Orals,Transdermals, and Other Estrogens in the Perimenopause

Cases

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Faculty/Presenter Disclosure

Faculty: Dr. Denise Black

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Case 4a

- 48 year old P2 presents with intermittent vasomotor symptoms of moderate severity
- She has a LNG-IUS 52 mg device in place. It was placed 3 years ago for the combined indication of contraception and heavy menstrual bleeding
- Since placement, her bleeding has decreased markedly. She now describes intermittent spotting only

Case 4a

- She describes these symptoms: for 3-4 months she will have profound vasomotor symptoms, difficulty sleeping, and irritability.
- She will then feel “normal” for a few weeks, then have an episode of vaginal spotting
- Following this, the vasomotor and other symptoms return. She is asking for treatment for these symptoms

Case 4a

- She is healthy, lean, and exercises regularly
- She is a non-smoker, and consumes 3-4 alcoholic beverages per week
- She takes no medication

- What is her diagnosis, and what are her treatment options?

Case 4a

- Diagnosis: most likely late perimenopause—not 12 months of amenorrhea, but symptomatic periods consistent with hypoestrogenism
- Hormonal treatment options: addition of estrogen therapy. Adequate endometrial protection in place (off label in Canada).
- Contraception still required
- Oral or transdermal estrogen?

Guidelines—Safety of Orals vs Td

- **SOGC 2014:** Women at increased VTE risk should be offered transdermal rather than oral estrogen
- **NAMS 2017:** Meta analysis of observational studies suggest that lower doses of oral or transdermal HT have less effect on risk of VTE; however, RCT data lacking
- **Endocrine Society:** For women at increased risk of VTE, we recommend a non-oral route of estrogen and progesterone for those with a uterus

VTE—Are Transdermal Estrogens Safer than Orals in the Average Risk Woman?

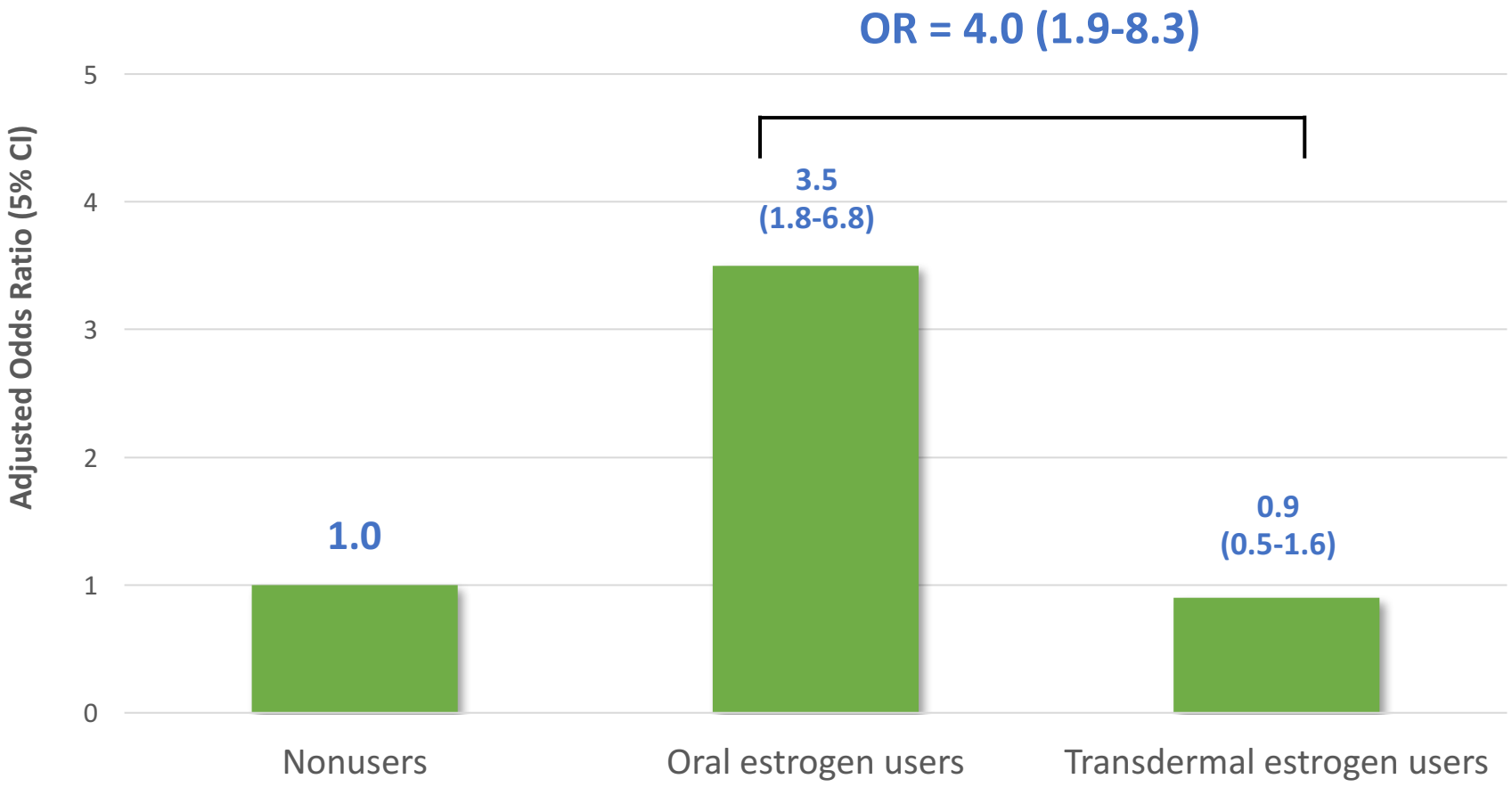
- With respect to VTE risk, only one study has done a head to head comparison at relatively equivalent doses using the same progestogen (KEEPs), with too few subjects to draw any conclusions.[1]

Observational studies suggesting better safety with Td did not use equivalent dosing, and did not control for the different progestogens used [2]

1. Harman et al, Ann Int Med 2014;161:249
2. Canonico et al Circulation 2007;115:840

Risk of VTE with Oral vs. Transdermal

ESTHER Study



ESTHER: Estrogen and Thromboembolism Risk Study

Scarabin PY, et al. Lancet 2003;362(9382):428-32.

ESTHER

- Estrogen dosing: average transdermal dose 50 ug patch, average oral dose 1.5 mg
- Low dose oral was up to 2 mg, low dose Td was <50 ug

Postmenopausal HT and Risk of VTE: Results of the E3n Trial

Treatment	Hazard ratios (95% CI)	
	Age-Adjusted	Multivariable Adjusted*
Never use (n=181)	1 [reference]	1 [reference]
Past use (n=66)	1.0 (0.7–1.3)	1.1 (0.8–1.5)
Current use of oral estrogens (n=81)	1.5 (0.9–2.3)	1.7 (1.1–2.8)
Current use of transdermal estrogens (n=174)	1.1 (0.7–1.6)	1.1 (0.8–1.8)
No progestogens use (n=26)	….	….
Current use of micronized progesterone (n=47)	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Current use of norpregnane derivatives (n=69)	1.7 (1.1–2.6)	1.8 (1.2–2.7)
Current use of nortestosterone derivatives (n=22)	1.4 (0.8–2.5)	1.4 (0.7–2.4)

*Adjusted for age, body-mass index, parity, educational level and time-period

Canonico et al. *Arterioscler Thromb Vasc Biol* 2010;30(2):340-5.

When to Consider Use of Transdermal Estrogen

A. Smokers

B. For patients with underlying medical conditions
- Higher risk of DVT or PE
- High triglyceride levels
- Gall bladder disease
- Hypertension

C. For "steady state" drug release
- Daily mood swings
- Migraine headaches
- Patients who do shift work

D. Inability to use oral tablets
- Stomach upset due to oral estrogen intake
- Problems with taking a daily pill

E. Patient choice of delivery system

Case 4b

- 41 year old P1, partner has had vasectomy
- Having hot flushes, night sweats, irritability, difficulty sleeping, anxiety, “rage”
- Menses irregular—coming between 3 and 5 weeks apart, sometimes heavy
- Healthy non-smoker currently on no medications
- Exam normal, pertinent investigations (including ultrasound) normal

Case 4b

- Diagnosis?
- Pathophysiology?
- Treatment options?

Case 4b

- Diagnosis—perimenopause, early
- Pathophysiology—widely fluctuating hormonal levels, with supraphysiologic estradiol production. Symptoms likely precipitated by sudden declines in hormone levels, not by hypoestrogenism per se
- Treatment: capturing aberrant ovarian cycling (generally with a low dose combined hormonal contraceptive, in the absence of contraindications)

Defining Menopause: the STRAW Staging System

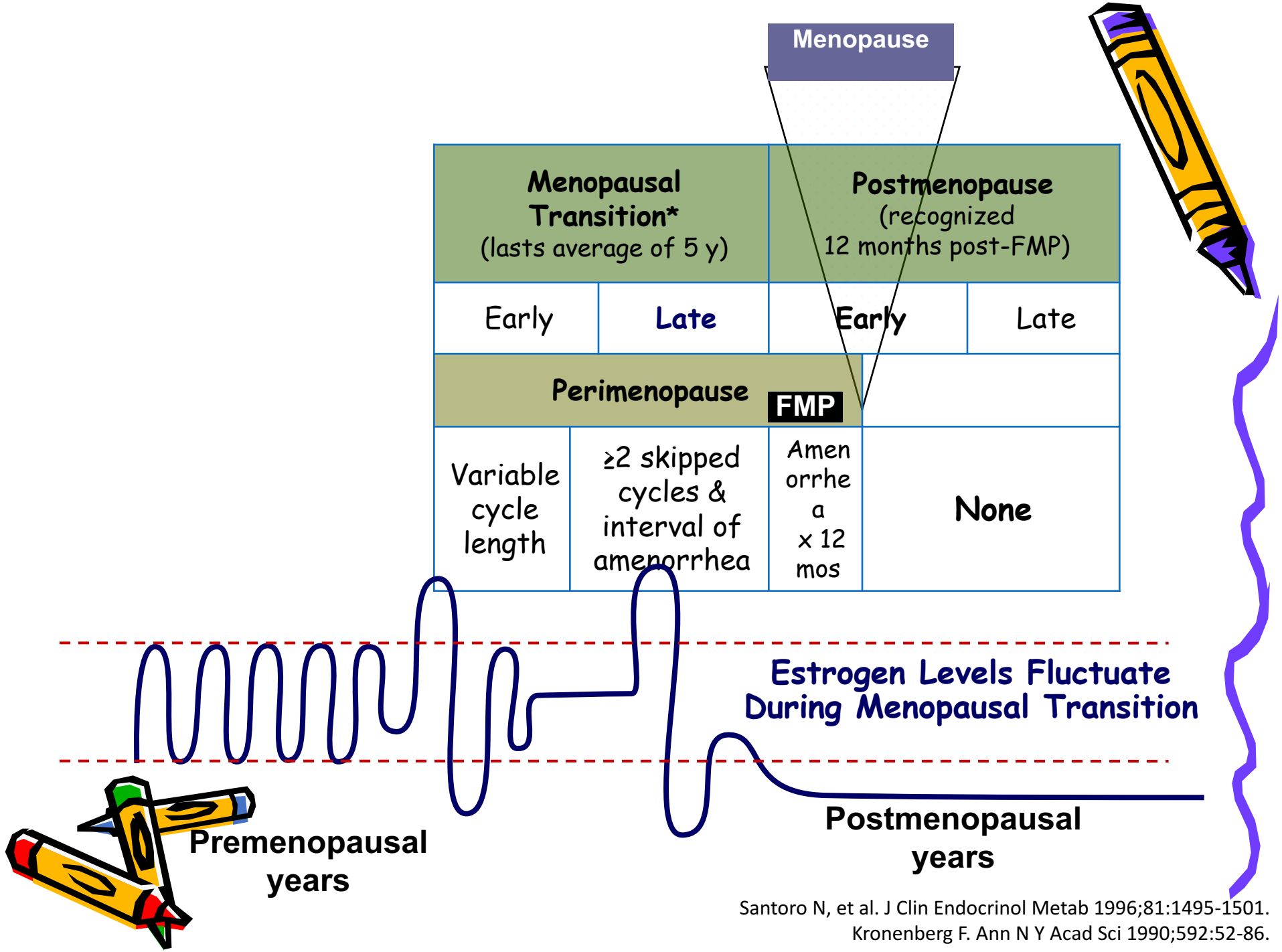
Final Menstrual Period (FMP)

Stages	**-5**	**-4**	**-3**	**-2**	**-1**	**+1**	+2
Terminology	**Reproductive**			**Menopausal Transition**		**Postmenopause**	
	Early	Peak	Late	Early	Late*	Early*	Late*
				Perimenopause			
Duration of Stage	Variable			Variable		**A** 1 yr	**B** 4 yrs / Until demise
Menstrual Cycles	Variable to Regular	Regular		Variable Cycle Length (>7 days different from normal)	≥2 skipped cycles & an interval of amenorrhea (≥60 days)	*Amenx12mos*	None
Endocrine	Normal FSH		Elevated FSH	Elevated FSH		Elevated FSH	

** Stages most likely to be characterized by vasomotor symptoms*

FSH: follicle-stimulating hormone.

Adapted from Soules et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Fertil Steril. 2001;76(5):874-878



Santoro N, et al. J Clin Endocrinol Metab 1996;81:1495-1501.
Kronenberg F. Ann N Y Acad Sci 1990;592:52-86.

Case 4c

- 48 year old P2, has tubal ligation
- Troublesome vasomotor symptoms for the last 6 months
- Amenorrheic for last 5 months
- Non-smoker
- Has elevated cholesterol and high triglycerides
- In both pregnancies had severe pre-eclampsia necessitating induction of labour at 34 weeks and 32 weeks
- Strong family history of heart disease

Case 4c

- Drinker of 10 alcoholic beverages per week
- BMI 28
- Has recently started a health and wellness program at her workplace

Case 4c

- Diagnosis? Likely late perimenopause—prolonged periods of amenorrhea and hypoestrogenic symptoms but not fufilling the criteria for post-menopausal
- Treatment options?
  - Lifestyle? Diet, exercise, limiting alcohol consumption
  - If HT desired, what combination?

Case 4c

- Considered at increased cardiovascular risk (increased triglycerides, overweight, relatively inactive, positive personal history for hypertensive disorders of pregnancy, positive family history)
- Treatment with estrogen should be transdermal (universal guideline agreement for CV high risk women)

Case 4c

- As per guidelines (IMS), micronized progesterone is preferred for high risk patients
- Cyclical is recommended (expert opinion) rather than continuous in the recently post-menopausal woman

Thank You

Discussion