Menopausal hormone therapy: current controversies

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Life expectancy and therefore prevalence of menopause has increased over time
Timeline of MHT development and use

1942
• FDA approves conjugated equine estrogen (CEE) for hot flushes

1960
• “Feminine Forever” – ERT promoted to prevent ‘living decay’

1970s
• endometrial cancer linked to unopposed oestrogen use leads to addition of cyclical progestogen

1980s
• MHT associated with lower CVD in epidemiological studies

1990s
• prevention of bleeding by continuous combined MHT

2000s
• RCT
Change in focus?

From prevention of “living decay” to prevention of chronic disease
Certainly a change in target age group
Desiderata = elimination of all menopausal symptoms, prevention of all post-menopausal disease, no promotion of disease

Let us skip to the WHI lessons rather than criticisms
All sorts of reasons to criticise it BUT highlighted 2 important take home lessons

1. The role of progestogen in risk and benefit for
   a) Breast cancer
   b) Cardiovascular disease

2. The difference between starting MHT late and starting early – ‘window of opportunity’

Langer R Climacteric 2017, 20, 91–96
All sorts of reasons to criticise it BUT highlighted 2 important take home lessons

1. The role of progestogen in risk and benefit for
   a) Breast cancer
   b) Cardiovascular disease

1. The difference between starting MHT late and starting early – ‘window of opportunity’
The most important legacy of the WHI study = spotlight on the role of progestogen (in WHI = medroxyprogesterone acetate)

Does it differ between progestogens?

Can we avoid progestogen therapy without hysterectomy?
What is the magnitude of breast cancer risk with MHT?

Using data from WHI
Increased risk estimated <0.1% per annum
or
incidence of <1.0 per 1000 women per year of use

Similar or lower than the risks associated with
• reduced physical activity
• obesity
• alcohol consumption.
Progestogens and breast cancer

The most important legacy of the WHI study = spotlight on the role of progestogen (in WHI = medroxyprogesterone acetate)

Does it differ between progestogens?
**E3N Study**

Increased incidence of breast cancer with addition of progestogen

Possible influence of type of progestogen

Note “dose effect” difference between different formulations

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**Fournier Breast Cancer Res Treat 2008**

<table>
<thead>
<tr>
<th>HRT type and duration of exposure (years)</th>
<th>Cases/PY</th>
<th>Relative risk (95%CI)</th>
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<tbody>
<tr>
<td>None</td>
<td>766/244,632</td>
<td>1 (ref)</td>
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<tr>
<td>Estrogen alone</td>
<td>76/20,347</td>
<td>1.29 (1.02-1.65)</td>
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<td>&lt;2</td>
<td>24/6,747</td>
<td>1.26 (0.83-1.89)</td>
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<td>[2-4]</td>
<td>18/5,705</td>
<td>1.13 (0.70-1.81)</td>
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<td>[4-6]</td>
<td>14/3,172</td>
<td>1.50 (0.88-2.56)</td>
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<tr>
<td>6+</td>
<td>13/3,301</td>
<td>1.31 (0.76-2.28)</td>
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<tr>
<td><em>p</em> for trend</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Estrogen + progesterone</td>
<td>129/40,537</td>
<td>1.00 (0.83-1.22)</td>
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<tr>
<td>&lt;2</td>
<td>18/8,697</td>
<td>0.71 (0.44-1.14)</td>
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<tr>
<td>[2-4]</td>
<td>33/11,647</td>
<td>0.95 (0.67-1.36)</td>
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<td>[4-6]</td>
<td>30/7,619</td>
<td>1.26 (0.87-1.82)</td>
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<td>6+</td>
<td>43/10,111</td>
<td>1.22 (0.89-1.67)</td>
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<td>1.16 (0.79-1.71)</td>
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<td>[4-6]</td>
<td>21/5,590</td>
<td>1.28 (0.83-1.99)</td>
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<tr>
<td>6+</td>
<td>35/7,876</td>
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<tr>
<td><em>p</em> for trend</td>
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<td>0.16</td>
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<td>Estrogen + other progestagens</td>
<td>527/104,243</td>
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<td>&lt;2</td>
<td>86/22,792</td>
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<tr>
<td>Weak estrogens</td>
<td>56/17,091</td>
<td>0.90 (0.68-1.18)</td>
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<tr>
<td>Others d / unknown HRT</td>
<td>82/21,071</td>
<td>1.27 (1.01-1.60)</td>
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<tr>
<td>Mixed e</td>
<td>538/130,594</td>
<td>1.25 (1.11-1.41)</td>
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Biological activities of progesterone and progestins

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<tr>
<th>Progestogen</th>
<th>Anti E</th>
<th>E</th>
<th>A</th>
<th>Anti A</th>
<th>Gluco</th>
<th>Anti min</th>
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<tr>
<td>Progesterone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
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<td>17α-OH-derivatives</td>
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<tr>
<td>Cyproterone acetate</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>MPA</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Spironolactone derivatives</td>
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<tr>
<td>Drospirenone</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>19-nortestosterone derivatives</td>
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<tr>
<td>Norethisterone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Levonorgestrel</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dienogest</td>
<td>±</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Schindler Maturitas 2003
Strategies to limit systemic progestogen exposure safely

- Hysterectomy
- Cyclical
t- Reduce dose
- TSECs
- Vaginal delivery
TSECs replace progestogen with a SERM which antagonises the oestrogen effect in selected tissues

- endometrium
- breast
Combining oestrogens and SERMs in the development of a TSEC

**Endometrium**
Uterine wet weight after 14 days’ treatment

**Breast**
Ductal tree invasion into the fat pad after 14 days’ treatment

Bazedoxifene, raloxifene and lasofoxfifene alone have antagonist effects on endometrial and breast tissue. Combined with CEE, BZA is most effective.

For

- Patient with troublesome mastalgia
- Patient with progestogen-sensitive moodiness
- Patient who is > 12 months past LMP
- Not enough evidence yet that it reduces breast cancer

Not for

- Patient at risk of VTE (although no increase seen in clinical trials)
- Patient who needs higher dose oestrogen
- Patient who is perimenopausal
Strategies to limit systemic progestogen exposure safely

- Hysterectomy
- Cyclical
- TSECS
- Vaginal delivery
- Reduce dose
Intravaginal application of Prometrium

- Why might you prefer it –
  - less systemic exposure for effective endometrial protection
- Posterior vagina (not anterior) has vascular connections with the uterus
- Relies on placement of Prometrium high in the posterior vaginal vault
  - needs to stay there and not fall out
- Associated with increased vaginal discharge
- What is the “recommended” dose
- OFF-LABEL

_Stute P Climacteric 2016_
Intravaginal application of Prometrium

*Cicinelli et al FertilSteril 2005*
- 3-year prospective study
- n = 30
- transdermal E2 gel 1.5mg daily + vaginal P 100mg alt die
- endometrium 2.7 +/- 0.5 vs. 3.4 +/- 0.9 mm at baseline
- endometrial biopsy showed endometrial atrophy

*Fernandez-Murga Climacteric 2011*
- Up to 12 months
- n = 64 (24 continued in study to 12m)
- Transdermal E2 25ug + vaginal P 100mg, both twice weekly
- Endometrial thickness at 12 m (n=27) 3.5 ± 1.0 mm

? Dosage 100mg alt die? - based on above studies
What about intravaginal oestrogen?
Intravaginal application of oestrogen for genito-urinary syndrome of the menopause

- Long-held belief has been that progestogen is not required
- Is this so?
- Does it rely on detailed knowledge of anatomy?
- Correct placement?
- Lower dosage?
- Short term use?
- Although many patients use it longterm
Safety of longterm vaginal oestrogen?

- Duration of studies
  - Most 12 weeks. Only one study went to 12m
- Safety data
  - Not all studies reported endometrial thickness or histology as safety data
- Endometrial thickness
  - Risk of endometrial thickening with creams 8-12%
  - no evidence of a significant difference between oestrogen tablets and oestrogen cream

Need to rethink intermittent course of progestogen in patients using longterm vaginal oestrogen

*Lethaby A Cochrane Database of Systematic Reviews 2016.*
All sorts of reasons to criticise it BUT highlighted 2 important take home lessons

1. The role of progestogen in risk and benefit for
   a) Breast cancer
   b) Cardiovascular disease

2. The difference between starting MHT late and starting early – ‘window of opportunity’
Early v late initiation of MHT

Differential effect of early v late MHT is not new

- Identified by Clarkson in primate studies
- Reinforced by findings in WHI

Explored further in
ELITE (Early versus Late Intervention Trial with Estradiol)
KEEPS (Kronos Early Estrogen Prevention Study)

Mikkola TS and Clarkson TB. Cardiovascular Research. 53(3): 605-619, 2002
KEEPS (Kronos Early Estrogen Prevention Study)

n = 727
Age 52.7 (2.6)
CAC <50 at baseline
Randomised
• CEE 0.45mg
• + Cyclical oral progesterone
• Transdermal 50ug
  + Cyclical oral progesterone
• Placebo
Endpoints at 4 years
• CIMT progression
• CAC score

No significant difference in change in CIMT or CAC

ELITE (Early versus Late Intervention Trial with Estradiol)

n = 643
<6y OR >10y post LMP
Rx
• Img oral oestradiol
  + cyclical vaginal progesterone
• Placebo
Endpoints at 5 years
• CIMT progression
• CAC score (ns)

Hodis NEJM 2016.

\[ p = 0.008 \]
MHT and cardiovascular disease

![Study and subgroup analysis diagram]

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Traffic rules for HRT

Start early – at least within 10 years of LMP

Proceed with caution in the face of some comorbidities e.g. prior DVT, migraine

Are there any stopping rules?
Are there any stopping rules?

“Use the lowest dose for the shortest amount of time
Less than 5 years recommended with combined therapy”

What are the safety data surrounding longterm therapy?

How long do they last?!
• 20% have few or no symptoms
• 60% have 4 - 8 years of symptoms
• 20% may have severe symptoms that continue into their 60s and 70s

Should we encourage patients to stop MHT?

The advice for short term treatment is based on breast cancer risk
Deaths in absolute numbers – breast cancer, IHD, stroke

ABS - AusStat
HRT discontinuation and vascular deaths

Higher risk of cardiac death in HRT stoppers compared with continuing HRT
• in 1\textsuperscript{st} year SMR (95%CI) 2.30 (2.12-2.50) and
• in later years SMR (95%CI) 1.26 (1.21-1.31)

Higher risk of stroke in HRT stoppers compared with continuing HRT
• in 1\textsuperscript{st} year SMR (95%CI) 2.52 (2.28-2.77) and
• in later years SMR (95%CI) 1.25 (1.19-1.31)

SMR= standardised mortality ratio
HRT discontinuation and vascular deaths

Is there a plausible biological explanation for this?

❖ withdrawal of non-genomic vasodilatory effects of oestrogen
❖ reduced oestrogen-induced nitric oxide gene expression
❖ withdrawal of inhibition of endothelin-1
❖ increased sympathetic and decreased parasympathetic activity associated with the return of hot flushes
❖ return of palpitations and arrhythmias associated with oestrogen withdrawal esp in women with long-QT syndrome

Mikkola J Clin Endocrinol Metab 2015
MHT discontinuation and bones

MHT effectively reduces osteoporotic fracture while it is being taken

*Eastell R JCEM 2019*
MHT discontinuation and bones

• Improved BMD and reduced fractures in observational and RCTs
• When treatment is stopped
  – lumbar spine BMD returns to untreated level within 1–2 years
  – bone turnover markers return to baseline or untreated levels
• In older women bone resorption returns to untreated levels without evidence of rebound
• in younger women urinary NTX increased above untreated levels returning to the untreated levels at 2 years

Does this remind you of denosumab?

McClung Osteoporosis Int 2016
Estetrol (E4) = natural estrogen, produced by the human foetal liver “Native Estrogen with Selective action in Tissues”

NK3R antagonists such as fezolinetant (ESN364) and NT-814

Chemokine receptor type 4 (CXCR4) modulator Q-122.
What is the relationship between oestrogen and hot flushes?

Prepubertal girls do not have hot flushes

GnRH agonist which suppresses gonadotrophins causes hot flushes – so not related to gonadotrophin surges

Oestrogen levels similar in symptomatic v asymptomatic women

Hot flushes may settle down with time even though oestrogen levels remain low

Falling oestradiol levels even if the absolute value is high may be associated with hot flushes (tachyphylaxis with oestradiol implants)

And yet, oestrogen therapy remains the most effective treatment for hot flushing

There must be a neurotransmitter which responds to oestrogen
Evidence for the role of KNDy neurones in thermoregulation

KNDy neurons

- form a bilateral network via the expression of NK3R
- project to the ME and GnRH terminals
- project to POA that controls heat dissipation effectors

Tacr3 gene encoding NK3R is expressed by warm-sensitive neurons in the medial POA
• E2 is a negative regulator of KNDy neurons, acting upstream of heat dissipation effectors
• absence of E2 negative feedback causes KNDy neurons to hypertrophy
• hyperactivity of KNDy neurons initiates heat dissipation and VMS.
Neurokinin 3 receptor antagonist phase 2 study pavinetant (MLE4901)

- LH pulse frequency did not change
- LH pulse amplitude higher with study drug cf placebo
- Rise in transaminase with study drug which returned to baseline with withdrawal
- Withdrawn from development

Prague Lancet 2017
Neurokinin 3 receptor antagonists in early phase studies

Fezolinetant (ESN364) (Ogeda/Astellas)
- 60 mg BD for 12 weeks
- 93% vs 54% reduction in HF frequency
- 70% vs 23% in severity (p < 0.001)

NT-814 (KaNDy/Nerre Therapeutics Ltd, UK)
- NK1R and an NK3R antagonist
- At 2 weeks
- 84% vs 37% reduction in HF frequency (p < 0.001).
- 50% vs 16% reduction in severity (p < 0.001)
If successful pharma development, manipulation of KNDy neurone may have wide-ranging application for symptoms in

• menopause management
• androgen deprivation therapy
• fertility applications in
  – Polycystic ovary syndrome
  – Functional pituitary-gonadalal suppression
In summary

• The symptoms and effects of menopause last for years
• Oestrogen is the most effective available management
• The addition of progestogen has an adverse effect on cardiovascular benefit and breast cancer risk
• Modification of progestogen type or delivery method, or elimination by use of SERM is being explored
• Minimisation of risk and maximisation of benefit for CVD and OP is related to an early start of therapy
• The available data do not support advising short term use
• Effective non-hormonal treatment may be on the horizon
Menopause: Hot topics for a cool climate

23rd Annual Australasian Menopause Society Congress

Hotel Grand Chancellor Hobart • 6 to 8 September 2019