Postmenopausal Bleeding

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Definition

- Not on HRT
  - PMB is bleeding occurring 12 months after permanent cessation of menses due to ovarian failure in women not taking HRT i.e. 12 months after the LMP.
- In those on HRT
  - 'Unscheduled bleeding' is defined as that still continuing 6 months after commencing therapy or after 6 months of amenorrhoea depending on the HRT regimen.

Significance

- Endometrial cancer is present in about 10% of those presenting with PMB (5.7%-11.5%.
- Referral needs to take account of other risk factors present.
  - Obesity
  - Previous history PCOS
  - Tamoxifen
  - Genetic predisposition to cancer.

Age Group (years)	Rates per 100,000 pa
<50	0.4
50-59	6.36
60-69	8.68
70-79	8.22
80+	7.28

PMB

- Consultations highest in 50-59 age group at 14.3/1000.
- When should referral take place?
- Don’t forget cervical cancer.

History

- Pattern of bleeding, is it abnormal?
- Other related symptoms and risk factors.
  - Duration and heaviness
  - Prior amenorrhoea
  - Compliance with HRT
  - Presence GI disease e.g. Crohns
  - Patient on drugs e.g. warfarin.

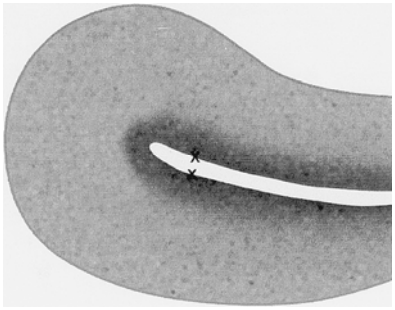
Examination

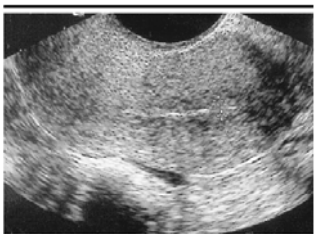
- Pelvic Examination
  - Speculum
    - Cervical cancer
    - Cervical polyps
  - Digital examination
    - Uterine size and mobility

Ultrasound

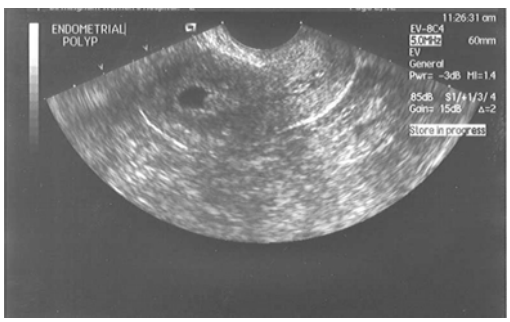
Transvaginal Ultrasound

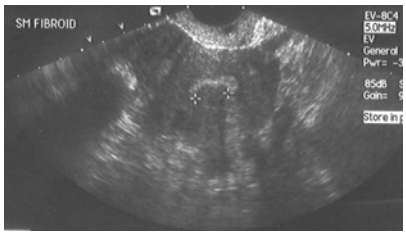
- Endometrial Thickness
  - The thicker the endometrium the greater the risk of pathology.
  - Double thickness of both endometrial surfaces.
  - Need to balance sensitivity and specificity i.e. the thinner the cut off, the less cases will be missed
- Pathology e.g. fibroids, polyps

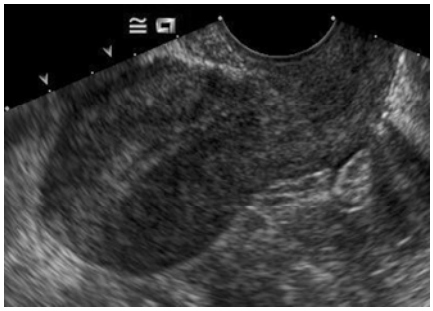




Bredella et al Radiology 1999







McHugo and Olliff Imaging 2006

Endometrial Thickness

- 5 mm of less reduces the risk by 84% (CI 54-94%).

TVUS

- 3 mm cut off
  - Never used HRT
  - Have not used HRT for over 1 year.
  - Using continuous combined
- 5 mm cut off
  - Current use of sequential HRT
  - Use of HRT in previous year

(SIGN Guideline)

Endometrial Biopsy

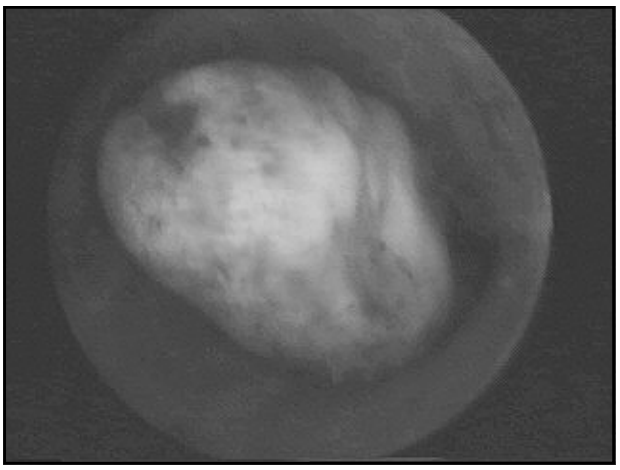
- Pipelle sampler
  - Procedure Failure rate of 10%
  - (importance depends on endometrial thickness)
  - Some cancers will be missed

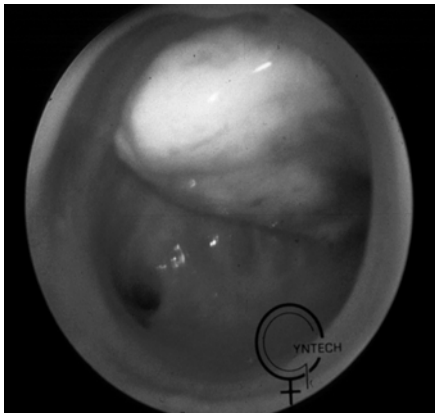
Endometrial Hyperplasia

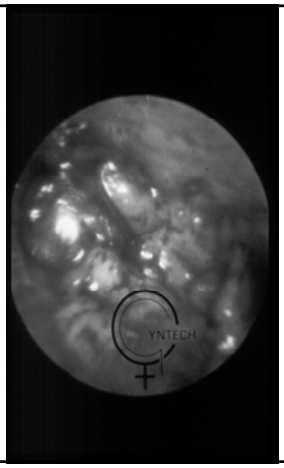
Reference	Simple	Complex	Atypical
Wentz et al 1974		26.7	88.9
Sherman 1978		19.8	57.1
Kurman et al 1985	1.1	3.4	29
Norris et al 1986		2	52

Saline Infusion Sonography

Hysteroscopy







Evaluation of the Uterine Cavity

- Critchley et al Evaluation of abnormal uterine bleeding. Health Technology Assessment 8. 2004
- Studied pre and postmenopausal women
- 200 post menopausal women and 326 moderate risk women
  - Perimenopausal over 45
  - Under 40 with risk factors
- USS, hysteroscopy and biopsy.

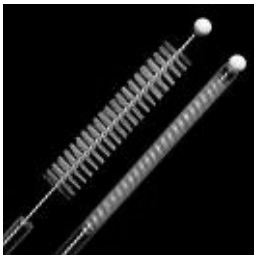
Demographic Details

Number of women	200
Mean age (SE)	57.6 (0.57)
Nulliparous %	13
Currently using HRT	30
Presenting complaint	
PMB	95
PCB	2
IMB	2
Irregular periods	5
Heavy periods	1
Other	2

HTA Study

- Randomised to:
  - Sampling by Tao Brush and Pipelle sampler
    - Randomised as to which done first
  - 'Visualisation' Procedure (postmenopausal women)
    - Ultrasound and biopsy (U + B)
    - Hysteroscopy and biopsy (H + B)
    - (perimenopausal had 1 of 4, U +B, H + B, H + B + U, B only)

Tao Brush



Sample details

- Tao Brush out-performed Pipelle in postmenopausal women.
- Higher adequacy rates when biopsy taken at hysteroscopy compared with blind biopsy (83 vs 61% for Tao Brush and 50 vs 36% for Pipelle) ie Brush 35% better.
- No difference according to which procedure carried out first.

Hyperplasia and Cancer

- 8 cancers, 5 in post menopausal women
- 3 atypical hyperplasias with 1 in postmenopausal group
- Simple hyperplasia in 1 postmenopausal women

Diagnosis

- 5 cancers identified by both methods.
  - 1 Pipelle and not TB (confirmed)
  - 2 by TB alone (1 atypical hyperplasia in a polyp and 1 unusual features)
- All hyperplasias detected by TB and 2 by Pipelle (1 not confirmed)

Patient Acceptability

- Preferred biopsy at time of hysteroscopy
- No adverse events with samplers
- More women prefered Tao Brush

Adverse Events

- None with ultrasound
- 16% with hysteroscopy
- 10% of women with Hysteroscopy and Biopsy
- 87% reassured by clinic visit
- Some women having biopsy alone would have preferred more investigations

Procedure Failure

- Pipelle Biopsy 15%
- Hysteroscopy 11%
- Pipelle provided adequate sample in 43% of postmenopausal women
- Tao Brush gave adequate sample in 72%
- Better samples when taken at hysteroscopy

Visualisation

- More successful visualisations for USS than Hysteroscopy in younger women but not in postmenopausal.
- USS better at detecting fibroids (32 vs 13%).
- Hysteroscopy better for polyps (13 vs 4%)

Cost-effectiveness

- Little difference
- Hysteroscopy>ultrasound (£88/woman)
- Ultrasound more acceptable to women
- Hysteroscopy not worse than biopsy

Bleeding on HRT

Bleeding on HRT

- 40-50% HRT users experience unscheduled bleeding
- Occurs with all types of HRT (30% cyclic HRT users and 50% on continuous combined visit a gynaecologist/GP with this problem. Affects 50% tibolone users)
- Commonest in early months of use
- Although numbers of HRT users has declined this is still a major problem.
- Tibolone has a better bleeding profile in first 9 months than cc HRT

Bleeding on HRT

- Poor compliance
- Poor absorption
- Drug interactions
- Coagulation defects
- Gynaecological disorders

HRT

- Unopposed oestrogen
- Sequential regimens
- Continuous combined

Endometrial Cancer and HRT

Type of HRT	Relative Risk (95% CI)
Unopposed oestrogen <1 year	1.4(1.0-1.8)
1-4 years	2.8(2.3-3.5)
5-9 years	5.9(4.7-7.5)
10+ years	9.5(7.4-12.3)
Sequential: ever versus never	1.3(1.1-5.5)
> 5 years	2.5(1.1-5.5)
CCT	0.8(0.5-1.4)

Unopposed Oestrogen

- Increases hyperplasia and malignancy
- Cancer risk related to dose and duration
- Increases cancer risk 15 fold and risk persists for 10 years after stopping treatment.

Combined HRT

- Risk cancer with continuous combined and tibolone is very low.
- Risk with intra-uterine progestagen is virtually non-existent
- Risk rises with sequential regimens after 5 years of use.
- Risk increases after 2 years with long-cycle regimens
- Uncertain if progestagen is needed with very low dose oestrogen

The Scottish Intercollegiate Guidelines Network (SIGN) recommend that 'the risk of endometrial cancer……in HRT users experiencing abnormal bleeding is sufficient to recommend referring all patients for investigation'

Hysteroscopy and Biopsy

- Gold standard for the investigation of PMB on HRT.
  - 18% polyps
  - 9% sub-mucous fibroids
  - <5% simple hyperplasia
  - <2% atypical hyperplasia/ endometrial cancer

SIGN recommendations

- Biopsy if bleed occurs before Day 6 of progestagen therapy
- New bleeding after amenorrhoea
- Heavy bleeding on continuous combined

but no clear data

TVUS

- For a cut-off of 5mm.
  - 99% negative predictive validity
  - 90% sensitivity
  - 48% specificity
  - Positive predictive value of 9% for predicting malignancy
  - Langer et al

Management

- Remove polyps
- Role fibroids uncertain
- Possibly less with low dose regimens
- No good evidence for changing dose of oestrogen or progestagen

Conclusions - Investigation

- Threshold for intervention low
- Hysteroscopy gold standard
- USS useful for evaluating need for hysteroscopy and can be used to screen out ultra low risk.
- Think about the Tao Brush

Conclusions - Management

- Repeat investigations if bleeding continues for further 1 year
- Usually no treatment required for those not on HRT
- For those on HRT:
  - Stop treatment
  - Change regimen
  - Increase progestagen component