presents highlights from
Some highlights

• The Evidence Base for HRT what can we believe? M Lhermite
  Risk factors for Breast Cancer C Antoine
  How to communicate with patients about the treatment risks and benefits? Harmonizing physician and patient. E Markowicz
  Herbal products: H Depypere
  Cardiovascular Effects of the Testosterone Patch; SPRMS and breast cancer prevention: A Pintiaux
  VSM & CVD, some news on osteoporosis and fractures, Dementia S. Rozenberg
In the center of the city, in the center of life, with passion for care

Respect  Quality  Solidarity  Innovation  Engagement

“Report of IMS Praha”

Serge Rozenberg UMC St Pieter Ziekenhuis
ULB-VUB  Belgium

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Conflict of interest & Disclosure

- Conflict of interest: none
- **Disclosure SR**
- Research funding IRIS- King Baudouin Fondation, Vesale research Foundation, Amgen, MSD
- Speakers bureau &/or Advisory Boards
- Abbot, Mylan, Pfizer, Will, Gedeon Richter, MSD, Amgen, Serylis Pharma,
Vasomotor Symptoms (VMS)

- Sensation of intense heat, sweating, flushing
- Hot flushes/night sweats
- >70% of women experience during menopause transition
  - 30% frequent or severe
**Trajectories of VMS (N=1455)**

Study of Women’s Health Across the Nation (SWAN)

- **Probability of VMS**
  - Years around final menstrual period
  - Low, 27.0%
  - Early onset, 18.4%
  - Late onset, 29.0%
  - High, 25.6%

(Repper ... Thurston, Menopause, 2016)
SWAN: Reported VMS and Subclinical CVD

VMS in past 2 weeks

*\( p < .05 \)

*IMT (mm)*

None | 1-5 Days | 6+ Days
---|---|---
0.69 | 0.72 | 0.73

Age, site, race, education, CVD risk factors, CVD meds, HT use, E2

(Thurston et al., 2011, Menopause)
Measurement of VMS

Physiologic

Electronic Diary
More VMS, Higher Subclinical CVD among Women with VMS

Adjusted for age, race, education, BMI, CVD risk factors, CV medications
<table>
<thead>
<tr>
<th>Factor</th>
<th>Variance in IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>4.7</td>
</tr>
<tr>
<td>Race</td>
<td>8.7</td>
</tr>
<tr>
<td>Education</td>
<td>1.0</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.5</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>0.20</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>0.13</td>
</tr>
<tr>
<td>Lipids</td>
<td>3.0</td>
</tr>
<tr>
<td>Medications</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Physiologic VMS Frequency</strong></td>
<td><strong>7.9</strong></td>
</tr>
</tbody>
</table>

VMS explain more variance in subclinical CVD than almost any other risk factor.
Altered Nervous System Activity During VMS

N = 215
p < .0001

Hot Flush

Parasympathetic control of heart

Minutes around Physiologic VMS

(Thorson et al., 20__ Menopause)
Trajectories of VMS (N=1455)
Study of Women’s Health Across the Nation (SWAN)

Probability of VMS

Years around final menstrual period

Low, 27.0%

Early onset, 18.4%

Late onset, 29.0%

High, 25.6%

(Tepper ... Thurston, Menopause, 2016)
WISE: Early Onset VMS Associated with Higher CVD Mortality

\[ p \text{ (log-rank)} = 0.030 \]

- Never VMS \( (n=93) \)
- VMS Onset \( \leq \) Age 42 \( (n=40) \)
- VMS Onset \( > \) Age 42 \( (n=121) \)

(Thurston et al., Menopause, in press)
Summary and Implications

- VMS start earlier, last longer than once thought
- VMS appear associated with markers of CVD risk
- Possibly......midlife marker of CVD risk
  - Aggressive risk factor reduction?
- Improve health of women
Menopausal symptoms and cardiovascular disease mortality in the Women's Ischemia Syndrome Evaluation (WISE)

- The Women's Ischemia Syndrome Evaluation enrolled women referred for coronary angiography for suspected myocardial ischemia.
- N= 254 women > 50 years, postmenopausal, with both ovaries, not taking hormone therapy underwent a baseline evaluation, were followed annually (median = 6.0 y), and the National Death Index was searched to ascertain CVD mortality (median = 9.3 y).
- Subset: brachial artery ultrasound for flow-mediated dilation (FMD). ROC
- Thurston et al [Menopause](https://doi.org/10.1097/MEN.0000000000000772). 2016 Sep 26. [Epub ahead of print]
Menopausal symptoms and cardiovascular disease mortality in the Women's Ischemia Syndrome Evaluation (WISE)

- Women reporting early onset VMS (HR = 3.35, 95% CI = 1.23-7.86, P = 0.005) and women who never had VMS (HR = 2.17, 95% CI = 1.02-4.62, P = 0.05) had higher CVD mortality than women with later onset symptoms (multivariable models). Women with early onset VMS had lower FMD than women with later onset symptoms (b = -4.31, SE = 2.10, P = 0.04, multivariable).

- **CONCLUSIONS:**
  - Women with signs and symptoms of ischemia who had VMS beginning early in midlife had higher CVD mortality and reduced endothelial function relative to women with later onset symptoms. Future research should evaluate the vascular phenotype of women with early midlife VMS.

- Thurston et al [Menopause.](http://example.com) 2016 Sep 26. [Epub ahead of print]
Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis.

• 32 studies were selected that included 310 329 women.

• RR (95% CIs) were 1.50 (1.28-1.76) for overall CHD, 1.11 (1.03-1.20) for fatal CHD, 1.23 (0.98-1.53) for overall stroke, 0.99 (0.92-1.07) for stroke mortality, 1.19 (1.08-1.31) for CVD mortality, and 1.12 (1.03-1.21) for all-cause mortality.

• Muka T et al JAMA Cardiol. 2016 Sep 14
Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis.

- Decreased risk of fatal CHD (RR, 0.87; 95% CI, 0.80-0.96) for women who had their onset of menopause at 50 - 54 years vs women < 50 years.

- Conclusions and Relevance:
  - The findings of this review indicate a higher risk of CHD, CVD mortality, and overall mortality in women who experience premature or early-onset menopause.

Muka T et al. *JAMA Cardiol.* 2016 Sep 14
### Table 2. Carotid-Artery Intima–Media Thickness (CIMT) Progression and Baseline CIMT.

<table>
<thead>
<tr>
<th>Measure and Postmenopause Stratum</th>
<th>Placebo (N = 299)</th>
<th>Estradiol (N = 297)</th>
<th>P Value†</th>
<th>P Value for Postmenopause Stratum Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rate of change in CIMT (95% CI) — mm/yr‡</td>
<td>0.0078 (0.0060–0.0096)</td>
<td>0.0044 (0.0026–0.0061)</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>Early postmenopause</td>
<td>0.0088 (0.0073–0.0103)</td>
<td>0.0100 (0.0085–0.0115)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Late postmenopause</td>
<td>0.75 (0.73–0.76)</td>
<td>0.75 (0.73–0.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline CIMT (95% CI) — mm</td>
<td>0.79 (0.77–0.81)</td>
<td>0.78 (0.77–0.80)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The median duration of follow-up was 4.8 years (range, 0.5 to 6.7); the median number of CIMT measures per participant was 10 (range, 2 to 13). In the early-postmenopause stratum, the median duration of follow-up was 5.0 years (range, 0.5 to 6.7) in the placebo group and 5.1 years (range, 0.5 to 6.2) in the estradiol group, and the median number of CIMT measures was 11 (range, 2 to 13) in each study group. In the late-postmenopause stratum, the median duration of follow-up was 4.6 years (range, 0.5 to 6.3) in the placebo group and 4.5 years (range, 0.5 to 6.1) in the estradiol group, and the median number of CIMT measures was 10 (range, 2 to 13) in each study group. CI denotes confidence interval.

† The P values shown are for the difference between estradiol and placebo within a given postmenopause stratum.

‡ Results were calculated with a mixed-effects model adjusted for the following randomization stratification factors: baseline CIMT (<0.75 mm or ≥0.75 mm) and hysterectomy status (yes or no). In the early-postmenopause stratum, data were available for 123 participants in the placebo group and 125 participants in the estradiol group. In the late-postmenopause stratum, data were available for 176 participants in the placebo group and 172 participants in the estradiol group.

Hodis et al NEJM 2016
World Menopause Day 2016

'Heart Health Matters,'
Epigenetic influence
Pregnancy terms

Placenta - The placenta is the organ that brings the baby nutrients and oxygen and carries away waste.

Uterus - The uterus (also called the "womb") is a tough, muscular organ that holds the baby during pregnancy.

Umbilical cord - The umbilical cord connects the baby to the placenta.

Cervix - The cervix is the bottom part of the uterus that leads to the vagina.

Fetus - This is what the baby is called while it is growing inside you.

Amniotic sac - This is a fluid-filled sac that lines the uterus and holds the baby.

Amniotic fluid - This is the fluid surrounding the baby in the uterus.

Vagina - The baby exits through here during a vaginal birth.
Epigenetic mechanisms in the developmental origins of osteoporosis
Implications for lifecourse prevention

Cyrus Cooper  OBE, DL, FMedSci

Professor of Rheumatology and Director, MRC Lifecourse Epidemiology Unit, University of Southampton; and
Professor of Epidemiology, University of Oxford; UK

15th World Menopause Congress, Prague; September 2016
Developmental origins of adult disease

Death rates from coronary heart disease among 15,726 men and women in Hertfordshire according to birth weight

Programming
Persisting changes in structure and function caused by environmental signals at critical periods during early development

David Barker 1936-2013
Building of peak bone mass
Maternal body build, smoking, activity and neonatal bone mass

Maternal smoking
P = 0.004

Walking speed (late pregnancy)
P = 0.002

BMI (pre-pregnancy)
P = 0.001

Tricep skinfold thickness (pre-pregnancy)
P = 0.002

Godfrey K et al J Bone Min Res (2001); Harvey N et al J DOHaD (20010)
Maternal vitamin D status and childhood bone mass

*Princess Anne Hospital Cohort Study, Southampton; Age 9yrs*

![Graphs showing correlation between maternal vitamin D status and various childhood bone measures.](image-url)
Maternal vitamin D and automated intrauterine femoral measurement using 3D ultrasound

Distal femur splaying index = cross-sectional area (cm²) / length (cm)

Mahon P et al. J Bone Miner Res 2010; 25: 14-19
Ioannou C et al. J Clin Endocrinol Metab 2012; 97: 2070-7
Yaqub M et al. Fetal Diag Ther 2013; e-pub

Maternal 25-OH vitamin D (34 weeks gestation, nmol/L)
Maternal vitamin D status and offspring whole body bone mineral at age 20 years
Western Australia Pregnancy (Raine) Cohort

Model 1: adjusted for season of blood sampling, sex and age at DXA
Model 2: Model 1 + maternal education, parity, ethnicity, maternal height and pre-pregnancy weight
Model 3: Model 2 + offspring height, lean mass and fat mass at 20 years

N=341, shown as mean±95% CI

Zhu et al. J Bone Miner Res 2014; 29: 1088-93
Maternal vitamin D and offspring birth weight

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvey et al</td>
<td>2008</td>
<td>6.51 (-0.68, 13.70)</td>
<td>39.59</td>
</tr>
<tr>
<td>Gale et al</td>
<td>2008</td>
<td>5.04 (-1.37, 11.47)</td>
<td>49.63</td>
</tr>
<tr>
<td>Farrant et al</td>
<td>2009</td>
<td>5.16 (-8.60, 18.92)</td>
<td>10.81</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>5.63 (1.11, 10.15)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Differences in birth weight (grams) per 10% increase in Vitamin D

Adjusted effect estimates

Adjustments: gest age; mat age; mat BMI; ethnicity; parity where possible

Harvey et al. HTAJ 2014; 18: 1-30
Vitamin D supplementation during pregnancy
Updated meta-analysis on maternal outcomes

• 15 trials of maternal supplementation; 23 ongoing/unpublished

• Improvement in serum 25(OH)D level
  – Mean difference 54.7nmol/l (36.6-72.9)

• Pre-eclampsia  HR 0.52 (0.25-1.05)
• Gestational DM    HR 0.43 (0.05-3.45)

Loss during adulthood
Bone mineral status in anorexia nervosa

Lawson et al Bone 2010; 46:458
Postmenopausal loss
Three generations of women in a Korean village. The elderly women have 'kyphosis' (or hunched back) which is a sign of vertebral fractures caused by osteoporosis. A family history of osteoporosis is an important risk factor for the disease.
Stop Development of Odanacatib for Osteoporosis

• increased risk of stroke
• Data presented at ASBMR September 2016.
Figure 1. Trial Regimens and Assessments.

Women were randomly assigned, in a 1:1 ratio, to receive subcutaneous injections of 210 mg of romosozumab or placebo once monthly for 12 months during the double-blind phase of the trial. Patients then received open-label denosumab, administered subcutaneously at a dose of 60 mg every 6 months for an additional 12 months; the initial group assignment was still blinded. Patients were stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). In a substudy of the overall population that involved 128 patients, bone mineral density was assessed at baseline and every 6 months. In a substudy of the overall population that involved 129 patients, the levels of bone-turnover markers were assessed at baseline, at day 14, and at months 1, 3, 3+14 days, 6, 6+14 days, 9, 12, 13, 18, and 24. After the 24-month trial period, patients continue to receive open-label denosumab in a 1-year extension study (data not shown).
Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Cosman et al NEJM 9/2016
Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Figure 2. Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.

The coprimary end points were the cumulative incidences of new vertebral fracture at 12 months and at 24 months (Panel A). The risk ratio was assessed among patients in the romosozumab group as compared with those in the placebo group at 12 months (end of the double-blind period) and at 24 months (by which time patients in both groups had received open-label denosumab for 12 months). Data from patients who underwent randomization and had a baseline radiograph and at least one radiograph obtained after the baseline visit are included here. Kaplan–Meier curves of the first clinical fracture (Panel B) and the first nonvertebral fracture (Panel C) from the time-to-event analysis are shown, including the double-blind period through 12 months and the period with open-label denosumab from 12 to 24 months. The insets show the same data on an enlarged y axis. Data from patients who withdrew from the trial or who reached the end of the reporting period without having a fracture were censored at the last observation time. P values are for results at 12 months and 24 months and are based on a Cox proportional-hazards model with adjustment for age and prevalent vertebral fracture, adjusted for multiple comparisons.

Cosman et al NEJM 9/2016
Romosozumab Treatment in Postmenopausal Women with Osteoporosis

- At 12 months, new vertebral fractures: 16/3321 patients (0.5%) in the romosozumab group, vs 59/3322 (1.8%) placebo (-73%; P<0.001).
- Clinical fractures: 58/3589 patients (1.6%) romosozumab vs 90/3591 (2.5%) placebo (-36%; P = 0.008).
- Non-vertebral fractures: 56/3589 (1.6%) romosozumab vs 75/3591 (2.1%) placebo (P = 0.10).
- At 24 months, vertebral fractures lower romosozumab + denosumaba vs placebo + denosumab (0.6% [21/3325] vs. 2.5% [84/3327] -75%; P<0.001).
- Adverse events: cardiovascular, cancer, balanced between the groups.
Sarcopenia-osteoposrosis
LIFESTYLE APPROACHES TO PREVENT FALLS, FRACTURES AND FRAIL BONES

Robin M. Daly PhD FSHA
Professor | Chair of Exercise and Ageing
Institute for Physical Activity and Nutrition (IPAN)
Deakin University, Melbourne, Australia
FACT #1

Osteoporosis ≠ Fracture

The real enemy is fragility fracture, not osteoporosis!

At least 30-50% of women aged 60+ years with a fracture do not have osteoporosis.
Most Fractures Are Due to Falls

Poor physical function is associated with an increased risk of hip fracture in older men, independent of BMD.
FACT #4: What’s New Sarco-osteoporosis

Normal Bone

Loss of bone mass, structure and strength

Loss of muscle mass, size and strength

Osteoporotic Bone
- Bone strength
- Bone mineral density
- Microarchitectural

Sarco-osteoporotic

Sarco-osteoporosis

Increased risk of falls and fracture
Increased morbidity and mortality
Loss of independence
Reduced quality of life

Healthy Young

Older Adult
New Algorithm for Sarcopenia

Slowness + Weakness + Low Lean Mass

1. Physical Function
   - Gait speed < 0.8 mph (4 or 6 p.m. walk)
     - Yes
     - Muscle strength
       - Men: < 26 kg
       - Woman: < 20 kg
       - If No, look for other causes of impaired function

2. Appendicular Muscle Mass
   - Appendicular L.M. (adjusted for BMI) or ACM
     - Men: < 0.7 BD
     - Women: < 0.5 BD
New Algorithm for Sarcopenia

Slowness + Weakness + Low Lean Mass

1. Physical Function

A Simple Question

Have you recently had a fall or are you worried about falling?

2. Mass

3. Appendicular Muscle Mass
Does Exercise Reduce Fracture Risk?

2012 Systematic Review and Meta-analysis

Clinical exercise trials that reported fracture number as the endpoint or observation.

Relative Risk of Overall Fracture

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Askham 2007</td>
<td>0.33 (0.67, 1.52)</td>
</tr>
<tr>
<td>Choi 2001</td>
<td>0.52 (0.30, 0.98)</td>
</tr>
<tr>
<td>Riviere 1997</td>
<td>1.47 (0.43, 4.88)</td>
</tr>
<tr>
<td>Kanzaka 2007</td>
<td>0.39 (0.09, 2.26)</td>
</tr>
<tr>
<td>Komorier 2010</td>
<td>0.49 (0.15, 1.55)</td>
</tr>
<tr>
<td>Komorier 2010</td>
<td>0.34 (0.15, 0.79)</td>
</tr>
<tr>
<td>Koopman 2006</td>
<td>0.34 (0.14, 0.80)</td>
</tr>
<tr>
<td>Nohr 2007</td>
<td>0.22 (0.01, 4.41)</td>
</tr>
<tr>
<td>Presinger 1996</td>
<td>0.97 (0.19, 5.05)</td>
</tr>
<tr>
<td>Robertson 2001</td>
<td>0.89 (0.18, 4.43)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.39 (0.51, 0.79)</td>
</tr>
</tbody>
</table>

P (heterogeneity) = 0.39

Overall fractures:
- Significantly 51% reduced risk

Vertebral fractures:
- Non-significant 44% risk
- Sensitivity analysis: 42% risk

(Statistical significance based on weighting for study quality)
Habitual Physical Activity

Adherence to the Physical Activity Guidelines and BMD

Data from NHANES 2007-2010 (n=19,486); Adults aged 20+ years

Men

Women

Physical activity guidelines: 2.5-5.0 and ≥5.0 × GL

GL = Physical activity guideline

Physical activity: 0 to 5.0 × GL

BMD: Bone mineral density
Dementia

• Meet the expert Victor Henderson
Patient concerns?

- Yes
- No

Informant concerns?

- Yes
- No

Clinician concerns for neuro-based impairment?

- Yes
- No

1. History (patient and informant)
   - Memory
   - Function
   - Medical and psychosocial
   - Medications
   - Family history

2. Examination
   - Cognition
   - Mood
   - Physical / neurological

3. Laboratory

Diagnosis & Management

Refer for neurologist evaluation

Follow-up as needed
Diagnosis / contributing factors

- Awareness of normal cognitive aging
- Depression or anxiety
  - Menopause as time of affective vulnerability
- Sleep disturbance
- Hot flashes (stress, sleep)
- Family stressors
  - Adolescent children, empty nest, aging parents, marital discord
- Career challenges
My screening cognitive exam

“Short Blessed” Orientation-Memory-Concentration Test

- Month
- Year
- Learn a name and address (5 items)  
  (John Brown, 42 Market Street, Chicago)
- Time of day (within 1 hour)
- Count backwards from 20 to 1
- Recite months of the year in reverse order
- Recall of name and address

Original reference:
Katzman R et al.,  
Am. J. Psychiatry  
1983;140:734

CERAD:  
Morris J et al.  
Neurology  
1989;39:1159
My screening cognitive exam

“Short Blessed” Orientation-Memory-Concentration Test

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- Year
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- Time of day (within 1 hour)
- Count backwards from 20 to 1
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Plus

- Clock drawing

CERAD:
Morris J et al.
Neurology
1989;39:1159

Original reference:
Katzman R et al.,
Am. J. Psychiatry
1983;140:734

2nd delayed recall of
“Management of Post-Menopausal Bleeding in women on MHT”

Serge Rozenberg UMC St Pieter Ziekenhuis
ULB-VUB Belgium

serge_rozenberg@stpierre-bru.be
Investigation of Women with Postmenopausal Uterine Bleeding: Clinical Practice Recommendations

- Munro MG\(^1\); Southern California Permanente Medical Group’s Abnormal Uterine Bleeding Working Group.
Take Home Messages

• Only selected women with bleeding associated with MHT require assessment of the endometrium.
• Uterine bleeding or spotting may be expected depending in part on the dose of MHT, in part on the schedule of progestin administration, and in part on the duration of therapy
• (Grade B)
Take Home Messages

• Women receiving doses of unopposed estrogen have a much higher incidence of endometrial hyperplasia and carcinoma, and require appropriate investigation of the endometrium
• (Grade A)
Take Home Messages

• It is not necessary to routinely evaluate the endometrium of women with uterine spotting or light uterine bleeding in the first 6 months of continuous estrogen and progestin MHT.

• Endometrial assessment of such women is recommended if spotting or bleeding persists > 6 months, although there is a very low incidence of endometrial hyperplasia or neoplasia

• (Grade B)
Take Home Messages

• Women receiving estrogen and cyclical progestins can be expected to have indefinite progestin withdrawal bleeding and require no further investigation provided that the dose and duration of cyclic progestins is adequate

• (Grade A)
Take Home Messages

• For women using cyclic progestins, bleeding outside the time of progestin withdrawal is considered abnormal and requires appropriate investigation

• (Grade B )
Take Home Messages

• It is apparent that EEC thresholds used for spontaneous bleeding can be applied to patients with HRT-related bleeding, but with a higher incidence of false-positive findings

• (Grade B )
Levonorgestrel Intrauterine Device as an Endometrial Cancer Prevention Strategy in Obese Women
A Cost-Effectiveness Analysis
How long does the bleeding last? How heavy is it?

- Heavy bleeding, even when experienced in the context of a cyclically administered progestin, may suggest the presence of intrauterine pathology.
Is there evidence of poor compliance?

• Some women take their medications sporadically or use their progestin in an unconventional fashion.
Is there a reason to suspect poor gastrointestinal absorption?

- Nausea, vomiting, or diarrhea?
- Incomplete absorption and resultant bleeding.
**Is there any evidence of hepatocellular disease?**

- The liver is responsible for metabolizing estrogen.
- Active or chronic hepatocellular disease: high levels of estrogen
- Heavy smokers
Is the patient receiving any other drugs?

• The intentional or inadvertent use of other gonadal steroids (estrogens with or without progestins) may explain unexpected bleeding.
More information?

- Irregular?: NO
- Heavy?: NO
- Risk factors?: NO
- Other medication?: No
- Exclude other pathologies?: Yes
- Endometrial thickness?: Yes (?)
Figure 1. Endometrial echo complex (EEC) measurement in the sagittal plane.
Study should include coronal or transverse plane as well. For demonstration purposes, the image is from a premenopausal woman.

Munro MG¹; Southern California Permanente Medical Group’s Abnormal Uterine Bleeding Working Group.
Figure 2. Typical measurement of normal postmenopausal endometrial echo complex (EEC) (< 4 mm) (arrowhead).

Munro MG¹; Southern California Permanente Medical Group’s Abnormal Uterine Bleeding Working Group The permanente Journal 2014.
Figure 3. Measurement of endometrial echo complex (EEC) when there is fluid in the cavity. Thickness of fluid (B) is subtracted from distance between base of opposing layers of endometrium (A). These should be in the same plane; they are separated slightly here for demonstration purposes.

Munro MG1; Southern California Permanente Medical Group’s Abnormal Uterine Bleeding Working Group The permanente Journal 2014.
• If everything is normal

• No further investigation needed
<table>
<thead>
<tr>
<th>Cause</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic endometrium</td>
<td>60-80</td>
</tr>
<tr>
<td>HRT</td>
<td>15-25</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>7-10</td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>5-10</td>
</tr>
<tr>
<td>Polyp(s) (endometrial or cervical)</td>
<td>2-12</td>
</tr>
<tr>
<td>Miscellaneous (uterine leiomyomas, cervicitis,</td>
<td>&lt;10</td>
</tr>
<tr>
<td>atrophic vaginitis, tamoxifen therapy, trauma,</td>
<td></td>
</tr>
<tr>
<td>anticoagulation)</td>
<td></td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy.

Bull et al 2012
### TABLE

**Postmenopausal bleeding: The differential diagnosis**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic endometrium</td>
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</tr>
<tr>
<td>HRT</td>
<td>15-25</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td><strong>7-10</strong></td>
</tr>
<tr>
<td>Endometrial hyperplasia</td>
<td>5-10</td>
</tr>
<tr>
<td>Polyp(s) (endometrial or cervical)</td>
<td>2-12</td>
</tr>
<tr>
<td>Miscellaneous (uterine leiomyomas, cervicitis, atrophic vaginitis, tamoxifen therapy, trauma, anticoagulation)</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

HRT, hormone replacement therapy.
More information ?

- Irregular ?
- Heavy ?
- **Risk factors ?**
- Other medication ?
- Exclude other pathologies ?
- Endometrial thickness ?
## Risk factors for endometrial cancer

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk (RR) (other statistics are noted when used)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>1.4% endometrial cancer prevalence in women 50 to 70 years old</td>
</tr>
<tr>
<td>Unopposed estrogen therapy</td>
<td>2 to 10</td>
</tr>
<tr>
<td>Tamoxifen therapy</td>
<td>2</td>
</tr>
<tr>
<td>Early menarche</td>
<td>NA</td>
</tr>
<tr>
<td>Late menopause (after age 55)</td>
<td>2</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2</td>
</tr>
<tr>
<td>Polycystic ovary syndrome (chronic anovulation)</td>
<td>3</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 to 4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Estrogen-secreting tumor</td>
<td>NA</td>
</tr>
<tr>
<td>Lynch syndrome (hereditary nonpolyposis colorectal cancer)</td>
<td>22 to 50% lifetime risk</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>13 to 19% lifetime risk</td>
</tr>
<tr>
<td>Family history of endometrial, ovarian, breast, or colon cancer</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: RR not available.

women at risk for endometrial cancer

- TVUS
- **Followed by** hysteroscopy and D&C or biopsy
- guidelines from the Society of Gynecologic Oncologists
Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding
• Is it a reliable technique?
The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis.

The sensitivity for the diagnosis of endometrial cancer (by Pipelle) in postmenopausal women was 99.6%.
The sensitivity for the diagnosis of atypical endometrial hyperplasia was 81%.
The specificity for all endometrial biopsy devices for the diagnosis of endometrial carcinoma was 98 to 100%.
< 5% : insufficient or no sample.

Dijkhuizen et al Cancer. 2000;89(8):1765
• Many postmenopausal women have a stenotic cervical canal, making outpatient endometrial sampling impossible
Bleeding from the uterus: Investigating uterine cavity

- Endometrial atrophy
- Myoma
- Polyps
- Adenomyosis
- Hyperplasia, simple, complex, atypia
- Endometrial cancer
Other Causes of Abnormal Uterine Bleeding

- Cervical or vaginal lesions
- Poor compliance
- Poor gastrointestinal absorption (for oral preparations)
- Drug interactions
- Coagulation defects
- Liver disease
- Nonreproductive tract origins (eg, urinary tract, gastrointestinal tract).
Vignette 5

• Mrs V is 51 years old. She is taking MHT (CEE 0.625 mg or 1 mg E2 + Progestin daily) since 2 months. Progestin is taken at an appropriate dose.

• She consults for bleeding.
Do we need to investigate her uterus?
Bleeding using E-P MHT

• Vaginal bleeding can be followed for the first six months after beginning continuous combined therapy.
• Endometrial biopsy is necessary if the bleeding persists beyond this point.
Background

• Approximately 40–60% of HT users experience unpredictable, unscheduled vaginal bleeding and spotting.
• Leading to discontinuation of therapy in up to 30%
• WHI: 40% of those randomized to combined HT were unblinded, most for irregular bleeding.
• M Hickey, S Agarwal 2009
Figure 3 Proportion of patients (%) with at least one bleeding episode in relation to time and to the used HT.

Rozenberg et al Human Reprod 2009
Continuous combined hormone replacement therapy with 1 mg 17beta-oestradiol and 5 mg dydrogesterone (Femoston-conti): endometrial safety and bleeding profile.

• 290 healthy, non-hysterectomised post-menopausal women receiving oral continuous combined 1 mg 17beta-oestradiol and 5 mg dydrogesterone (Femoston-conti) for 1 year.

• 1 woman developed simple hyperplasia without atypia (failure rate 0.4%). % women without bleeding: 71% during the 1st cycle to around 80% end of the study.

• Overall, 41% of the women were amenorrhoeic throughout the study.

• Quereux C¹, Pornel B, Bergeron C, Ferenczy A.

Ultra low dose continuous combined hormone replacement therapy with 0.5mg 17beta-oestradiol and 2.5mg dydrogesterone: protection of the endometrium and amenorrhoea rate.

- Open, multicentre study: n= 446
- Aspiration endometrial biopsies were performed at baseline and after 1 year
- 1 case of simple hyperplasia (incidence of 0.27% ;95% CI: 0.01-1.48%) per protocol sample (n=395).
- The overall rate of amenorrhoea in the full sample (n=446) and 14% had only one or two bleeding/spotting episodes. The rate of amenorrhoea in months 10-12 (n=413) was 88%.
- The number of bleeding/spotting days per cycle fell during the study. The mean number of bleeding/spotting days was 5.8 and the mean number of days without bleeding was 358.2. Spotting alone was the most prevalent bleeding intensity, whilst heavy bleeding was rare.
Short and long term effects of tibolone in postmenopausal women.

• ....When compared to equipotent doses of combined HT, tibolone reduced vaginal bleeding (15 RCTs, n = 6342; OR 0.32, 95% CI 0.24 to 0.42) but was less effective in relieving the frequency of vasomotor symptoms (two RCTs, n = 545; OR 4.16, 95% CI 1.50 to 11.58).

• AUTHOR'S CONCLUSIONS:
  • Tibolone, used at the daily dose of 2.5 mg, may be less effective than combined HT in alleviating menopausal symptoms although it reduced the incidence of vaginal bleeding.

Rates of Bleeding/Spotting and Amenorrhea Similar to Rates with Placebo

• High and similar cumulative rates of amenorrhea at year 1 among women treated with CE 0.45/BZA 20 and placebo; and was higher than seen in women treated with CE 0.45/MPA 1.5

• Noncumulative rates of spotting and bleeding/spotting were similar among women treated with CE/BZA or placebo and consistently higher in women treated with CE 0.45/MPA 1.5

Women who have uterine bleeding after a period of amenorrhea should have endometrial biopsy, due to the relatively increased incidence of intrauterine pathology (eg, hyperplasia, carcinoma, fibroids, polyps).
• Assessment should also be performed in women with bleeding that is refractory to hormonal manipulation (such as decrease of E2 or increase in progestin dose, or change of regimen).
• Is TVUS useful for evaluating the endometrial thickness?
Prediction of endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm

729 women with postmenopausal bleeding

371 women eligible for inclusion

358 women excluded:
- Endometrium ≤ 4.4 mm (n = 290)
- Endometrium not measurable (n = 46)
- Fluid in the uterine cavity (n = 20)
- Transvaginal examination not possible (n = 2)

110 women excluded:
- No endometrial sampling performed (n = 30)*
- Postprocessed images not available (n = 30)†
- Only Endorette sampling (n = 21)‡
- Insufficient material for diagnosis (n = 21)
- Only D&C despite focal lesions in the cavity (n = 7)
- Bicornuate uterus (n = 1)§

261 women included in the study
Prediction of endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm
Prediction of endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm
Table 3 Results of univariate and multivariate logistic regression analyses with regard to predicting endometrial malignancy in women with postmenopausal bleeding and sonographic endometrial thickness ≥ 4.5 mm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate logistic regression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.057</td>
<td>1.027-1.088</td>
<td>0.0005</td>
</tr>
<tr>
<td>HRT</td>
<td>0.305</td>
<td>0.142-0.654</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of warfarin</td>
<td>0.123</td>
<td>0.016-0.928</td>
<td>0.005</td>
</tr>
<tr>
<td>ET</td>
<td>1.121</td>
<td>1.078-1.167</td>
<td>0.0005</td>
</tr>
<tr>
<td>Vascularity index</td>
<td>1.082</td>
<td>1.059-1.105</td>
<td>0.0005</td>
</tr>
<tr>
<td>VAS score</td>
<td>1.061</td>
<td>1.046-1.076</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Multivariate logistic regression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.061</td>
<td>1.030-1.093</td>
<td>0.0005</td>
</tr>
<tr>
<td>HRT</td>
<td>0.338</td>
<td>0.154-0.744</td>
<td>0.004</td>
</tr>
<tr>
<td>Use of warfarin</td>
<td>0.085</td>
<td>0.011-0.662</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.053</td>
<td>1.019-1.087</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of warfarin</td>
<td>0.077</td>
<td>0.008-0.716</td>
<td>0.003</td>
</tr>
<tr>
<td>ET</td>
<td>1.110</td>
<td>1.066-1.157</td>
<td>0.0005</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.045</td>
<td>1.004-1.088</td>
<td>0.031</td>
</tr>
<tr>
<td>Any type of HRT</td>
<td>0.305</td>
<td>0.108-0.862</td>
<td>0.017</td>
</tr>
<tr>
<td>ET</td>
<td>1.060</td>
<td>1.018-1.103</td>
<td>0.002</td>
</tr>
<tr>
<td>VAS score</td>
<td>1.058</td>
<td>1.041-1.075</td>
<td>0.0005</td>
</tr>
<tr>
<td>Model 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.072</td>
<td>1.028-1.118</td>
<td>0.001</td>
</tr>
<tr>
<td>HRT</td>
<td>0.264</td>
<td>0.086-0.806</td>
<td>0.012</td>
</tr>
<tr>
<td>ET</td>
<td>1.088</td>
<td>1.044-1.133</td>
<td>0.000</td>
</tr>
<tr>
<td>Vascularity index</td>
<td>1.092</td>
<td>1.064-1.121</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Odds ratios were calculated for endometrial thickness expressed in mm, age in years and vascularity index in percent. ET, endometrial thickness; HRT, hormone replacement therapy; Model 1, age, use of warfarin, HRT; Model 2, age, use of warfarin, ET; Model 3, age, HRT, ET, VAS score; Model 4, age, HRT, ET, vascularity index; VAS, visual analog scale.
Should we measure endometrial thickness in asymptomatic women?
Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding

Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding

Invitation letter distributed \( (n = 2951) \)

Invitation letter reached the invitee \( (n = 2785) \)

Reply letter returned stating willingness to participate \( (n = 757) \)

Willing to participate \( (n = 694) \)

Eligible and examined \( (n = 514) \)

Included \( (n = 510) \)

Invitation letter did not reach the invitee because of a change of address \( (n = 166) \)

Reply form not returned \( (n = 2028) \)

Decided not to participate \( (n = 63) \)

Did not fulfill eligibility criteria \( (n = 180) \)

Excluded due to technical problems \( (n = 4) \)
Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding

None on HRT
Transvaginal ultrasound examination of the endometrium in postmenopausal women without vaginal bleeding

• About 10% of gynecologically asymptomatic postmenopausal women have a sonographic endometrial thickness $\geq 5.0$ mm. Our results support conservative management of such women.

Capacity of endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women: a systematic review and meta-analysis

• Do not justify the use of endometrial thickness as a screening test for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic postmenopausal women not using HRT.

TVUS

- **In Women on hormone therapy**
  - Not useful screening tool
  - Only to assess adnexal pathology, or if abnormal bleeding occurs and an endometrial biopsy cannot be easily obtained.
  - In the case of abnormal bleeding in women on cyclic progesterone, it is best to obtain the TVUS early in cycle, when the endometrium is expected to be at its thinnest.
  - Persistent bleeding **always** requires endometrial biopsy regardless of ultrasound findings.
  - We tell patients that bleeding is common when ET is initiated and should decrease over time. If it does not, and if it becomes heavier, or bleeding occurs after a long period of no bleeding, then a biopsy is indicated.