HRT: Controversies and Current Practice

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Welsh Obstetrics & Gynaecology Society
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Objectives

• The relevance of Menopause to the modern gynaecologist
• The Place of HRT in it’s management
• Is HRT safe?
• Practical advice about HRT prescribing
• Testosterone
• Resources
Why is the Menopause Important to Gynaecologists?

- It is a natural event (mean age 52)
- It is an immediate consequence of BSO
- Menopausal symptoms can have significant impact on Quality of Life
- Long-term health implications
- Premature ovarian insufficiency (POI) is an easily correctable endocrine condition with significant long-term health risks
- Predominantly dealt with in Primary care but they need advice and support…….
Current Situation

- 11 million women in UK over 45
- > 1/3rd want support for menopausal symptoms and most want more information
- Services very variable
- Controversy and uncertainty about HRT last 15 years
- Knowledge and training gap
- Recent National and International recommendations
- NICE guidance published Nov 13th 2015
  www.nice.org.uk/guidance/ng23
The Impact of the Menopause
Short-term

Vasomotor symptoms:
- experienced by 60 – 80% women
- 25% women experience significant symptoms
- Mean duration 7 years,
- 10-20% go on flushing well into their 60’s
- impact on sleep, mood and QoL
The Impact of the Menopause
Other Symptoms

• Insomnia, tiredness, mood swings, irritability,
• Anxiety, Palpitations
• Headaches
• Connective tissue; skin/hair, changes, joint aches
• Cognitive function; “foggy head”, difficulty making decisions, poor concentration
• Low self esteem, difficulty coping
• “not myself” “lost my spark”
The Impact of the Menopause
Medium-term

Genitourinary syndrome of the menopause (GSM):
• Uro-genital atrophy
  – Dyspaerunia
  – Recurrent UTI’s
  – PMB

• Peak incidence of urinary incontinence and prolapse
The Impact of the Menopause
Longer term problems

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Menstrual Problems</th>
<th>Menopause</th>
<th>Urogenital Atrophy &amp; Prolapse</th>
<th>Osteoporosis</th>
<th>Cardiovascular Disease</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-50</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>50-55</td>
<td></td>
<td>Menopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-65</td>
<td></td>
<td></td>
<td>Urogenital atrophy &amp; prolapse</td>
<td>Osteoporosis</td>
<td>Cardiovascular disease</td>
<td>Dementia</td>
</tr>
<tr>
<td>&gt;75</td>
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</tbody>
</table>

“Menopause presents an opportunity to review modifiable risks for later disease processes”
Managing the Menopause

- Holistic approach
- Lifestyle opportunities
- Reducing modifiable risk factors

- Other prescription drugs
- Complimentary and Alternative therapies
- Vaginal Oestrogens
- HRT
Oscillations in the development of a new drug

The new wonder drug

Promising reports

Rational prescribing

It's poison!

Great idea

Adapted from Laurence Clinical Pharmacology 1973
Inspiration from Scott’s Parabola, BMJ 2001;323:1477
International Recommendations on HRT

• Endocrine Society Statement
  Journal of Clinical Endocrinology & Metabolism 2010

• International Menopause Society Statement
  Climacteric 2013

• British Menopause Society Recommendations
  Menopause International 2013 (2016)

• NICE guidance on Menopause Nov 13th 2015
  www.nice.org.uk/guidance/ng23
What HRT Does do:

• Relieves menopausal symptoms and improves quality of life
• Reverses uro-genital atrophy
• Prevents osteoporosis and reduces fracture risk
• Reduces Cardiovascular disease risk
Oestrogens and Cardiovascular Disease

5. Time frame: cardiovascular mortality in Mayo Clinic Study (<45 y)

Rivera et al., Menopause 2009
Cardiovascular Effects of HRT

- Loss of oestrogen associated with increased risk
- Risk not seen if oestrogen replaced
- Use of oestrogen in early postmenopause (< 6yrs) reduces longterm cardiovascular disease events
- Starting oestrogen >10 yrs postmenopause may increase risk of cardiovascular events
- “window of opportunity”
  Schierbeck L, BMJ 2012
  Hodis H et al NEJM 2016
Finnish Cohort Study
Mikkola TS et al. Menopause 2015

Observational nationwide Study 489,105 women using HRT 1994 to 2009

In HRT users
- CHD death reduced 18 - 54%
- Stroke death reduced 18 - 39%
- All cause mortality reduced 12 - 38%
- Risk reduction related to length of oestrogen exposure

Per 1000 women using any HRT for at least 10 years
- 19 fewer CHD deaths
- 7 fewer stroke deaths
Neurological Effects

Decline in cognitive function, memory and wellbeing within weeks of oophorectomy in peri-menopausal women
Sherwin 1988, Farrag A 2002

Mayo Clinic cohort (BSO 1950-87 n=1075) 90% FU

BSO increased risk:
- Parkinsonism HR 1.80 (1.00-3.26)
- Dementia HR 1.70 (1.15-2.15)
- Anxiety HR 2.29 (1.13-3.95)
- Depression HR 1.54 (1.04-2.26)

Risk increased with younger age of oophorectomy

Risk not seen in women given ERT
Individualising HRT

**Benefits**
- Menopausal symptoms
- Sexual function
- Osteoporosis
- CVD
- Neurological

**Risks**
- Breast Cancer
- VTE
- Stroke
- Ovarian Cancer?
“I don’t want to take HRT because I’ve heard it’s too dangerous”

“I’ve been told I have to come off it as I’ve had it for 5 years”
### Difference in breast cancer incidence /1000 menopausal women over 7.5 years (95% CI)

Baseline risk in the UK over 7.5 years: 22.48 /1000

Adapted form NICE CG23

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Past Users</th>
<th>Current users</th>
<th>Treatment &lt; 5 yrs</th>
<th>Treatment 5 -10 yrs</th>
<th>&gt; 5yrs since stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oestrogen alone</strong></td>
<td><strong>RCT</strong></td>
<td>-</td>
<td><strong>4 fewer (-11 to +8)</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>Observational</strong></td>
<td>0 (-5 to +8)</td>
<td><strong>6 more (+1 to +12)</strong></td>
<td><strong>4 more (+1 to +9)</strong></td>
<td><strong>5 more (-1 to +14)</strong></td>
</tr>
<tr>
<td><strong>Oestrogen + Progestogen</strong></td>
<td><strong>RCT</strong></td>
<td>-</td>
<td><strong>5 more (-4 to +36)</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>Observational</strong></td>
<td>3 fewer (-11 to +12)</td>
<td><strong>17 more (+14 to +20)</strong></td>
<td><strong>12 more (+6 to +19)</strong></td>
<td><strong>21 more (+9 to +37)</strong></td>
</tr>
<tr>
<td><strong>Any HRT</strong></td>
<td><strong>RCT</strong></td>
<td>-</td>
<td><strong>9 fewer (-16 to +7)</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>Observational</strong></td>
<td>0 (-1 to +2)</td>
<td><strong>18 more (+12 to +25)</strong></td>
<td><strong>11 more (+3 to +22)</strong></td>
<td><strong>23 more (+8 to +45)</strong></td>
</tr>
</tbody>
</table>
Breast Cancer and HRT:
NICE MENOPAUSE GUIDANCE NG23 (Nov 2015)

- All women have an individual baseline risk
- Multi-factorial disease
- E alone – very little or no change in risk
- E + P - associated with small increased risk
- Any increase in risk is related to treatment duration and returns to baseline after stopping
- HRT is a promoter rather than initiator of breast cancer cells
- Provide *absolute* risk estimates rather than risk ratios and percentage change in risk
# Breast cancer risk

<table>
<thead>
<tr>
<th>KEY</th>
<th>Relative risk of breast cancer</th>
<th>Number of women developing breast cancer over the next 5 years, per 1,000 women</th>
<th>Number of extra (<em>or less</em>) cases of breast cancer over the next 5 years, per 1,000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HRT</td>
<td>1</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Combined HRT (estrogen plus progestogen)</td>
<td>1.26</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Estrogen only HRT</td>
<td>0.73</td>
<td>11</td>
<td>-4</td>
</tr>
<tr>
<td>Obese, older than 50 years (BMI greater than 35)</td>
<td>2</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Alcohol - 2 or more units/day</td>
<td>1.5 - 2</td>
<td>23 - 30</td>
<td>8 - 15</td>
</tr>
</tbody>
</table>

Figures from Women's Health Initiative trial for women aged 50-79 years
HRT Safety- thrombotic risk

Increased thrombotic risk with oral therapy (2 - 4 x) not seen with transdermal oestrogens

- Esther study  (J Thromb Haemostasis 2006)
  oral RR 4.3 (2.6-7.2) transdermal RR 1.2 (0.8 – 1.7)

- Women with additional risk factors e.g obesity, Factor V Leiden - further 3-8 fold increase with oral E, unchanged with transdermal

- Varying effect of Progestogen addition
  E + NETA 1.7 x, E + MPA 2.7 x, E + mP 1.1 X
Number of Events per 10,000 Women per Year (E only)

HRT and Stroke

French cohort study (50-60 yrs):
• Oral oestrogen RR 1.58 (1.01-2.49)
• Transdermal RR 0.83 (0.56-1.24)
• Synthetic progestogens increased risk
• Micronised progestogen zero risk

Canonica et al Stroke 2016
Risks with HRT
Per 1000 women aged 50-59 over 7.5 years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>E</th>
<th>E + P</th>
<th>Any HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>26.3</td>
<td>6 fewer</td>
<td>5 more</td>
<td>6 fewer</td>
</tr>
<tr>
<td>Stroke</td>
<td>11.3</td>
<td>0</td>
<td>6 more</td>
<td>3 fewer</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>22.48</td>
<td>4 fewer</td>
<td>5 more</td>
<td>9 fewer</td>
</tr>
<tr>
<td>Fragility fracture</td>
<td></td>
<td></td>
<td></td>
<td>23 fewer</td>
</tr>
</tbody>
</table>
Breast Cancer Risk v type of HRT: EN3 EPIC cohort (European Prospective Investigation into Cancer and Nutrition) – 5.8y FU
Fournier et al Int J Cancer 2005

<table>
<thead>
<tr>
<th>Exposure Category</th>
<th>Person Years</th>
<th>Multivariate adjusted risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen alone</td>
<td>9698</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<tr>
<td>Estrogen + synthetic progestogen</td>
<td>46242</td>
<td>1.4 (1.2-1.7)</td>
</tr>
<tr>
<td>Estrogen + micronised progesterone</td>
<td>20685</td>
<td>0.9 (0.7-1.2)</td>
</tr>
</tbody>
</table>
HRT – Who should be offered it?

- Symptomatic menopausal women
- Premature Ovarian insufficiency – at least until 50
- Asymptomatic women under 60 at increased risk of osteoporosis
- Personalise care: review indications and risk/benefit balance on a regular and individual basis
How Long?

• For most women 2-5 years is sufficient
• (At least until 50 for women with POF)
• **No specific time limit**, but reappraise risk/benefit regularly
• Vaginal Oestrogens can be continued indefinitely

Stopping HRT

• Dose can be lowered gradually
• Add in vaginal oestrogens if indicated
• Consider bisphosphonates if high risk of Osteoporosis
Vaginal Oestrogens

Rapidly reverses atrophic changes

Now licensed for indefinite use

Minimal systemic absorption

10mcg (low dose) vagifem
(I year equivalent to single 1mg tablet)

Ospemifine – SERM with vaginal effects Goldstein et al Climacteric 2013

Laser Thermablation: CO2 or Yag
Gambacciani 2015
Female Testosterone Therapy

• Postmenopausal ovary is androgen secreting
• No correlation between T levels and low sexual desire

Benefits and Harms of Testosterone Therapy

• 35 randomized trials (n = 5053) Elraiyah et al JCEM 2014
• Significant improvement in various domains of sexual function and personal distress in postmenopausal women
• Main benefit in oophorectomised women but maybe effective in others

No licensed Testosterone preparations for women

• Currently use 1/5th to 1/7th gel/day
• Off label, no long term safety data
Summary

- The Menopause is relevant to all Gynaecologists
- Women with premature ovarian Failure need special focus and should have HRT at least up till age of 50
- For women to be offered information and treatment for short term symptoms
- For the vast majority of early post-menopausal women (<60), HRT is a safe and effective option for the relief of menopausal symptoms and prevention of osteoporosis
- Our role as gynaecologists is to provide up to date information, advice and guidance and support our patients and colleagues in primary care
Resources

For Doctors and Nurses:
• British Menopause Society: www.thebms.org.uk
• Post Reproductive Health RCOG – 15/16th November 2016
• Annual Meeting Warwick 6/7th July 2017
• NICE: www.nice.org.uk/guidance/ng23

For patients
• Women’s Health Concern: www.womens-health-concern.org
• Menopause Matters: www.menopausematters.co.uk
• Manage my Menopause: www.managemymenopause.co.uk