Prescribing Hormone Replacement Therapy (HRT)

Christina Jang
No disclosures
Prescribing HRT

REGISTRARS
History of prescribing HRT

- 1890’s: ‘change of life’ considered favourably
  - Herbs, belladonna, cannabis, opium
- 1899: ‘Ovariin’ powder – pulverized, dessicated cow ovaries
- 1920: Serge Voronoff
  - Monkey ovaries grafted into women
- 1923: Allen & Doisy isolated on ovarian extract - ‘folliculin’
- 1933: ‘Emminen’– conjugated estrogen from urine of pregnant women
- 1942: ‘Premarin’ first marketed
1960’s: Robert Wilson

- Menopause is a disease state, HRT is the cure

- Premarin became 5th leading prescription drug in US
Husbands, too, like "Premarin"

The physician who puts a woman on "Premarin" when she is suffering in the menopause usually makes her pleasant to live with once again. It is no easy thing for a man to take the stings and barbs of business life, then to come home to the comrade of a woman "going through the change of life." If she is not on "Premarin," that is. But have her begin estrogen replacement therapy with "Premarin" and it makes all the difference in the world. She experiences relief of physical distress and also that very real thing called a "sense of well-being" returns. She is a happy woman again—something for which husbands are grateful.

"Premarin," conjugated estrogens (equine), a complete natural estrogen complex, is available as tablets and liquid, and also in combination with megestrol acetate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y. • Montreal, Canada
2003 Women’s Health Initiative (WHI)

- NIH initiated study
- Recruited >161,000 post-menopausal women aged 50-79
- 4 separate clinical trials
  - Estrogen + Progestogen, Estrogen only, Ca VitD, Low fat diet
- + 1 observational study
- Aimed at evaluating the long term benefits and risks of HRT
  - Use of E+P linked to breast cancer and heart disease
  - Wiped US$850 million off HRT market overnight
The Menopause

• Permanent cessation of menstrual periods

• Average age 51 years (range 45-60)

• Younger age of menopause
  • Smokers
  • Type 1 diabetes
  • Women who have never had children
  • Women with more regular cycles

• Medically induced: surgery, chemotherapy, radiotherapy

• Loss of fertility and ovarian hormonal production
The Menopause

• Symptoms
  • Hot flushes
  • Night sweats
  • Mood swings
  • Sleep disturbance
  • Urogenital symptoms
Primary Ovarian Insufficiency

• Incidence: 1 in 1000 by age 30
  1 in 100 aged 40

• Diagnostic criteria
  • Younger than age 40
  • Oligo /amenorrhoea for 6 months
  • 2 FSH levels in menopausal range at least a month apart

• Cause usually unknown

• 5-10% become pregnant after diagnosis

• Associated with increased risk of premature death, cardiovascular disease, mood disorders, fractures
Indications for HRT

1. Relief of menopausal symptoms

2. Treatment of women with primary ovarian insufficiency

3. Treatment of women with secondary hypogonadism
Benefits of HRT

1. Hot flushes
   • 75% reduction in frequency and 87% reduction in severity
   • No difference between various types of estrogens

2. Female sexual function
   • Improvement in vulvovaginal atrophy

3. Mood and Depression
   • Probably benefit in women with depression but not non-depressed women
Benefits of HRT – Bone

- Prevents postmenopausal bone loss
- Improvement in BMD as effective as bisphosphonates
- WHI (E+P)²
  - 24% ↓ all fractures
  - 33% ↓ hip fractures

Improvement of BMD with E+P¹

¹Wells G et al, Endocr Rev 2002
²Cauley JA, JAMA 2003
Which one to use?
Considerations

• Local vs systemic treatment

• Oral vs Non-oral therapy

• Choice of progestogen
Basic Principles (1)

• Women with intact uterus
  • Estrogen + Progestogen

• Women who have had a hysterectomy
  • Estrogen alone
1. **Women <24 months since last period**
   - Continuous estrogen + cyclical progestogen

2. **Women >24 months since last period**
   - Continuous estrogen + continuous progestogen
Estrogen and Progesterone
Estrogen

• Development of female organs

• Majority made by the ovary
  • Smaller amounts made in liver, adrenal gland
  • Also from conversion of testosterone → oestrogen

• Estrogen deficiency leads to symptoms
Naturally occurring estrogens

Estrone E1

Estradiol E2
=17β-oestradiol

Estriol E3
## Estrogen Preparations in HRT

<table>
<thead>
<tr>
<th>Estradiol</th>
<th>Conjugated Equine Estrogens (CEE)</th>
<th>Ethinyl Estradiol</th>
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</thead>
<tbody>
<tr>
<td>- Estradiol, estradiol valerate, estradiol hemihydrate</td>
<td>- Mixture of 10 conjugated estrogens from pregnant mares</td>
<td>- Found in OCP</td>
</tr>
<tr>
<td>- Structurally similar to ‘natural’ estradiol</td>
<td>- 0.3, 0.625mg preparations</td>
<td>- Supraphysiological doses 20mcg, 30mcg</td>
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<tr>
<td>- 1mg, 2mg preparations</td>
<td>- Can’t be measured</td>
<td>- 5mcg EE = 1mg Estradiol</td>
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<tr>
<td>- E can be measured</td>
<td>- Can’t be measured</td>
<td>- Can’t be measured</td>
</tr>
</tbody>
</table>
Oral Estrogen

- Metabolised by liver
  - hepatic ‘first pass' effect
  - ~30% of activity is lost
- Increases TBG, CBG
- Increases HDL
- Increases procoagulation factors

- Suitable if skin problems/allergies

Preparations

- Estrogen alone
  - *Progynova* = estradiol 1mg, 2mg
  - *Premarin* = CEE 0.3, 0.625mg
- Combined cyclic
- Combined continuous
Transdermal Estrogen

• Estradiol in patches and gel
• No first pass effect
• Patches applied once or twice a week
• Skin rash

• Sandrena Gel:
  • applied daily

Preparations

• Estrogen only
  \( Estradot = \) Estradiol 25, 37.5, 50, 75, 100mcg

• Estrogen + continuous Progestogen
  \( Estalis \) continuous 50/140, 50/250

• Estrogen + cyclical Progestogen
  \( Estalis \) sequi  50/140, 50/250
Vaginal preparations

**Vagifem**

- Ideal if local symptoms only
- Estradiol 25mcg
- DON’T need to add a progestogen
- Initially one daily for 14 days
- Maintenance one twice a week
Progesterone

• Made by corpus luteum after ovulation (also adrenal, placenta)
• Prepares endometrial lining for implantation
• Fall in progesterone levels trigger menstruation
Classification of Progestogens

• Natural
  • Progesterone

• Structurally similar to Progesterone
  • Medroxyprogesterone acetate
  • Dydrogesterone

• Structurally similar to Testosterone
  • Norethisterone acetate
  • Drospirenone
  • Levonorgestrel
Dosing Progestogen

1. Cyclical regimen - higher dose for shorter time

- Estrogen
- Progestogen
  - Provera 10mg

Day 1 | Day 12 | Day 28

2. Continuous regimen – lower dose throughout cycle

- Estrogen
- Progestogen
  - Provera 5mg

Day 1 | Day 28
Progestogen preparations

Oral

• *Provera* = medroxyprogesterone acetate

Patches (combination with E)

IUD: *Mirena*

• Levonorgestrel 52mg over 5 years
• Good option if contraception needed
<table>
<thead>
<tr>
<th>Type of HRT</th>
<th>Product</th>
<th>Presentation</th>
<th>PRS</th>
<th>Dose (indicated for HRT)</th>
<th>Company</th>
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</thead>
<tbody>
<tr>
<td>Combined Continuous</td>
<td>Angeliq 1/2</td>
<td>Tablet</td>
<td></td>
<td>1 mg E2 / 2 mg Estradiol</td>
<td>Bayer</td>
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<tr>
<td></td>
<td>Klisig</td>
<td>Tablet</td>
<td></td>
<td>2 mg E2 / 1 mg NETA</td>
<td>Novo Nordisk</td>
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<td></td>
<td>Klasance</td>
<td>Tablet</td>
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<td></td>
<td>Premila</td>
<td>Tablet</td>
<td></td>
<td>0.625 mg CEE / 2.5 mg MPA</td>
<td>Pfizer</td>
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<tr>
<td></td>
<td>Estelle Continuous</td>
<td>Patch</td>
<td></td>
<td>50 mcg E2 / 140 mcg NETA</td>
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<td></td>
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<td>50 mcg E2 / 250 mcg NETA</td>
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<td>Combined Estro</td>
<td>Triaseqens</td>
<td>Tablet</td>
<td></td>
<td>1 mg, 2 mg E2 / 1 mg NETA</td>
<td>Novo Nordisk</td>
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<td></td>
<td>Hevacotin</td>
<td>Tablet</td>
<td></td>
<td>2 mg E2 / 10 mg Progestogen</td>
<td>Abbott</td>
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<td></td>
<td>Estril</td>
<td>Tablet</td>
<td></td>
<td>50 mcg E2 / 140 mcg NETA</td>
<td>Novartis</td>
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<tr>
<td></td>
<td>Estrol</td>
<td>Tablet</td>
<td></td>
<td>50 mcg E2 / 250 mcg NETA</td>
<td>Novartis</td>
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<tr>
<td>Cestrogen only</td>
<td>Fregene</td>
<td>Tablet</td>
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<td>1 mg, 2 mg, Estradiol Valerate</td>
<td>Bayer</td>
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<td></td>
<td>Estridem</td>
<td>Tablet</td>
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<td>1 mg, 2 mg, Estradiol</td>
<td>Novo Nordisk</td>
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<tr>
<td></td>
<td>Premarin</td>
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<td>0.5 mg, 0.025 mg CEE</td>
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<td>Ovral Tablets</td>
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<td>1 mg Estradiol</td>
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<td>Zimmerman</td>
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<td>2 mg Estradiol</td>
<td>Abbott</td>
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<td></td>
<td>Climara</td>
<td>Patch</td>
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<td>26 mcg, 52 mcg, 78 mcg Estradiol</td>
<td>Bayer</td>
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<td>Petrastrin Mix</td>
<td>Patch</td>
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<td>Patch</td>
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<td>56, 37.5, 60, 100 mcg Estradiol</td>
<td>Novartis</td>
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<tr>
<td></td>
<td>Estrogen</td>
<td>Gel</td>
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<td>1 mg/g Estradiol</td>
<td>Asacon</td>
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<tr>
<td>Other</td>
<td>Livial</td>
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<td>2.5 mg Tibolone</td>
<td>MSD</td>
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<tr>
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<td>MSD</td>
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<tr>
<td>Progestogen only</td>
<td>Micronor</td>
<td>LUS</td>
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<td>50 mcg Levonorgestrel</td>
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<td>8 mg Norethisterone</td>
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<tr>
<td></td>
<td>Prometa</td>
<td>Tablet</td>
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<td>5 mg, 10 mg MPA</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>Plante</td>
<td>Tablet</td>
<td></td>
<td>5 mg, 10 mg MPA</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>Medroxyprogesterone</td>
<td>Suspension</td>
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<td>10 mcg MPA</td>
<td>Vanduzer</td>
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<td>Vaginal Estrogen Only</td>
<td>Cestrin Osuna</td>
<td>Pessary</td>
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<td>5 mcg Estradiol</td>
<td>MSD</td>
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<tr>
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<td>Viginal</td>
<td>Pessary</td>
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<td>25 mcg Estradiol</td>
<td>Novo Nordisk</td>
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<td></td>
<td>Cestrin Cream</td>
<td>Cream</td>
<td></td>
<td>1 mg/g Estradiol</td>
<td>MSD</td>
</tr>
</tbody>
</table>
Management of the menopause

• Up-to date with mammogram and Papsmear

• DEXA

• Start with standard doses of estrogen ± progestogen
  • Oral 1-2mg, patch 50mcg

• Low dose Vaginal E for women with urogenital symptoms only

• Aim for short time frame (3-5 years)
Side effects

Estrogen
• Breast tenderness
• Nausea

Progesterone
• Mood: anxiety, irritability, depression
• Headache
• Breast pain or tenderness
• Abdominal pain or bloating

Vaginal bleeding
• Very common, will usually settle
• May need to increase dose of Progestogen
• Need to investigate if persists beyond 6 months
Management of Primary Ovarian Insufficiency

• Aim of treatment
  • Relieve symptoms of estrogen deficiency
  • Reduce risk of long term complications

• Aim to mimic normal ovarian function
  • Transdermal estrogen + cyclical progestogen

• Oral Contraceptive Pill not recommended\(^1\)
  • Dose of hormone excessive
  • Risk of thromboembolic events
  • Case reports of pregnancy while on OCP

• Treat with hormone therapy until age 50

POI – Hormone Management

• What dose of estrogen therapy to start off with?

• Prevention of long term complications crucial
  • Oral estradiol 1mg and 0.5mg increases BMD at spine and FN\textsuperscript{1}
  • Improved BMD with transdermal E 100mcg in women with POI\textsuperscript{2}

• ? Role for measuring E levels
  • Mean E2 during menstrual cycle = 367pmol/L
  • Significant reduction of bone resorption with E2 >220pmol/L\textsuperscript{3}

• 50mcg patch $\rightarrow$ 150-180pmol/L
  100mcg patch $\rightarrow$ 260-360pmol/L

\textsuperscript{1}Gambacciani M et al Maturitas 2008
\textsuperscript{2}Crofton PM et al. Clinic Endo 2010
\textsuperscript{3}Reginster J et al. Calcif Tissue Int 1992
Secondary hypogonadism

• Very little evidence

• Oral estrogen reduces IGF1 compared to transdermal\textsuperscript{1}
  • OCP – need 55-70\% higher GH dose
  • Oral estrogen – need 20-30\% higher GH dose

➢ Transdermal E preferred

\textsuperscript{1}Filipsson H et al. Eur J Endocrinol 2009
\textsuperscript{2}Birzniece V et al. Nat Rev Endocrinol 2012
HRT – the bad stuff
Breast Cancer

• Greatest fear for women using HRT

• Evidence that use of E+P is linked to a higher risk

• Women’s Health Initiative
  • E+P arm of trial ended after 5.2 years

• Main Criticisms of WHI
  • Older (mean age 63y), overweight/obese
  • Many were past users of HRT
  • 3.5% were 50-54y with mod-severe symptoms
  • CEE 0.625mg + MPA 2.5mg
Estrogen + Progestogen

Unweighted HR = 1.49
(95% CI, 1.13-1.96)
Weighted Z = -3.86
Weighted P < .001

Estrogen alone

HR, 0.77
(95% CI, 0.59-1.01)
Breast Cancer

• 26% of women in E + P trial were past users of HRT

• Cumulative exposure to hormones is relevant
HRT and Breast Cancer

• Progestogen appears to play a role

• Risk is lower with micronised progesterone and Dydrogesterone when compared to Medroxyprogesterone acetate and Norethisterone\(^1\)

\(^1\) Fournier A, Breast Cancer Res 2008
Table 3  Relative risks for invasive breast cancer by type of HRT and duration of exposure, compared with HRT never-use

<table>
<thead>
<tr>
<th>HRT type and duration of exposure (years)</th>
<th>Cases/PT (^a)</th>
<th>Relative risk (^b) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>766/244,632</td>
<td>1 (ref)</td>
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<tr>
<td>Estrogen alone</td>
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<tr>
<td>&lt;2</td>
<td>246,747</td>
<td>1.26 (0.83-1.89)</td>
</tr>
<tr>
<td>[2-4]</td>
<td>182,705</td>
<td>1.13 (0.70-1.81)</td>
</tr>
<tr>
<td>[4-6]</td>
<td>140,172</td>
<td>1.50 (0.88-2.56)</td>
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<tr>
<td>6+</td>
<td>135,301</td>
<td>1.31 (0.76-2.28)</td>
</tr>
<tr>
<td>(p\ for trend)</td>
<td></td>
<td>0.73</td>
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<tr>
<td>Estrogen + progesterone</td>
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<tr>
<td>&lt;2</td>
<td>188,697</td>
<td>0.71 (0.44-1.14)</td>
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<tr>
<td>[2-4]</td>
<td>331,1647</td>
<td>0.95 (0.67-1.36)</td>
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<tr>
<td>[4-6]</td>
<td>307,619</td>
<td>1.26 (0.87-1.82)</td>
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<tr>
<td>6+</td>
<td>431,111</td>
<td>1.22 (0.89-1.67)</td>
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<tr>
<td>(p\ for trend)</td>
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<td>0.04</td>
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<tr>
<td>Estrogen + dydrogesterone</td>
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<tr>
<td>&lt;2</td>
<td>166,923</td>
<td>0.84 (0.51-1.38)</td>
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<tr>
<td>[2-4]</td>
<td>288,697</td>
<td>1.16 (0.79-1.71)</td>
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<tr>
<td>[4-6]</td>
<td>215,590</td>
<td>1.28 (0.83-1.99)</td>
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<tr>
<td>6+</td>
<td>357,376</td>
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<td>Estrogen + other progestagens</td>
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<tr>
<td>&lt;2</td>
<td>882,2702</td>
<td>1.36 (1.07-1.72)</td>
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<td>[2-4]</td>
<td>134,30189</td>
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<td>[4-6]</td>
<td>106,19,942</td>
<td>1.70 (1.44-2.23)</td>
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<tr>
<td>6+</td>
<td>156,23,817</td>
<td>1.65 (1.62-2.35)</td>
</tr>
<tr>
<td>(p\ for trend)</td>
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<td>0.01</td>
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<tr>
<td>Weak estrogen (^c)</td>
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<tr>
<td>Others (^d) / unknown HRT</td>
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<tr>
<td>Mixed (^e)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Fournier A, Breast Cancer Res 2008
Breast Cancer – ‘Gap time’

• Time between onset of menopause and initiation of HRT

<table>
<thead>
<tr>
<th>Gap Time</th>
<th>E + P</th>
<th>E alone</th>
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<tbody>
<tr>
<td>&lt;5 y</td>
<td>1.77 (1.07 – 2.93)</td>
<td>1.12 (0.39 – 3.21)</td>
</tr>
<tr>
<td>&gt;5 y</td>
<td>0.99 (0.74 – 1.31)</td>
<td>0.58 (0.36 – 0.93)</td>
</tr>
</tbody>
</table>

• Hypothesis
  • Breast cancer cells deprived of E become sensitive to pro-apoptotic effect of E
HRT and Breast Cancer - summary

- E+P particularly with synthetic Progestogens is associated with an increased risk, possibly within 3-5 years of initiation
  - Risk back to baseline within 3 years of cessation
  - Progesterone and dydrogesterone do not appear to increase risk

- Difficult to provide estimate of absolute risk because risk varies with individual woman
  - Duration of use, type of progestogen, Gap time

- Women closer to time of menopause to initiation of HRT appear to be at highest risk
HRT and Cardiovascular disease

• WHI initial reports linked use of HRT to increase in risk of CV disease\(^1\)

• Findings were of borderline significance

\(^1\)Manson JE et al, NEJM 2003
HRT and Cardiovascular disease (2)

• Timing hypothesis
  • Effects of HRT are modified by timing of initiation
• No significant change in risk if initiated close to menopause¹
• Hypothesis
  • Oral E increases proinflammatory markers that act on atheromatous plaque

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1 Rossouw JE et al, JAMA 2008
HRT and Cardiovascular disease - summary

• HRT is not recommended for CHD risk reduction

• Use of HRT for other indications should not be hampered by concern that it increases CHD in younger recently menopausal women

• Unclear if cardiovascular outcomes applicable if using other forms of estrogen including lower dose, transdermal, or different progestogens
HRT and thromboembolic disease

• Strong evidence that oral estrogen increases thromboembolic (TE) risk
• No evidence that transdermal estrogen increases risk
  • Based on observational studies, no RCT’s
• Risk is multiplicative with age, higher BMI, thrombophilias, surgery and immobilisation
• Overall risk for oral E is 2 fold
  • Baseline rate 15/100 000 woman years
  • HRT risk = 30/100 000 woman years
References / Resources

• Executive Summary: Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement
  • Santen RJ et al. JCEM July 2010

• Jean Hailes Foundation website

• A Practitioner’s Toolkit for the Management of the Menopause
A Practitioner’s Toolkit for the Management of the Menopause

Developed by the Women’s Health Research Program
School of Public Health and Preventive Medicine
Monash University, 2014

The supporting notes for the Practitioner’s Toolkit for Managing the Menopause are published, with free access, in Climacteric, the Journal of the International Menopause Society.


Endorsed by the Australian Menopause Society, the International Menopause Society and the Jean Hailes Foundation.
HRT in breast cancer survivors

<table>
<thead>
<tr>
<th></th>
<th>HABITS</th>
<th>Stockholm</th>
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<tbody>
<tr>
<td>n</td>
<td>434</td>
<td>378</td>
</tr>
<tr>
<td>Median follow up (yr)</td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td>HR – recurrence</td>
<td>3.3 (1.5 – 7.4)*</td>
<td>0.82 (0.34 – 1.9)</td>
</tr>
<tr>
<td>% node positive disease</td>
<td>25.9</td>
<td>16</td>
</tr>
<tr>
<td>Regimen</td>
<td>‘local practice’</td>
<td>73% E alone or cyclical progestogen every 3 months</td>
</tr>
</tbody>
</table>

- Overall not recommended
HRT and ovarian cancer

• Meta-analysis published February 2015
• Over 12000 women from 52 epidemiological studies
• Use for 5 years from around age 50 years
  ➢ ~1 extra ovarian cancer per 1000 users
  ➢ if prognosis is typical, ~ 1 extra ovarian cancer death per 1700 users

• WHI: Only RCT; results not statistically significant
Tibolone

- Synthetic steroid hormone, alternative to HRT
- 2.5mg tablets
- Metabolites have oestrogenic, progestogenic and androgenic activity

- Low incidence of breast cancer, no increase in mammographic density
- No increase in risk of VTE

- Increases breast cancer recurrence in breast cancer survivors
- Increased risk of stroke in women > 60y
Progestogen / Dydrogesterone preparations

• *Femoston* = Estradiol 2mg + dydrogesterone 10mg (cyclical)

• *Femoston conti* = Estradiol 1mg + dydrogesterone 5mg (continuous)

• *Utrogestan* = micronized Progesterone 100mg, 200mg*
• Duphaston = dydrogesterone 10mg*

*currently not TGA approved in Australia, access via SAS or as authorized presriber