Common Cases and Conundrums in Menopause care

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Financial Disclosures

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- Speaker fees:
  - Amgen
  - Bayer
  - Merck
  - Novartis
  - Novo-Nordisk
  - Warner-Chilcott
- Advisory Boards
  - Lilly
  - Amgen
  - Novartis
  - Pfizer

Goals

- To review some of the common challenges in menopause care including:
  - Premature menopause
  - Patients with relative contraindications to hormone therapy
  - Breast cancer survivors
- Provide an evidence based approach to managing some of these problems

Nomenclature

- Menopause: Final menstrual period, determined after 1 year without menses
- Perimenopause: change of 7 or more days of the menstrual cycle, FSH fluctuates
- Premature Menopause: menopause prior to the age of 40 (2SD below average)
  - may be spontaneous or induced by disease, medication, irradiation, or surgery
- Primary ovarian insufficiency: irregular menses and elevated FSH >40 in women under age 40

Mrs. Young

- 36 year old G1P1 who initially presented with secondary infertility and severe pain
- Had an abnormal U/S which prompted laparoscopy showing stage 4 endometriosis
- Opted for conservative surgery at which time bilateral large endometriomas were removed
- Pain much improved, but no periods, moderate hot flushes, mild vaginal atrophy, and FSH 50+ after surgery

Mrs. Young

- Mother had breast cancer age 59, no other family members with breast cancer
- Family history of osteoporosis in grandmother who had a hip fracture
- Normal body habitus, non smoker
- Decides she would like a pregnancy but does not want interventions
- What's next?

Mrs. Young

- Hormone replacement with premature menopause:
  - Standard of care to provide hormone replacement
  - Preparation used depends on reproductive and menstrual goals and degree of symptoms
  - Does not increase risk of breast cancer, stroke, heart disease
  - Reduces osteoporosis and heart disease risk
  - OCP regimens provide regular menses and contraception
  - HT does not prevent pregnancy
  - Recently menopausal women-cyclic HT may be preferable

ACOG Committee Opinion 698, Obstet. Gynecol. VOL. 129, NO. 5, MAY 2017

Mrs. Young

- Hormone therapy with a history of endometriosis:
  - Combined HT in standard doses does not appear to cause regrowth of endometriotic tissue
  - A small subgroup of women may experience recurring pain and other symptoms during unopposed ET after hysterectomy and BSO but addition of a progestin is not routine in these patients
  - No evidence that progestin only therapy is preferential

SOGC Managing Menopause No. 311, September 2014

Mrs. Young

- Duration of hormone use for patients with a history of premature menopause
  - Hormones should be supplemented until the average menopause age of 50-52
  - After that, ongoing hormone therapy should depend on symptoms and risk/benefit
  - Earlier initiation of HT does not increase CV risk

ACOG Committee Opinion 698, Obstet. Gynecol. VOL. 129, NO. 5, MAY 2017

Summary

- Patients with ovarian failure and menopause prior to the age of 40 should receive hormone replacement
- Standard OCP's or hormone therapy preparations can be used depending on the goal
- The risks in this population are minimal and not the same as hormones in older women
- Endometriosis is not expected to recur with EPT, OCP or ET (in patients with hysterectomy)
- Case outcome

ACOG Committee Opinion 698, Obstet. Gynecol. VOL. 129, NO. 5, MAY 2017
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Mrs. Ohno

- 54 year old G2P2, last period 24 months ago
- Lawyer at a large firm
- Had DUB during perimenopause, biopsy showed simple hyperplasia managed with a Mirena IUD, repeat biopsy N
- BMI 38.3, IGT and mild hypertension, no CVD
- Has gained 15 pounds since menopause, fairly sedentary lifestyle, non smoker, no EtOH
- Hot flushes causing embarrassing sweats during client meetings, and sleep very disrupted, suffering from "brain fog"

Mrs. Ohno

Prevalence of Self-Reported Obesity among Males and Females 18 Years and Older, by Age Group, 2007

Relative risk of Type 2 Diabetes with increasing BMI in men and women

www.publichealth.gc.ca
Colditz GA et al. Ann Intern Med. 1995

Mrs. Ohno

- What is the impact of menopause on weight gain?
  - SWAN Over 3 years of follow up:
    - Body weight rose by a mean of 2.1 +/- 4.8kg
    - Waist increased by 2.2 +/- 5.4 cm
    - Increase with age was independent of menopause
  - Metabolic syndrome increases:
    - OR 1.45/year of perimenopause (1.35-1.46)
    - OR 1.24/year after menopause
    - Increase with menopause was independent of age
  - Menopause is associated with changes in fat distribution and the appearance of abdominal fat

Imke Janssen , Archives of Internal Medicine 2008;168(14):1568-1575
Sowers MF et al., Menopause: Biology and Path.. 2000, pp. 175–188.

Mrs. Ohno

- What is the impact of obesity on menopause?
  - Higher % body fat, but not lean mass, was related to an increased likelihood of VMS
  - Women who gain weight during menopause are more prone to symptoms
    - Gains in body fat from one year to the next were associated with an increased likelihood of VMS at the subsequent visit
    - OR for hot flushes in SWAN was 1.27 for each SD increase in percent body fat

Thurston et al., Obstet Gynecol Clin North Am. 2011 Sept ; 38(3): 489–501
Thurston RC, et al. Am J Epidemiol 2008;167(1):78–85.
Thurston RC, et al. Am J Epidemiol 2009;170(6):766–74

Mrs. Ohno

- Obese women have an increased risk of:
  - Cardiovascular disease
  - VTE
  - Breast cancer
  - Endometrial cancer
    - aromatization of ovarian androgens in adipose tissue

Lambrinoudaki et al., Maruritias 66 (2010) 323-26

Mrs. Ohno

- Would you be comfortable offering her HT?
  - WHI: MetS at baseline in women without prior cardiovascular disease, diabetes, or hypertension at baseline identifies women who are more likely to have had adverse coronary outcomes on HT (OR 2.26)

Cushman M, et al., JAMA. 2004 Oct 6;292(13):1573-80

Mrs. Ohno

- What would I do?
  - I would probably start her on a low dose transdermal estrogen
  - I would recommend and initiate aggressive weight reduction interventions
  - consider liraglutide, or orlistat, ? Bariatric surgery
  - Reassess regularly for progress
- WHAT?????

Mrs. Ohno

- Risk of breast Ca is probably not increased further by HT
- Low absolute risk of CVD, VTE in young women

Kuhl, Maturitas 51(1): 83-97 (WHI)
SOGC Managing Menopause No. 311, September 2014

Timing Hypothesis

Pamela Ouyang et al., J Am. Col. Cardiology, Vol 47:9, 2 (2006), Pages 1741–1753

Differences between Oral and transdermal Estrogen

	Oral Estrogen	Transdermal Estrogen
Clotting factors	↑	No change
Saturation of bile with cholesterol	↑	No change
Triglycerides	↑	↓
HDL	↑	Modest ↑
LDL	↓	No change
CRP	↑	No change
SHBG	↑	No change
TBG	↑	No change

Thromb Haemost. 2001 Apr;85(4):619-25.

Mrs. Ohno

- Menopro app

EMAS Position on managing obese postmenopausal women

- Obese women seeking HT should be counseled about their individual baseline risk of CVA, VTE and breast Ca
- Lowest effective estrogen dose should be used (eg CEE 0.3, Es 0.5-1 or transdermal 25-50ug)
- Transdermal E2 is suggested as it has been associated with lesser risk of VTE
- Observational studies suggest that MP may be associated with lower VTE risk

Lambrinoudaki et al., Maruritias 66 (2010) 323-26
Schenck-Gustafsson K et al., Maturitas. 2011 Jan;68(1):94-7
2016 IMS Recommendations Climacteric 2016; 19:109-50

Mrs. Ohno

- Mirena for endometrial protection
  - In contraception users, amenorrhea delayed with increasing BMI
  - Causes regression of endometrial hyperplasia in select groups of women
- Mirena with ET
  - As affective as other systemic progestin regimens
  - More spotting in the first 3-6 months of use
- ? Reasonable to use, but prepare to biopsy as needed and maybe add or change progestin

Stoegerer-Hecher E, 2012 Feb;28(2):119-24
Way & Holland., Climacteric. 2011 Dec;14(6):622-32
Somboonporn W et al, Menopause. 2011 Oct;18(10):1060-6

Mrs. Ohno

- Benefits of weight reduction:
  - Improved health prognosis: VTE, CVD, DM
  - Reduced risk of endometrial and breast Ca
  - Reduction in VMS
  - Reduction of incontinence

Lambrinoudaki et al., Maruritias 66 (2010) 323-26

Summary

- Obesity is common and obese women have more VMS
- Individualized risk assessment is required and tools are available to help you
- Patients are at increased risk of VTE, CVD and breast and ovarian cancer at baseline
- Weight reduction can reduce VMS and improve health outcomes
- Transdermal estrogen and MP are preferred though evidence is still not definitive
- Endometrial protection is important

Mrs. Ohno

Mrs. Pink

- 52 year old G3P3, diagnosed with invasive ductal carcinoma of the left breast managed with lumpectomy, chemotherapy and radiation
- Was still having periods at time of Dx, initially managed with Tamoxifen, recently started Anastrazole for prevention of recurrence
- Otherwise healthy no other medications
- No family history of heart disease or OP
- Bothersome VMS interfering with QOL

NAMS Recommendations

- NAMS advises to not recommend:
  - Over-the-counter supplements
  - Herbal therapies
  - Vitamins
  - Relaxation
  - Calibration of neural oscillations
  - Chiropractic intervention
- These are risk free but have no evidence for efficacy:
  - Cooling techniques
  - Avoiding "triggers"

NAMS Position Paper 2015, Menopause, Vol. 22, No. 11, 2015

NAMS Recommendations

- Level II evidence suggests these may be beneficial
  - Weight loss
  - Mindfulness-based stress reduction
  - S-equol derivative of soy
  - Stellate ganglion block
- NAMS Recommended prescription therapies:
  - FDA-approved low-dose paroxetine salt
  - Other SSRIs and SNRIs yielding significant VMS reductions in large RCTs
  - Gabapentin and pregabalin

NAMS Position Paper 2015, Menopause, Vol. 22, No. 11, 2015

Specifically not recommended in breast cancer survivors

- High dose Vitamin E
- Dong Quai
- Black Cohosh
- Phytoestrogens
- Homeopathic treatments

L'espérance S et al., Support Care Cancer. 2013 Feb 25
Fritz et al., Support Care Cancer. 2013 Feb 25

Considerations in breast cancer survivors

- CYP2D6 is the enzyme responsible for metabolizing Tamoxifen into its active metabolite
- sertraline, paroxetine and fluoxetine are stong inhibitors of the activitity of this enzyme
- fluvoxamine and citalopram are weaker inhibitors
- This interaction is not observed with Venlafaxine
- Interactions do not apply to AI therapy

Goetz et al.. *Breast Cancer Res Treat*. 2007;101:113-121.
Jeppesen U, *Eur. J. Clin. Pharmacol.* 51(1), 73–78 (1996).

SUMMARY

- Special populations require different considerations when managing menopausal complaints
- Patients with early menopause should have hormone replacement until around age 50 unless contraindicated
- Patients with relative contraindications to HT including obesity deserve counselling and individualization of therapy
- Patients with contraindications to HT should be counselled about the current evidence for non hormonal therapies

Thank you!