# *MENOPAUSE AND HRT IN LIGHT OF THE 2015 NICE GUIDELINES*

LJR February 2016

# *Menopause*

- Menopause is a clinical diagnosis in ***healthy women over 45 years*** who have ***not had a period for at least 12 months*** and are not using hormonal contraception, or who do not have a uterus and have menopausal symptoms.
- The average age of menopause in the United Kingdom is ***51 years,*** although 1% of women experience premature ovarian insufficiency (menopause before the age of 40 years). ***Eight out of 10 women experience perimenopausal symptoms***, most commonly hot flushes and night sweats, which typically last about four years. Quality of life may be severely affected.
- Twenty five percent of women have severe menopausal symptoms, which can seriously affect a woman's quality of life. Millions of women worldwide now live 30-40% of their lives after the menopause.

# *REVIEW: LATEST EVIDENCE ON USING HORMONE REPLACEMENT THERAPY IN THE MENOPAUSE*

*Bakour, Williamson. The Obstetrician and Gynaecologist:2015;17:20-8*

# *Studies into the risk/benefits of HRT*

- **1970's epidemiological studies**; found lower incidence of CVD in women taking HRT, criticism of study – bias as healthy women more likely to take HRT
- **HERS**; looked at 2y prevention of HRT in women with CVD average age 66.7, found no benefit, more VTE and more gallbladder disease
- **WHI**; evaluated the effect of HRT on healthy women 50-79y in combined HRT arm found more breast cancer, heart disease, VTE and stroke (not seen in the oestrogen only arm) again criticism that the population was older than usual
- **Million women study**; 50-64 uk, more breast cancer in the combination arm, again some bias and study failings eg data missing
- **2012 cochrane systemic r/v** echoed previous studies (as most of data came from these studies) – more vte/cvd/stroke/breast cancer/gall bladder disease and dementia in >65's, again mean age >60 so ?how representative. Reduced fractures

# *Summary of evidence*

- Lack of representative data, evidence showing some harm of HRT
- MRHA advice stood until recent NICE guidelines
  - *For most women, short term treatment will be sufficient to relieve vasomotor symptoms; for others, HRT may need to be continued for longer. For all women, the lowest effective dose should be used for the shortest possible time, and the need to continue HRT should be reviewed at least yearly, taking into consideration the change in balance of risks and benefits*

# *Changing viewpoints?*

- Shapiro et al published several papers in the journal of family planning and reproductive health care analysing the big studies above and criticising methodology and findings in 2011 – 2012
- ie. No new evidence but just some debunking of previous study findings
- Following the WHI report there was an 80% reduction in the use of HRT
- More the feeling that the continued negative attitude to the use of HRT for symptom relief is not justified

- Menopause adversely affects quality of life and an informed discussion of the risk/benefit ratio on an individual basis is appropriate
- NICE guidance contains a recommendation that HRT can be used for symptom control for up to 5 yrs

# MENOPAUSE: DIAGNOSIS AND MANAGEMENT OF MENOPAUSE. (NICE GUIDELINE 23) 2015

**Summary of benefits and risks of hormone replacement therapy (HRT) started before 65 years to treat menopausal symptoms (NICE)**

# *Benefits*

- **Relief of vasomotor symptoms**, **musculoskeletal symptoms, low mood, and sexual difficulties** (systemic HRT)
- **Relief of urogenital symptoms** (topical or systemic HRT)
- **Osteoporosis prevention** (systemic HRT). The absolute risk of any fragility fracture is 69/1000 women over 3.5 years in women not using HRT; in those using systemic HRT, 23 fewer women per 1000 (95% confidence interval −10 to −33) would be at risk. This benefit is maintained during treatment but reduces once treatment stops

# *Risks*

- **Unscheduled vaginal bleeding**: common during first 3 months; report to a healthcare professional if it occurs after the first 3 months
- **Venous thromboembolism (VTE)**: absolute risk is 12.5/1000 over 5 years in women not using HRT. In those using oral HRT, 10 (6 to 14) more women per 1000 would be at risk. *Transdermal HRT is not associated with increased risk of VTE*
- **Stroke**: small increased risk in women taking oral but *not transdermal oestrogen*
- **Breast cancer**: absolute risk is 22.5/1000 over 7.5 years in women not using HRT. In those using *oestrogen and progestogen*, 5 more women (−4 to 36) per 1000 are at risk; in those using oestrogen alone, 4 (−11 to 8) fewer women per 1000 are at risk. The increased risk of breast cancer while taking oestrogen plus progestogen disappears once HRT is stopped

# *No change in risk*

- **Coronary heart disease** (CHD): the risk of CHD is not increased in women who use HRT compared with non-users (when started under the age of 60)

- *The impact of HRT that is started after 65 years was outside the scope of the guideline
- ***Dementia, risks with HRT unknown***

# *Patient information on the risks/benefits of HRT and decision tools:*

- There are tables in the NICE guideline detailing the rates of CVD/stroke/breast cancer and fragility fracture. Example to follow
- http://www.nice.org.uk/guidance/ng23/chapter/recommendations
- Also diagramatic representation of risks to share at:
- http://mylan.blob.core.windows.net/download-centre/making-an-informed-choice.pdf

# Table 3 Absolute rates of breast cancer for different types of HRT compared with no HRT (or placebo), different durations of HRT use and time since stopping HRT for menopausal women

| | | Difference in breast cancer incidence per 1000 menopausal women over 7.5 years (95% confidence interval) (baseline population risk in the UK over 7.5 years: 22.48 per 1000 [1] ) | | | |
|---|---|---|---|---|---|
| | | Current HRT users | Treatment duration <5 years | Treatment duration 5–10 years | >5 years since stopping treatment |
| **Women on oestrogen alone** | RCT estimate[2] | 4 fewer (-11 to 8) | No available data | No available data | 5 fewer (-11 to 2) |
| | Observational estimate[3] | 6 more (1 to 12)[4] | 4 more (1 to 9) | 5 more (-1 to 14) | 5 fewer (-9 to -1) |
| **Women on oestrogen + progestogen** | RCT estimate[2] | 5 more (-4 to 36) | No available data | No available data | 8 more (1 to 17) |
| | Observational estimate[3] | 17 more (14 to 20) | 12 more (6 to 19) | 21 more (9 to 37) | 9 fewer (-16 to 13)[5] |

**HRT, hormone replacement therapy; RCT, randomised controlled trial**

**For full source references, see Appendix M in the full guideline.**

**[1] Office for National Statistics (2010) breast cancer incidence statistics.**

**[2] For women aged 50–59 years at entry to the RCT.**

**[3] Observational estimates are based on cohort studies with several thousand women.**

**[4] Evidence on observational estimate demonstrated very serious heterogeneity without plausible explanation by subgroup analysis.**

**[5] Evidence on observational estimate demonstrated very serious imprecision in the estimate of effect.**

# *Summary Of The Nice Guidance: Menopause; Diagnosis And Management Of Menopause*

# *Diagnosing Menopause*

- For **women >45y** a diagnosis of menopause based on history ie absent/irregular periods and menopausal symptoms. **No need to check FSH**
- For **women <45y** where menopause is suspected check **FSH, 2 readings 4-6 wks apart**
- Avoid checking FSH in women using combined contraceptives or high dose progesterone eg. depo

# *Summary Of Nice Guidance For Symptom Management*

- Explanation and advice incl. individualised risk benefits discussion
- Options
  - HRT
  - Non hormonal
  - CBT
- Contraception

# *Vasomotor Symptoms*

- HRT for up to 5y
- Not ssri/clonidine first line
- Isoflavones/black cohosh – some evidence but concerns about safety of preparations, drug interactions

# *Psychological symptoms*

- HRT
- CBT
- No clear evidence of SSRI's or SNRI's in women with menopausal symptoms who have not been diagnosed with depression (based on low to moderate quality evidence and the expertise of the GDC)

# *Urogenital atrophy*

- Topical oestrogen, continued as long as needed to relieve symptoms (can use in combination with systemic HRT if needed)
- Moisturisers and lubricants, alone or in addition to topical oestrogen

- Altered sexual function
  - Consider testosterone if HRT alone not sufficient to treat low libido…..???

# *Hrt: Practical Considerations*

A woman presents with problematic menopausal symptoms….

# *History*

- Lifestyle
- past medical history
- mental health
- Identify any relative contraindications to HRT
  - Existing cardiac disease
  - Active liver disease
  - SLE
  - Previous breast cancer
  - Previous ovarian/endometrial cancer
  - Undiagnosed vaginal bleeding
  - Personal/FH VTE
- ?still needing contraception (for 2y after last period if <50y and 1y after last period if >50)

- Examination
  - BP
  - BMI

- Investigations, not necessary if typical symptoms and >45y

# *Management*

- Beneficial **lifestyle changes**
  - Avoid sudden temperature changes eg. hot drinks
  - Reduce caffeine/alcohol intake
  - Avoid spicy foods
  - Increase exercise
  - Wear clothes in layers
  - Relaxation techniques
  - Cooling devices; facial spray/cool pads
  - Absorptive nightwear
- **Individualised discussion of the risks/benefits of HRT**. NB; for patients with relative contraindications to HRT discussion with specialists may be of help
- **Options** other than HRT (as per NICE) also gabapentin for flushes recommended in rcog pils as evidence based benefit

# *Choice Of HRT (or choices, choices, choices of HRT!)*

- **No uterus** – easier: oestrogen only

- **Uterus** – must have combination oestrogen and progesterone due to risks of endometrial hyperplasia with unopposed oestrogen (include subtotal hysterectomy in this group in case any residual endometrium at resection margin)
  - Still having periods or within 12 months of last period? Go for a cyclical preparation. Will continue to have scheduled bleeding
  - More than 12 months since last period? Go for continuous combined preparation or Tibolone

# *Which route?*
# *Oral HRT*

- easy,
- familiar
- cheap

but

- can have gi side effects and 1st pass effects of or on other drugs,
- increased risk VTE and stroke compared to transdermal

# *Which route?*
# *Transdermal HRT*

- less effect on lipids/clotting pathways
- Use first line if;
    - Migraine
    - Diabetes
    - Controlled hypertension
    - Gall bladder disease
    - Hyperlipidaemia
    - Obesity
    - Smoking
    - Risk factors for VTE
    - Varicose veins

# *Which route?*

- **Vaginal symptoms the main problem?** – use topical oestrogens, little systemic absorption so no need for progesterone. (can use at the same time as systemic HRT if vaginal symptoms still a problem)

- **Oral plus mirena**; licensed for 4y as endometrial protection but FSRH consider mirena to be effective in this respect for 5 yrs. (more evidence needed re risks)

# *Review at 3 months*

- Generally start with low dose oestrogen
- If still getting symptoms at 3 months – increase oestrogen
- If progesterone side effects consider changing preparation or mirena
  - more androgenic progesterones; norethisterone, levonorgestrel
  - less androgenic progesterones: micronized progesterone, medroxyprogesterione, dydrogesterone
- BP
- Review risk factors
- If irregular bleeding persists 3m after initiation of HRT r/v and consider referral

# *Once Established On HRT Can Review Annually*

- Women wishing to stay on HRT >5y should be encouraged to switch to continuous combined HRT due to avoid and increased risk in endometrial hyperplasia seen in women on long term sequential therapy. [2.]
- As a rule, women aged 54 yrs would be advised to switch (80% of women at this age are postmenopausal). [2.]

# *Stopping HRT*

- Reducing gradually reduces short term symptoms but has no overall effect on longer term symptoms

# *Special Groups*

# *Increased Risk Of VTE*

- Oral HRT does increase the risk of VTE
- Transdermal route does not
- Consider transdermal route for women at increased risk of VTE including women with a BMI >30 (NICE)

# *CVD*

- HRT is an options for women with cardiovascular risk factors as long as these are optimally managed

# *FH Breast cancer*

- NICE; Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer

  - Women with a family history of breast cancer who are considering taking, or already taking, HRT should be **informed of the increase in breast cancer risk with type and duration of HRT.**
  - Advice to individual women on the use of HRT should vary according to the **individual clinical circumstances** (such as asymptomatic menopausal symptoms, age, severity of menopausal symptoms, or osteoporosis).
  - HRT usage in a woman at familial risk should be restricted to **as short a duration and as low a dose as possible. Oestrogen-only HRT should be prescribed where possible.**
  - A woman having an early (natural or artificial) menopause should be informed of the risks and benefits of HRT, but **generally HRT usage should be confined to women younger than age 50 years if at moderate or high risk**

# *FH Breast cancer cont.*

- When women with no personal history of breast cancer have either a ***BRCA1*** or ***BRCA2*** mutation or a family history of breast cancer and they have had a **bilateral salpingo-oophorectomy before their natural menopause, offer them HRT** up until the time they would have expected natural menopause. **[new 2013]**

## PMH Breast Cancer
## NICE: early and locally advance breast cancer guideline

- **Discontinue hormone replacement therapy** (HRT) in women who are diagnosed with breast cancer.
- **Do not offer HRT routinely to women with** menopausal symptoms and a **history of breast cancer**. HRT may, in exceptional cases, be offered to women with severe menopausal symptoms and with whom the associated risks have been discussed. [specialist].

## PMH Breast Cancer

## NICE: early and locally advance breast cancer guideline

- The selective **serotonin re-uptake inhibitor** antidepressants paroxetine and fluoxetine may be offered to women with breast cancer for relieving menopausal symptoms, particularly hot flushes, but not to those taking tamoxifen (Interaction, also interacts with st john's wort).
- Clonidine, venlafaxine and gabapentin should only be offered to treat hot flushes in women with breast cancer after they have been fully informed of the significant side effects.

# *PMH Breast cancer summary*

- HRT use will depend on patient choice, stage of disease, receptor status, medication (would render aromatase inhibitors inactive)
- *[Specialist assessment if considering HRT]*
- Safe following risk reducing surgery with mastectomies / BSO for BRCA 1+2

# *Premature Ovarian insufficiency*

- NICE definition of prem ovarian insufficiency = Menopause <40y
- Other sources : premature = menopause <45y
- Practically would recommend HRT for women with menopause <45y as benefits>risks until the age of average menopause ie 51y (or at least age 50y)
- At increased risk of CVD and osteoporosis but lower risk of breast cancer
- Using HRT under 45y is not thought to increase the risk of breast cancer above the population risk for their age.[2.]

# *Audit Ideas (NICE)*

- Patients with BMI >30 prescribed oral HRT (less risk of VTE with transdermal)
- FSH requests – how many in women >45y or on combined hormonal contraception or high dose progesterone

# *Future research (NICE)*

- In women who have been treated for breast cancer, what is the safety and effectiveness of alternatives to systemic HRT as treatments for menopausal symptoms?
- In women with a previous diagnosis of breast cancer, what is the impact of systemic HRT usage on the risk of breast cancer recurrence, mortality, or tumour aggression?
- What is the difference in the risk of breast cancer in menopausal women on HRT with progesterone, progestogen, or selective oestrogen receptor modulators?
- How does the HRT preparation affect the risk of VTE?

# *Future research (NICE)*

- What is the impact of estradiol combined with the levonorgestrel releasing intrauterine system on the risk of breast cancer and VTE?
- What are the effects of early HRT use on the risk of dementia?
- What are the main clinical manifestations of premature ovarian insufficiency and the short term and long term impact of the most common therapeutic interventions?

# *References*


1. **Practice Guidelines; Diagnosis and Management of Menopause: A Summary of the NICE guidelines**. BMJ 2015;351:h5746
2. **Review: Latest evidence on using hormone replacement therapy in the menopause**; *Bakour, Williamson. The Obstetrician and Gynaecologist:2015;17:20-8*
3. **Menopause: diagnosis and management of menopause.** (NICE guideline 23) 2015.
4. **Early and locally advanced breast cancer: diagnosis and treatment.** (Clinical guideline 80.) 2009.
5. **Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer.** (Clinical guideline 164.) 2013.