HRT and Menopause

Mr N Pisal
Consultant Gynaecologist
Whittington & Portland Hospital
Menopause and HRT
Menopausal Symptoms

- 94% get some symptoms, 25% get severe symptoms
- Hot flushes & sweats
  - 74% experience, most common symptom
- Headaches
- Tiredness
- Irritability
- Poor memory
- Sleep disturbance
- Depression, anxiety, Mood swings
- Loss of libido
- Dry skin
- Vaginal atrophy
- Osteoporosis.....
Carol found her own way of coping with the hot flushes
HRT

- Very effective at treating symptoms of menopause.

- Until recent studies (Women’s Health Initiative and Million Women Study), HRT was widely used for long periods.
The girls who are destined to grow up into tomboys

Fizzy drinks leave a bitter aftertaste for the young

Surgery could cause dementia

The world is singing her praises

HRT scare prompted by 'flawed' studies

News

The contraceptive pill and HRT are among the most widely used treatments to prevent breast cancer. But recent studies have suggested that HRT may increase the risk of breast cancer in women over 50.

The following study was published in the British Journal of Obstetrics and Gynaecology. It is based on data from the Million Women Study, which involved 3,922,285 women aged 50-69 in the United Kingdom. The study found that women who took HRT for more than 10 years had a higher risk of breast cancer than those who did not.

The study was sponsored by the National Institute for Health Research and the National Cancer Research Institute. The researchers said their findings could have implications for women considering HRT.
## WHI study (av age 63)

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR (E2 only)</th>
<th>RR (E+P)</th>
</tr>
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<td>CHD</td>
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Selected clinical outcomes by participant age

Outcome by Age, y
Coronary Heart Disease
- 50-59
- 60-69
- 70-79

Stroke
- 50-59
- 60-69
- 70-79

Venous Thromboembolism
- 50-59
- 60-69
- 70-79

Invasive Breast Cancer
- 50-59
- 60-69
- 70-79

Global Index
- 50-59
- 60-69
- 70-79

Hazard Ratio

JAMA 2004;291:1701-1712
WHI studies: Coronary heart disease
HRT and CHD: absolute risk by age

Taken from: Rossouw et al. JAMA. 2007;297:1465-1477

n=27,347
Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial

Louise Lind Schierbeck registrar, Lars Rejnmark associate professor, consultant, Charlotte Landbo Tofteng staff specialist 1, Lis Stilgren consultant 2, Pia Eiken consultant, senior endocrinologist, Leif Mosekilde professor, senior consultant, Lars Køber professor, consultant, Jens-Erik Beck Jensen associate professor, consultant

1Department of Endocrinology, Hvidovre Hospital, Kettegård alle 30, 2650 Hvidovre, Denmark; 2Department of Medicine and Department of Endocrinology and Internal Medicine, Århus University Hospital, Århus, Denmark; 3Department of Endocrinology, Svendborg Hospital, Svendborg, Denmark; 4Department of Cardiology, Nephrology, and Endocrinology, Hillerød Hospital, Hillerød, Denmark; 5Department of Cardiology, Rigshospitalet, Copenhagen, Denmark

Main outcome measure The primary endpoint was a composite of death, admission to hospital for heart failure, and myocardial infarction.

Results At inclusion the women on average were aged 50 and had been postmenopausal for seven months. After 10 years of intervention, 16 women in the treatment group experienced the primary composite endpoint compared with 33 in the control group (hazard ratio 0.48, 95% confidence interval 0.26 to 0.87; P=0.015) and 15 died compared with
The Danish Osteoporosis Prevention Study (DOPS)

Primary endpoint and mortality and major risks for HRT in the total population during randomisation phase (up to year 2002).

- Mortality, heart failure, MI
- Mortality
- DVT
- Stroke
- Breast cancer
- Other cancer

HR

0
1
2
3

Schierbeck L L et al. BMJ 2012;345:bmj.e6409
HRT and breast cancer risk

- Combined HRT increased breast cancer risk more than Oestrogen only HRT
- Risk increases with duration of HRT
- Risk seems to go back to normal within 5 y of stopping HRT
WHI study (av age 63)

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Risk for post-menopausal women (mean age 63) developing breast cancer over a five year period (15 out of 1000)

Risk to general population

Additional risk for CC HRT users: 4 cases / 1000 (Not significant in latest analysis)

“Significant reduction in breast cancer risk in CEE alone study”
La Croix AZ et al JAMA 2011; 305:1305-14
Breast cancer risk: The progestogen matters!

**E3N French Cohort Study**

- **Baseline risk without HRT**
  - Relative risk (95% CI): 1.00 (0.83–1.22)
- **Estrogen/progesterone**
  - Relative risk (95% CI): 1.16 (0.94–1.43)
- **Estrogen/dydrogesterone**
  - Relative risk (95% CI): 1.69 (1.50–1.91)
- **Estrogen/other progestogens**
  - Relative risk (95% CI): 1.0

**Baseline risk without HRT**

- **Baseline risk without HRT**
  - Standard incidence ratio (95% CI): 1.69
- **Estradiol/dydrogesterone**
  - Standard incidence ratio (95% CI): 1.13 (0.49–2.22)
- **Estradiol/MPA**
  - Standard incidence ratio (95% CI): 1.49–1.79
- **Estradiol/NETA**
  - Standard incidence ratio (95% CI): 1.88–2.18
- **Estradiol/other progestogens**
  - Standard incidence ratio (95% CI): 2.03 (1.76–2.04)

Significantly different from the risk without HRT

Not statistically significantly different from risk without HRT

“Breast cancer risk was lower with natural progesterone / dydrogesterone”

**Figure 5:** Standardised incidence rates for endometrial cancer per 1000 women in the study cohort over a 5-year period, according to body-mass index and type of HRT last used.
Risk of VTE with HRT

Risk in current users is 3-4 x higher than in non-users
one case in 5000 users per year

The baseline risk of VTE between the ages of 50 and 70 is higher

Increased risk appears to be concentrated in new users

VTE risk is not increased with transdermal E (oral 3.5 vs TRD 0.9)
ESTHER study - Lancet 2003;362:428-432
### Table: HRT and risk of VTE; systematic review and meta-analysis

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<th>Study Type</th>
<th>OR (Pooled)</th>
<th>95% CI (Pooled)</th>
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<tr>
<td><strong>Observational studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral oestrogen</td>
<td>2.5</td>
<td>1.9-3.4</td>
</tr>
<tr>
<td>Transdermal</td>
<td>1.2</td>
<td>0.9-1.7</td>
</tr>
<tr>
<td><strong>Randomised controlled trials</strong></td>
<td></td>
<td></td>
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<td>Oral oestrogen</td>
<td>2.1</td>
<td>1.4-3.1</td>
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Other benefits of HRT

• Urogenital Atrophy\(^1\)
  • Highly effective for vaginal and urinary symptoms

• Cognitive\(^2\)
  • 30% reduction in dementia incidence if HRT started early

• Colon Cancer\(^3\)
  • 44% reduction in CEE + P WHI (RR 0.56 0.38-0.81)

Ideal HRT regimens

- Estradiol gel or patch
  - Estradot patches 25-100mcg
  - Oestrogel 2-4 apps
  - Sandrena gel 0.5-2.0mg/day

- Progesterone/Progestogens
  - Oral: Utrogestan cc100mg, sc200mg 12/28
  - Vaginal: Utrogestan, Crinone 8%, Cyclogest
  - Mirena

- Closest combined oral regimen
  - Femoston range 1:10, 2:10, Conti 1:5, Conti low dose 0.5:2.5
Mirena: HRT

- **Mirena**: HRT / PMS (4yr license)
  - NB: poss prog SEs / bleeding

- “On the way” – “Baby” Mirena 12 & 16 mcg systems (3y & 5y)
Vaginal Oestrogen

- Vaginal symptoms may persist despite HRT
- Highly effective for local symptoms
- Vagifem now licensed for indefinite usage

- Creams
  - Ovestin (0.1% estriol) / Gynest (0.01% estriol)

- Rings
  - Oestradiol: Estring – 2 yr license

- Vag Tabs
  - Vagifem (10mcg) Total dose = 1.14mg/year
Key points (HRT)

• **Combined HRT** has different profile compared to **oestrogen alone** (lipids, CHD)

• An increase in **breast cancer** risk is related to
  • the duration of use and
  • concurrent use of progestogens.

• **Transdermal oestrogen** have different metabolic profiles and side-effects (VTE risk)

• Mirena or Utrogestan  + Transdermal Oestrogen
Livial

- Active ingredient Tibolone
- Mimics action of Oestrogen + Progesterone + Testosterone
- Bleed-free
- Can be used after 54 or 2 years after menopause
- Increases risk of breast cancer (but thought to be less than combined HRT)
HRT should be part of the overall strategy

- Increase weight-bearing exercise
- Calcium + VitD3 supplements (Adcal D3)
- Reduce alcohol intake
- Quit smoking
Bone Health
Osteoporosis

- Affects two million women in the UK
- 300,000 people in the UK suffer a fragility fracture per year including
  - 76,000 hip fractures
- Numbers increasing
Risk factors

• H/o fracture following a minor fall
• Early menopause (aged less than 45)
• H/o amenorrhoea > 1yr

• Smoking + alcohol
• Corticosteroids for three months or more
• Rheumatoid arthritis or coeliac disease

• BMI < 19
DEXA Scan

• Minimal radiation from a DEXA scan, less than one-tenth the dose of a standard chest X-ray.
• Safe and relatively inexpensive

• Baseline study at 50y of age + repeat every three years
Prevention of fractures

- FRAX tool
  - Early detection and treatment

- Regular weight-bearing exercise
- Adcal D3
- Reduce risk of falling / improve balance etc
Menopause and HRT

Regulatory View 2013
- Minimum effective dosage for shortest duration with annual reappraisal
- HRT should be used for prevention of osteoporosis only in women who are unable to use other medicines that are authorised for this purpose.

Menopause/Osteoporosis/Endocrine Society View
- HRT should be used first line in women younger than 60y for prevention and Rx of osteoporosis

Screening after 50
Ovarian Screening

- CA125
- TVS

- Only 85% of all and 50% of early ovarian cancers will have raised CA125
- False positives with endometriosis, fibroids etc
- There will be a proportion of interval cancers even if you screen annually

- Screening can be used where risk is increased
Post menopausal woman with ovarian cyst

TVS + CA125

Simple, unilateral, <5cm CA125<30

Conservative Mx in primary care

Repeat TVS + CA125 every 4 months for 1y

Repeat TVS + CA125 every 4 months for 1y

Resoluion or No change

Suspicious features on scan OR >5cm

Refer urgently

Cyst increases in size or develops suspicious features

Discharge
Red Flag Symptoms
Red Flag Symptoms

- Post-menopausal bleeding
- New onset of pelvic or abdominal pain
- Persistent abdominal distension (women often refer to this as 'bloating')
- Feeling full (early satiety) and/or loss of appetite
- Increased urinary urgency and/or frequency.
Sexual Health and Contraception
• Low libido
• Vaginal dryness
• Increased risk of STI
Sexually transmitted infections double in older population in ten yrs

2 February 2012
St BMJ editorial: Sexual health and the older adult
Increased risk of STI

- Less likely to use condoms
- Less likely to be screened
- More likely to start a new relationship
- Atrophic vaginitis: Risk of tears and transmission
- Immune senescence
HSDD

• Intrinsa patch 300 microgram/24hr
• Twice weekly testosterone patch

• Testim gel (1 pea-sized blob to be applied once a day or once every other day, 1 tube should last for at least 8 days)

• Livial
Vaginal dryness

- Atrophic vaginitis
- Local oestrogen pessaries, cream or ring

- Vagifem 10mcg vaginal tablets or ovastin cream
  - Once at night for two weeks
  - Followed by twice a week for maintenance

- Lubrication such as Sylk / KY
Vaginal oestrogen

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Summary

- HRT indicated for menopausal symptoms
- Breast cancer risk seems to be associated with long term use oral progesterone? could be avoided with Mirena
- Transdermal oestrogen reduces risk of VTE
- Oestrogel: Ability to easily titrate the dose with symptoms
- STI on the increase in this age group
- Prevention of osteoporosis
- Screening with CA125 + TVS for ovarian cancer, but has limitations
Thank You

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