MENOPAUSE MANAGEMENT IN THE BRCA PATIENT

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OBJECTIVES

- Discuss the importance of menopausal management in BRCA carriers who have undergone prophylactic risk-reduction surgery.
- Discuss treatment options in BRCA carriers who have had breast cancer.
- Discuss treatment of genitourinary syndrome of menopause
- Explore some special considerations.

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A NOTE ON HORMONES

- Please keep in mind that not all “hormones” are created equal.
- When interpreting studies, it is important to consider:
  - which estrogen was used - conjugated equine estrogen or 17-beta estradiol; systemic versus local/vaginal
  - which progestogen was used - a progestin or progesterone
  - duration, timing, doses, route all matter and may alter risks
- Risks associated with hormone therapy in naturally post-menopausal women cannot be extrapolated to surgically, premature menopausal women

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OBJECTIVES

- **Discuss the importance of menopausal management in BRCA carriers who have undergone prophylactic risk-reduction surgery:**
  - Why do these women need hormonal therapies?
    - Symptoms
    - Long-term negative health outcomes
  - Is hormonal therapy safe?
    - Will these therapies cause an increased cancer risk?

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WHY DO SURGICALLY MENOPAUSAL WOMEN NEED HORMONES?

- Because the symptoms are awful.
- Because they will live longer, healthier lives if they are given hormone replacement.

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SYMPTOMS OF SURGICALLY MENOPAUSAL WOMEN

- Women who undergo surgical menopause, when compared to their naturally-menopausal counterparts, tend to have more severe symptoms:
  - Vasomotor symptoms
  - Decreased quality of life
  - Decline in sexual health

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SYMPTOMS OF SURGICALLY MENOPAUSAL WOMEN

- Hormone therapy is the gold standard for menopausal management.

Finch 2011 - in young women, HRT improves vasomotor symptoms compared to RRSO without HRT

Madalinska 2006 - HT associated with fewer:

- hot flashes (20% vs. 41%)
- cold sweats (23% vs. 38%)
- night sweats (25% vs. 39%)

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SYMPTOMS OF SURGICALLY MENOPAUSAL WOMEN

- Hormone therapy is the gold standard for menopausal management.
- Rebbeck 1999:
  - Prospective study of 114 mBRCA carriers
  - Women taking HRT had fewer vasomotor symptoms (P = 0.0003)
  - Higher sexual functioning (P = 0.015)
  - Fewer hot flashes, including lower frequency and severity of symptoms.

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SYMPTOMS OF SURGICALLY MENOPAUSAL WOMEN

- Surgical menopause is associated with significant bothersome sexual symptoms:
  - RRSO associated with more vaginal dryness (28%), dyspareunia (35%), less pleasure and less satisfaction (Elit 2001, Robson 2003)
  - Twice as likely to have hypoactive sexual desire disorder (Dennerstein 2006)
  - Sexual activity returns to baseline with HRT after 1 year (Fang 2009)
  - HRT does not ameliorate decline in sexual functioning (Finch 2011)

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LONGTERM HEALTH OUTCOMES OF SURGICAL MENOPAUSE

- The negative impact on longterm health has been well documented in patients who undergo surgical menopause (ie, premature menopause):
  - Cardiovascular disease
  - Osteoporosis
  - Cognitive decline

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LONGTERM HEALTH OUTCOMES OF SURGICAL MENOPAUSE

- Cardiovascular Disease:
- Mayo Clinic Cohort showed those with BSO under 45 had increased mortality due to cardiovascular disease with HR 1.44
  - 1.84 if no estrogen used
  - 0.65 if HRT
- In contrast, all cause mortality reduction from BSO

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LONGTERM HEALTH OUTCOMES OF SURGICAL MENOPAUSE

- Cardiovascular Disease:
- Michelsen 2009 –
  - Patients with RRSO had increases in metabolic syndrome OR 2.46 (95% CI 1.63 - 3.73)
  - Also increased central obesity, altered lipids, elevated fasting glucose and elevated blood pressure
- Shukla 2011
  - BRCA1-positive women may be at an increased risk for cardiovascular disease due to abnormal function of BRCA1 gene on cardiomyocytes in mice

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LONGTERM HEALTH OUTCOMES OF SURGICAL MENOPAUSE

- Bone Health:
- Cohen 2012
  - Women with RRSO before age 50 years had high rates of osteopenia (62%) and osteoporosis (9%)
- Chapman 2011
  - Women ≥2y of menopause had 30% more osteopenia and osteoporosis vs women who took HRT
- DXA is indicated for women who have menopause before 45 years of age according to the clinical practice guidelines in Canada

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LONGTERM HEALTH OUTCOMES OF SURGICAL MENOPAUSE

- Cognition and Mental Health:
- Increased risk of dementia 25 years after premenopausal BSO (HR 1.46)
  - Worse if under 49 at OR and HRT delayed until over 50 (HR 1.89)
- 40% decrease in dementia for women on ERT
- Premenopausal BSO had an increased risk of parkinsonism (HR 1.78), increased with younger age at oophorectomy

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IS HORMONE THERAPY SAFE?

- Women remain fearful of hormone therapy despite its benefits
- Risks difficult to assess, especially in special populations (eg, premature/surgical menopause, BRCA mutation carriers)
- Markov Model - BRCA carriers having mastectomy and oophorectomy prophylaxis at age 30, plus HRT to age 50 = 0.79 years gained (Armstrong 2004)

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IS HORMONE THERAPY SAFE?

- HRT, BRCA and Breast Cancer Risk:
  - Case-control study by Eisen, showed no increased risk of breast cancer among BRCA patients who used HRT (2008):
    - 472 BRCA1+
    - OR for breast cancer associated with ever use of HT = 0.58 (95% CI = 0.35 to 0.96; P = .03)
  - Rebbeck 2005 (PROSE study)
    - 462 BRCA1/2 carriers
    - HRT after RRSO did not alter the reduction in breast cancer risk associated with RRSO (HR = 0.37; 95% CI, 0.14 to 0.96)

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IS HORMONE THERAPY SAFE?

- HRT, BRCA, and Breast Cancer Risk:
- Kotsopoulos 2016 –
  - 432 matched pairs of women with mBRCA1 mutation
  - Mean duration of HRT 4+ years
  - OR for breast cancer for HRT to never users = 0.80 (95 % CI 0.55-1.16; P = 0.24)

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IS HORMONE THERAPY SAFE?

- HRT, BRCA and Ovarian Cancer Risk:
  - Kotsopoulos 2006 – OR with ovarian cancer and ever use of HRT was 0.93 in mBRCA (95% CI = 0.56-1.56)
  - Guidozzi 2009 – RCT looking at HRT after ovarian cancer in all comers
    - No difference in disease free interval (P = 0.785) and overall survival (P = 0.354)

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OBJECTIVES

- **Discuss treatment options in BRCA carriers who have had breast cancer.**
  - Review HABITS and Stockholm trials
  - Explore non-hormonal, alternative therapies

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HABITS TRIAL

- Hormonal Replacement Therapy After Breast Cancer—Is It Safe?
- 442 followed for a median of 4 years
- New breast cancer in
  - 39/221 (17.6%) in the HRT arm
  - 17/221(3.2%) women in the control arm
  - (HR 2.4; 95% CI 1.3 to 4.2)
- The new breast cancer events in the HT arm were mainly local events
- No evidence for a higher breast cancer mortality rate

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STOCKHOLM TRIAL

- 10 year follow up of the Stockholm randomized trial:
  - 378 women followed for a median of 10.8 years
  - 188 of the women reported using oral HRT for a mean duration of 2.6±1.2 years
  - Women in the non–HRT group were allowed to use local vaginal estrogen
  - Found increased risk for recurrence only in the contralateral breast
    - HRT users 7.4%
    - Non–HRT users 2.1%
    - HR of 3.6 (1.2–10.9). .
  - No significant difference in new breast cancer events or breast cancer deaths
  - Prematurely closed owing to HABITS
  - Aimed to minimize progestin use

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SCREENING VS. MASTECTOMY

- In patients who are choosing breast cancer screening, i.e., mammography, MRI, clinical breast exams, it is important to remember that the goal of this approach is to catch an early cancer.
  - For young patients who are diagnosed with breast cancer, it is important to remember that the use of hormone therapy is not recommended.
  - This should be a consideration when patients are choosing between screening and prophylactic mastectomy.

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ALTERNATIVE PRESCRIPTIONS TO HORMONAL THERAPY

- Antidepressants - some clinical trial data to support use, often lower doses and faster onset of action than when used for depression
  - Venlafaxine, paroxetine, others
- Gabapentin - start low dose and titrate upwards, be aware of side effects
- Clonidine - 0.05mg PO BID
- Oxybutynin - 2.5 - 5mg PO BID

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ALTERNATIVE NON-PRESCRIPTIONS TO HORMONE THERAPY

- Soy - shows benefit in patients that are able to break down metabolites
- Exercise, weight loss - limited data specifically supporting relief of VMS
- Other “natural” products - studies limited, must be wary of safety and efficacy

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OBJECTIVES

- **Discuss treatment of genitourinary syndrome of menopause**
  - Understand the importance and prevalence of genitourinary syndrome of menopause
  - Differentiate between systemic and local estrogen therapies
  - Explore non-hormonal approaches to management

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GENITOURINARY SYNDROME OF MENOPAUSE

- Prevalence is high, and many patients do not mention symptoms to their health care providers
- Impact on quality of life is significant
- Symptoms are not all sexual - urinary symptoms are common and bothersome

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GENITOURINARY SYNDROME OF MENOPAUSE

- Local therapies are lower dosing compared with systemic
- Very little systemic absorption - remain well in menopausal range
- Does not require progestogen
- Breast cancer patient on Aromatase Inhibitor may be the only group unable to use

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GENITOURINARY SYNDROME OF MENOPAUSE

- Alternative management options:
  - "Utilize"
    - Vibrators, dilators
    - Sexual activity - with or without company!
  - "Moisturize"
    - Lubricants
    - OTC products for regular use

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OBJECTIVES

- **Explore some special considerations:**
  - Discuss the advantage of hysterectomy, from a hormone replacement perspective
  - Discuss the use of testosterone in hormone replacement therapy

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SPECIAL CONSIDERATIONS - ADVANTAGES OF HYSTERECTOMY

- From a hormone-replacement perspective:
  - Negating the need for a progestogen likely reduces a portion of the risk of developing breast cancer associated with the use of long-term hormonal therapy (WHI)
  - However, there are other ways to mitigate this potential risk:
    - Specific drug selected
    - Dosing regimen - cyclic or continuous

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SPECIAL CONSIDERATIONS - TESTOSTERONE THERAPY

- Not approved by Health Canada for use in women
- Must be used off-label, with close clinical follow-up
- Good data to support efficacy for treatment of hypoactive sexual desire disorder in women, especially those surgically menopausal
- Poor longterm data on breast safety

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CONCLUSIONS

- For the BRCA patient who underwent prophylactic surgical menopause:
  - Hormone therapy is appropriate.
  - Hormone therapy is considered safe.

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CONCLUSIONS

- For the BRCA patient who has had breast cancer:
  - Alternative therapies to systemic hormones exist.
  - Many patients may still use local estrogen therapy.

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RESOURCES

- North American Menopause Society
  - menopause.org
- Society of Obstetricians and Gynecologists of Canada
  - menopauseandu.ca
- The Daisy Network
  - Patient centred resource for POI patients
  - daisynetwork.org

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