Menopause: Clinical Scenarios

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Outline:

- Understand basic principles of menopause management.
- Understand use of MHT and its contraindications

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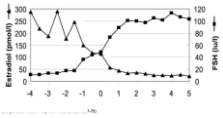
Definition of Menopause

- Permanent cessation of menstruation resulting from loss of ovarian follicular activity
- Diagnosis is clinical – signs, symptoms, 12 months since last menstrual period (LMP).
  - Associated with significant hormonal variability over time
  - Overall, **decline in estrogen levels and rise in FSH levels** over the menopausal transition



  - Premature Menopause occurs before age 40 in 1% of women

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Burger *et al.*, JCEM 84(11): 4025–4030, 1999

Using Menopausal Hormone Therapy

- The principal indication for MHT is alleviation of troublesome vasomotor symptoms
- The dose and duration of MHT should be consistent with treatment goals
- Estrogen only is appropriate therapy for women after a hysterectomy
- Estrogen plus a progestogen should be used when the uterus is present
- MHT should be part of an overall strategy aimed at improving midlife health
- Current safety data do not support the use of MHT in breast cancer survivors
- Topical low dose estrogen is preferred for those women whose symptoms are limited to vaginal dryness and dyspareunia

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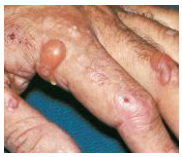
IMS Recommendations on Management of Mid life Women's health and MHT
Baber R et al Climacteric 2016

Global Consensus Statement on MHT
De Villiers T et al. Climacteric 2016;19:313-5

Contra indications MHT

- Undiagnosed PV Bleeding
- Hormone dependent cancers
- Active liver disease
- Pregnancy
- Active thromboembolic disorder
- Active myocardial infarction
- Porpyhria cutanea tarda



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Case 1 : Jan

- **52 years old. LMP 15 months ago**
- **Married,**
- **Non smoker, 10G EtOH daily.**
- **2 children, 28,26, no obstetric issues.**
- **Worsening hot flushes, night sweats, poor sleep, 'moody', skin crawling, some vaginal dryness**
- **Affecting her work and QoL**
- **Nil medication**

- **Past history:**
- **menarche age 12**
- **OCP use until age 45 (husband vasectomy)**
- **lap cholecystectomy**
- **Family history: mother #NOF/ hyperthyroidism**
- **Normal examination**
- **Pap-smear normal**
- **Breast screen mammogram- NAD**

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Jan is menopausal: the history makes the diagnosis!

Do:

- Take a good personal and family history including conditions that may affect management.
- Check menopausal symptoms;
  -symptom score card can help
  (Some symptoms may not be due to menopause).
- Reinforce key mid life preventative health messages

Don't:

- Check FSH, LH, oestradiol or testosterone in a woman **at the normal age of menopause**
- Blood test results will not influence management decisions
- Early cessation of menses is the exception
- Management is usually based on clinical signs and symptoms.

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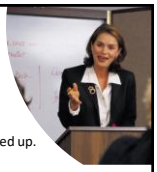
Introducing Annette, aged 48 years

- Married, banker, 3 children.
- No co-morbidities, uterus intact.
- Physical exam NAD, BMI 22
- Vasomotor symptoms day and night
- No sleep, difficult to work
- Irregular periods for 11 months
- FH unremarkable

"I need hormones, Doctor"

Annette



- Annette is perimenopausal (< 12 months amenorrhoea).
- Blood tests not required
- Arrange appropriate screening. (CST, Mammogram).
- Does she need contraception? If so consider COC or Mirena plus E2.
- Annette's irregular bleeding is probably 'normal' but must be followed up.
  - If not regular after 3-6 months of hormone therapy - ultrasound
- **MHT Options**
- Start with a low dose to minimize side effects (bleeding, breast tenderness)
- Sequential MHT in the perimenopause:(e.g. Femoston sequi, Trisequens, Estalis sequi)
- Tailored combination of an estrogen and a progestogen for 10-14 days per month. (e.g. estrofem or E2 patches plus prometrium 200mg for 10-14 days per month)
- Consider switching to continuous combined therapy after 6-12 months

Case 3: Cherie

- **22yo university student**
  - Menarche age 16
  - Never been sexually active
  - Spotting for 1 day every 3-4 months
- 8 months of amenorrhea
  - No significant vasomotor symptoms

Past History
- Nil; no surgery, non-smoker

Family history
- No early menopause,
- No intellectual disability

Examination
- Height 164cm, BMI 22
- BP 124/70
- Tanner stage 4 breast and pubic hair development

Case 2: Cherie has secondary amenorrhoea

DD: Pregnancy, Hyperprolactinaemia, Hypothalamic amen., Menopause, PCOS

- *Investigate for POI in any young woman with 4 months irregular menses*
- FSH 56 IU; PRL normal, BhCG neg., Estradiol <18 pmol/L
- Repeat FSH after 6 weeks - still raised (61IU): - ***Cherie has POI***
- i.e. The presence of menopausal level serum gonadotropins in association with irregular menses in women younger than 40.
- Commonly idiopathic but multiple causes and associations .
- Results from decreased number of follicles during development or an accelerated rate of follicular loss
- Untreated POI is associated with increased incidence osteoporosis, heart disease, cognitive impairment and premature death
- The cornerstone of treatment is MHT at least until normal age of menopause.

www.eshre.org.eu/guidelines

Rafique, Sterling and Nelson. Obstet Gynecol Clin Nth Am 2012;39:567-86

Causes of POI

Genetic	Immunological	Infections	Metabolic	Iatrogenic
X monosomy	Hypothyroid	Mumps	17 hydroxylase deficiency	Ovarian surgery
X Trisomy	Addisons	TB	Galactosemia	Chemotherapy
FMR 1 mutation	Diabetes	Malaria		Radiotherapy
Deletions	Coeliac	Shigella		
Translocations	APS 1 and 2	Varicella		
FOXL 2	ITP, Candidiasis	CMV		
FSH, LH	SLE, RA, Sjogrens	HSV		
GALT, Inhibin	Chronic Hepatitis			

- The majority are idiopathic or iatrogenic

Fragile X Syndrome

- An X linked genetic condition causing intellectual disabilities, learning difficulties and various physical characteristics. It is the commonest known cause of autism.
- 1:150 women are carriers of a faulty FMR 1 gene of whom 25% will develop POI.
- FH of POI or family members with intellectual disabilities may point to FMR 1
- As with idiopathic POI, female FX carriers may spontaneously conceive.
- Genetic screening is important to identify these women as, should they conceive, they are at risk of bearing a child with FXS.

Case 3: Cherie has POI

- **Follow up tests**:
- Chromosomal analysis and fragile X pre-mutation testing normal
- Adrenocortical and thyroid antibodies normal, TSH normal
- Pelvic US- normal uterus/ inactive ovaries
- Diagnosis: Idiopathic POI
- Assessment of osteoporosis and CVD risk
- Consider AMH particularly when fertility is an issue
- Counselling is critical
- Start treatment – Combined MHT (might need higher doses)
  - Combined OC in long cycles (more acceptable, probably contraceptive)

www.eshre.org.eu/guidelines

Rafique, Sterling and Nelson. Obstet Gynecol Clin Nth Am 2012;39:567-86

Case 4: Louise

- Age 48, married, 2 children, normotensive.
- No significant Family History. BMI 26
- Significant flushes, sweats, sleep disturbances.
- LMP 13 months ago
- History of focal and non focal migraine some of which are linked to menstrual cycle.
- Migraines worse since menopause

- **Told she cannot take MHT.**

Migraines in women

- Prevalence in women 17% but peaks at 30% around age 40
- Migraines may be related to estrogen withdrawal or to fluctuating levels.
- Migraine with aura more common when estradiol levels are high.
- Hormone related migraines are typically focal.
- After the menopause:
- 45% of women with hormone related headaches worsen, 15% improve, 35% no change.
- MHT is not contra-indicated in women with focal and non focal migraine

Pavlovic et al Neurology 2016;87:49-56

Using MHT in women with migraine

- Louise can use MHT.
- Aim to keep hormone levels stable as fluctuations promote headache.
- Transdermal estradiol e.g. estradot
- Continuous progestogen – e.g. micronized progesterone (prometrium)
- Use the lowest effective dose
- In women with REM activated sleep migraine oral estrogen at night may help.

Pavlovic et al Neurology 2016;87:49-56

Case 5: Bo

- 51, married, 3 children, generally well.
- PH lower leg DVT after complicated knee surgery 10 years ago.
- No known FH,
- Slim, normotensive, non smoker.
- Severe Vasomotor Symptoms not responding to a range of complementary and prescription options
- Told she cannot take MHT

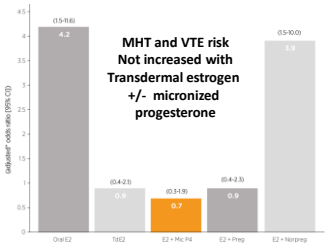
Annualized rate per 1000 woman-years

	Estrogen + Progestin (n=8506)	*Placebo (n=8102)*	*Adjusted hazard ratio (95%CI)*
Venous thrombosis	3.5	1.7	2.06 (1.57-2.70)
Deep venous thrombosis	2.6	1.3	1.95 (1.43-2.67)
Pulmonary embolism	1.8	0.8	2.13 (1.45-3.11)
Procedure related	0.6	0.5	1.09 (0.63-1.91)

VTE risk was increased for women taking oral MHT in WHI.
Absolute increased risk 1 per 1000 w/yr

Archer D and Oger E. Climacteric 2012;15:235-240

MHT and VTE risk by route of administration and type of progestogen



Canonico et al Circulation 2007

Scarabin Y-P Climacteric 2018;21:341-345

Using MHT after a VTE

- Bo may use MHT – lowest dose and transdermal is best!
- Use progesterone (prometrium) rather than synthetic progestins

US Endocrine Society Statement 2015:

- VTE due to past immobility, surgery or bone fracture is not necessarily a contraindication to transdermal therapy.
- Pts with a thrombophilia, VTE due to OCP or MHT should avoid MHT.
- Good history, details of previous VTE, thrombophilia screen.
- Similar guidelines for obese hypertensive smokers diabetics

Stuenkel C et al J Clin Endocrinol Metab. 2015;100:3975-4011

Case 6: Bridget

- 39, married, 2 children good general health.
- FH. Mum, sister both breast cancer. Mum's sister ovarian cancer aged 49
- Genetic screening has detected a BRCA1 mutation.
- Bridget has had risk reducing surgery (BSO) leading to a premature surgical menopause.
- She now has severe vasomotor symptoms.
- She has elected to use surveillance to monitor her breasts for disease.
- No benefit from complementary therapies

BRCA mutation carriers

- Not rare: 1:400 women.
- By age 50, if untreated, 20% will have ovarian CA and 50% breast CA.
- Menopause specific QoL is compromised after RRBSO
- Counselling prior to surgery and integrated care v important: Should the uterus go?
- Most guidelines support the use of MHT until the normal age of the menopause.
- Discuss alternative treatments including Life style, CBT, SSRI (Lexapro, Paxil), SNRI (Efexor, Pristiq), GABA, Clonidine (Catapres) Stellate ganglion block,

The effect of short term HRT on BrCa risk in women undergoing prophylactic BSO for BRCA1 or BRCA2 mutations

- Prospective Cohort of 462 disease free women with BRCA1/2 mutations
- 155 underwent BSO, 307 did not.
- Post operative follow up of 3.6 years
- BSO led to a significant reduction in BrCa Risk. RR 0.40, 95%CI 0.18-0.92)
- Use of HRT after BSO did not affect BrCa Risk. RR 0.37, 95%CI 0.14-0.96)

Rebbeck T et al J Clin Oncol. 2005;23:7804-7810

Use of MHT and risk of breast cancer in BRCA1 Carriers

Case Control study of 472 matched women

Measured Parameter. MHT : Controls	Multivariate Odds Ratio
Surgical menopause	0.48 (0.19-1.21) ns
Natural Menopause	0.68 (0.37-1.21) ns
Menopause before age 45	0.50 (0.23-1.10) ns
Menopause after age 45	0.62 (0.32-1.21) ns
Age at Diagnosis <45	0.49 (0.23-1.04) ns
Age at Diagnosis >45	0.63 (0.34-1.16) ns
< 3 years use of MHT	**0.63 (0.34-1.16) ns**
> 3 years use of MHT	**0.51 (0.24-1.08) ns**
Current MHT use	**0.63 (0.37-1.07) ns**
Past MHT use	**0.43 (1.16-1.17)***

No increase in Breast Cancer risk associated with MHT use or duration of use

Eisen A et al. HRT in carriers of the BRCA 1 mutation. J N C I 2008;100:1361-1367

Hormone therapy in women at high risk of breast cancer: Summary

- MHT does not add to the risk of breast cancer associated with benign breast disease[1] or a family history of breast cancer[1,2,3]
- Women with BrCa gene mutations are at greatly increased risk of breast cancer but MHT does not further exaggerate that risk[5]
- MHT following risk reduction surgery in BRCA 1,2 carriers does not increase breast cancer risk[4,5]
- MHT remains an option for treatment of severe vasomotor symptoms however any decision to use MHT must be based on a thorough risk:benefit analysis

1.Rippy L Marsden J Climacteric 2006;9:404-15
2.Sellars T et al Ann Intern Med 1997;127:973-80
3.Gramling R et al Epidemiology 2009;20:752-6
4.Rebeck T et al J Clin Oncol 2005;23:7804-10
5.Eisen J et al J Nat Cancer Inst. 2008;100:1361-67

Conclusions

- Remember the importance of the mid life health check and appropriate screening.
- The menopause is a normal physiological event, its consequences may not be so.
- Any woman with > 4 months irregular menses should be investigated for POI.
- MHT remains the most effective treatment for troublesome vasomotor symptoms.
- When initiated within 10 years of the LMP, MHT is a very safe intervention.
- Women with focal migraine may use MHT. Low dose transdermal is preferred.
- A history of VTE is not always a contraindication to use of transdermal MHT.
- Carriers of BRCA mutations may use MHT following RRBSO without increasing cancer risk.
- Treatment should always be individualized and review should be at least annually.