentiation
  - Prl
  - Breast development
  - Milk production
Circulatory Levels Of Pituitary & Steroid Hormones

Post Meno Pausal Woman (Progesterone undetectable)
Pre Meno Pausal Woman (1st week of menstrual cycle)

Circulatory levels of Pituitary and steroid Hormone
Alterations In Mean Circulating Hormone Levels During Menopause Transition
Estradiol is the dominant hormone:
95% from ovary & 5% from peripheral conversion.
Hormonal Changes – Late Reproductive Age

Rise in early cycle FSH
• Attributed to a fall in antral follicle, fall in production of inhibin B
• AMH is also reduced 2-10 fold
  - Predicting length of time to menopause
• Erratic estrogen levels, fall in progesterone levels

Fig. Perimenopausal hormone production. The arrow size indicates the levels of hormone secretion. FSH, follicle-stimulating hormone.
Age-related Hormonal Level Changes

**Estrogen:**
- 75% reduction from age 35-50

**Progesterone:**
- 35% reduction from age 35-50

**AUB:**
- At menopause, there is relatively high estrogen compared to progesterone.
Estradiol: Adrenal & Peripheral Sites

- FSH is markedly elevated
- Inhibin B, AMH often remains undetectable estrogen
- Main circulating hormone at postmenopause is estrone
Depletion of ovarian follicles

- Primordial follicle numbers fall to a critically low level (<1000)
- Transition to predominantly abnormal ovulatory or anovulatory cycles
- Women often experience slightly shorter cycles (by 2-4 days)
- 60-70% cycles are anovulatory
Physiological changes of the menopause are a consequence of changes in both the ovaries and hypothalamus.
Steroid Basic: Cholesterol

- Steroid hormones are all derived from cholesterol
- Cholesterol contains cyclopentanoperhydrophenanthrene ring
Biosynthesis

Cholesterol (27 carbons) → Pregnane derivatives (21 carbons) → Progestins Corticoids

Pregnane derivatives (21 carbons) → Androstan derivative (19 carbons) → Androgens

Androstan derivative (19 carbons) → Estrane derivatives (18 carbons) → Estrogens
Major Circulating Estrogens In Women

- Three major naturally occurring circulating estrogens in women:
  - Estrone (E1)
  - Estradiol (E2) most potent
  - Estriol (E3) least potent
Estrogen Biosynthesis In Women

Source - ovary, adrenal cortex, peripheral tissues

Adrenal

Ovary

Aromatase

Rate limiting factor

Physiologic
- Brain
- Breast
- Skin
- Blood vessel

Pathologic
- Brain cancer
- Endometriosis

A. Androstenedione

17β-HSD

Aromatase

Skin

Adipose tissue

Peripheral tissues

Circulation

E₂

E₁, E₂

E₁

E₃

A
Aromatization of androgens to estrogens in various target organs may differ in each individual—Influenced by weight, age, stress, sex

Bioavailability of estrogens—2% is free and bioavailable

Levels of SHBG

Biological activity of estrogen metabolites
Potency of the estrogen depends on the nuclear retention time

- **17-beta estradiol (E2)** - Most potent has the longest retention time of 6-24 hours
- **Estriol** - Least potent has a retention time of only 1-4 hours
- **Estradiol** is 10 times more potent than estrone and 80 times more potent than Estriol
Estrogens: Nature’s Intelligent Protective Mechanism

Predominant circulating type of estrogen depends on the stage of a woman’s life reflecting the need of the potency of the hormone

• Estradiol  E1 - most potent (reproductive phase)
• Estrone   E2 - low potency (menopause)
• Estriol    E3 - least potent (pregnancy)
• Estetrol   E4 - low potency estrogen present during pregnancy, produced from fetal liver
Absorption, Fate, And Elimination Of Estrogens
Estrogen

- Reproductive function
- Non-reproductive function
Effects Of Estrogen – Physiological And When In Excess

EFFECTS OF ESTROGEN – Physiological and when in excess

Physiological effects

- Breast
  Programs milk production

- Liver and heart
  Controls cholesterol

- Uterus
  Prepares for fetus

Harmful effects

- Breast
  Increases cancer risk

- Uterus
  Increases cancer risk

Bone
  Preserves strength
Deficiency Of Estrogen – Possible Effects
Estrogen Receptors
Estrogen Receptors

Estrogen Target Tissues

- Central nervous system: ERα, ERβ
- Cardiovascular system: ERα, ERβ
- Liver: ERα
- Breast: ERα, ERβ
- Bone: ERα, ERβ
- Gastrointestinal tract: ERβ
- Urogenital tract: ERα, ERβ
Estrogen Receptors

- ER α is expressed: Liver
- ER β is expressed most highly in: Lungs, kidney, bladder, intestines
- Many cells express both ER α and ER β, which can form either homo- or heterodimers: CNS, blood vessels, bone, heart, breast, ovary, uterus, testes, prostate
Molecular Action Of Estrogen

Different response in different tissues
Variable Response To Endogenous Estrogens

- Distribution, heterogeneity and function of α and β receptors
- Aromatization of androgens to estrogens in various target organs may differ in each individual
- Bioavailability of estrogens depends on levels of SHBG
- Tissue levels of estrogen
- Biological activity of sex steroid metabolites
Optimum Health - Level Of Estrogen

Optimum Levels of Estrogen = Optimum Health

Health is NOT found at the extremes

Hormone Deficiency
- VMS
- CVD
- Osteoporosis
- Mood changes
- Amenorrhea
- Genitourinary syndrome

Optimum Hormone Levels

Hormone Excess
- Breast and uterine cancer
- Fibroids
- Endometriosis
- Gall bladder disease
- Venous thromboembolism
Changes At Menopause

Physical changes
Effect On Bone
Effect Of Estrogen On Brain
Estrogenic Effect On Neurotransmitters
CNS

- Receptors in cortex, limbic system hippocampus, pre-optic area & amygdala

- Modify the synthesis release and metabolism of neurotransmitter

- Increased cholinergic tone
Declining Estrogen – Genital Tract

- < Blood flow
- > PH
- < Collagen synthesis
- Sensory neurological impairment
Beneficial Effects Of Estrogens On CVS

- Positive effect on endothelial cell function
- Relaxation of the vascular smooth muscle
- Improve cardiac contractility and coronary artery blood flow
Effects Of Estrogens Therapy On Lipid Metabolism

- Estrogens slightly elevate serum triglycerides and slightly reduce total serum cholesterol levels
- Increase HDL levels and decrease the levels of LDL and Lipoprotein(a)
- Beneficial alteration of the ratio of HDL to LDL is an attractive effect of estrogen therapy in postmenopausal women
Window Of Opportunity For Hormone Therapy

Effects of estrogen on vessel wall at different stages of menopause transition

- **Premenopause**
  - Benefits of endogenous estrogens

- **Perimenopause**
  - Primary benefits of HT

- **Post menopause**
  - Harmful effects of HT
Effects Of Estrogen On Body Fat, Glucose And Insulin Metabolism

- Promotes and maintains gynecoid body fat distribution
- Improves glucose and insulin metabolism
Effects Of Estrogens On Bile

• Alter bile composition by increasing cholesterol secretion & decreasing bile acid secretion
• This leads to increased saturation of bile with cholesterol and appears to be the basis for increased gallstone formation in some women
• Decline in bile acid biosynthesis may contribute to the decreased incidence of colon cancer in women receiving combined estrogen-progestin treatment
Consequences Of Estrogen Excess

- Endometrial Hyperplasia
- Endometrial Polyp
- Gall bladder / stones
- Fibroid
- Venous thromboembolism
- Carcinoma Breast
- Carcinoma Uterus
Natural Estrogens Used For Menopausal HT

- 17 beta estradiol
- Estradiol valerate
- Conjugated equine estrogens
- Estriol
Natural Estrogens Used For Menopausal HT

17β-estradiol

Minimal load on liver

Estradiol Valerate
Metabolizes in the liver to 17β - estradiol + valeric acid

Conjugated Equine Estrogens
A mixture of Estrone & Equilin Sulphate (200 compounds), thus 2-3 times extra load on liver

Estradiol hemihydrate is the 17 beta isomer of estradiol
5 As compared to CEE * and EV # Conjugated Equine Estrogens * Estradiol Valerate
Synthetic Estrogens – Not Used For MHT

- Ethinyl estradiol, mestranol
- 750-1000 times more potent than natural estrogens
- Enhances hepatic effects which increases synthesis of clotting factors, angiotensin, SHBG

Except in perimenopause, premature menopause
Basic: Module 2

Progesterone
Progesterone

• Involved in female menstrual cycle, supports pregnancy, and embryogenesis in the womb
• Source: corpus luteum, adrenal cortex and placenta
• Progesterone is not measurable in menopausal women
## Classification of Progesterone—

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>Micronized progesterone</td>
</tr>
<tr>
<td>Retroprogesterone</td>
<td>Dydrogesterone</td>
</tr>
<tr>
<td>Progesterone derivative</td>
<td>Medrogestone</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone derivatives (pregnanes)</td>
<td>Medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, cyproterone acetate</td>
</tr>
<tr>
<td>17-Hydroxynorprogesterone derivatives (norpregnanes)</td>
<td>Gestonorone caproate, nomegestrol acetate</td>
</tr>
<tr>
<td>19-Norprogesterone derivatives (norpregnanes)</td>
<td>Demegestone, promegestone, nesterone, trimegestone</td>
</tr>
<tr>
<td>19-Nortestosterone derivatives (estranes)</td>
<td>Norethisterone = norethindrone, norethisterone acetate, lynestrenol, ethinodiol acetate, norethinodrel</td>
</tr>
<tr>
<td>19-Nortestosterone derivatives (gonanes)</td>
<td>Norgestrel, levonorgestrel, desogestrel, etenogestrel, gestodene, norgestimate, Dienogest</td>
</tr>
<tr>
<td>Spirolactone derivative</td>
<td>Drospirenone</td>
</tr>
</tbody>
</table>
Progesterone differs in their actions depending on their receptor binding affinity.
Progestogens: Receptor-binding Activity: MHT

All progestogens have protective effect on the endometrium, but not all progestogens have the same receptor-binding effect

<table>
<thead>
<tr>
<th>Progestogen</th>
<th>Progestogenic</th>
<th>Estrogenic</th>
<th>Androgenic</th>
<th>Anti-androgenic</th>
<th>Glucocorticoid</th>
<th>Anti-mineralocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dydrogesterone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MPA</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tibolone</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+ Effective; ± Weakly effective; - Not effective
Progestogen Risk Differences-Receptor Binding Effect

Evidence of difference in risk with EPT - varies with different progestogens and progesterone

• For cardiovascular events
• Differences in lipid profiles
• Breast cancer
• Thrombogenic potential
Progesterone is used in HT at menopause to prevent endometrial hyperplasia & endometrial cancer.
<table>
<thead>
<tr>
<th>Progestogens</th>
<th>Transformation dose mg per day p.o.</th>
<th>Ovulation inhibition mg/day p.o.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>200-300</td>
<td>300</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>10-20</td>
<td>&gt;30</td>
</tr>
<tr>
<td>MPA</td>
<td>5-10</td>
<td>10</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>0.15</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Androgens

- Androgens are a group of chemically related sex steroid hormones:
  - Testosterone, Dihydrotestosterone, Androstenedione, Dehydroepiandrosterone, Dehydroepiandrosterone sulfate
- Sources in postmenopause: Ovary, adrenal & peripheral tissues
Androgens In The Female

• Substrate for production of estrogen
• Libido and sexuality
• General well being, CVS, bone, breast, cognitive function
Clinical Implications Of Androgens

Testosterone levels:

• Higher than estradiol concentrations in postmenopausal women
• Lower in postmenopausal than in premenopausal women, least in oopherectomized women
Clinical Implications Of Androgens

Testosterone:

- Estradiol production in female physiology
- Acts as a circulating pro-hormone and converts into estradiol and dihydrotestosterone (DHT), a major source of estradiol after menopause
- Testosterone levels vary in each individual of the same age, hence estrogen levels too may be different
Clinical Implications Of Androgens

- Serum androgen levels are not representative of the total bioavailable androgens in the body
- Bioavailability of testosterone is the function of SHBG
- Only free testosterone which is unbound to SHBG is functional
- Androgen deficiency may present when estrogens are in excess or SHBG is high
Tibolone is a selective tissue oestrogenic activity regulator.
Kinetics
Metabolism of Tibolone

- Rapid and extensive absorption
- Rapid metabolism to
  - 3α-OH-tibolone
  - 3β-OH-tibolone
  - Δ4-isomer of tibolone
- Excretion is mainly as conjugated (sulfated) metabolites
- Kinetics are not affected by food or renal function
Tissue-Specific Effects Of Tibolone’s Metabolites

Specific binding affinities of tibolone and its primary metabolites

<table>
<thead>
<tr>
<th>Tibolone/ Metabolites</th>
<th>Oestrogen Receptor</th>
<th>Progestogen Receptor</th>
<th>Androgen Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibolone</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3-alpha-hydroxy tibolone/3-beta-hydroxy tibolone</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$\Delta^4$ Tibolone</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+ Stimulatory effect; - Suppressive effect; ? Unknown effect
Selective Estrogen Receptor Modulator - (SERM)

A drug that acts like estrogen on some tissues but blocks the effect of estrogen on other tissues
SERM-
Selective Estrogen Receptor Modulator

• Raloxifene is a benzothiophene series of antiestrogens to be labeled a SERM
• Lasofoxifene
• Droloxifine
• Idoxifene and
• Toremifene are similar SERM agents (but they are still considered experimental)
SERM-Raloxifene

- Agonist -- Bone
  -- Lipid metabolism

- Antagonist -- Uterine endometrium
  -- Breast tissue

Not to be used for management of vasomotor symptoms
5) Speroff textbook on reproductive endocrinology
7) Schindler AE. Maturitas. 2003;46(S1):7-16.
References

10) Tibolone summary of product characteristics. Available at: www.medicines.org.uk
14) Harrison’s book on endocrinology.