HRT and the Menopause

Tony Parsons

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Declaration of interest

- 40 years of firm conviction that the menopause needs to be taken more seriously
- Various research studies partly supported by the pharmaceutical industry
- Lectures at meetings and conferences supported by pharmaceutical companies
- NICE Menopause Guidelines Development Group 2015
Demographics

1850
* Age at menopause - 45 yrs
* Life expectancy - 45 yrs

2018
* Age at menopause - 52 yrs
* Life expectancy - 83 yrs
* Today > 35% life = post menopausal
Impact of menopause on future health

* Obesity, metabolic syndrome and diabetes
* Cardiovascular disease
* Osteoporosis and chronic arthritis
* Dementia, cognitive decline and depression
* Cancer
* Autoimmune disorders
No FSH - >45yrs with menopausal symptoms

> 45yrs do not use – AMH*, Oestradiol, Inhibin A,B, Antral follicle count

OCP or high dose prog – do not use FSH (?)

Consider FSH age 40-45, with menopausal symptoms

FSH x 2 mandatory when menopause suspected < 40
Back to Basics

* Who should be offered HRT?
* Advantages (benefits)
* Disadvantages (risks)
* What do you give?
* Duration of use?
* When / how to stop?
Why Consider HRT?

- Quality of Life
- Treatment of Symptoms
- Prevention of Long-term Chronic Conditions
Menopausal Symptoms

-nothing diagnostic, nothing impossible
Consider alternatives to HRT first?

- Why?
  - Less likely to work - see BMS and NICE for prescribable and OTC alternatives
  - Often unknown safety and efficacy if OTC
  - May be unethical if it deprives individual from receiving more effective treatment
MORE HARM THAN GOOD?
The Moral Maze of Complementary and Alternative Medicine

Edzard Ernst
Kevin Smith

Springer
Estrogen withdrawal does not explain the aetiology of hot flushes

- There are no correlations between hot flush occurrence and plasma, urinary and vaginal levels of estrogens
- Nor are there differences in plasma levels between asymptomatic and symptomatic women
- Role of neurokinins

Estrogen withdrawal is necessary to explain the occurrence of hot flushes but is not, by itself, sufficient to do so
Prevalence of moderate to severe vasomotor symptoms

Gartoulla 2015
Hot flushes may continue years after menopause

Ages 29 to 82 Years

Number of years women report having hot flushes as estimated by a survey of 501 untreated women who experienced hot flushes.

Mean age of natural menopause was 49.5 years; mean age of surgical menopause was 43.7 years.

Kronenberg F. Ann NY Acad Sci. 1990;592:52-86. Used with permission.
Flushes in older women (over 60)

* Smoking
* BMI over 25

* May be a cardiovascular risk factor
Vasomotor symptoms and cardiovascular mortality

- Women’s Ischaemia Syndrome Evaluation
- 254 women, >50, postmenopausal, both ovaries, no HRT
- CVD mortality
- Early onset VMS – HR 3.35 (CI 1.23 – 7.86)
- Never VMS - HR 2.17 (CI 1.02 – 4.62)
- Flow mediated dilation lower in early onset VMS

Thurston R et al, 2017
Incidence of GSM

* 15% premenopausal women
* 10 – 40% postmenopausal
* 10 – 25% women taking systemic HRT
* 2/3 by age 75
* Under-reported and undertreated
Hypertension and risk of stroke

Danish Nurse Study

Lokkegaard et al Arch Neurol 2003;60:1379
Effect of Oestrogen lack

- Change in BMI, fat distribution
- Inc LDL cholesterol
- Decreased HDL
- Increase TGs
- **Blood pressure**
- Glucose/insulin metabolism
- Endothelial dysfunction
- 4 fold increased risk CVD
- POI—53% inc risk CHD
Ovarian conservation and long-term health outcomes

Hazard Ratios for bilateral oophorectomy (all statistically significant at 95 % level)

- **Total mortality** 1.12
- Fatal plus nonfatal CHD 1.17
- Stroke 1.14
- Breast cancer 0.75
- Ovarian cancer 0.04 (NNT=220)
- Total cancer 0.90
- Lung cancer 1.26 (NNH=190)
- Total cancer mortality 1.17
Age at menopause and risk of Ischaemic Stroke

* Framingham Heart Study
* Observational study
* 1430 women stroke-free until age 60
* Natural menopause
* No HRT

* Menopause before age 42 HR 2.03 (1.16-3.56)
* Average age at stroke 80
Testosterone

- T levels do NOT fall rapidly at the menopause
- T levels fall steadily from age 30
- There is no significant change at menopause but the ratio between estrogen and testosterone changes and SHBG levels may fall
Leading Causes of Death Perceived by Women

- Breast Cancer (39%)
- Heart Disease (18%)
- Other Cancer (13%)
- Lung Cancer (2%)
- Other/Don’t Know (16%)
- Smoking (1%)
- Stress (2%)
- Ovarian Cancer (9%)
- Old Age (1%)
Actual Causes of Death Among U.S. Women

- Heart Disease (45%)
- Other (25%)
- Lung Cancer (5%)
- Breast Cancer (4%)
- Ovarian Cancer (<2%)
- COPD (4%)
- Pneumonia (4%)
CVD in women

[Graph showing the incidence of CVD in women compared to men across different age groups (20-34 yrs, 35-44 yrs, 45-54 yrs, 55-64 yrs).]
CVD in women

- Different clinical presentation
- Often present late
- Other medical problems
- Poorly represented in trials
- Fewer interventions
- Coronary microvascular disease, women 4x more than men
- Worse prognosis following MI:
  - 38% women die in 1 year, 25% men
  - In 6 years, further MI in 35% women, 18% men
More treatment for lipids/BP
More percutaneous coronary interventions
A lot less smoking in last 40 years
Less dairy fat consumption
Higher fresh fruit intake
(although 1/3 still eat less than 5 portions)
But … obesity and diabetes are increasing and threatening to increase mortality rates again
Incidence of CVD: relation to menopause status

The Framingham Study

- Incidence (per 1000 women)
  - Age (years)
  - n = 2873

Adjusted women-to-men ratios of hazard ratios for association between risk factors and incident myocardial infarction.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Ratio of HR (95% CI)</th>
<th>Ratio of HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood pressure</strong></td>
<td>1.09 (1.02 to 1.16)</td>
<td>1.01 (0.95 to 1.08)</td>
</tr>
<tr>
<td>Systolic per 20 mm Hg</td>
<td></td>
<td></td>
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<tr>
<td>Diastolic per 10 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1.83 (1.33 to 2.52)</td>
<td>1.45 (1.12 to 1.88)</td>
</tr>
<tr>
<td>Elevated blood pressure v no hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 hypertension v no hypertension</td>
<td></td>
<td></td>
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<tr>
<td>Stage 2 hypertension v no hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>1.05 (0.91 to 1.20)</td>
<td>1.55 (1.32 to 1.83)</td>
</tr>
<tr>
<td>Former v never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current v never</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>By smoking intensity</strong></td>
<td>1.23 (0.80 to 1.90)</td>
<td>1.42 (1.11 to 1.83)</td>
</tr>
<tr>
<td>1-9 cigarettes per day v never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19 cigarettes per day v never</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20 cigarettes per day v never</td>
<td>2.01 (1.57 to 2.57)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>2.91 (1.56 to 5.45)</td>
<td>1.47 (1.16 to 1.87)</td>
</tr>
<tr>
<td>Type 1 v no diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 v no diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>0.97 (0.91 to 1.03)</td>
<td>0.89 (0.76 to 1.03)</td>
</tr>
<tr>
<td>Body mass index per 5 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight v healthy weight</td>
<td>0.93 (0.79 to 1.09)</td>
<td></td>
</tr>
<tr>
<td>Obese v healthy weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>1.14 (0.62 to 2.09)</td>
<td></td>
</tr>
<tr>
<td>History of atrial fibrillation v no history</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td>1.13 (0.98 to 1.31)</td>
<td>1.14 (0.97 to 1.34)</td>
</tr>
<tr>
<td>Middle v high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low v high</td>
<td></td>
<td></td>
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Elizabeth R C Millett et al. BMJ 2018;363:bmj.k4247

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Effect of ERT on Coronary Atherosclerosis: timing of initiation

<table>
<thead>
<tr>
<th>Premenopausal Years</th>
<th>Postmenopausal Ovariectomy Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Healthy diet</td>
<td>CEE + atherogenic diet</td>
</tr>
<tr>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>2. Atherogenic diet</td>
<td>CEE + atherogenic diet</td>
</tr>
<tr>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>3. Healthy diet</td>
<td>Atherogenic diet + Healthy diet</td>
</tr>
<tr>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

Plaque Area (% of placebo)

?6 -10 Year Human Equivalent

Time

Effect of hormone therapy on atherosclerosis varies with stage of reproductive life.

Premenopause → Perimenopause ← Postmenopause

- ~5% (15-25 yrs)
- ~15% (25-35 yrs)
- 35-45 yrs
- 45-55 yrs
- 55-65 yrs
- 65 yrs

Benefits of Endogenous $E_2$  Primary Benefits of HT  No Benefits of HT

Smoking

* Increased menopausal symptoms (vasomotor, insomnia, psychological)

* Increased CVD risk

* Increased osteoporosis risk

* Mechanisms—toxicity to ovarian follicles, reduced estrogen, earlier age of menopause
Cardio protection at 50?

- Observational studies
- Update on WHI
- KEEPS
- DOPS
- ELITE
- NICE Guidance
HRT and Cardiovascular Protection

23 good observational studies

**BUT**

* Not randomised
* Mainly unopposed oestrogen (and we now know E+P does not have same beneficial effects on lipids)
* Healthy cohort effect
CHD: primary prevention

* low-dose aspirin reduces CVA risk

* no reduction in CHD risk with low-dose aspirin

* no reduction in CHD mortality with statins

* reduction in CHD risk with HRT

Hodis and Mack. Menopause 2007; 14: 1-14
Further analyses of WHI

- Starting HT within 10 years of menopause
  - 24% reduction in CHD
  - 30% reduction in overall deaths
- Slight increase in stroke risk at all ages
- Coronary artery calcium
  - Mild-to-moderate 40% reduced
  - Severe 60% reduced
Does the timing of HRT matter?

- Meta-analysis of 30 trials
- 27,000 participants

- Odds ratio for mortality differed with age at enrolment
  - Under 60 - 0.61
  - Over 60 - 1.03

- [Nurse’s Health Study  HRT within 2 years of LMP - 0.61]
Effect of HT on cardiovascular events in recently post menopausal women (Danish Osteoporosis Prevention Study)

* Results – 11 years study followed to 16 years
* Risks during treatment (hazard ratios) for
  * Primary endpoint 0.48 *
  * Death 0.57
* During follow-up
  * Primary endpoint 0.61 *
  * Death 0.66
CEE plus MPA (non-hysterectomised group)
  * CHD hazard ratio **1.19** [0.95 - 1.45]
CEE alone (hysterectomised group)
  * CHD hazard ratio **0.94** [0.78 – 1.14]

* No change in all-cause mortality
Direct Effects of Oestrogen Replacement on the Heart (Sanghvi et al, 2018)

- In users of HRT for more than 8 years
  - Smaller LV volume
  - Smaller AV volume
  - Lower LV stroke volume
- Biggest effect in over-65s
Risk of stroke with various types of menopausal hormone therapies

- Cohort Study
- 980,003 women aged 51-70
- 20,199 strokes (78% ischaemic)

- Risk increased with oral only (RH 1.16, 1.12-1.22)
- No risk with transdermal at standard doses

Lokkegaard et al 2017
Observational data from Finland

- Observational nationwide Study Finland
- 489,105 women using HRT, 1994 to 2009
- CHD death reduced by 18 to 54% in users (positively related to HRT exposure time)
- Stroke death reduced by 18 to 39% in users (not clearly related to exposure time)
- All cause mortality reduced by 12 to 38% in users
- All risk reduction comparable starting before, at or after age 60

Mikkola 2016
Increased cardiovascular mortality after HT discontinuation before 60

Mikkola 2015
Cardiovascular mortality in first year after stopping therapy

- Mikkola TS et al 2015
- 332,202 Finnish women
- 2 million woman-years of follow up
- All causes of death recorded
- 30% confirmed by autopsy
- Death rates compared to age-standardised background population
Effects of HT on myocardial infarction

Tuomikoski 2015 NAMS meeting
Take home messages – estrogen and the heart

* Estrogen is strongly cardio protective in premature ovarian insufficiency

* Estrogen appears to protect the heart in women in their 50s who do not have established cardiovascular disease

* Women in their 60s with menopausal symptoms can safely be treated with HRT but if starting consider cardiovascular risk factors and use transdermal route

* Don’t stop HRT unnecessarily, especially before age 60
Lifetime risk of Dementia for a 45-year old

- Men
- Women
Annual risk of AD for HT Users and Nonusers

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>70</td>
<td>0.02</td>
<td>0.02</td>
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<tr>
<td>75</td>
<td>0.04</td>
<td>0.04</td>
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<tr>
<td>80</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>85</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>90</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>95</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>100</td>
<td>0.12</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Cognitive decline

- BSO < age 48 HR 1.6
- BSO > age 48, no increased risk
- E replacement blocks accelerated ageing cascade
- Age < 50, E strongly protective
- Age 50-59, E moderately protective
- Age > 65 if started late, E deleterious

Presented EMAS May 2015
VTE risk - summary

* Baseline risk for VTE 1.0 per 1,000 women per year (@50)
* Oral HRT – extra 1.5 events /1,000 women/ yr
* May be different effect from doses and progestogen types – MPA higher risk, progesterone and dydrogesterone lower

* No significant increase with transdermal
* NICE recommends transdermal if BMI >30

* Time to reconsider pre-op advice?
HRT and VTE recurrence

* 1023 consecutive postmenopausal women aged 45 to 70, previous confirmed VTE, between Jan 2000 to Dec 2008
* Followed up average 79 months
* Oral estrogens—HR 6.4
* Transdermal estrogens—HR 1.0

HRT and Breast Cancer

- Probable increased risk associated with most progestogens – (possibly not progesterone or dydrogesterone) – no risk with oestrogen alone
- Duration related after normal menopause age only
- No obvious association with dose
- Accelerator rather than initiator
- Extra risk gone 5 years after initiation
What do we give?
(Informed patient choice)
Route

- Transdermal safest and most cost effective
- No increase in thrombotic risk at standard doses (NICE 2015)
- May limit progestogen choices

- Vaginal – no contraindications
  - May be needed in addition to systemic in 20-25% of women
Regimens

* Unopposed oestradiol

* Sequential (SEPT)
  * How many days prog?
  * How often?

* Continuous combined (CCEPT)
**Oestrogen**

- Conjugated Equine
  - Oral only
  - Possible lower breast cancer risk (WHI)
  - Mix of oestrogens including SERMS

- **Oestradiol**
  - Usual first choice
  - All routes available
  - Needs progestogen for women with uterus (including endometrial ablation)
  - Vaginal preparations do not require progestogen
Progestogens

- Progestogens protect endometrium
- But may increase thrombotic risk – some more than others
- Small increase in breast cancer risk (possibly not with progesterone or dydrogesterone)
- Wide choice with oral
- Limited choice with ready-made transdermal combinations (i.e. only NET and LNG with patches)
How long?

- All guidelines agree
  - “no arbitrary duration of use”
- Balance perceived benefits versus risks (if any)
- Possible short-term disadvantage to stopping before 60
How to Stop

* Gradually or abruptly?
  * No good data but advantages to weaning off
  * ? No difference at one year after stopping
  * More severe symptoms at first with abrupt stop
  * Don’t keep trying to stop
    * Increased thrombotic risk
    * Possible cardiac risk
    * Half-life of symptoms is at least 3 years
Resources

British Menopause Society - www.thebms.org.uk

Menopause Matters - www.menopausematters.co.uk

Manage my menopause -
www.managemymenopause.co.uk

NICE - https://www.nice.org.uk/Guidance/NG23

Thank you!