Case 2: Breast Cancer in the perimenopause

FAIRMONT HOTEL VANCOUVER, CANADA 6–9 JUNE 2018

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Financial Disclosures

Speaker Bureau: Merck, Amgen, AMAG, Pfizer, Bayer

Advisory Board: Merck, Amgen, Pfizer, Mithra, AMAG,GSK

Other: CTV Medical Consultant

“The Three Seasons of Survival”

Acute

Extended

Permanent

Fitzhugh Mullan NEJM 1985

Needs of Breast Cancer Survivors

Late effect	Risk
Recurrence	0-100%
2nd primary	1-2%
Psychological distress	30%
Lymphedema	10-25%
Premature menopause, infertility and osteoporosis	45%
Estrogen deprivation	>50%

Needs of Breast Cancer Survivors

Late effect	Risk
Weight gain	50% 2.5-5Kg 20% 10-20Kg
CVS disease	0.5-1% CHF
Fatigue	30% 1-5 yrs after diagnosis
Cognitive impairment	30%
Familial risk	5-10%

Symptom Management

- ✓ Women with breast cancer have many adverse symptoms, of which some are specific to premenopausal patients
- ✓ Hot flushes: non-hormonal drugs, such as antidepressants and anti-seizure compounds
- ✓ Vaginal dryness and dyspareunia-Non-estrogenic vaginal lubricants
- ✓ Cancer-related fatigue- exercise

Loprinzi, C. L., S. L. Wolf, et al. (2008). "Symptom management in premenopausal patients with breast cancer." Lancet Oncol **9(10): 993-1001**

Meet Joan

- 52, 3 years post ER/PR positive breast cancer
- TAHBSO, Bilateral Mastectomy
- Chemotherapeutic regime
- On arimidex

Concerns

- Hot flashes and night sweats
- What are her options?

Nonprescription Products Have Limited Data to Support Efficacy in Relieving Vasomotor Symptoms

Agent	Study Design	Efficacy	Adverse Events
Soy-derived isoflavones[1]	Systematic review of 25 randomized controlled trials of phytoestrogens (≥4 weeks) involving 2,348 symptomatic women	7 of 8 soy food trials, 3 of 5 soy extract trials, and 3 of 5 red clover trials showed no significant difference from placebo	Most common adverse events were gastrointestinal disorders
Black cohosh[2]	N=80 late perimenopausal or postmenopausal women; 160 mg/day	No significant difference from placebo	Both groups reported gastrointestinal symptoms; nausea and vomiting; fatigue, asthenia, or malaise; and headaches
Evening primrose oil[3]	N=56 menopausal women; 4000 mg/day for 6 months	No significant difference from placebo	Minimal side effects, including slight nausea
Dong quai[4]	N=71 menopausal women; 4.5 g/day for 6 months	No significant difference from placebo	Both treatment groups reported burping, gas, and headaches
Ginkgo biloba[5,6]	N=87 menopausal women; 120 mg/day for 6 weeks[5] N=31 menopausal women; 120 mg/day for 1 week[6]	No significant difference from placebo	None reported
Ginseng[7]	N=384 menopausal women; 100 mg/day for 4 months	No significant difference from placebo	Both treatment groups reported influenza or colds, headaches or migraines, and gastrointestinal disorders
Vitamin E[8] Alpha E, Amino-Opti-E, Aquasol E, Aquavite-E, Centrum® Singles-Vitamin E, E Pherol, E-400 Clear, Nutr-E-Sol	N=120 women with a history of breast cancer; 800 IU/day for 4 weeks in a crossover design	No significant difference from placebo	Both groups reported headaches, fatigue, and nausea

There are limited data comparing the above referenced products to one another or to approved FDA treatments. Therefore, comparative efficacy cannot be determined based on the above.

1. Krebs EE, et al. *Obstet Gynecol.* 2004;104:824-836.
2. Newton KM, et al. *Ann Intern Med*. 2006;145:869-879.
3. Chenoy R, et al. *BMJ.* 1994;308:501-503.
4. Hirata JD, et al. *Fertil Steril.* 1997;68:981-986.
5. Elsabagh S, et al. *J Psychopharmacol.* 2005;19:173-181.
6. Hartley DE, et al. *Pharmacol Biochem Behav.* 2003;75:711-720.
7. Wiklund IK, et al. *Int J Clin Pharmacol Res.* 1999;19:89-99.
8. Barton DL, et al. *J Clin Oncol.* 1998;16:495-500.

Recommend: NonRx

Two mind-body therapies have level I evidence showing positive effects

- Cognitive behavioral therapy (CBT) protocols (MENOS 1 and MENOS 2)
- Clinical hypnosis: Elkins protocol

North American Menopause Society. *Menopause*. 2015;22(11).

Recommend: Prescription Therapies

- FDA-approved low-dose paroxetine salt
- Other SSRIs and SNRIs yielding significant VMS reductions in large RCTs
- Gabapentin and pregabalin

North American Menopause Society. *Menopause*. 2015;22(11).

Other SSRIs, SNRIs

- Large RCTs show significant VMS reductions with
  - Paroxetine
  - Escitalopram
  - Citalopram
  - Venlafaxine
  - Desvenlafaxine

North American Menopause Society. *Menopause*. 2015;22(11).

Prescription Therapies: Choice

Depends on

- Prior effective therapy
- Patient history
- Adverse events profile and tolerance of adverse effects
- Co-administered medications

North American Menopause Society. *Menopause*. 2015;22(11).

Concerns

- Vaginal dryness

Concerns

- Vaginal dryness options…….
- Moisturizers and Lubricants
- Vaginal estrogen
- Vaginal DHEAS
- Laser therapy

Concerns

- Sexual issues

Menopause: The Journal of The North American Menopause Society
Vol. 25, No. 6, pp. 1-13
DOI: 10.1097/GME.0000000000001121

Consensus Recommendations

Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health

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Abstract

The objective of The North American Menopause Society (NAMS) and The International Society for the Study of Women's Sexual Health (ISSWSH) Expert Consensus Panel was to create a point of care algorithm for treating genitourinary syndrome of menopause (GSM) in women with or at high risk for breast cancer. The consensus recommendations will assist healthcare providers in managing GSM with a goal of improving the care and quality of life for these women. The Expert Consensus Panel is comprised of a diverse group of 16 multidisciplinary experts well respected in their fields. The panelists individually conducted an evidence-based review of the literature in their respective areas of expertise. They then met to discuss the latest treatment options for genitourinary syndrome of menopause (GSM) in survivors of breast cancer and review management strategies for GSM in women with or at high risk for breast cancer, using a modified Delphi method. This iterative process involved presentations summarizing the current literature, debate, and discussion of divergent opinions concerning GSM assessment and management, leading to the development of consensus recommendations for the clinician.

Genitourinary syndrome of menopause is more prevalent in survivors of breast cancer, is commonly undiagnosed and untreated, and may have early onset because of cancer treatments or risk-reducing strategies. The paucity of evidence regarding the safety of vaginal hormone therapies in women with or at high risk for breast cancer has resulted in avoidance of treatment, potentially adversely affecting quality of life and intimate relationships. Factors influencing decision-making regarding treatment for GSM include breast cancer recurrence risk, severity of symptoms, response to prior therapies, and personal preference.

We review current evidence for various pharmacologic and nonpharmacologic therapeutic modalities in women with a history of or at high risk for breast cancer and highlight the substantial gaps in the evidence for safe and effective therapies and the need for future research. Treatment of GSM is individualized, with nonhormone treatments generally being first line in this population. The use of local hormone therapies may be an option for some women who fail nonpharmacologic and nonhormone treatments after a discussion of risks and benefits and review with a woman's oncologist. We provide consensus recommendations for an approach to the management of GSM in specific patient populations, including women at high risk for breast cancer, women with estrogen-receptor positive breast cancers, women with triple-negative breast cancers, and women with metastatic disease.

Key Words: Atrophic vaginitis – Breast cancer – Breast cancer risk – Breast cancer survivors – Genitourinary syndrome of menopause – Vulvovaginal atrophy.

Received March 21, 2018; revised and accepted March 22, 2018.

Concerns

- Experiences a degree of distress and depression

Breast Cancer and Depression: Tamoxifen and Antidepressants via Cytochrome P450 2D6

- ✓ Women taking tamoxifen for the treatment or prevention of recurrence of breast cancer are likely to take antidepressants either for a psychiatric disorder or for hot flashes

- ✓ Some antidepressants inhibit the metabolism of tamoxifen to its more active metabolites by the cytochrome P450 2D6 (CYP2D6) enzyme, thereby decreasing the anticancer effect

Desmarais, J. E. and K. J. Looper (2009). "Interactions between tamoxifen and antidepressants via cytochrome P450 2D6." J Clin Psychiatry **70(12): 1688-1697**

Interactions between tamoxifen and antidepressants via cytochrome P450 2D6

	2D6 interaction	
Fluoxetine	+++	Strong :to be avoided
Paroxetine	+++	Strong :to be avoided
Citalopram	+	Mild
Escitalopram	+	Mild: studies lacking
Bupropion	+++	Strong : to be avoided
Sertraline	++	Moderate
Fluvoxamine	++	Moderate 2D6 and 3A4: studies lacking
Venlafaxine	-/+	Minimal
Desvenlafaxine	-	Minimal: studies lacking
Mirtazapine	+	Minimal: studies lacking

Desmarais, J. E. and K. J. Looper (2010). "Managing menopausal symptoms and depression in tamoxifen users: implications of drug and medicinal interactions." Maturitas **67(4): 296-308**

Desmarais, J. E. and K. J. Looper (2009). "Interactions between tamoxifen and antidepressants via cytochrome P450 2D6." J Clin Psychiatry **70(12): 1688-1697**

Concerns

- What about bone loss?
- Is depression an additional risk factor for her bones?

Depression as a Risk Factor for Osteoporosis

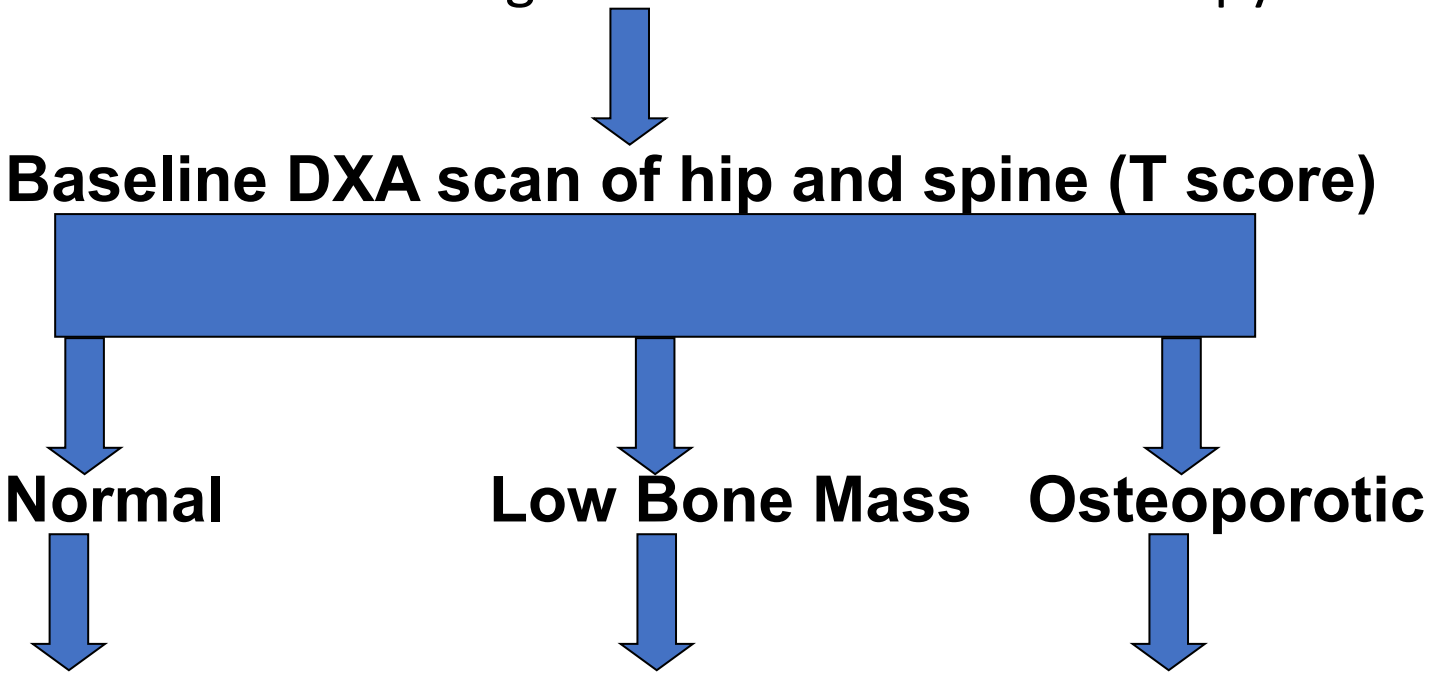
- ✓ Association between depression and low bone mineral density

- ✓ Depression may induce bone loss and osteoporotic fractures
  - ✓ Via specific immune and endocrine mechanisms
  - ✓ Potential effect of specific antidepressants
  - ✓ Possible role of poor lifestyle

Cizza, G., S. Primma, et al. (2009). "Depression as a risk factor for osteoporosis." Trends Endocrinol Metab **20(8): 367-373**

Management of MSK health

Women starting aromatase inhibitor therapy



Concerns

- She is worried about her heart health

Concerns

- She is worried about getting cancer again

Evidence Based Interventions

Late effect	Interventions
Recurrence and 2nd primary	Mammo/hx/px[22]
Psychological distress	Psychosocial interventions[4]
Lymphedema	MLD, compression, complex decongestive therapy[4]
Premature menopause [7]	Assessment of sexual reproductive technologies [4] Bone health programs
Estrogen deprivation	Diet/exercise and drugs promising

Evidence Based Interventions

Late effect	Interventions
Weight Gain	Diet /exercise
CVS disease	Prevention strategies, cardiac work up
Fatigue	Exercise promising
Cognitive impairment	No evidence
Familial risk	Genetic counseling [1]

Discussion

Perimenopause—Challenges and Solutions
Case 3: CVD and Diabetes during Perimenopause

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Nothing to Declare

I have no financial relationships to disclose.

THE LANCET

Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants

*NCD Risk Factor Collaboration (NCD-RisC)**

Summary

Background One of the global targets for non-communicable diseases is to halt, by 2025, the rise in the age-standardised adult prevalence of diabetes at its 2010 levels. We aimed to estimate worldwide trends in diabetes, how likely it is for countries to achieve the global target, and how changes in prevalence, together with population growth and ageing, are affecting the number of adults with diabetes.

Methods We pooled data from population-based studies that had collected data on diabetes through measurement of its biomarkers. We used a Bayesian hierarchical model to estimate trends in diabetes prevalence—defined as fasting

Lancet 2016; 387: 1513-30

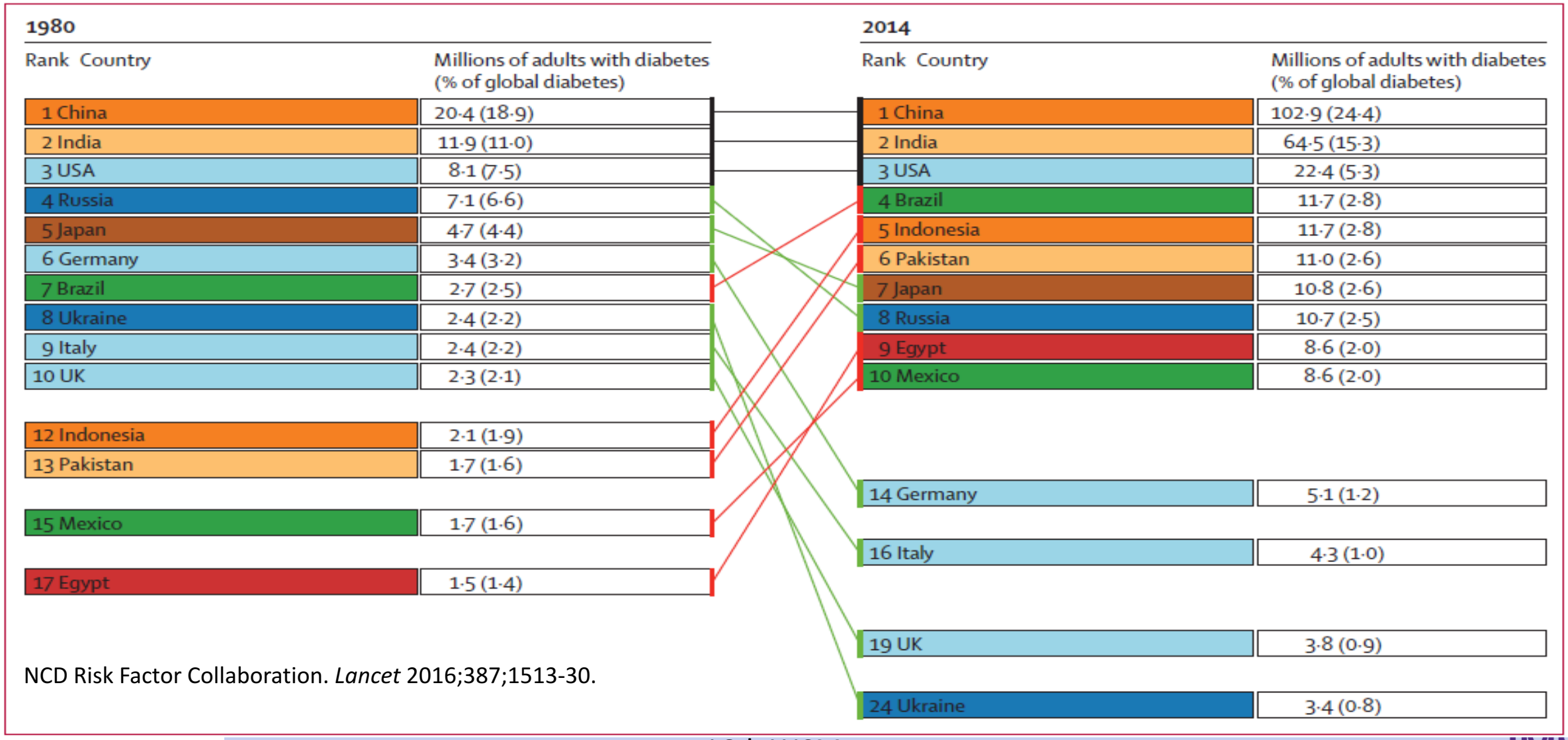
Published Online
April 6, 2016
http://dx.doi.org/10.1016/S0140-6736(16)00618-8

See Comment page 1485

See Perspectives page 1505

NCD Risk Factor Collaboration. *Lancet* 2016;387;1513-30

Ten Countries with the Largest Number of Adults with Diabetes in 1980 and 2014



NCD Risk Factor Collaboration. *Lancet* 2016;387;1513-30.

National Diabetes Statistics Report

> 100 Million US Adults Affected

- As of 2015, in the U.S.
  - 30.3 million 9.5 % diabetes
  - 84.1 million > 33.3 % pre-diabetes
- Age related DM prevalence
  - 18-44 y 4 %
  - 45-64 y 17 %
  - ≥ 65 y 25 %

www.cdc.gov/media/releases/2017/p0718-diabetes-report.html

Criteria for Diagnosis of Diabetes

- FPG ≥ 126 mg/dL 7.0 mmol/L
- 2-h PG ≥ 200 mg/dL 11.1 mmol/L
- **A1C ≥ 6.5 % 48 mmol/mol**
- Random PG ≥ 200 mg/dL 11.1 mmol/L symptoms

Diabetes Care 2018;41(Suppl 1)S13-S27

Criteria for Diagnosis of Prediabetes

- FPG ≥ 100-125 mg/dL 5.6 - 6.9 mmol/L
- 2-h PG ≥ 140-199 mg/dL 7.8-11.0 mmol/L
- A1C ≥ 5.7-6.4 % 39-47 mmol/mol

***Diabetes Care* 2018;41(Suppl 1)S13-S27**

Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults

Consider for all adults BMI ≥ 25* with ≥ 1 added risk:

- First-degree relative with DM
- High-risk race/ethnicity
- Hx of cardiovascular disease
- HTN ≥ 140/90 or Rx HTN
- HDL < 35 (0.90 mmol/L) and/or TG > 250 (2.82 mmol/L)
- Polycystic ovary syndrome
- Physical inactivity
- Insulin resistance: severe obesity, acanthosis nigricans
- Prediabetes test yearly
- Gestational diabetes every 3y

***Diabetes Care* 2018; 41(Suppl 1):S13-S27. *Asian Americans, BMI ≥ 23)**

Criteria for Testing for Diabetes or Prediabetes in Asymptomatic Adults

- Testing should **begin at age 45 years** for all patients[1]
- **Repeat testing** at a minimum of **3 year intervals** if results are normal[1]
- In a Swedish public health program, age at DM diagnosis was 4.6 y lower in those who were screen-detected[2]
  - Clinical detected cases had worse health outcomes[2]

Diabetes Care 2018; 41(Suppl 1):S13-S27. *Asian Americans, BMI ≥ 23); 2. Feldman AL, _Diabetologia_ 2017

Challenges of Perimenopause and DM

- Symptoms of estrogen withdrawal can initially be confused with those of hypoglycemia
- Blood glucose control often deteriorates during the luteal phase—perimenopausal hormone fluxes create havoc
- Weight gain challenges glucose, BP, and lipid control
- Menstrual irregularities are of added concern as risk of endometrial cancer is elevated

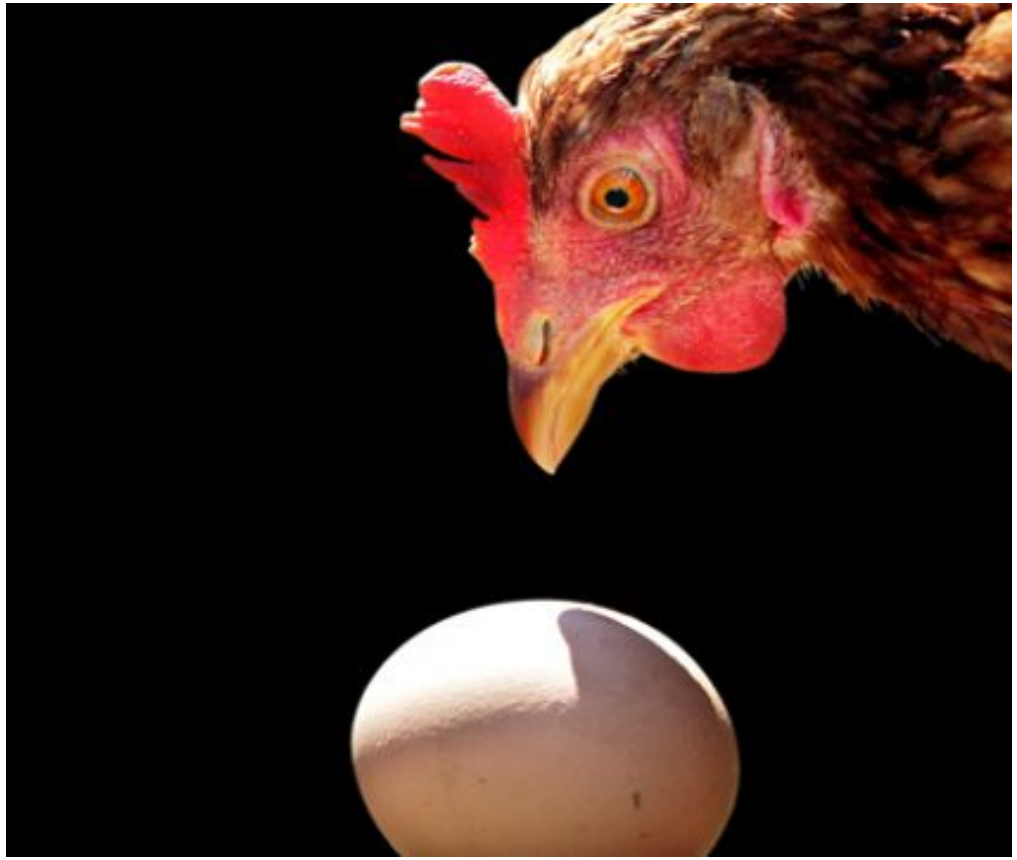
Menopause and Diabetes Risk

- Natural menopause, occurring at the average age, does not appear to increase DM risk[1,2]
- Duration of reproductive life span may contribute to DM—both shorter (< 30 yr) and longer (≥ 45 y)[3,4]
- Hysterectomy is associated with increased DM risk; oophorectomy did not confer added risk[5]

1. Stuenkel CA, *Climacteric*, 2017; 2. Mauvais-Jarvis F, *Endocrine Reviews*, 2017; 3. LeBlanc ES, *Menopause*, 2017; 4. Muka T, *Diabetologia*, 2017; 5. Luo J, *Am J Epidemiol,* 2017.

Menopause and Diabetes Risk

- The exact effect of menopause on glucose homeostasis, independent from chronological aging, is still controversial[1,2]
- Relationships between early menopause and diabetes (among other CVD risk factors) may be bidirectional[3]



1.Stuenkel CA, *Climacteric*, 2017; 2. Mauvais-Jarvis F, *Endocrine Reviews*, 2017; 3. Manson JE and Woodruff TK, *JAMA Cardiol*, 2017.

Vasomotor Symptoms and DM Risk

- In Australian Longitudinal Study, early severe VMS were associated with DM risk; OR 1.55 (1.11-2.17)[1]
- In 2 large cohort studies, VMS were associated with increased risk of Type 2 DM[2]
- In the WHI studies, VMS were associated with DM, particularly night sweats, possibly related to sleep disturbance[3]

Herber-Gast GC, *Menopause*, 2014; 2. van Dijk GM, *Maturitas*, 2015; 3. Gray KE, *Menopause*, 2018

Women with Diabetes

- Diabetes is considered by the AHA to be a CHD risk equivalent
- RCT evidence of CVD outcomes with MHT in women with DM is mostly lacking
- RCT of MHT show neutral or beneficial effects on glucose control
- Evidence inadequate to make firm recommendations

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011.

Recommendations for Treating VMS with MHT in DM

Organization	Citation	Bottom Line
NAMS	Menopause, 2017	Not addressed
IMS	Climacteric, 2016	Not addressed
UK NICE	Post Reprod Health, 2015	MHT not adverse for glucose control Consider MHT after taking comorbidities into account
Endocrine Society	JCEM, 2015	Evidence for safety inadequate Some women may be candidates for MHT after assessing CVD risk Prefer TD E2 and MP
Canadian Menopause Society	JOGC , 2014	May prescribe MHT for symptom relief
ACOG	Practice Bulletin, 2014	Not addressed

Stuenkel CA, *Climacteric*, 2017; *updated June, 2018*.

Women with Diabetes

- An individualized approach to treating menopausal symptoms could be considered
- Low threshold to recommend nonhormonal therapies, particularly in women with concurrent CVD
- Some women with DM, after evaluation of CVD risk, may be candidates for MHT
- Prefer transdermal estrogen and micronized progesterone—more metabolically 'friendly'

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011.

Approach to Patient with VMS Considering MHT

EVALUATE CARDIOVASCULAR RISK

HIGH *

CONSIDER OTHER OPTIONS

ACCEPTABLE

*** Includes known CHD, CVD, PAD, etc.**

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011.

Cardiovascular Risk Assessment

- Both the Endocrine Society[1] and NAMS[2] are aligned in recommending quantifying 10 year CVD risk
- Use the AHA/ACC risk calculator or other validated country or population-specific instrument
- If resources allow, CAC determination can contribute to risk assessment if ≥ 40 y[3]
- Cardiovascular 'age' is a concept under development[4]

1. **Stuenkel CA, *JCEM*, 2015; 2. NAMS HTPS, *Menopause*, 2017; 3. American Diabetes Association, *Diabetes Care,* 2018; 4. Santen RJ, *Menopause,* 2017**

Evaluate Cardiovascular Risk

10-yr CVD Risk	Years since Menopause Onset	
	≤ 5 y	6 to 10 y
Low (<5%)	MHT ok	MHT ok
Moderate (5 to 10%)	MHT ok (Choose Transdermal)	MHT ok (Choose Transdermal)
High** (≥10%)	Avoid MHT	Avoid MHT

Stuenkel CA, et al. *J Clin Endocrinol Metab* 2015; 100:3975-4011; NAMS HTPS, *Menopause*, 2017

Treatment of Menopausal Symptoms in Young Women with Diabetes

10-yr CVD Risk	Years since Menopause Onset	
	≤ 5 y	6 to 10 y
Low (<5%)	MHT ok	MHT ok
Moderate (5 to 10%)	MHT ok (Choose Transdermal)	MHT ok (Choose Transdermal)
High** (≥10%)	Avoid MHT	Avoid MHT

and normal weight

Oral MHT OK

or if obese

TD preferred

Mauvais-Jarvis F, et al. *Endocrine Reviews,* 2017

Sex Differences in the CVD Consequences of DM

Compared with men:

- CVD risk profile is more adverse in women
- Women with DM have 2-fold excess risk CHD
- MI occurs earlier and has higher mortality
- Revascularization rates lower; survival less
- Rates of incident heart failure higher
- DM is stronger risk factor for stroke and PVD

Regensteiner JG, et al. *Circulation* 2015; 132:2424-2447.

Recommendations for CVD Risk Factor Management in T2DM

Risk	Recommendation
Nutrition	Individualize; Mediterranean diet
Obesity	Surgery BMI $\geq$ 40 or $\geq$ 30 glucose
Blood glucose	$A_{1C} \leq 7.0\%$ (53 mmol/mol)
Blood pressure	Rx to achieve BP < 140/90
Cholesterol	$\geq$ 40y Rx moderate intensity statin
Low-dose aspirin	$\geq$ 50y +1 risk, Rx 75-162 mg/d

American Diabetes Association. *Diabetes Care,* 2018

What about new drugs for CVD risk reduction in T2DM?

Secondary Prevention Benefit in RCTs

LDL lowering as adjunct to statin therapy

- Ezetimibe
- PCSK9 inhibitor: evolocumab, alirocumab

Glucose lowering agents

- SGLT2 inhibitors: **empagliflozin,** canagliflozin*
- GLP-1 agonists: **liraglutide**, semaglutide

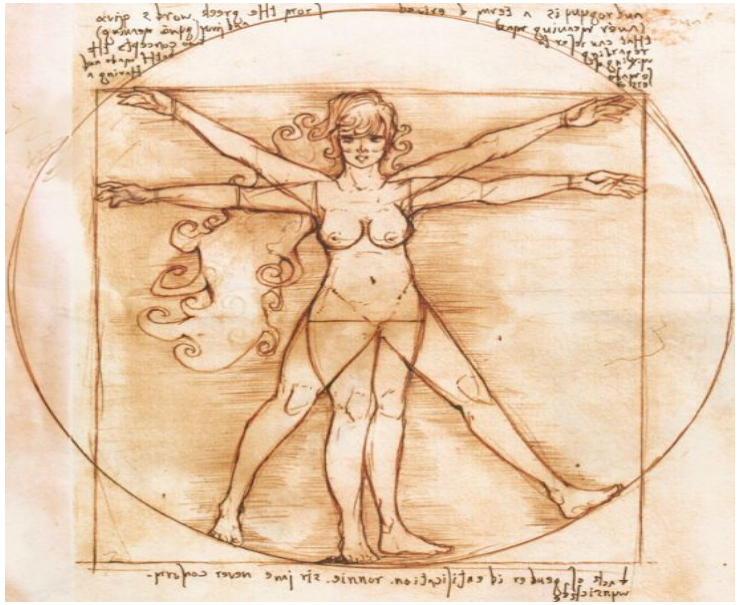
Anti-inflammatory agents

- Interleukin-1 beta blocker: canakinumab

American Diabetes Association. *Diabetes Care,* 2018; *2-fold increased amputations; bold FDA approved for CVD event reduction. Dapagliflozin effective in obs study in lower risk patients.

Health Considerations for Women with DM

- Osteoporosis and fracture risk
- Cancer risk: breast, colorectal, and endometrial
- Obstructive sleep apnea common
- Cognitive decline and depression
- Genitourinary syndrome of menopause



Stuenkel CA, *Climacteric*, 2017

Prevention or Delay of Type 2 Diabetes

For patients with prediabetes, refer for intensive diet and exercise behavioral counseling

- Target loss of 7% initial body weight
- Increase moderate-intensity physical activity t
- Technology-assisted tools (internet based or mobile apps)

- Metformin may be considered BMI ≥ 35, age
  - Monitor Vitamin B12 deficiency (anemia or neuropathy)

***Diabetes Care* 2018;41(Suppl 1)S51-S54**

MHT for Prevention of DM?

- Not government approved for this indication
- Not appropriate due to complex risks and benefits
- Not addressed by most society guidelines
- Not the end of the story…

Stuenkel CA, *Climacteric*, 2017; Mauvis-Jarvis F, *Endocrine Reviews*, 2017

CVD and DM in the Perimenopause

Summary and Conclusions

- Diabetes is a burgeoning health concern, amenable to reversal with lifestyle interventions and weight loss
- The interaction of menopause and diabetes is complex
- Cardiovascular morbidity and mortality are the most serious health sequelae for women with DM
- Myriad health concerns require additional clinical emphasis and study to define optimal management

Discussion

Nutrition Break

Menopausal Hormone Therapy Regimens in the Perimenopause

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Robert Reid Disclosures

Relationships with commercial interests:

Advisory boards: Bayer, Merck, Mithra

Speaker's Bureau: Pfizer

Objectives

- After this presentation participants will be able to:
  - Describe the erratic onset of menopausal symptoms that may characterize the perimenopausal transition
  - Define the particular situation and select hormone therapy appropriate to the underlying pathophysiology

Perimenopausal Menstrual Interval Variation

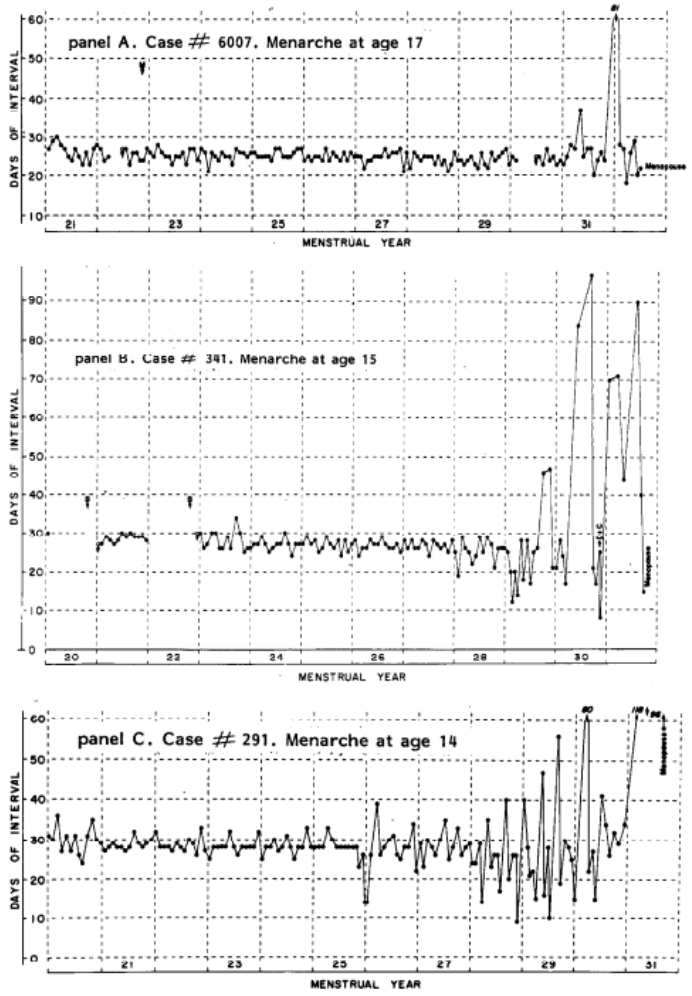


Fig. 5. Three menopausal transitions of contrasting durations.

Treloar AE. Menstrual cyclicity and the pre-menopause. Maturitas 1981; 3(3-4): 249-64

Menstrual Interval Variation Through Reproductive Years

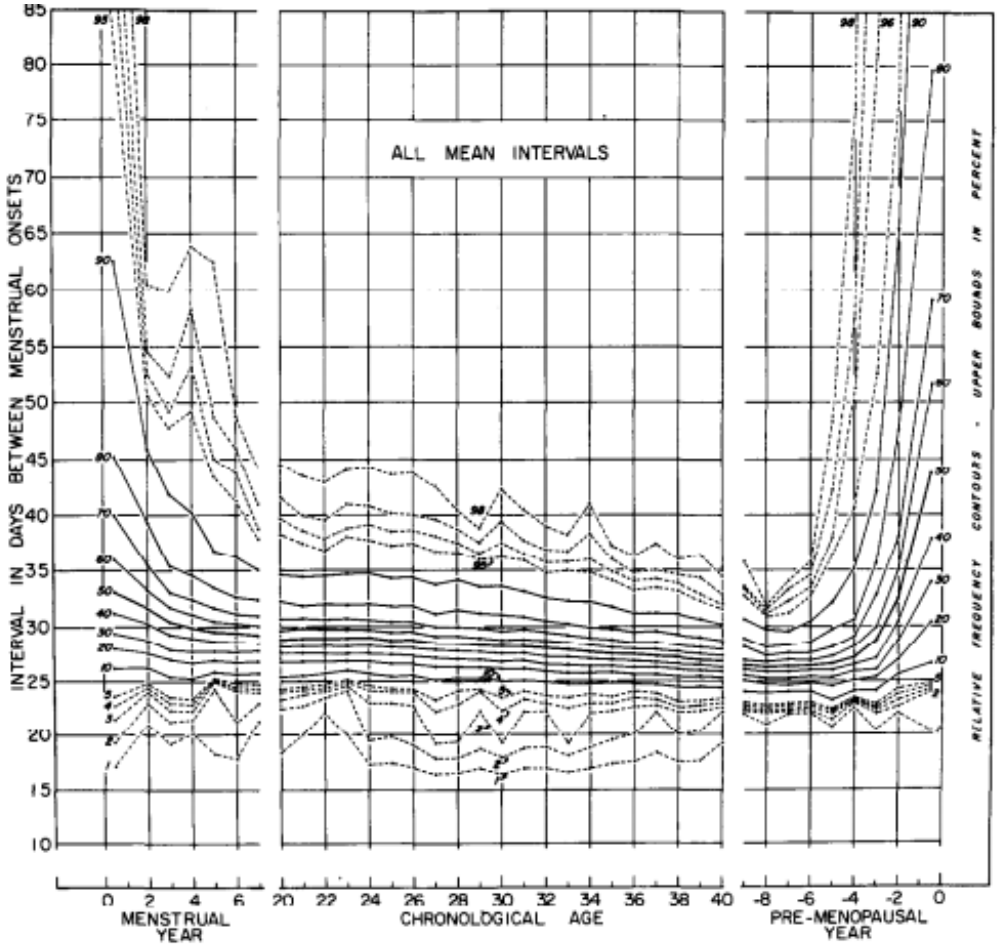
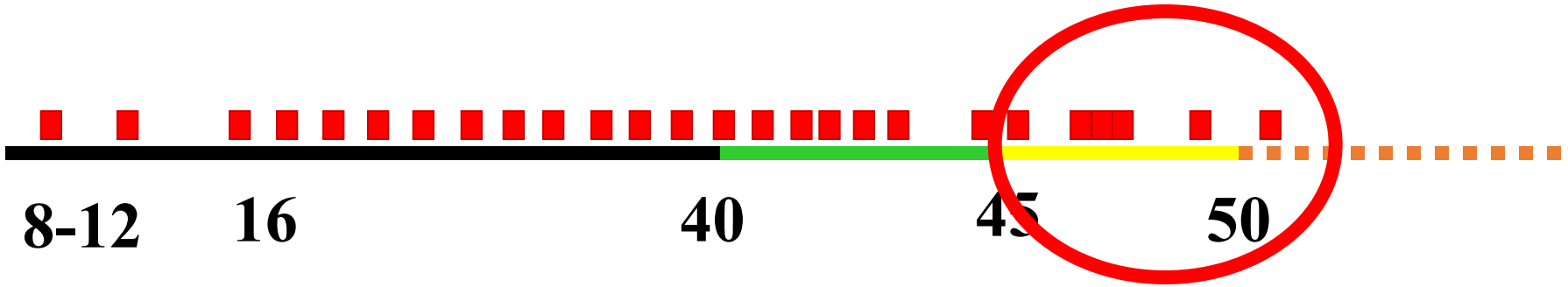


Fig. 1. Contours for the distribution of mean intervals for all person-years of experience.

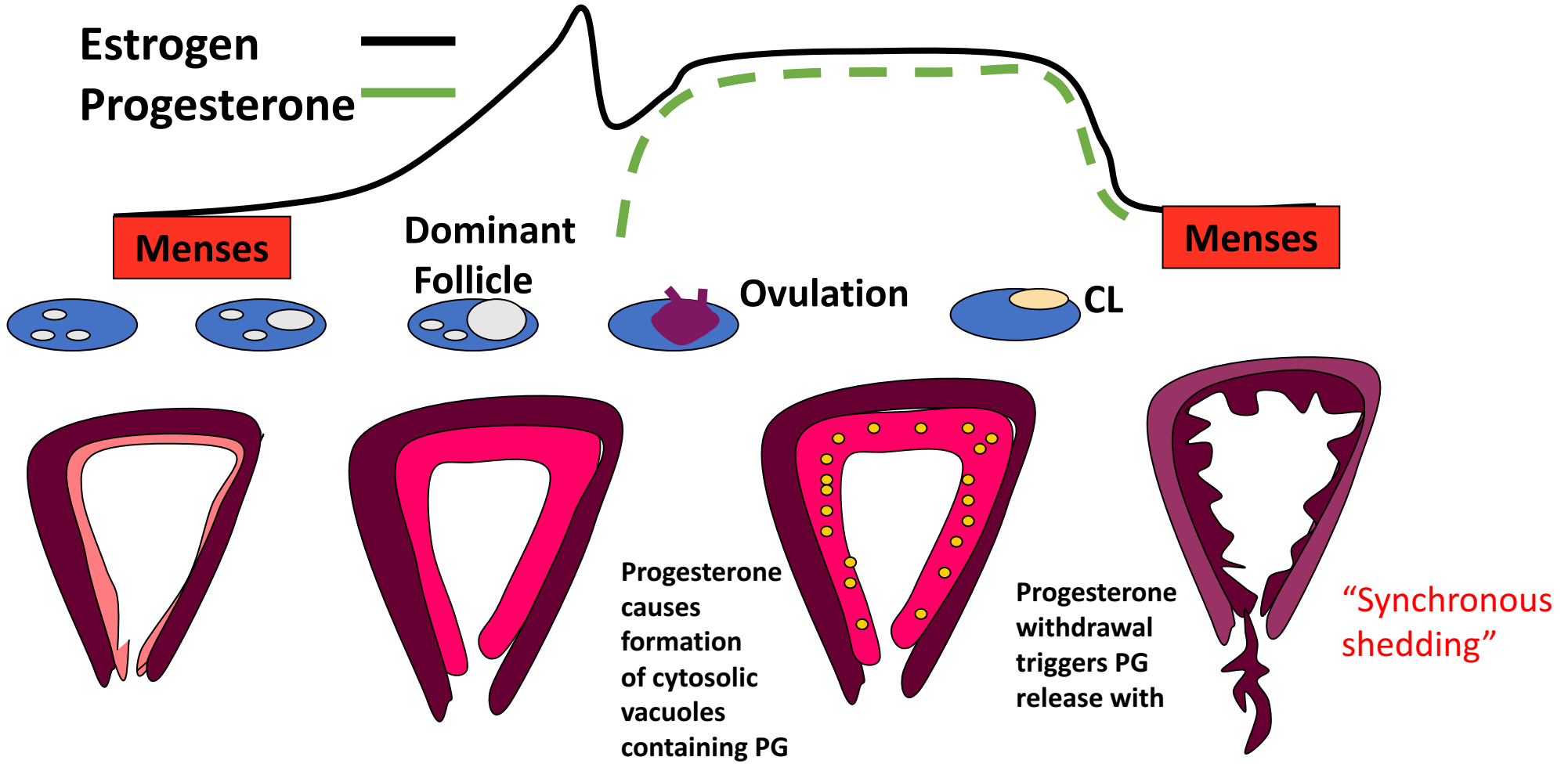
Treloar AE. Menstrual cyclicity and the pre-menopause. Maturitas 1981; 3(3-4): 249-64

Menstrual Cyclicity Over a Lifetime

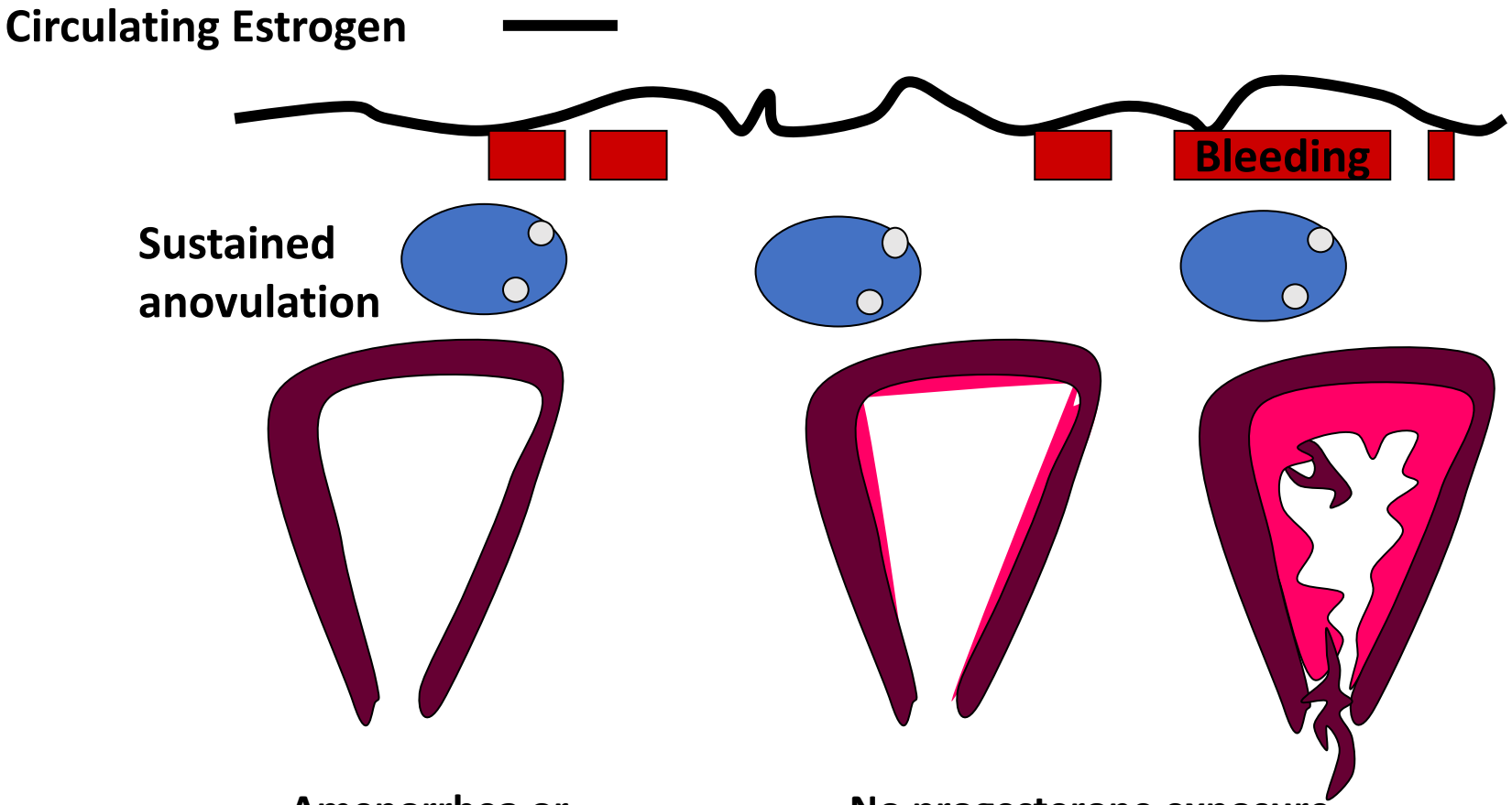


Thelarche indicates first estrogen exposure	Regular monthly cycles- every 28 –30 d	Shortened follicular phase- 22-24 day cycles	Irregular unpredictable cycles	Menstrual periods cease

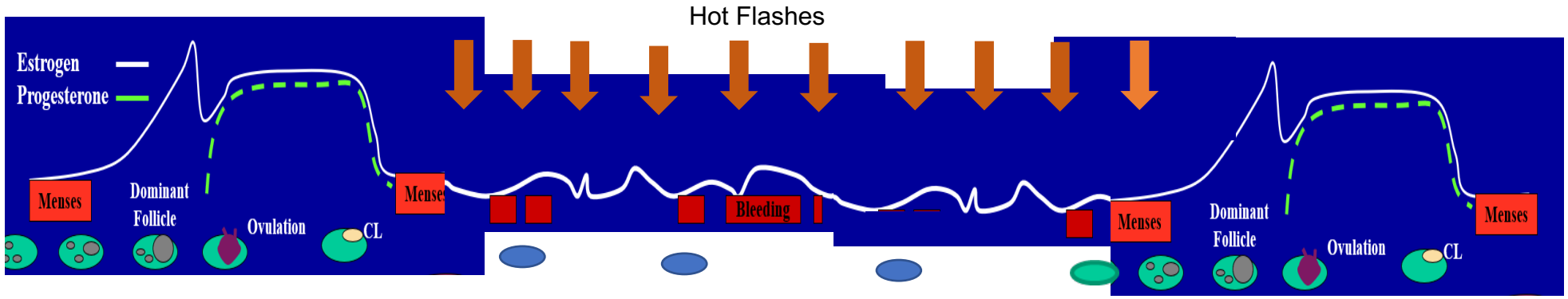
Ovulatory Cycles



Perimenopausal Anovulatory Cycles



Perimenopause: a Time of Unpredictability



Occasional ovulation mixed with periods of ovarian quiescence

The few remaining follicles are those that are most resistant to FSH stimulation

As FSH levels rise these follicles activate and estrogen levels rise
With cessation of hot flashes

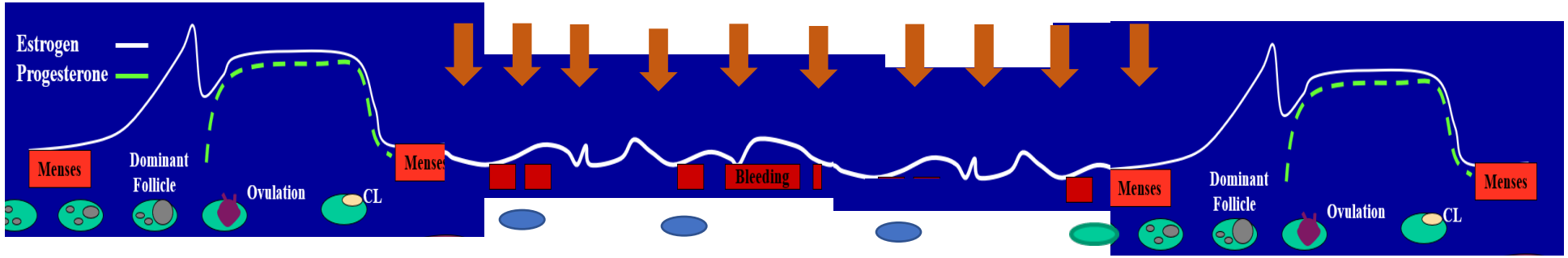
Clinical Situations for HRT in Perimenopause

1. Hormone therapy for the woman with irregular menses and periodic VMS
   a) With contraindications to CHC
   b) Without contraindications to CHC
2. Women with pre-existing insertion of LNG IUS for bleeding control who subsequently develops VMS
3. Women less than 1 year from LMP with amenorrhea and continuous VMS

Defining the Clinical Situation

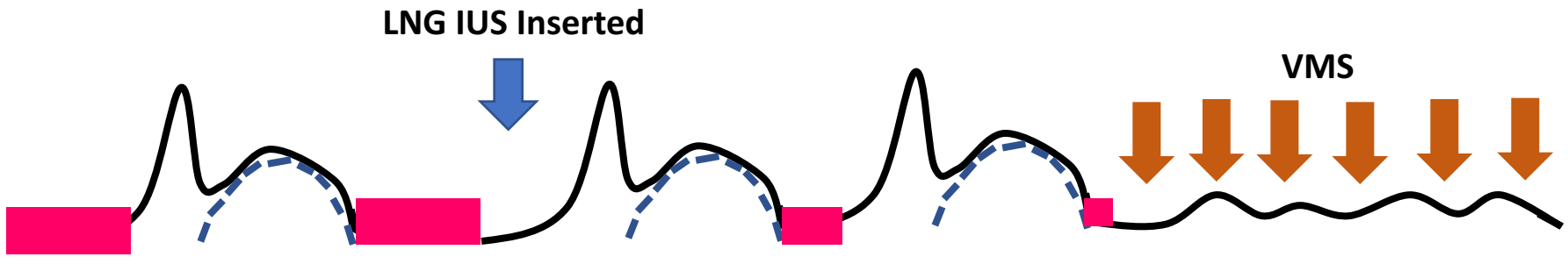
- Not always precise
- FSH not helpful beyond age 45
  - in younger women may help differentiate POI from other causes of amenorrhea
- Duration of amenorrhea
  - After 6 months amenorrhea about 50% have had FMP; at 12 months 90%
- Need for cycle control or contraception?

1. Hormone Therapy for the Woman with Irregular Menses and Periodic VMS



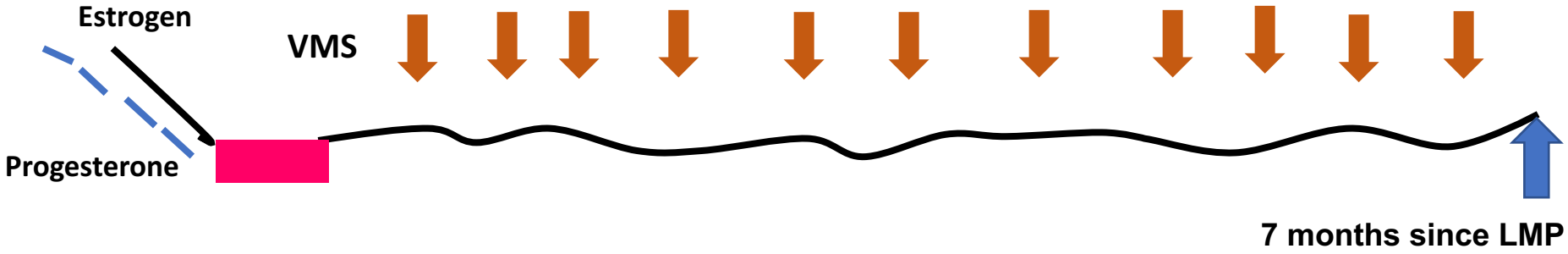
- In this situation CHC levels of hormones are required to override occasional spontaneous ovulation thus maintaining cycle control while preventing VMS
- Also affords contraception and some non- contraceptive benefits (bone protection, reduced risk of endometrial and uterine cancer)
- If a contraindication to CHC:
  - LNG IUS for contraception and bleeding control
  - Systemic estrogen for VMS
- If no contraindication to CHC:
  - Consider extended cycle or continuous CHC

2. VMS Developing in a Woman with LNG IUS for HMB



- LNG providing cycle control and contraception
- Off label addition of systemic estrogen for control of VMS

3. Continuous VMS and Amenorrhea but Not Meeting Criteria for Menopause



- Do not need to wait for 1 year of amenorrhea to start treatment for VMS
- Start with standard menopausal HRT and only switch to CHC (or LNG IUS and estrogen if contraindications to CHC exist) for troublesome bleeding (periodic menses)

Conclusions

- Do your best to define the individual situation based on history (age, duration of amenorrhea, onset and severity of VMS)
- Select a therapy that will relieve VMS while also addressing issues of cycle control and contraception (if needed)

Discussion