Hormone replacement therapy in the menopause

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King Abdullah University Hospital

Outlines

Introduction

- Menopause
- Definitions
- The physiologic changes
- Symptoms associated
- Diagnosis

Hormone replacement therapy (HRT)

- Indications for HRT
- Contraindications to HRT
- HRT regimens
- Topical HRT
- Tibolone
- Side effects

Latest evidence

- What we know so far: the main large studies
- Effect of HRT on CVS events in *recently* postmenopausal women
- Premature ovarian insufficiency
- Thrombosis risk
- Other benefits of HRT
- Non-hormonal treatments
- HRT in survivors of gynaecological and breast cancer

Clinical approach

- History
- Physical examination
- Investigation
- Differential diagnosis
- Practical guidance on HRT prescribing (Figure , tables)

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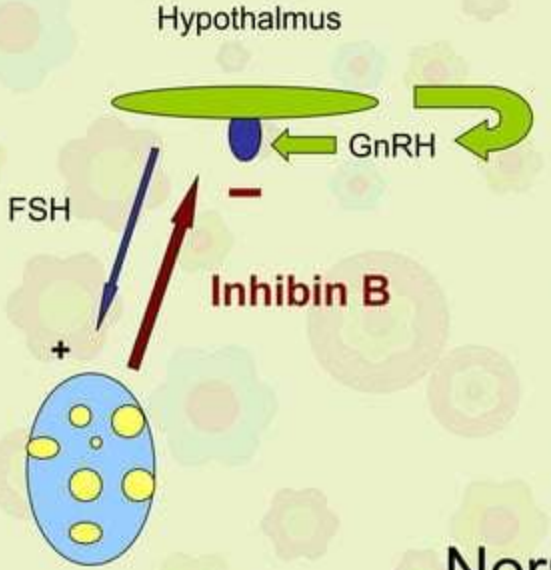
Menopause: Definitions

- *Clinically*: Amenorrhoea of 12 months
- *WHO*: permanent cessation of menstruation, resulting from the loss of ovarian follicular activity
- The Climacteric phases ?
- Surgical menopause ?
- At 50 years (standard deviation + / - 4 years)
- Early menopause: before 45 years ~ risk factors ??
- Premature ovarian failure (POF): before 40 years ??
- Osteoporosis: reduced bone mass per unit volume

The physiologic changes of Menopause

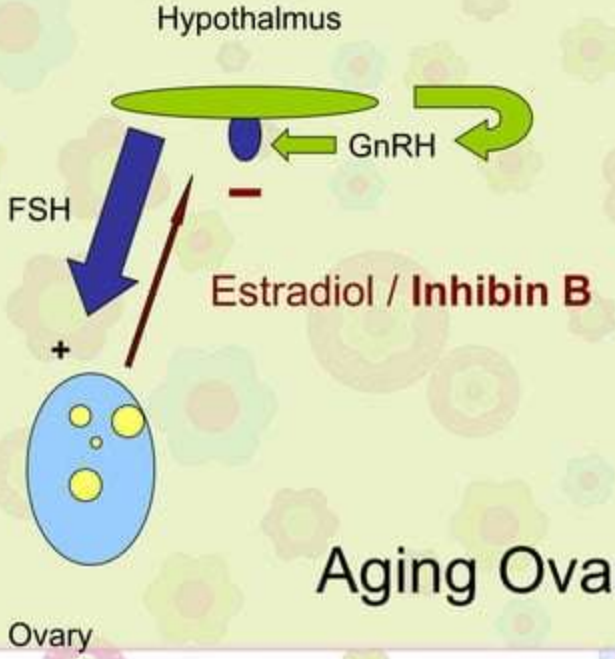
Hormonal Changes



Normal Ovary

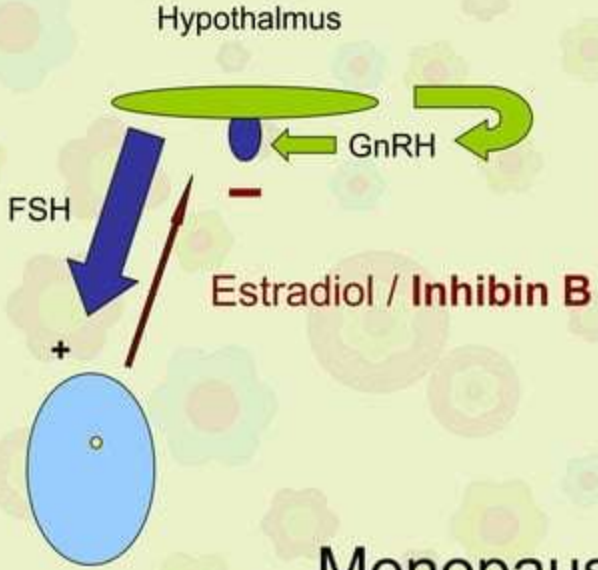
The physiologic changes of **Menopause**

Hormonal Changes

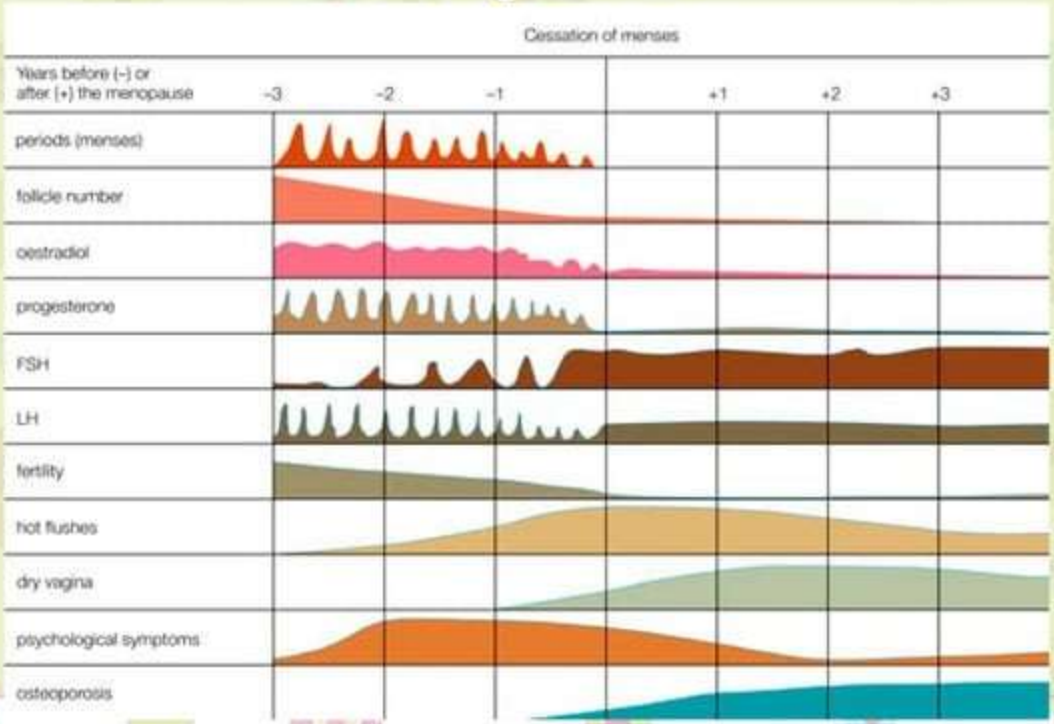


The physiologic changes of Menopause

Hormonal Changes



The physiologic changes of **Menopause**



Symptoms associated with Menopause

Table 1. Clinical manifestations of menopause

Symptoms	Type of health issue
Vasomotor symptoms	Hot flushes
Neuropsychiatric symptoms	Sleep disturbance
	Depression and mood disturbance
	Memory and attention deficits
Genitourinary symptoms	Vaginal dryness
	Sexual dysfunction
	Frequent urinary tract infections
	Urinary incontinence
Musculoskeletal symptoms	Joint pain
Long-term health issues	Osteoporosis
	Coronary artery disease

- In about 70% of women
- Severely in about 20%
- a median duration of 5.2 years
- 10% of women -> more than 10 years

Symptoms associated with Menopause

Symptoms related to hormone deficiency during postmenopause include:

Estrogen	Progesterone	Testosterone
• Headaches	• Muscle weakness	• Low libido
• Fatigue	• Irregular heartbeat	• Decreased sexual desire
• Hot flashes	• Vaginal infections	
• Joint pain	• Mood swings	• Low mood
• Mood swings	• Anxiety	• Lack of energy
• Memory lapses	• Headaches	

"The Menopausal Metabolic Syndrome"

- **Lipid Triad**
  - **Hypertriglyceridemia**
    ↑ LDL Cholesterol
  - ↓ HDL Cholesterol
- **Abnormalities in Insulin**
  - **Insulin resistance**
    ↓ insulin elimination
  - ↓ insulin secretion
  - Hyperinsulinemia
  - **HT reduces onset of DM and improves insulin resistance**
- **Other Factors**
  - **Endothelial dysfunction**
    ↑ visceral fat
    ↑ uric acid
  - ↓ SHBG
  - ↑ blood pressure

Menopause: Diagnosis

- ***Healthy women aged over 45 years = > clinical symptoms,***

1. vasomotor symptoms and irregular periods
2. Ammenorrhea at least 12 months and are not using hormonal contraception

- ***If without a uterus = > clinical symptoms***
- in ***women aged 40 to 45 years*** with menopausal symptoms, including a change in their menstrual cycle = >***serum FSH and estradiaol is diagnostic (30iu\ml)***
- in women aged under 40 years in whom menopause is suspected = > ***serum FSH and estradiaol is diagnostic***
- in women using combined oestrogen and progestogen contraception or high-dose progestogen => ??

NG23 ~ NICE 2015

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Indications for HRT

- Relief of menopausal symptoms (short-term)

- Prevention/treatment of osteoporosis (long-term)

·ACOG suggests not using MHT for the prevention of chronic disease (osteoporosis, CHD, or dementia) ,but *they now recommend bisphosphonates for* osteoporosis treatment

- Premature ovarian failure

Contraindications to HRT

1. Existing cardiac disease (*Absolute*)
2. Active liver disease
3. Systematic lupus erythematosus
4. Previous breast cancer
5. Previous endometrial cancer
6. Undiagnosed vaginal bleeding
7. Previous personal/family history of venous thromboembolism

Informed consent !

Box 2. Conditions that are not contraindications to HRT

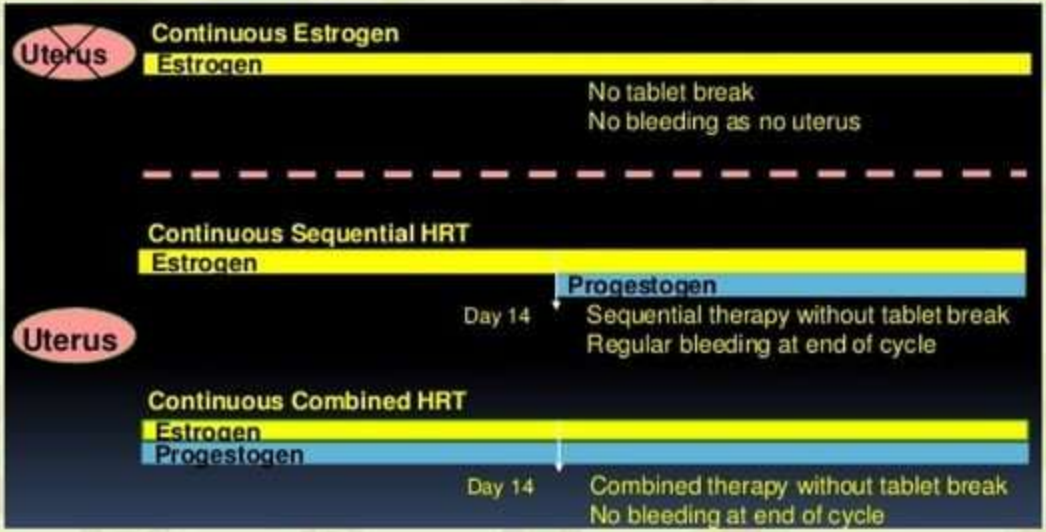
- Asthma
- Past history of benign breast disease
- Previous abnormal smears/cervical cancer
- Contact lens wearers
- Depression
- Diabetes
- Controlled blood pressure
- Hyperlipidaemia
- Melanoma
- Multiple sclerosis
- Obesity
- Renal failure
- Sickle cell anaemia
- Smoking
- Thyroid disease
- Osteoporosis prevention in young women with premature ovarian insufficiency

HRT REGIMENS

Tips

- Estrogen , HRT vs cOCP ?!
- Progestogen or micronised progesterone?! Six months?
- Orally or transdermally.
- Mirena ? Women who cannot tolerate oral progestins
- Supplemental testosterone ?!
- Vaginal progesterone regimens ?
- Conjugated estrogen/bazedoxifene ?

HRT REGIMENS



HRT REGIMENS

HRT REGIMENS

EPT Regimen	Estrogen	Progesterone
Cyclic – sequential	Day 1-25	Last 10-14 days of ET cycle
Cyclic- combined	Day 1-25	Day 1-25
Continuous - sequential	Daily	days every month 10-14
Continuous – long sequential Women who cannot tolerate oral progestins	Daily	days every 3-6months 14
Continuous - combined	Daily	Daily
Tibolone	Daily	

(estrogen plus a progestogen = EPT)

Topical HRT: vaginal estrogen

- vulvovaginal atrophy (now referred to as "genitourinary syndrome of menopause" [GSM])
- Cornification and regeneration of the vaginal epithelium.
- Improves lubrication and sexual function.
- Systemic absorption is insignificant.
- May reduce symptoms of urgency of micturition and recurrent urinary tract infections.
- Additional systemic progestogen is not required
- In such cases both topical and systemic may require
- Safety in breast cancer ??, The benefits to the genitourinary tract along with improved sexual intimacy may outweigh the risk.

Tibolone

- Steroid, Metabolites are active
- Selective tissue estrogenic activity regulator.
- Mildly, progestogenic and androgenic properties
- Unsuitable in perimenopausal women, ↑ breakthrough bleeding.
- Breast cancer ?? No data

Side effects

- **Estrogen include:**

1. bloating
2. breast tenderness
3. swelling
4. nausea
5. leg cramps
6. headaches
7. indigestion
8. vaginal bleeding

- **Progestogen include:**

1. breast tenderness
2. swelling
3. headaches or migraines
4. mood swings
5. depression
6. acne
7. tummy (abdominal) pain
8. back pain
9. vaginal bleeding

Weight gain and HRT ??

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What we know so far: the main large studies

A. The Heart and Estrogen/progestin Replacement Study (HERS) I & II

- The first study to identify if HRT prevented recurrence of coronary heart disease (CHD) in women with established CHD
- Randomised to conjugated equine estrogens (CEE)/medroxy progesterone
- The treatment did increase the risk of venous thromboembolism (VTE)
- A follow-up study of this cohort, the HERS II in 2002 concluded that this benefit did not persist and stated ***that HRT should not be used for secondary prevention in women with established heart disease.***

~ Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002;

~ Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women JAMA 1998

What we know so far: the main large studies

B. The Women's Health Initiative Study

- To evaluate the effect of HRT on healthy postmenopausal women with a particular interest in cardiovascular outcomes.
- Randomised to CEE and medroxy progesterone acetate or placebo
- Women who had had a hysterectomy were randomized to CEE only or placebo
- In 2003 the combined arm of the study was closed -> Increase in breast cancer, heart disease, stroke and VTE events were reported, while a reduction in fracture rate, bowel cancer and diabetes were the advantages gained
- The reanalysis of this study in 2007 demonstrated that giving HRT to women within 10 years of the menopause was associated with fewer risks and a reduction in cardiovascular events
- 'the window of opportunity'

~ Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003

What we know so far: the main large studies

C. The Million Women Study

- Women aged 50–64 years in the UK attending the NHS *breast screening* programme were invited and subsequently followed by completion of a *questionnaire*.
- A *significant increased risk of breast cancer was seen in the women on combined HRT (estrogen and progestogens)* and less so with estrogen only and tibolone.
- **Problems:**

1. the breast cancers already present at the time of entry into the study were not excluded
2. patients on HRT concerned for their wellbeing were more likely to attend
3. the rapid onset of the breast cancer development did not fit the biological course of the disease
4. significant amounts of data, such as menopausal status, time since menopause, age at menopause and body mass index changes were missing during the follow-up questionnaires.

~ Breast cancer and HRT in the Million Women Study. Lancet 2003

~ Commentary regarding recent Million Women Study critique and subsequent publicity. Menopause Int 2012

What we know so far: the main large studies

D. 2012 Cochrane Collaboration systematic review

- Assessed the clinical effects of using HRT for 1 year or more
- Twenty-three randomised double-blind studies were included involving 42 830 women aged 26–91 years.
- Since 70% of the data were derived from the Women's Health Initiative and HERS
- The randomised studies included all estrogens, with or without progestogens
- *None of the studies focused on younger, recently diagnosed postmenopausal women.*
- the findings agreed with the large publications, with an increased risk of VTE, CVD, stroke, breast cancer, gall bladder disease and dementia in women over 65 years old.
- *the review concluded that there was no indication to use HRT for primary or secondary prevention of CVD or dementia or for protection of cognitive function.*
- *There was a significant benefit and reduction in the risk of bone fracture after 5 years of use*
- The study had insufficient data to assess the risk of long-term HRT use in perimenopausal women or postmenopausal women younger than 50 years of age

~Long term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2012

Effect of HRT on CVS events in *recently* postmenopausal women

- A randomised study by Schierbeck et al. that was carried out in Denmark in 1990–1993, has been the first one to address the correct timing and the long-term effect of HRT on *CVD in recently postmenopausal women*
- The number of patients was relatively small, with 502 patients randomly selected to receive HRT and 504 to receive no treatment.
- The publication of adverse reports from other trials led to the discontinuation of the intervention at 11 years but follow-up was continued for a total of 16 years.
- After 10 years, women on HRT were *found to have had a significant reduction in mortality and CVD-related events, with no apparent increased risk of VTE, stroke or cancer*. The health benefits were seen for up to 6 years after stopping.

Thrombosis risk

- the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk
- the risk of VTE associated with HRT is greater for oral than transdermal preparations
- the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk.
- Consider transdermal rather than oral HRT for menopausal women who are at increased risk of VTE, including those with a BMI over 30 kg/m2.
- Consider referring menopausal women at high risk of VTE (for example, those with a strong family history of VTE or a hereditary thrombophilia) to a haematologist for assessment before considering HRT.

~GTG 2013

Box 4. Indications for use of the transdermal route first line

- Personal preference
- Migraine
- Diabetes
- Controlled hypertension
- Existing gall bladder disease
- Hyperlipidaemia hypertriglyceridemia
- Obesity
- Smoking
- Previous venous thromboembolism known thrombophilias
- Varicose veins

Premature ovarian insufficiency

- ≤ 40 years + symptoms + elevated FSH levels on 2 blood samples taken 4–6 weeks apart.
- Earlier onset of both CVD episodes and osteoporosis
- ↓breast cancer risk compared with their menstruating peers.
- it is strongly advised that these women should consider taking HRT, at least until the age of 50 ~ NICE 2015
- HRT may have a beneficial effect on blood pressure when compared with a combined oral contraceptive
- **Bisphosphonates** are not considered first-line treatment for ***prevention*** of osteoporosis in younger women

Other benefits of HRT

- Improvement of low mood
- Protection against loss of connective tissue
- Reduction of bowel cancer in women using HRT
- Neuroprotective, preserving cognitive function and reducing the risk of Alzheimer's disease.
- Some protection against Parkinson's Disease

~The British Menopause Society & Women's Health Concern recommendations on hormone replacement therapy. Menopause Int 2013

Non-hormonal treatments

- **Clonidine, selective serotonin reuptake (if not on tamoxifen)**
- **Selective noradrenaline reuptake inhibitors for example, *venlafaxine*, (unlicensed indication for vasomotor symptoms), *mood lability or depression***
- **Gabapentin ?**
- **Aromatase inhibitors ?**

Box 5. Self-help tips and coping strategies[a]

- Avoid sudden temperature change (hot drinks)
- Reduce caffeine/alcohol intake
- Avoid spicy foods
- Increase exercise
- Wear layers of clothes to be able to take off and put on when necessary
- Practise relaxation techniques
- Use cooling devices e.g. facial spray, cold pillows/pads in bed
- Wear absorptive night attire

[a]Long-term trials of alternative over-the-counter treatments have not been evaluated

HRT in survivors of gynaecological and breast cancer

All except endomerial & breast CA	• No evidence of increased recurrence
Endometrial cancer *Gynecol Obstet Invest* 2008	• Lack of conclusive data, no specific recommendations • HRT after EMC treatment does not appear to have an adverse effect on EMC. • Consider all possible benefits and theoretical risks of recurrence or mortality in each individual to provide the best of care for the patients.
Breast cancer	• HABITS trial • At present it is contraindicated

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Clinical approach: History

1. Age
2. Menstrual history
3. Menopausal symptoms
4. Mental state symptoms
5. Sexual history
6. Use of contraception
7. Urinary symptoms
8. Social history (smoking, relationships…)
9. Medical history (liver disease, SLE, migrane, CVD, VTE, or HTN)
10. Surgical history(gyne operations)
11. Family history (cancers, CVD, or osteoperosis)

Clinical approach: Physical examination

1. Blood pressure
2. Weight and hight
3. Breast palpation
4. Abdominal palpation
5. Vaginal examination
6. Pap smear

Clinical approach: Investigation

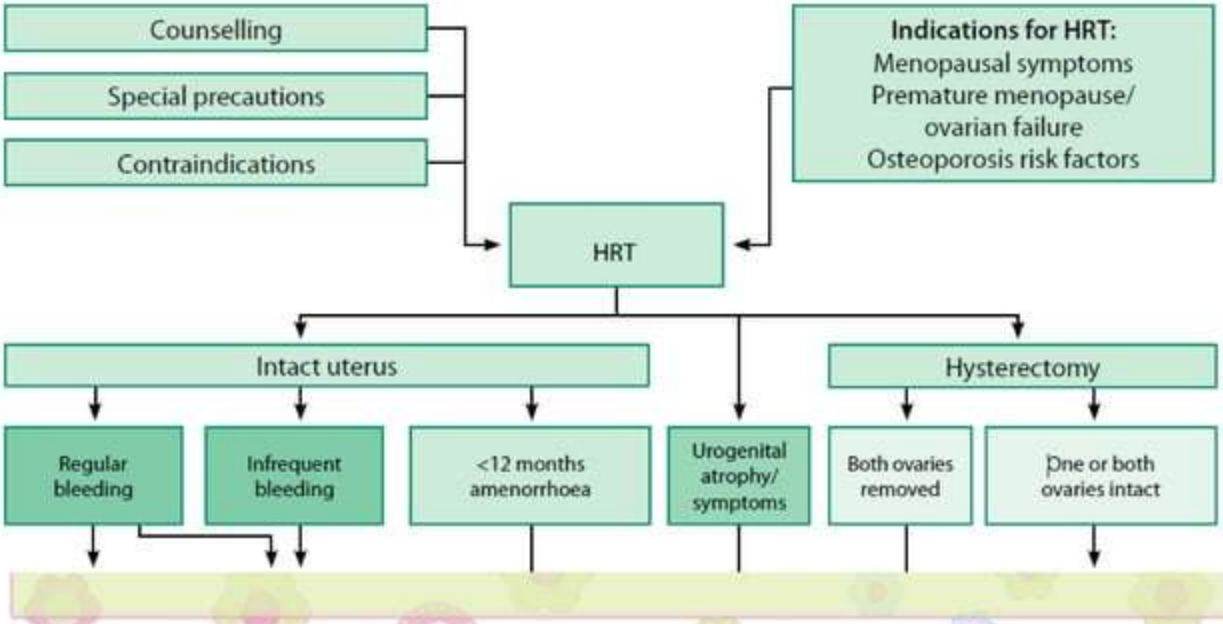
1. Pap smear
2. Urine analysis
3. Full blood count
4. Lipid profile
5. Thyroid function test
6. Liver and kidney function tests
7. Mamography (all women, preferably before and annually)
8. Diagnostic hysteroscopy wih bx (undiagnosed vaginal bleeding)
9. Bone density study
10. If diagnostic in doubt: serum FSH & Estradiol

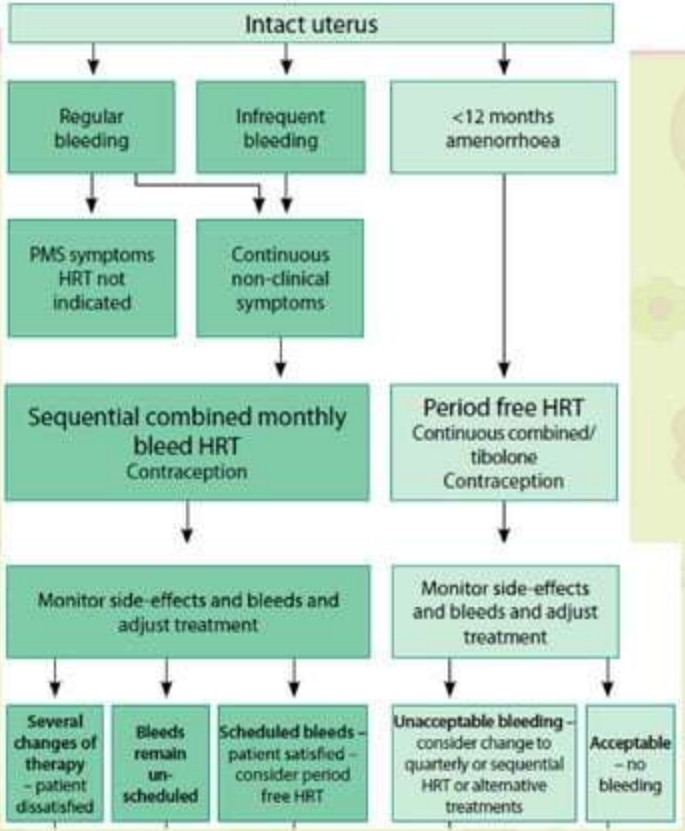
Clinical approach: Differential diagnosis

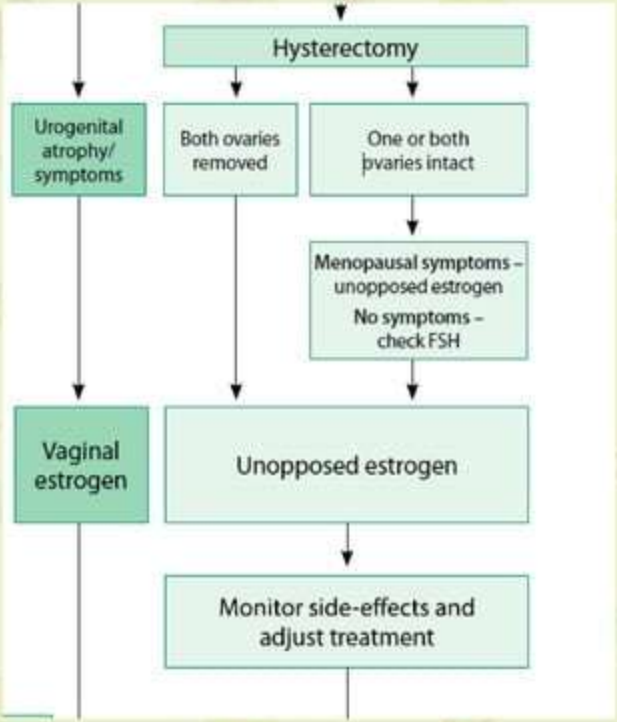
1. Depression
2. Anemia
3. Thyroid dysfunction
4. Hyperparathyrodisim
5. Gynecological disorders

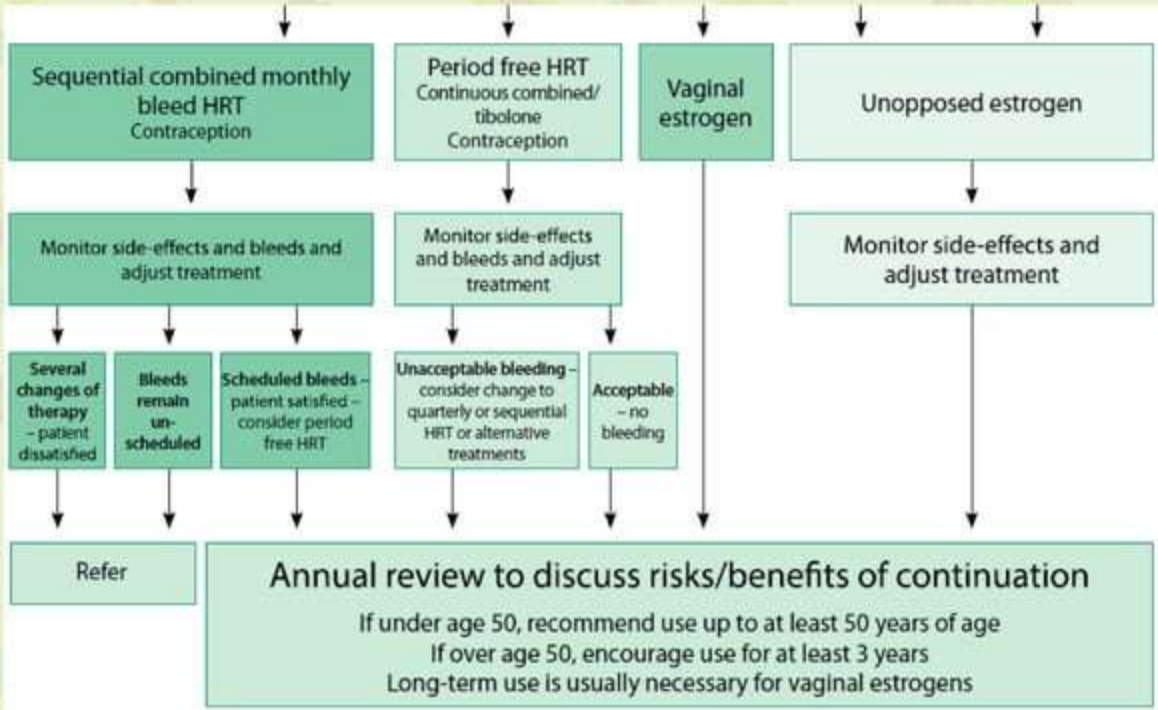
   - dysfunctional uterine bleeding

Practical guidance on HRT prescribing




Intact uterus
Regular bleeding
Infrequent bleeding
<12 months amenorrhoea
PMS symptoms HRT not indicated
Continuous non-clinical symptoms
Sequential combined monthly bleed HRT
Contraception
Period free HRT
Continuous combined/ tibolone
Contraception
Monitor side-effects and bleeds and adjust treatment
Monitor side-effects and bleeds and adjust treatment
Several changes of therapy – patient dissatisfied
Bleeds remain un-scheduled
Scheduled bleeds – patient satisfied – consider period free HRT
Unacceptable bleeding – consider change to quarterly or sequential HRT or alternative treatments
Acceptable – no bleeding


Hysterectomy
Urogenital atrophy/ symptoms
Both ovaries removed
One or both ovaries intact
Menopausal symptoms – unopposed estrogen
No symptoms – check FSH
Vaginal estrogen
Unopposed estrogen
Monitor side-effects and adjust treatment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Refer
Annual review to discuss risks/benefits of continuation
If under age 50, recommend use up to at least 50 years of age
If over age 50, encourage use for at least 3 years
Long-term use is usually necessary for vaginal estrogens

Route / Starting estrogen

- Transdermal 17-beta estradiol → oral 17-beta estradiol → conjugated estrogens.
- equally effective for symptom relief (and bone density).
- metabolic effects differ (oral estrogens) :

1. ↑ in serum triglycerides
2. ↑ C-reactive protein
3. ↑ sex hormone-binding globulin (SHBG) ↓ free testosterone concentrations → a negative impact on libido and sexual function, but this has not been proven.
4. ↑ TBG and ↓ bioavailable T4
5. ↑ cortisol-binding globulin (CBG), ↑ in total serum cortisol

- The risks of VTE and stroke appear to be higher with oral when compared with transdermal estrogen

Dose

- oral 17-beta estradiol [0.5 mg/day]
- 0.025 mg of transdermal estradiol → 0.0375 mg → 0.05 mg (reassessment monthly)
- **bilateral oophorectomy**: require higher doses up to 0.1 mg transdermal estradiol for the first two to three years after surgery; the dose can subsequently be tapered down.
- Estrogen should be administered continuously
- oral micronized progesterone (200 mg/day for 12 days of each calendar month).

Factors affecting oral estrogen metabolism

- Anticonvulsant drugs (phenytoin, carbamazepine) ?
- T4 replacement therapy?
- Concurrent acute alcohol ingestion?
- end-stage renal disease ?

- **Duration of therapy:**

1. short-term use → not more than five years or not beyond age 60 years
2. recurrent, bothersome hot flashes → nonhormonal options → extended use of hormone therapy

- **Monitoring with mammography**

ACOG Recommend annual mammogram , even in used short term

- **Use of oral contraceptives during the menopausal transition:**

1. the ages of 40 and 50 years, desire contraception, need control of bleeding,
2. OC containing 20 mcg of ethinyl estradiol
3. should be avoided in obese perimenopausal women

- **Stopping hormone therapy& Tapering :**

1. Tapering has not been proven to be more effective than stopping treatment abruptly
2. ACOG suggests a gradual taper, one approach is to decrease the estrogen by one pill per week every few weeks

Problems management

- Persistent menopausal symptoms ?
- Persistent breast tenderness ?
- Heavy withdrawal bleeding ?
- Bleeding during progesterone therapy ?
- No bleeding ?
- Irregular bleeding ?
- Intolerance of bleeding ?
- Premenstrual symptoms ?

Table 1. Simplifying decision selection of HRT in low-risk women

Condition	Type of HRT
Perimenopausal women	Continuous estrogen/cyclical progestogen
Hysterectomised women	Estrogen only
Women with subtotal hysterectomy	Estrogen only if no endometrium identified histologically at the lower resection margin CCT should be used if endometrium seen
Endometrial ablation	Either cyclical or CCT ?combined continuous
Progestogen-sensitive	Mirena plus systemic estrogen Micronised progesterone
Early menopause	May require higher estrogen dose
Older woman	Start with lowest dose and adjust
Potential malabsorption	Non-oral route
Postmenopausal, low libido	Try tibolone as first choice
Non-responders to standard treatment: young with surgical induced menopause	Subcutaneous implants of estrogen*

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- D[illegible]e by [illegible]n Yaseen MBBS, 4th year OG
- S[illegible] Rawan Obaidat Gyneoncologist.

thank you!