HORMONE THERAPY

A BALANCED VIEW??

Prof Greta Dreyer
Definitions

- HRT hormone replacement therapy
- HT genome therapy
- ERT estrogen replacement therapy
- ET estrogen
- EPT estrogen progesterone therapy
Logical indications for HRT

• Perimenopausal symptoms:
  – Flashes
  – Dryness
  – Sleeping or mood disorders

• Osteoporosis
• QOL
• Depression
Decision to treat

• Certainty of diagnosis:
  – Clinical = good enough
  – FSH>30

• Severity of symptoms = indication
• No Contra-indications

• Idea of pro's and con's
• Idea of planned duration
• Holistic approach, preventative medicine
Holistic approach to the menopausal woman

• Modify lifestyle:
  – Exercise
  – Smoking
  – Alcohol
  – Obesity
  – Diet
  – Stress
Holistic approach

• Alternative medications proven to impact:
  – HT treatment
  – ACE I
  – LDA
  – Statins
  – Bisphosphonates
  – Calcium

• About: The risks & benefits of:
  – Estrogen plus progestin in
  – Healthy postmenopausal women

• 16608 women with uterus
• Used for 5.2 yrs
• Age 50-79
• CEE 0.625mg & MPA 2.5mg vs placebo

• Stopped early: Risks > Benefits

• Other leg:
  – 11739 on estr alone
  – Without uteri
  – Ends 3/2005
  – Health benefits outweights risks??
  – CEE 0,625mg vs placebo
  – Ongoing

- Outcome measures per 10000 women yrs:
  - Cancer:
    - Breast
    - Colon
    - Other
  - Stroke: RR1.4 = 40% incr risk (21 vs 29)
  - Other TE events
  - Coronary heart diseases
  - Fracture and osteoporosis
Atherosclerosis issue

• Atherosclerosis Studies:
  – Progression equal
  – On angiography

• Estrogen alone:
  – Without statins
  – Slows progression
Clinical outcome measures - influences on CVD - WHI, HERS:

- HERS study:
  - Secondary prevention of CHD
  - 2763 used for 4,1 yrs
  - CEE & MPA
  - Failed to show benefit
  - Increased events in first (2) year
  - CVS and stroke
Clinical guidelines after WHI - study:

• Re-evaluation - long term use:
  – Continued benefit vs automatic renewal of script?
  – Increased risk with long term use:
    • Clotting tendency
    • Breast cancer
    • CHD
Clinical guidelines after WHI - study:

- Re-evaluation - long term use:
  - Options to consider:
    - Stop
    - Lower dosages
    - Alternative medications
    - Continue use - active decision
Important remaining issues:

- Estrogen only - better??
- Different regimens and routes
- Lower doses for reduced side effects
- Unopposed vs apposed
- Tibolone
- SERMs
-- PART 2 --

• This part of the lecture is additional information
ESTROGEN therapy
PRO’s and CON’s

• Prevention of skeletal complications
  – Fractures
  – Pain
  – Shortening

  – Prevention vs
  – Treatment
  – Cost effective!
ESTROGEN therapy
PRO’s and CON’s

• Non-skeletal benefits
  – Climacterium
  – Dementia
  – Carbohydrate metabolism
  – Lipid profile
  – Decrease in some cancers
  – Vascular status
ESTROGEN therapy
PRO’s and CON’s

• Thrombo-embolic disease
  – increased risk RR 3.6
  – Trans-dermal?
  – Dose dependant
  – AGE dependant
ESTROGEN therapy
PRO’s and CON’s

• Heart and blood vessels
  – Menopause is major risk factor for disease
  – Difficult to evaluate evidence
  – Interaction with existing risk factors
  – Age and type of HT differs widely
  – Clotting risk on existing vascular disease in elderly women major problem!

  – Possible prevention in younger women not sufficiently proven
PROGESTOGEN therapy
PRO’S’s and CON’S’s

• Colon cancer prevention
• Endometrial cancer prevention
• Increased effect on bone
• Decreased effect on lipids and CVS
• Breast cancer
  – Risk increased with ~ 2% of the existing risk after 5 years of use
  – Risk disappears after cessation of use
PROGESTOGEN-HORMONES
Classification

• A group of substances that are able to create a secretory pattern of estrogen primed endometrium
• According to derivation from parent compound.
• Natural progestins and various synthetic progestins
# Classification

<table>
<thead>
<tr>
<th>Parent compound</th>
<th>Progestin</th>
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<tbody>
<tr>
<td>Progesterone</td>
<td>Micronised progesterone</td>
</tr>
<tr>
<td>Retroprogesterone</td>
<td>Dydrogesterone</td>
</tr>
<tr>
<td>17α-Hydroxyprogest (pregnanes)</td>
<td>MPA, Megestrol acetate</td>
</tr>
<tr>
<td>17α-Hydroxyprogest (norpregnanes)</td>
<td>Nomegestrol acetate</td>
</tr>
<tr>
<td>19-Norprogesterone derivatives</td>
<td>Trimegestone</td>
</tr>
<tr>
<td>19-Nortestosterone derivatives</td>
<td>Norethisterone, LNG</td>
</tr>
<tr>
<td>Spirinolactone derivatives</td>
<td>Drospirenone</td>
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</table>
Pharmacological Profiles of Progestogens

<table>
<thead>
<tr>
<th>Compound</th>
<th>Progestogenic activity</th>
<th>Androgenic activity</th>
<th>Anti-androgenic activity</th>
<th>Anti-aldosterone activity</th>
<th>Gluco-corticoïd activity</th>
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<tbody>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>-</td>
<td>(+)</td>
<td>+</td>
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</tr>
<tr>
<td>Drospirenone</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Cyproterone</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>(+)</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
<td>-</td>
<td>(+)</td>
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<tr>
<td>Norethisterone</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
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<td>Tibolone</td>
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<td>+</td>
<td>-</td>
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<td>-</td>
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<td>Norgestimate</td>
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<td>(+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>+</td>
<td>-</td>
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</tr>
</tbody>
</table>

Symbols: + relevant activity, (+) activity not clinically relevant, - no activity
HORMONES and BONE
Estrogen:
- Stimulatory effect on osteoblasts
- Positive effect on collagen
- Prevents bone resorption
- Significantly reduces bone turnover
  - inhibition of bone remodelling or architectural change
  - inhibits differentiation of osteoclasts
Modes of action
anti-osteoporosis interventions

➡️ BONE FORMATION  ➡️ BONE RESORPTION

Pre-OB
Replication

Pre-OC
Differentiation

BMI

OB
Bone-forming activity

OC
Bone-resorbing activity

# Published data on range of anti-fracture efficacy of bone agents

## Table: Anti-fracture efficacy of bone agents

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Raloxifene</th>
<th>Estrogen</th>
<th>Strontium ranelate</th>
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</thead>
<tbody>
<tr>
<td><strong>Osteopenia</strong></td>
<td>NS</td>
<td>NS</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Vertebral Fx</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Peripheral Fx*</td>
<td>NS</td>
<td>√</td>
<td>NS</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Hip Fx</td>
<td>√</td>
<td>√</td>
<td>NS</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>≥ 80 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vertebral Fx</td>
<td>---</td>
<td>√</td>
<td>---</td>
<td>---</td>
<td>√</td>
</tr>
<tr>
<td>Peripheral Fx</td>
<td>---</td>
<td>NS</td>
<td>---</td>
<td>---</td>
<td>√</td>
</tr>
</tbody>
</table>

* Intention to Treat Population (ITT)

- **NS**: Non-significant fx reduction vs placebo
- **---**: No data
- **√**: Significant fx reduction vs placebo

### Notes:

- Intention to Treat Population (ITT)
- Non-significant fx reduction vs placebo
- No data
Estrogen and the prevention of osteoporosis

- Most effective in first few years after the menopause
- Estrogen therapy that begins after age 60 and continues appears to offer a nearly equivalent bone-conserving benefit and might indeed be more cost-effective
Estrogen and the prevention of osteoporosis

• Many years of estrogen therapy are needed
• Worthwhile reduction in the fracture risk.
• After seven to ten years of use, reduction in fractures of the spine, hip and wrist more than 50%
• catch-up bone loss occurs after estrogen is discontinued
Estrogen and the prevention of osteoporosis

• HRT uptake and continuation is increased after demonstration of osteoporotic risk
• BMD is better maintained when estrogen replacement is combined with an adequate intake of calcium
• lower doses of oestrogen in combination with adequate calcium has adequate effect
Estrogen and the treatment of osteoporosis

• Estrogen therapy increases or preserves bone density in all areas of the skeleton

• Long-term use of estrogen replacement reduces the risk of hip fractures by 50-60% and the risk of vertebral fractures by 90%

• delayed estrogen replacement is unquestionably effective when continued for around 10 years or more
Estrogen and the treatment of osteoporosis

- Efficacy well established
- Relatively low acquisition cost
- Non-skeletal benefits
- HRT considered one of the first-line pharmacologic therapies for the treatment of established osteoporosis in post-menopausal women.
Estrogen and the treatment of osteoporosis

- Can effectively be combined with other anti-resorptive agents
  - Bisphosphonates
  - calcitonin for an additive therapeutic effect on
    - BMD
    - fractures and height loss
- When used as therapy for established osteoporosis, therapy should often continue indefinitely.
OTHER SEX HORMONES AND ANALOGUES

• Progestogens
  – Responsible for increase in breast cancer risk
  – lowest effective dose
  – women with a uterus only
  – Negative cardiovascular effects
  – No important effect on bone
OTHER SEX HORMONES AND ANALOGUES

• Phyto-estrogens
  – Not currently recommended

• Androgens and anabolic steroids
  – increase bone density
  – negative effects on serum lipids, cardiovascular morbidity, liver function and hirsutism
  – frail, elderly patients
  – advanced osteoporosis
  – management of acute vertebral fractures.
OTHER SEX HORMONES AND ANALOGUES

Tibolone
- prevent postmenopausal bone loss
- neutral on the endometrium and breast
- effective control of menopausal symptoms
- fracture data not available

SERMs
- prevent postmenopausal
- reduce the incidence of vertebral fractures
- risk of venous thromboembolism
- lower incidence of breast cancer
- climacteric symptoms
Risks and concerns of estrogen replacement therapy

• Breast cancer
  – Risk increased by approximately two percent per year of use after 5 years
  – Risk only increased when adding progestin

• Thrombo-embolic disease
  – Increased 3.6 fold

• Cardiovascular system
  – Cardiac morbidity
  – Stroke
HORMONES and the BREAST
BREAST CANCER:

- Hormone-related
  - Sex ratio
  - Hormonal risk factors

- Non-hormonal risk factors

- Epidemiological risk factors – not very helpful for the individual
BREAST CANCER –
hormonal risks:

• Gender

• Long reproductive span

• Obesity

• PCOS, infertility, anovulation

• ‘Long term’ use of combined HRT
BREAST CANCER – hormonal risks:

Protective factors:

• Early or surgical menopause

• Low BMI

• Anti-hormones
BREAST CANCER –

hormonal risks:

• Gender

• Long reproductive span

• Obesity

• PCOS, infertility, anovulation

• ‘Long term’ use of combined HRT
BREAST CANCER – non-hormonal risks:

- AGE
- Smoking
- Large breasts
- Diet high in animal fats
- White or Indian race
BREAST CANCER –
non-hormonal factors:

Protective factors:

• Exercise

• Anti-oxidant intake

• Fruit & vegetable intake

• Black race, oriental diet
Demographics – hereditary breast cancer:

FAMILY HISTORY

• Multiple cancers, >2 cases
• Mean age younger, below 40 yrs
• Multifocal or bilateral breast cancer
• Male breast cancer
• Multiple primary cancers, breast and ovarian cancer
# Risk Factors for Breast Cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>First pregnancy (&gt;30 yrs)</td>
<td>1.48</td>
</tr>
<tr>
<td>Body mass index (&gt;29.68 kg/m²)</td>
<td>1.48</td>
</tr>
<tr>
<td>College graduate</td>
<td>1.36</td>
</tr>
<tr>
<td>Alcohol use (&gt;5 g/d)</td>
<td>1.16</td>
</tr>
<tr>
<td>Delayed menopause</td>
<td>1.14 (5 yrs)</td>
</tr>
<tr>
<td>HRT (current)</td>
<td>1.12 (5 yrs)*</td>
</tr>
</tbody>
</table>

HORMONE THERAPY
CONCLUSION
Therapeutic regimens:

- Hysterectomised women, only estrogen preparations
- Young postmenopausal women
  - sequential regimen
  - orally or transdermally
- Later postmenopause
  - continuous combined
  - amenorrhoea
ESTROGEN REPLACEMENT therapeutic guidelines:

• **Dosage**
  – lower dosage will be equally effective when combined with calcium therapy

• **Route of administration:**
  – transdermal route
  – optimise patient satisfaction

• **Clotting risk:**
  – Consider as contra-indication
  – Combine with anti-coagulants
Special indication:

- Early oophorectomy
- Premature ovarian failure
  - Low dose OC
  - Decreases all the risks of early ovarian failure
ESTROGEN REPLACEMENT: “best practise”

• Per indication
• Individualize
• Dyration of treatment
  – Symptoms – short term
  – Osteoporosis >7 years
• Progestogen separate question
  – Local?
  – Low dose?