Cathy

Waking up flushed and sweaty several times a night left Cathy feeling tired all day. But when she began to feel hot on and off during the day as well, she went to see Dr. Kent.

Dr Kent with stethoscope

Menopause and Hormone Therapy Guidelines

MENOPAUSE

The word "**menopause**" literally means the "end of monthly cycles" from the Greek word *pausis* (cessation) and the root *men-* (month)

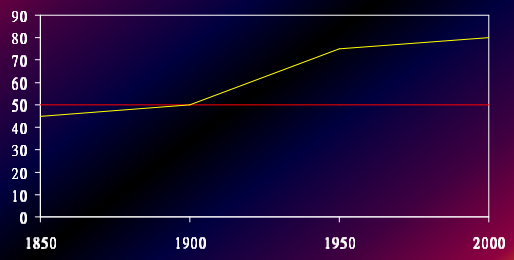
The word "**menopause**" was created to describe this change in human females, where the end of fertility is traditionally indicated by the permanent stopping of monthly menstruation or menses

Menopause is a term used to describe the permanent cessation of the primary functions of the human ovaries:

- The ripening and release of ova and the release of hormones that cause both the creation of the uterine lining and the subsequent shedding of the uterine lining (a.k.a. the menses or the period).
- Menopause typically (but not always) occurs in women in midlife, during their late 40s or early 50s, and signals the end of the fertile phase of a woman's life.

Menopause is defined as the time when there has been no menstrual periods for 12 consecutive months and no other biological or physiological cause can be identified.

Life expectancy and age of menopause



Climacteric

The phase in the aging process of women marking the transition from the reproductive stage of life to the non-reproductive stage

Menopause

The final menstrual period and occurs during the climacteric. The average age of menopause is 51.

Menopause

- Premature menopause
- Surgical menopause
- Natural menopause

Target organs of oestrogen

- Bone
- Urogenital
- Vasomotor
- Heart
- Eyes
- Teeth
- Breast
- Colon

Menopausal symptoms

Psychological
(Early symptoms)

- **IRRITABILITY**
- **DEPRESSION**
- **TIREDNESS / POOR SLEEP**
- **ANXIETY**
- **LOSS OF LIBIDO**
- **FORGETFULNESS**
- **LOSS OF CONCENTRATION**

Menopausal symptoms

Physical
(Intermediate symptoms)

- Vasomotor symptoms: hot flushes, night sweats and palpitation
- Urogenital atrophy: vaginal dryness, dyspareunia, pruritus vulvae, urinary frequency, urgency, and recurrent cystitis

Menopausal symptoms

- Diseases which may occur much later because of oestrogen loss:
  - Osteoporosis
  - Cardiovascular disease
  - Dementia of the Alzheimer's type
  - Cancers

Osteoporosis

- Oestrogen deficiency
- Peak bone mass at 30-35 years old
- Bone loss at a rate of 0.5-1% per year afterward
- Bone loss at a rate of 2-3% per year for 10 years after menopause
- Osteoporosis is associated with fracture (femoral neck, vertebral body and distal radius)

Cardiovascular disease

- Rapid increase in mortality and morbidity from cardiovascular disease after menopause
- Epidemiological evidence suggests that HRT is associated with 50% reduction in cardiovascular risk in menopausal women
- There is no prospective randomised data to show that HRT is effective in the primary prevention of cardiovascular disease.

Management of menopause

- Advise on a healthy life style
- Psychological support
- Hormone therapy

Prevention of osteoporosis

- Change lifestyle risk factors
- Exercise
- Adequate calcium / vitamin D intake
- Hormone Replacement Therapy
- Alendronate
- Raloxifene

Prevention of cardiovascular disease

- Healthy life style
- Diet
- Avoid smoking
- Control of hypertension, diabetic and hyperlipidaemia
- ?Hormone Replacement Therapy (Not effective for secondary prevention. ? Primary prevention)

Treatment:
Is there a '*Magic Potion*'?
(Like that of Getafix)

Hormone therapy

- Informed choice
- Risks and benefits of taking HRT
- Role of doctor: weighing up the pros and cons for individual woman

Indications for HRT

- Relief of menopausal symptoms
- Long term prevention of osteoporosis

Absolute contraindications

- Pregnancy
- Undiagnosed abnormal vaginal bleeding
- Active or recent blood clot or myocardial infarction
- Suspected or active breast or endometrial cancer
- Active liver disease with abnormal liver function tests
- Porphyria cutanea tarda

Hormone Replacement Therapy
Routes of administration of oestrogen

- Oral
- Transdermal
- Implants
- Local vaginal preparation

Oral therapy

- Main oestrogens used in oral post-menopausal oestrogen therapy are
  - Conjugated equine oestrogens (CEE),
  - oestradiol and
  - oestradiol valerate,
  - although esterified oestrogens, mestranol, oestriol and oestropipate, are also but seldomly used.
- Tibolone: a steroid hormone that has oestrogenic, progestogenic and androgenic properties.

HT Therapy

The appropriate dose of oestrogen varies with the indication for therapy.

For menopausal symptoms, it can be raised until a minimum effective dose is found:

Oestrogen	Bone sparing/ average symptom relieving dose (mg)	Maximum dose (mg)
oestradiol valerate	2	4
piperazine oestrone sulphate	1.25	2.5
oestriol	2	4
conjugated equine oestrogens	0.625	1.25
micronised oestradiol	2	4

Transdermal therapy

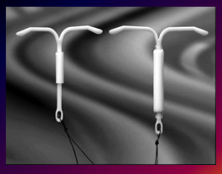
- Patches (oestrogen only or combined preparation)
- Skin irritation may be a problem but new matrix patches and the gels are usually well tolerated
- Route of choice for women with risk factors for venous thrombo-embolism, liver disease or gastro-intestinal problems
- Climara: a skin patch that contains estradiol

Oestrogen implants

- Now less widely used
- Implants should be given no more than every 6 months

Progestogen

- Oral or transdermal form
- Levo-norgestrel releasing intra-uterine system - **Mirena**



Oral progestogens

- C21 progestone derivatives : dydrogesterone or medroxyprogesterone acetate (MPA)
- C19 nor-testosterone derivatives: norethisterone acetate or levonorgestrel
- Drosperinone: progestogen derivative with antimineralocorticoid activity

Progestogen	*Regimen (dose for endometrial protection)*	
	12/28 days (mg)	*continuous* (mg)
medroxyprogesterone acetate	10	2.5-5.0
norethisterone	1.25	0.35 - 1.25
norethisterone acetate	1	N/A
dydrogesterone	10-20	10
levonorgestrel	0.09	0.03-0.06
cyproterone acetate*	2	1

Typical HT preparations

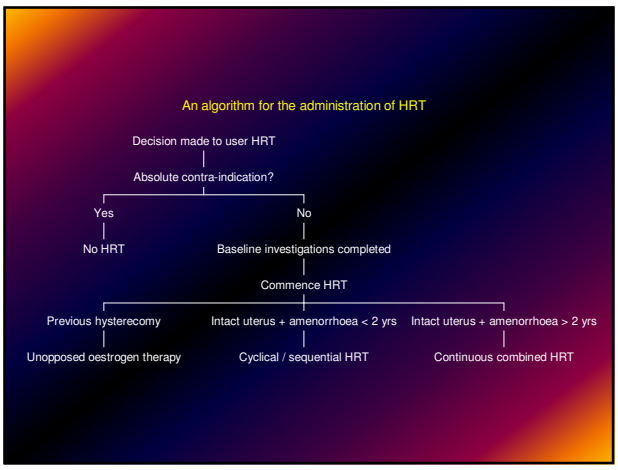
- **Activel: (estradiol and norethindrone)**
- **Angeliq: (estradiol and drospirenone)**

Local vaginal therapy

- Useful for local vaginal dryness and symptoms of urgency
- Contraindication to systemic HRT but require oestrogen for local symptoms
- E.g. Premarin Vaginal Cream

HRT regimens

- Women who have had a hysterectomy only need to take oestrogen
- Women with an intact uterus must take progestogen for endometrial protection to prevent endometrial cancer or hyperplasia
- Regular surveillance of endometrium is required for women (extreme intolerance of progestogen) on unopposed oestrogen



HRT regimens

- Sequential preparation: progestogen added for 12-14 days each month. Some women will not bleed on sequential preparations and this is not a cause for concern provided that the progestogen is taken correctly.
- Continuous combined HRT: give oestrogen and progestogen daily. These preparation induces endometrial atrophy. Intermittent bleeding and spotting are common in the first few month of use. More suitable for women who are at least one year since their last spontaneous period.

Side effects of HRT

- Nausea
- breast pain
- heavy or painful withdrawal period
- premenstrual syndrome type of side effects
- weight gain?

Management of irregular bleeding

- Sequential regimen: bleeding should occur at around the time of progestogen withdrawal (on or after day 11). Bleeding occurs at other time or persistent irregular bleeding should be investigated.
- Continuous combined regimen: amenorrhoea should be achieved 4 months after start of treatment. Spotting during the first few months is common. Spotting which occurs after a period of amenorrhoea should be investigated.

Risk of HRT

- Breast cancer
- Thrombo-embolism

The Million Women Study

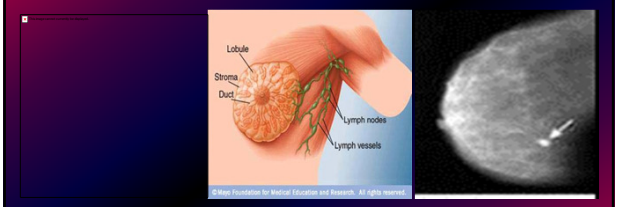
- **A national study of women's health, involving 1.3 million UK women aged 50 and over(between 1996 and 2001). The study looked at how HRT affects a woman's breasts and other aspects of her health. 66 National Health Service Breast Screening Centres were involved.**

Women's Health Initiative (WHI) study

- **WHI Study in the United States began in 1997 and was scheduled to be completed in 2005. However, researchers halted the study on May, 2002 because they felt that the health risks for participants taking HRT outweighed the possible benefits of HRT.**

HRT and breast cancer

RISK OF BREAST CANCER



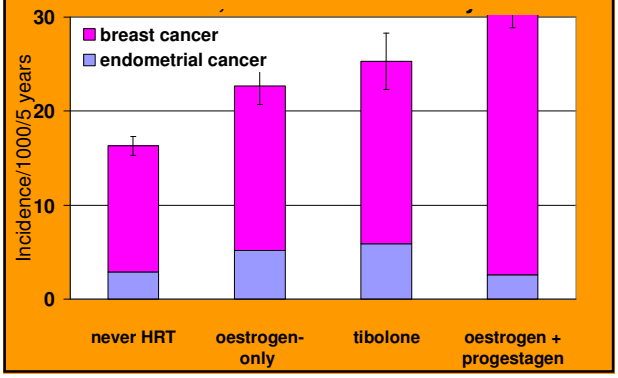
HRT and breast cancer

- Breast cancer is a hormone dependent cancer and its relationship with HRT is a complex one.

- Continuous combined HRT was associated with an increased breast cancer risk if used for four years or more
- However this increased risk disappears within 5 years once use is discontinued
- Use of Tibolone is associated with an increased risk of invasive breast cancer .

(Women's Health Initiative study 2002), (The Million Women Study 2003)

THE MILLION WOMEN STUDY



RISK OF OVARIAN CANCER

- Incidence of ovarian cancer increased with increasing duration of use of HRT(estimated duration of use at time of diagnosis, 7.7 years)

(The Million Women Study April 24, 2007)

RISK OF COLORECTAL CANCER

- Combined HRT use is associated with decreased risk of colorectal cancer

HRT AND VENOUS THROMBOEMBOLISM
RCOG 2004

- It is recommended that, in women with a previous VTE, with or without an underlying heritable thrombophilia, oral HRT should usually be avoided

- It is recommended that, when a woman who is on HRT develops a VTE, HRT should be discontinued
- In high risk women with an underlying thrombophilic trait HRT is not recommended
- SERMs should be considered to carry the same risk of thrombosis as oestrogen-containing HRT

- Prior to commencing HRT, a personal history and a family history assessing the presence of VTE in a first- or second-degree relative should be obtained
- HRT should be avoided in women with multiple pre-existing risk factors for VTE.

- It is recommended that, if a woman requires to continue on HRT after a VTE, long-term anticoagulation should be considered

Coronary heart disease (CHD)

- HRT is contraindicated for secondary prevention of further coronary disease because of lack of documented efficacy and a possible early excess mortality

- Heart and Estrogen/progestin Replacement Study (HERS) reported that standard doses of EPT increased the risk of CHD in the first year of therapy

(Grady D et al. JAMA. 2002)

- Randomised controlled trials have found an increased risk of CHD in women who started combined oestrogen-progestogen therapy more than 10 years after menopause.
- Newly menopausal women, have a lower relative risk compared with older women

(Rossouw JE. JAMA 2007)

Stroke

- In randomised controlled trials, oestrogen-only and combined HRT increased the risk of stroke (mostly ischaemic) compared with *placebo.*

Hendrix SL, et al. Circulation 2006

- In Tibolone users; The LIFT(long term intervention on fractures with tibolone) study identified a significantly (2·2-times) increased risk of stroke, mostly ischaemic, risk increased from the first year of treatment

(Cummings SR. BMJ 2006)

HRT and Osteoporosis

- HRT and Bisphosphonates has positive effects on bone density in postmenopausal women whether or not they have osteoporosis

- Maintaining HRT use decreases the risk of vertebral and non-vertebral fractures in women after surgical menopause ,early postmenopausal women and in women with established osteoporosis

- **Selective Estrogen Receptor Modulators (SERMs) may be useful in the prevention of vertebral fractures in women who cannot use HRT or bisphosphonates**

Duration of treatment

Menopausal symptoms

- Duration of treatment will depend upon the women's preference and the presence of risk factors
- In the absence of risk factors, HRT can be stopped after 2 years

Prevention of Osteoporosis

- 10 years after HRT has been stopped, bone density and fracture risk are similar in women who had used HRT and those have not
- Long term treatment (>10-15 years) is required to prevent osteoporosis
- Constant reassessment (general health, risk factors and life expectancy) is required.

Monitoring of women on HRT

- Compliance of treatment, symptoms control, side effects and bleeding pattern
- Cervical smear

Monitoring of women on HRT

Visits	Tests
First	History and physical examination, Blood pressure, FSH/LH, lipid profile, liver function test, bone biochemistry, mammography and urinanalysis
At each visit	Blood pressure Urinanalysis
Every 2 years	Physical examination, lipid profile, liver function test, determination of fasting glucose level, mammography
As indicated	Bone mineral density

Bleeding pattern

Other options for management of menopausal symptoms and prevention of osteoporosis

Tibolone

- Steriod hormone
- The parent compound and its metabolites can all bind to steroid receptos
- Oestrogenic, progestogenic and androgenic properties
- Different hormonal effects predominate in different tissues.
- Oestrogenic: climacteric symptoms, bone and lipid
- Progestogenic: endometrium
- Androgenic: libido
- Breast: less breast pain and no change in breast density on mammography

Non-hormonal treatment

- Antidepressant's can lower the number and severity of hot flashes. They may also help with irritability, depression, and moodiness.
- Clonidine can reduce the number and severity of hot flashes. Some women have side effects related to low blood pressure.
- Gabapentin can reduce the number and severity of hot flashes. Possible side effects include sleepiness, dizziness, and swelling.

Conclusion

Research Continues, Recommendations May Change

1-Decisions regarding HRT therapy must be made between the woman and her physician on an individual basis.

2-HRT must be used for as short a time as possible with lowest effective dose .

3- HRT has long-term risks including breast cancer and venous thromboembolism.

4-HRT has not been proven to be beneficial in primary and secondary prevention of coronary heart disease in fact may result in a small increased rate of CHD.

5- The low dose hormone replacement therapy is as effective as the standard dose HRT, and may have a favorable side effect profile

6- HRT is the most effective treatment of menopausal symptoms .

7- For patients at risk of osteoporosis, other preventive therapies such as bisphosphonates and SERM are available. However, for women at risk of osteoporosis who also have vasomotor menopausal symptoms, HRT can be of benefit .

8- The decision to prescribe HRT should be based on a thorough evaluation of the potential benefits and potential risks of treatment

9-Evidence for the risks of HRT in women who had premature menopause is limited and the balance of benefits and risks may be more favourable than in older women .

It is uncertain whether the results of WHI and MWS can be applied to younger postmenopausal women taking appropriate doses and regimens – the average participant age ≈ 61

(British Menopause Society Council 12 February 2008)

10-There is a lack of evidence to confirm benefits or to highlight possible adverse effects of HRT alternative therapies

So what was in Getafix's 'Magic Potion'

- **Mistletoe:** Mistletoe is the vital ingredient of the potion. It is a fungus that grows on Oak trees, it is said to have magical properties. It can only be cut by a golden sickle.
- **Roots:** Doesn't say what kind of roots.
- **Lucky Plants:** Such as a four leaf clover.
- **Fish:** Can only be fresh fish (i.e. not Unhygenix's)
- **Black Gold (Petroleum):** Only a few drops are needed. Getafix originally imported this from Ekonomikrisis until he forgot to bring some. After a series of tests, Getafix discovered Beetroot Juice could be used instead.
- **Carrots:** Self explanatory
- **Salt:** Just a pinch will do.
- **Honey and Mead:** To keep evil spirits away


The hilarious
celebration
of women and
The Change.
Menopause
The Musical