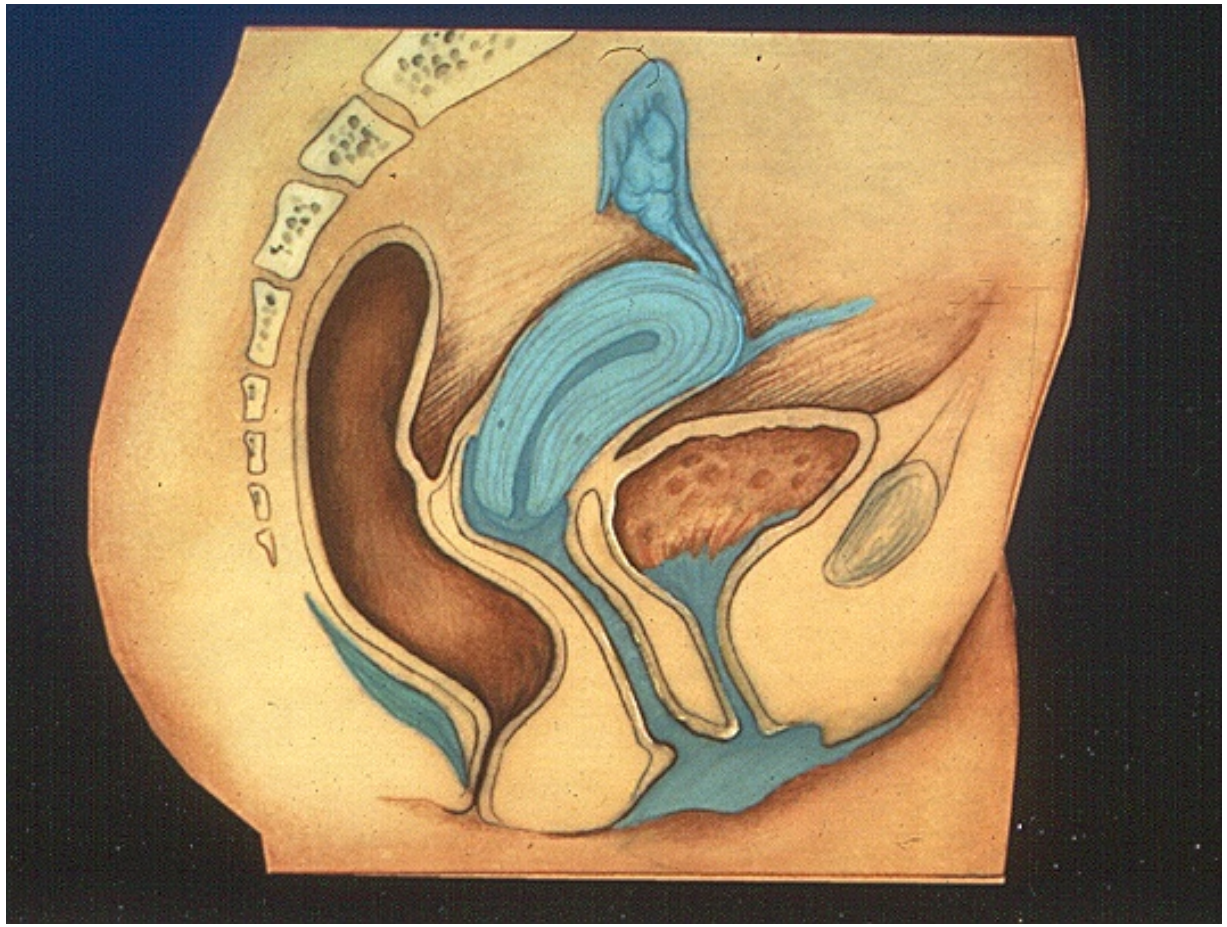
What I want to talk about

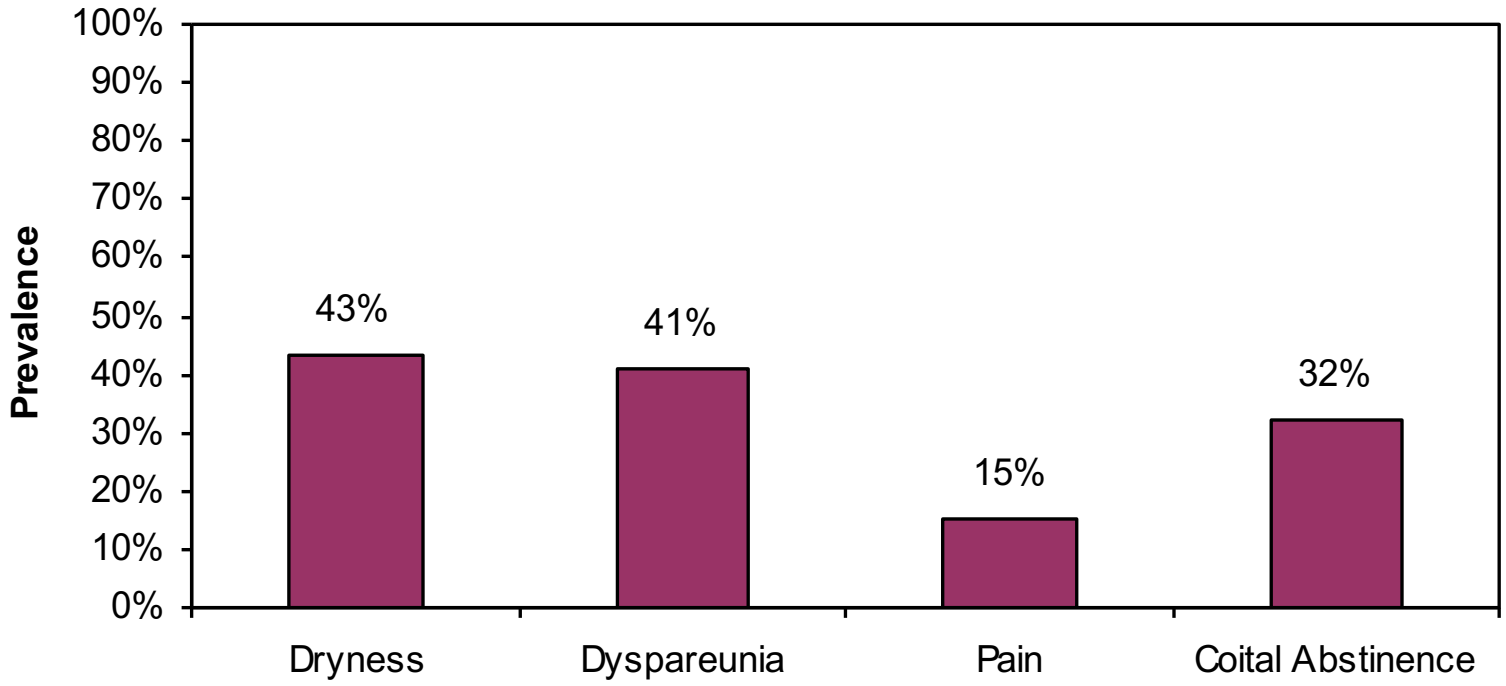
- Limited database
- Endocrine changes
- Neurological changes
- Bone and joint changes
- Urogenital changes

Estrogen-sensitive pelvic tissues



Vaginal Symptoms

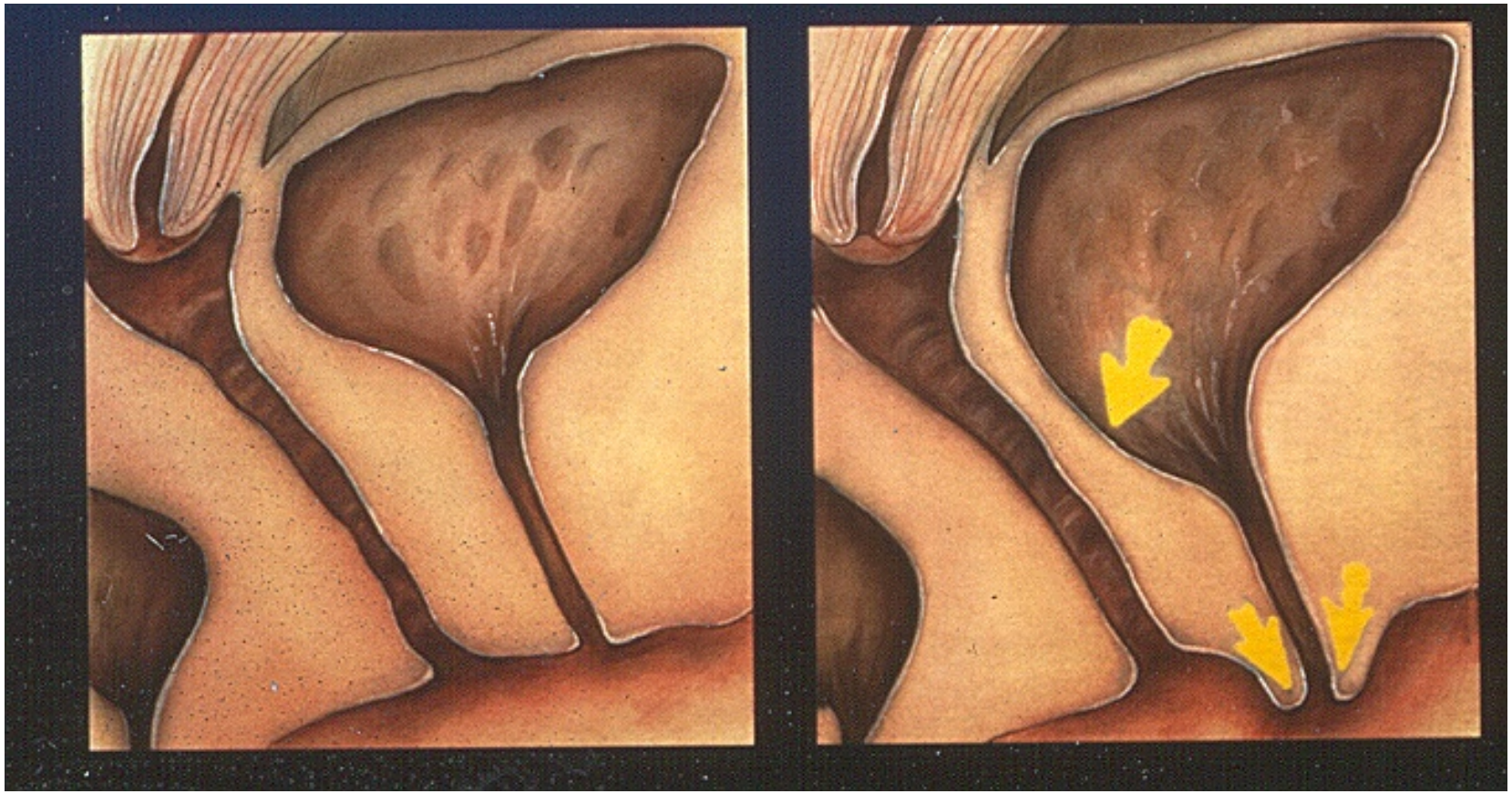
1280 women aged 61 and living in Uppsala



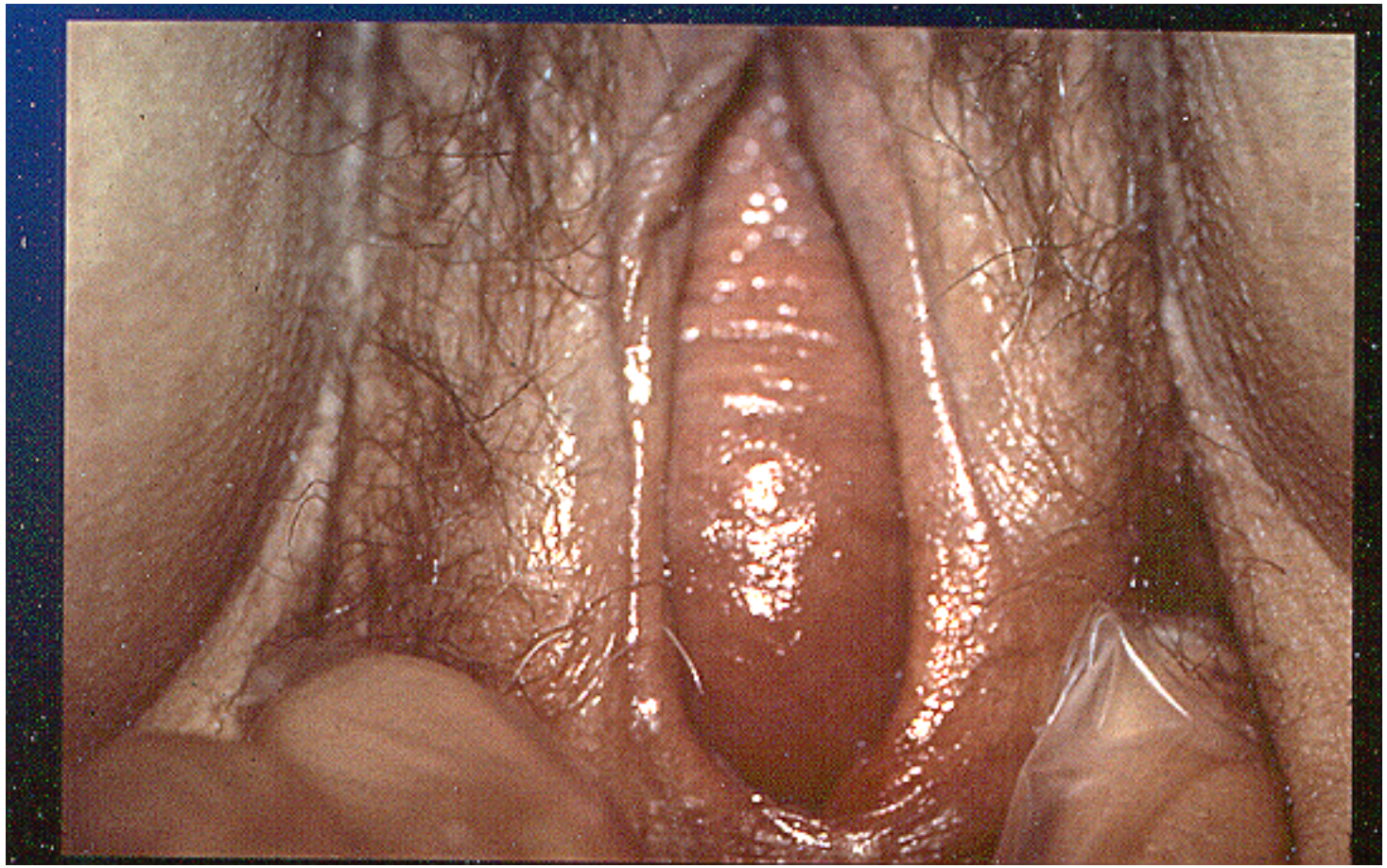
59% sexually active, 34% on estrogen therapy

Stenberg A, et al. *Maturitas* 1996;24:31-6

Anatomical changes associated with urogenital aging



Cystocele



Urinary symptoms

1280 women aged 61 and living in Uppsala

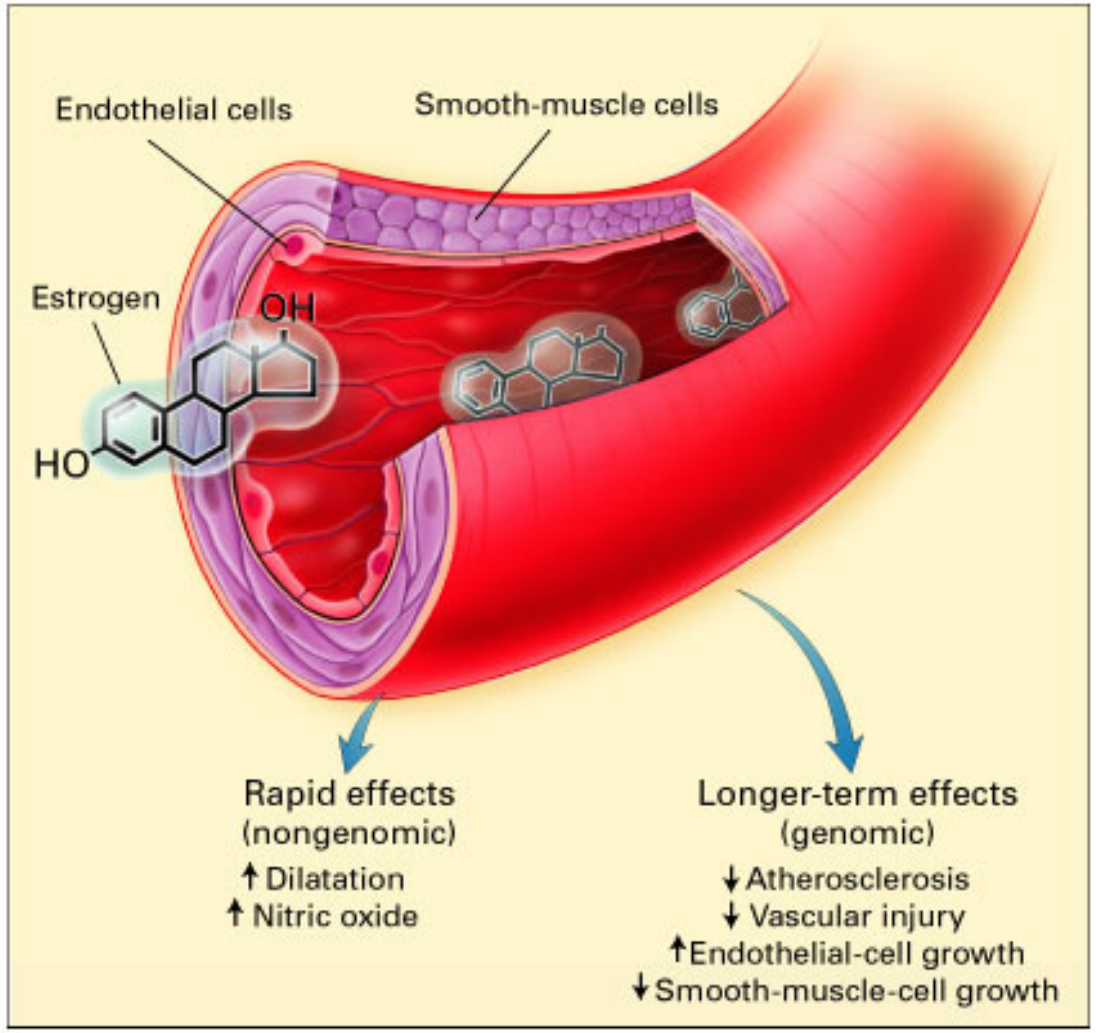
- 73% had some degree of urinary incontinence (33% more severe)
- 49% had some degree of stress incontinence (25% more severe)
- 67% had changed voiding habits
- 8% had urinary frequency
- 4% had had >2 UTIs in the past year

Stenberg A, et al. *Maturitas* 1996;24:31-6

What I want to talk about

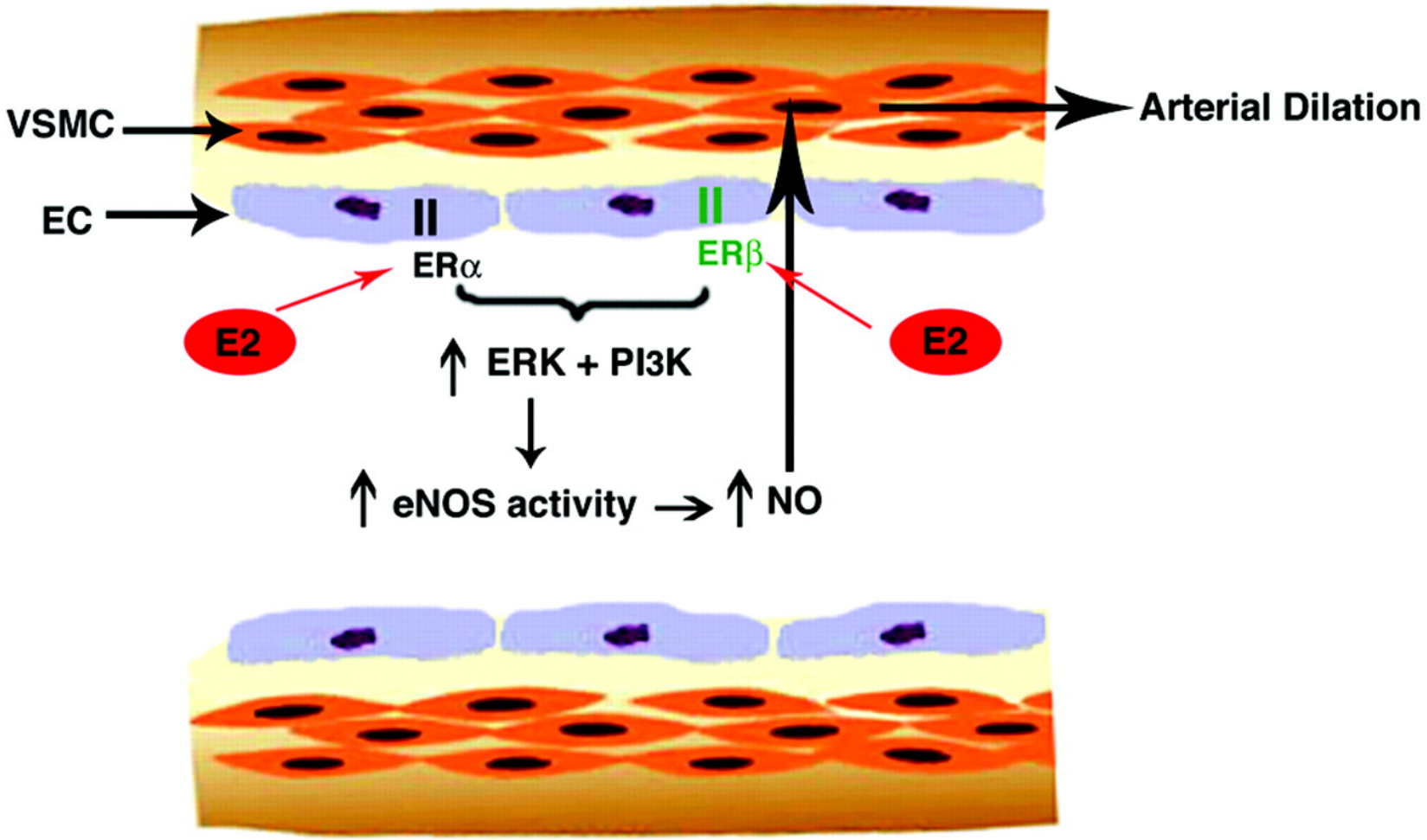
- Limited database
- Endocrine changes
- Neurological changes
- Bone and joint changes
- Urogenital changes
- Cardiovascular changes

Estrogen's arterial effects



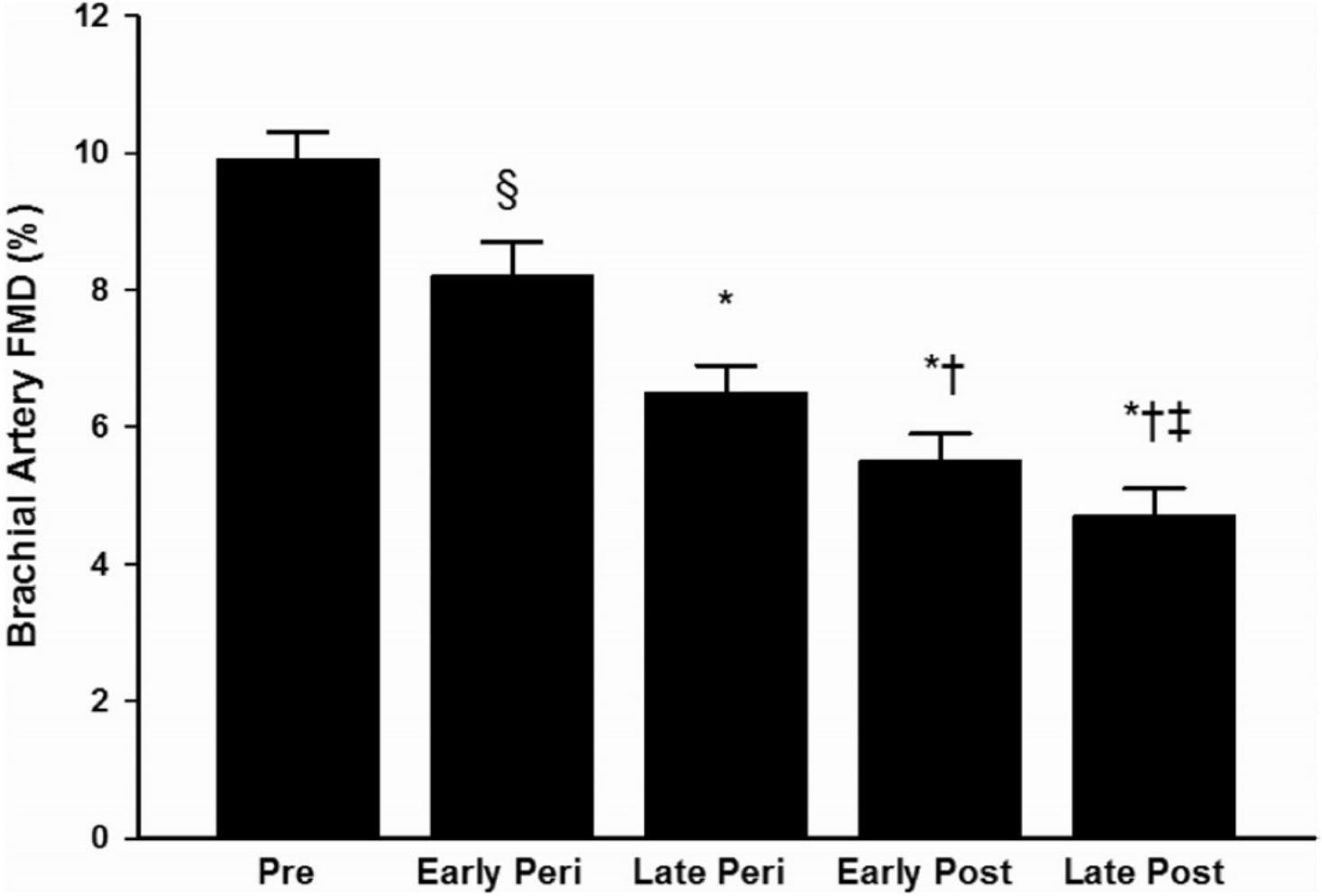
Mendelsohn & Karas. *N Engl J Med* 1999;340:1801-11

Estradiol vasodilator effects in arteries



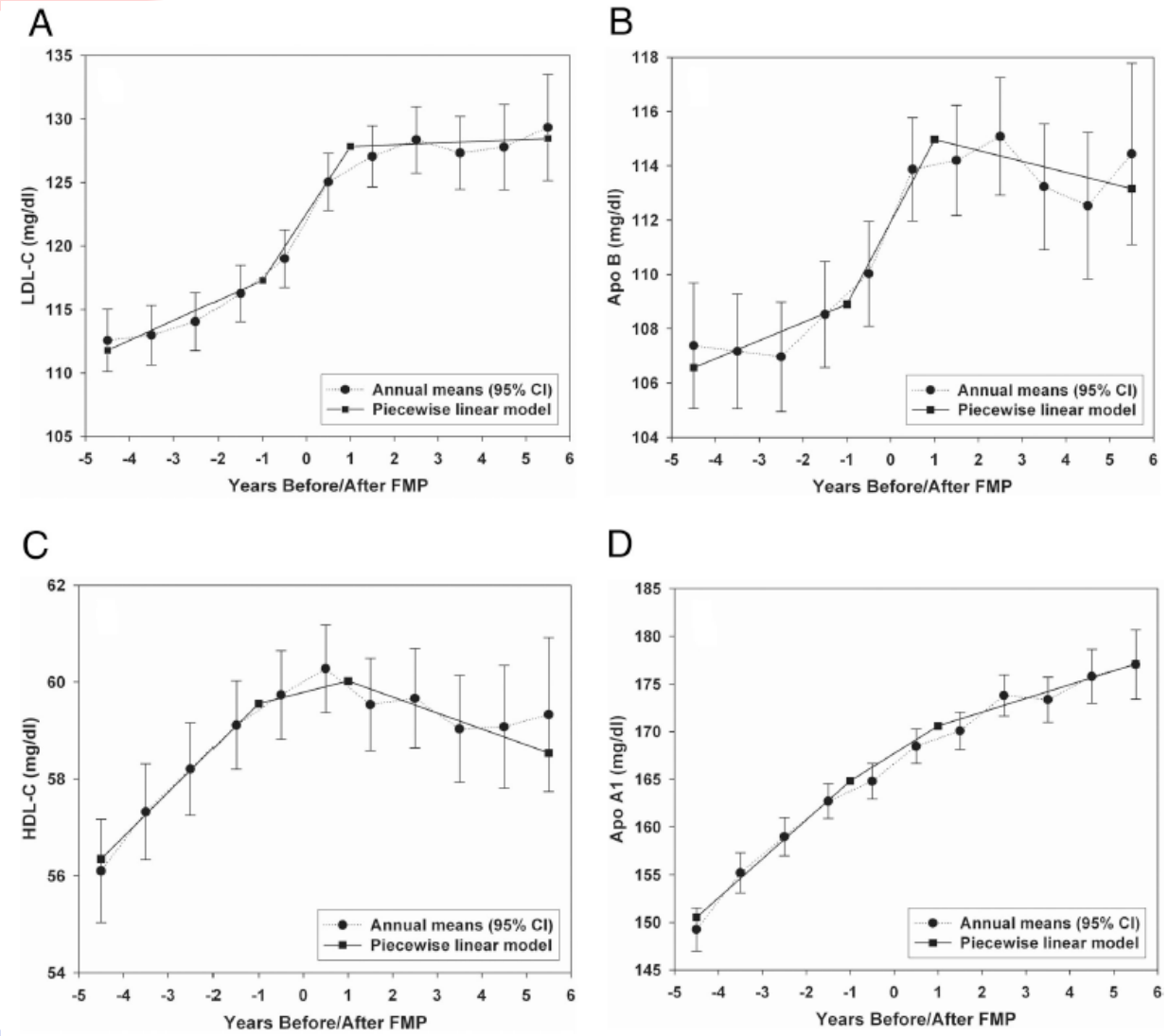
Xiaomei Guo et al. *J Biol Chem* 2005;280:19704-10

Vascular endothelial-dependent vasodilatation across the menopausal transition



Moreau KL et al. *J Clin Endocrinol Metab* 2012;97:4692-4700

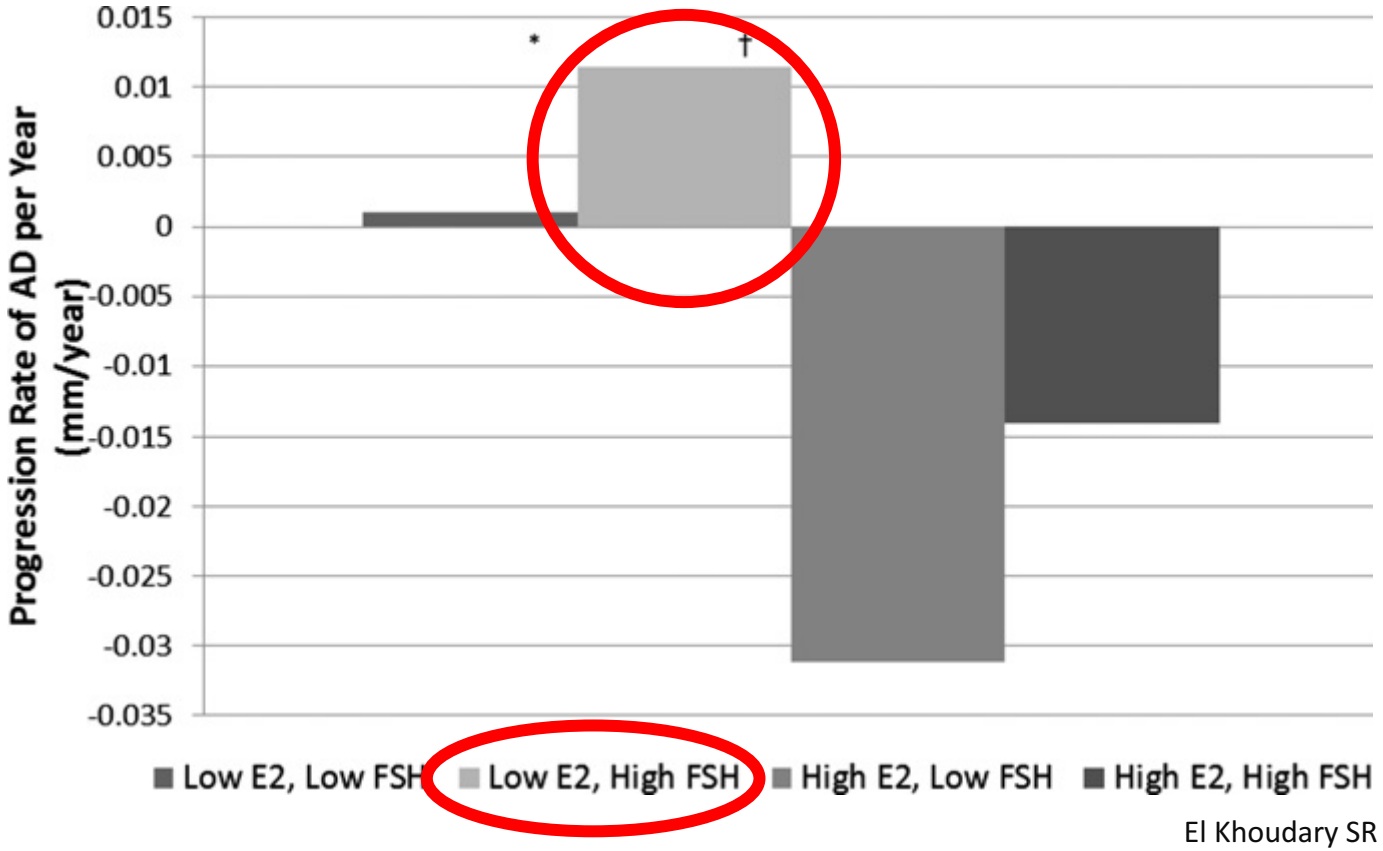
Changes in mean lipid levels over menopausal transition (SWAN)



1054 women
sampled annually for
a mean of 9 years

Matthews KA et al *J Am Coll Cardiol* 2009;54:2366-73

Change in atherosclerosis by levels of E_2 and FSH during menopausal transition (SWAN)



El Khoudary SR et al. *Atherosclerosis* 2012;225:180-6

Changes and potential for modification

Endocrine effects

- Estradiol levels decline with four distinct trajectories and ethnic variations identified
- FSH levels rise
- Inhibin B levels decline
- AMH levels decline
- Testosterone levels show broader scatter
- DHEA-S levels rise during perimenopause and early postmenopause, then return to baseline

Changes and potential for modification

Neurological effects

- Cognitive function declines, with declines in cognitive speed and verbal memory
- Estrogenic regulation of neuronal glucose metabolism and estrogenic neuroprotection both decline
- Mood change (chiefly depression) prevalent in perimenopause
- Sleep disturbance and vasomotor symptoms

Changes and potential for modification

Bone and joint effects

- Increased osteoclast activation, leading to increased bone resorption and accelerated fracture rates
- Increased chondrocyte inflammation, impaired subchondral bone remodelling, leading to increased rates of osteoarthritis

Urogenital effects

- Mucosal atrophy in vagina, bladder trigone, and urethra, leading to vaginal irritation, dyspareunia, urinary symptoms and altered voiding habits

Changes and potential for modification

Cardiovascular effects

- Progressive reduction in vascular endothelial-dependent vasodilatation over menopausal transition
- Menopause-associated rises in mean levels of LDL-cholesterol, Apo A1, and Apo B, and fall in mean HDL-cholesterol
- Increase in atherosclerosis in hypoestrogenic women

Menopausal physiology

Case Presentation

Diagnosis and Management of the Perimenopause

IMS Precongress Workshop

Vancouver BC

June 5, 2018

Wendy Wolfman MD FRCS(C)FACOG

Professor of Ob/Gyn University of Toronto

Director of Menopause Unit Mt. Sinai Hospital

What is Happening to Me?

Ms Miserable
47 yr old G1 P1 healthy sexually active lawyer

Symptoms

- Menses every 23 days-3 mo. Lasting up to 14 days
- Sore breasts before erratic menses
- Worsening of migraines before menses
- New onset hot flashes
- Difficulty coping and working
- New difficulty sleeping
- Decreased sexual interest

Diagnosis of Perimenopause or transition-symptoms

- clinical diagnosis
- subtle changes in menses--first symptoms
- Suspect in anyone with menstrual irregularity (7 days) and other symptoms typically over 40-
- Late perimenopause > 2 missed cycles or > 60 days of amenorrhoea-
- Average age 47.5 yrs, Mean length 5 years ,may start 8 years before
- Menopause defined retrospectively after 12 mo amenorrhoea
- **Includes most symptomatic years**
- Earlier onset associated with longer transition

Perimenopause Review -Annals of Int Medicine 2015

STRAW+10

	Menarche					FMP (0)				
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

Harlow SD *Menopause* 2012;19:387-95

Diagnosis-Evaluations

- Not a disease
- Ovarian reserve decreased
  - Day 3 FSH > 10-15 mIU/ml borderline
  - Decreased antral follicle count in follicular phase-fewer than 2-10 AF cycle day 2-4
  - AMH declines < .5 ng/ml
- FSH > 25IU/L consistently and LH increase
- **LAB tests not necessary for diagnosis**

Annals of Internal Medicine 2015
NAMS Clinician's guide 5 th edition

Symptoms and signs of high estrogen levels

- Annovulatory cycles-Light and infrequent bleeding or Long cycle length with heavy prolonged bleeding
- “worsening PMS”
  - Sore breasts
  - Mood changes
  - Headaches
- Growth of fibroids
- Increased risk of endometrial hyperplasia

Symptoms of the Perimenopause-low estrogen stage

- **Menstrual Irregularity**
- Decreased fertility
- **Vaginal changes and urinary symptoms**
- Joint aches
- Migraines

- **Weight gain**
- **Sleep problems**
- **Vasomotor Symptoms**
- **Mood changes, difficulty concentrating, irritability, depression**
- **Decreased sexual interest**

All may affect quality of life

Treatments-General Principles

- Patients may have many symptoms that fluctuate
- **No treatment unless symptoms present**
- In general address bleeding issues first
- Rule out underlying significant diseases especially pregnancy or endometrial cancer or other malignancy
- Address each symptom individually
- If no contraindication see if one medication can treat most of symptoms

1. Abnormal Uterine Bleeding

- > 90% have 4-8 yrs of unpredictable cycle change before FMP
  - 32% lighter, 29% heavier, 24% shorter and 20% longer
- Evaluate if too frequent (timing)< 20 days, too heavy(volume) > 80ml or continuous> 7-8 days (regularity)
- Skipping patterns frequent
- 10% stop suddenly
- Pattern of infrequent and lighter usually not concerning

ACOG Practice Bulletin 2012 Ob Gyn 2012
Mitchell Menopause 2000

What is normal?

TABLE 7

Suggested "normal" limits for menstrual parameters in the midreproductive years.

Clinical dimensions of menstruation and menstrual cycle	Descriptive terms	Normal limits (5^{th} to 95^{th} percentiles)
Frequency of menses (d)	Frequent	<24
	Normal	24–38
	Infrequent	>38
Regularity of menses, cycle-to-cycle variation over 12 mo (d)	Absent	—
	Regular	Variation ± 2–20 days
	Irregular	Variation >20 days
Duration of flow (d)	Prolonged	>8.0
	Normal	4.5–8.0
	Shortened	<4.5
Volume of monthly blood loss (mL)	Heavy	>80
	Normal	5–80
	Light	<5

Note: Limits are based primarily on the data of Treloar et al. (7), Hallberg et al. (11), Snowden and Christian (21), and Belsey and Pinol (26).

Fraser. International definitions of abnormal menstrual bleeding. Fertil Steril 2007.

Evaluation

- Good history
- Orderly Physical examination-careful exam external genitalia, urethra, rectum, vagina, cervix bimanual
- Pap, cervical cultures if indicated
- EB usually indicated in this age group
- βHCG, CBC, TSH, possibly prolactin
- TVUS
- HSG
- MRI

AUB: Uniform Classification of Etiologies

Polyp
Adenomyosis
Leiomyoma
Malignancy & Hyperplasia

Structural Abnormality

Coagulopathy
Ovulatory Dysfunction
Endometrial
Iatrogenic
Not Yet Classified

No Structural Abnormality

Treatments of AUB

- 1. Acuity of presentation
- 2. Cause of AUB
- 3. Patient's wishes for fertility
- 4. Shared decision making
- **5. In general medical methods first-** goal is to temporize if possible until menopause -tranexamic acid, antiprostaglandins, OCP's, progestins, iron therapy
- 6. Progestin IUD
- 6.Hysteroscopy +- polypectomy or Endometrial ablation
- 7. Surgical-myomectomy, hysterectomy

2. Vasomotor Symptoms

- Sensation of heat starting in torso and rising up neck and head lasting 1-7 min or up to 60 min up to to 50/day
- Occur in 60-80% in late perimenopause and early postmenopause
- Occur in 16% women 10 yrs prior to FMP ,32% yr before FMP
- 10-15% severe-probably genetically determined
- Categories of Hot Flashes
  - 1.Early onset with decline after menopause
  - 2. Onset near LMP with later decline
  - 3.early onset with persistent high frequency
  - 4. persistently low frequency

Tepper PG Menopause 2016
Woods N NAMS 2017
Thurston Menopause 2017
Freeman Menopause 2008

Differential Diagnosis

- **Hormone Excess**
  - Thyroid excess
  - Carcinoid
  - Pheochromocytoma
- **Anxiety disorders**
- **Pharmaceuticals**
  - Chronic opioids
  - Opiate withdrawal
  - SSRI's
  - Nicotinic acid
  - Calcium channel blockers
  - Estrogen blockers of action and synthesis
- **Dietary factors**
  - Alcohol
  - Spicy Food
  - Food additives
- **Chronic infection**
- **Others**
  - Postgastric surgery dumping syndrome
  - Mastocytosis and mast cell disorders
  - Some CA's-medullary thyroid ; pancreatic islet-cell; renal cell, lymphoma

C Stuenkel et al J Clin Endocrinol Metab Nov 2015

Start with General Measures for Hot Flashes- for mild ones only

- Cold showers, fans, Lower room temp < 64°
- Dress in layers, Cotton and moisture wicking clothing
- Avoid alcohol and spicy foods
- Exercise and Weight control
- Red clover, isoflavones??
- Acupuncture , yoga
- Hypnosis
- CBT

Simon JA Menopause 2013 Elkin GR Menopause 2013
Elkin GR J Clin Oncol 2008
Lesi G J Clin Oncol 2015
Hardy C Menopause 2018

Non-hormonal prescription treatments for VMS

- SSRI's-range 37-60% efficacy
  - venlafaxine 37.5-75mg and desvenlafaxine 50 mg
  - paroxetine 7.5- 12.5mg-salt approved in US for VMS
  - Escitalopram 10-20 mg
  - sertraline, citalopram and fluoxetine mixed results
- Clonidine-40% effective - .025 po bid-.1 mg
- Gabapentin 300 mg tid- up to 2400mg /day
  - -try up to 900 mg qhs for nighttime flashes
  - Pregablin also efficacious (75-150 mg bid)

Freeman JAMA 2011
Loprinzi J Clin Oncol 2009
Joffe Am J Obst Gynecol 2010
Pandya Lancet 2005

Practical tips for Hormones and Treating Symptomatic Women with menses

1. Try low dose BCP for symptoms if no risks < 51
2. Try LNG-IUS 52mg-especially if menses are heavy (after biopsy) and add E2
3. Can use estrogen alone if patient has regular menses
4. Use sequential HRT regimen if skipping menses

   -Patients on sequential can have withdrawal bleeds after P

   Late in transition can use continuous combined-expect some bleeding

Sleep Problems

- 12,603 aged 40-55-38% difficulty sleeping
- Highest in late perimenopause (45%) and surgical (48%)
- Risk factors –stress, poor health, nocturia, depression, hot flashes, cognitive change, obesity
- Diagnosis- history and sleep study-rule out sleep disorder
- Treatment- sleep hygiene, CBT, and HT, exercise, antidepressants, hypnotics

Kravitz HM Menopause 2003
Freedman RR Menopause 2011
De Zambotti M Menopause 2013
Gao C Menopause2018

Mood in perimenopause

- Symptoms- Depressed mood, anxiety ,panic attacks, stress ,decreased sense of well-being, loss of control, sadness, irritability, tearfulness, fatigue, anhedonia, wt loss, insomnia, hypersomnia, increased guilt, diminished ability to think, recurrent thoughts of death > 2 wks
- OR 1.8-2.9 -Present in up to 23 %- even in previously not depressed
- Risk factor-previous history of depression, PMS or postpartum depression, oophorectomy ,longer perimenopause or severe symptoms
- Diagnosis: Beck Depression Inventory –see if criteria of DSM V are met

Schmidt P Menopause 2006 Cohen LS Arch Gen Psych 2006 Hickey M Menopause 2016
Freeman EW Menopause 2010 Marsh WK Menopause 2017 Bromberger JT J Affect Disord 2016

Treatment of Mood

- Clinical depression-psychotherapy and antidepressants
- Antidepressants-SSRI's and SNRI's highly effective including fluoxetine, sertraline, venlafaxine, desvenlafaxine, citalopram ,escitalopram, duloxetine, and mirtazapine
- Treat menopausal symptoms and sleep problems
- Hormonal therapy-PRCT trials show that Estrogen enhances mood in perimenopausal women with depression-can use OCP's or estrogen
- Refer if symptoms severe or uncertain diagnosis

Joffe H J Womens Health Gen Based Med 2001 Soares Menopause 2017
Joffe H J Clin Psychiatry 2007 Gleason CE *PLoS Med 2015*
Soares CN J Clin Psychiatry 2003 Soares Arch Gen Psychiatry 2001

Decreased Sexual Desire

- Multifactorial-general health, relationship and partner, pain, previous sexual history, body image, stress, incontinence, medications,pain etc
- -occur in 40% midlife women but 12% distressed
- Independent decrease within 20 mo of FMP
- Independently associated with declines in estrogen and testosterone (gradual decline)
- Diagnosis: validated Watts Sexual Function Questionnaire or Female Sexual Function Index

Shifrin J Obstet & Gynecol 2008
Avis Menopause 2015 Simon Ob & Gyn 2017

Treatment of Sexual Problems

- Take time to take complete history,
- Discuss issue and educate about changes in sexual function
- (PLISSIT model)
- Modify sexual technique and experiment
- Enhance relationship with partner
- Improve health and body image
- Pharmacologic interventions –**treat pain if due to atrophy- moistuizers, lubricants, local estrogen and DHEA, transdermal estrogen**
- Consider flibanserin, testosterone and bupropion

NAMS Guideline 2014
IMS Guideline 2018

Discussion