CANADIAN MENOPAUSE SOCIETY
SOCIÉTÉ CANADIENNE DE LA MÉNOPAUSE

PROCEEDINGS
from

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SIGMA
Canadian Menopause Society
103-1089 W Broadway
Vancouver, BC, Canada
V6H1E5

www.sigmamenopause.com
sigmamenopause@gmail.com
T: 604-736-7267

Forward to Readers

September 11-13, 2015 marked the 2nd Sigma Canadian Menopause Conference. Hosted in Toronto, this event brought together the finest speakers and innovators in menopause management from across the continent and across the pond.

Recognizing the importance of nurturing young practitioners, several awards were made available to young physicians. Sigma presented five Young Menopause Scholar awards to trainees in fellowship programs or recent graduates from fellowship programs, including one international scholar.

With generous support from Pfizer Canada, twenty – four deserving young physicians were awarded Sigma/Pfizer Young Physician Awards in Menopausal Health.

These young practitioners have collaborated to produce this Conference Proceedings synopsis. Inside you will find a summary of the highlights of every session presented at the conference. For those who were able to attend, this document will be able to act as a reminder and fact finder. For those unable to attend, this will be an opportunity to share in some of the important knowledge shared during this event.

As you read this document, you will appreciate many different writing styles: however, the unmistakable undercurrent of enthusiasm unites all the pieces.

Thank you to the young Scholars and young Physicians for their important contributions, and to our industry sponsors for their support.

From the desk of
Dr. Denise Black, Editor-in-Chief

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FROM NAMS PERSPECTIVE
DR. MARGERY GASS

Over the last several years, NAMS (North American Menopause Society) has published position statements with regards to key topics in menopause management. These are described briefly below:

2012:

NAMS published a position statement on the use of hormone replacement therapy. The statement supports the use of hormone therapy for the relief of bothersome menopausal symptoms. It may also be used for patients to prevent osteoporosis in select patients. It cautions the use should be for only as long as needed for symptom control, and mentions an increase in breast cancer risk with combined estrogen and progestogen use after three to five years. It does not support the standard use of custom compounded hormone therapy.

2013:

NAMS published a position statement on the treatment of vulvovaginal atrophy (VVA) (or "genitourinary syndrome of menopause - GSM). If first-line over-the-counter treatments fail, patients should use local vaginal estrogen to treat symptoms (Ospemipene is another option for American patients). Cancer (breast and endometrial patients) should consult with their oncologists. Short term data do not support the need for concomitant progestogen therapy with local vaginal estrogen.

Estrogen use after the age of 65 is complicated. The Beers list (initially created in 1991) in the US is a contributing factor. This is a list of medications that have been deemed potentially harmful or inappropriate for patients over the age of 65. Systemic estrogen

therapy is on this list. Many physicians are leery to prescribe estrogen to their older patients, because the Beers list is used by evaluators (individual and system-based) to measure prescribing practices. Healthcare providers can receive letters telling them that how they are practicing is not within recommended guidelines (according to the Beers list)!

NAMS has written a rebuttal to the Beers list dilemma. It points out that many women have bothersome, significant symptoms after the age of 65. Initiation of hormone therapy is safest if started shortly within the menopausal transition. However, the Society states that it supports the "judicious use of hormone therapy for women after the age of 65". It also suggests that the Beers list might put estrogens in another category: "use with caution". NAMS supports the ongoing use of the lowest effective dose of MHT, provided the woman understands the risks, that she is under proper supervision, and she perceives a benefit from the therapy. It is a judgement made based on clinical decisions, between the patient and her care provider.

Dr. Gass also addressed several myths with regards to menopausal use of hormone replacement. She points out that hormones are not the fountain of youth, and are not prescribed to curb the aging process. She then reminds us that if any drug (or intervention) is to be used for primary prevention, it had better have a good safety profile, as the users in question may or may not have developed the disease as part of their natural history.

With regards to heart disease in women, she points out that heart disease increases as women age, and not as a direct outcome of menopause per se.

MHT- HOW LONG & HOW MUCH

When it comes to bone loss as women age, this is also a "natural" process, more so than it is pathologic. There is a rapid loss of bone that happens at the time of the menopausal transition, but this may be an equivalent loss to the extra mass that was accumulated in early adulthood. MHT also has a much higher number-needed-to-treat versus other commonly prescribed "bone meds", such as bisphosphonates.

Some final points mention that MHT is not a perfect solution. There are common side effects to the therapy, such as bleeding and breast tenderness. Patients may also undergo extra investigations, when compared to their peers not on similar therapies. Finally, there are potentially other harms of HRT including gallbladder disease, unknown cognitive detriments in some populations, and urinary incontinence.

HER MAIN TAKE-HOME POINT:

"The lowest dose of HT should be used for the shortest duration needed to manage menopausal symptoms. The decision to use HT should incorporate the woman's personal risk factors and her quality-of-life priorities in this shared decision."

(Notice she did not give a time or dose limit to this statement. It tells us to use clinical judgement based on individual patient needs and circumstances.)

MHT- HOW LONG & HOW MUCH

FROM SOGC PERSPECTIVE
DR. JENNIFER BLAKE

On duration, the SOGC 2014 Canadian Consensus Statement: Managing Menopause states that no clear recommendation on duration of therapy exists. Each woman should decide when it is time to stop MHT. In women with persistent menopausal symptoms, extended use may be required.

On dose, the SOGC Canadian Consensus Statement states that the lowest effective dose must be used. Women using standard dose should be advised to decrease the dose after a few years.

MHT AND BREAST CANCER:

The health care provider should periodically review the risks of MHT in light of the association between duration of use and breast cancer risks.

Duration of use is only one of the factors to consider in breast cancer risk:

- Choice of estrogen may be important. CEE alone has been shown to decrease breast cancer risk.
- Choice of progestogen may be a factor. Observational studies have suggested that use of progesterone, rather than a synthetic progestin, may reduce risk.
- Choice of regimen may impact risk as well. Continuous use of progestogen carries a greater breast cancer risk than sequential progestogen use.

MHT DOSING

There appears to be a dose-response relationship between stroke risk and MHT.

SUMMARY: Review MHT to reduce to lowest effective dose. On dose there is no simple answer: it is about balancing many competing and interacting risk and mitigating factors.

FROM IMS PERSPECTIVE
DR. NICK PANAY

On duration of therapy for MHT, the IMS states that women can have the option of MHT for as long as they derive symptomatic benefit and are aware of the risks for their regimen and personal circumstances. Women can try without MHT every few years, but symptoms in some women may last for many years and should be treated with the lowest effective dose of MHT.

For women with POI, the mainstay is estrogen and progestogen replacement, to be continued at least until the average age of natural menopause. Untreated POI increases the risk of CVD, osteoporosis, cognitive decline, dementia, and Parkinsonism.

DURATION OF THERAPY—CHD:

- MHT does not increase coronary events in women < 60 years of age, or within ten years of menopause. There is evidence that estrogen therapy may be cardioprotective if started around the time of menopause. Three recent trials have demonstrated this:
- DOPS (Danish Osteoporosis Study), 10 years in duration, showed a significant reduction in mortality and hospitalizations for MI and CHF in users of MHT.
- KEEPs (4 years in duration) showed no difference in CIMT between MHT treated and untreated groups.
- ELITE (6+ years in duration) showed the early treatment group had a reduction in progression of CIMT.

DURATION OF THERAPY—BONE

- No mandatory time limit for duration of MHT, although the protective effect of MHT declines after cessation of therapy.

MHT- HOW LONG & HOW MUCH

DURATION OF THERAPY—VTE

The risk of VTE increases with age. In higher risk women, lower dose transdermal estrogen therapy should be considered over oral.

DURATION OF THERAPY—STROKE

Stroke risk correlates with age. Stroke is a rare event before age 60. MHT increases the risk of ischemic stroke, significant after the age of 60.

DURATION OF THERAPY—MORTALITY

The most recent Cochrane analysis showed that women initiating MHT within 10 years of menopause had a reduction of all cause mortality of 0.70 (0.52-0.95) and a reduction of CV mortality of 0.52 (0.29-0.96).

DURATION OF THERAPY—COGNITIVE AGING

Overall, no significant cognitive benefits or harms of MHT were demonstrated, except for short term cognitive benefits shown in surgically menopausal women offered MHT right after oophorectomy.

DURATION OF THERAPY—BREAST CANCER RISK

The possible increased risk of breast cancer associated with MHT is small (<1 per 1000 women per year of use). This number is similar or lower than the impact of common lifestyle factors such as decreased physical activity. The data from the WHI demonstrated no increased breast cancer risk in first time users of MHT during the 5-7 years since initiation of therapy.

MHT- HOW LONG & HOW MUCH

DURATION OF THERAPY—GSM

Treatment of GSM needs to be continued indefinitely to maintain benefit.

SUMMARY:

There is no reason to place mandatory limitations on duration of MHT. Continuation of therapy is at the discretion of the woman and her health care provider.

DOSING:

Dosing and POI

Women with POI need higher doses of estrogen

Dosing and Stroke

Lower doses have smaller risks.

Dosing and Bone

Evidence exists for protection against loss of BMD with lower than standard doses of estrogen.

Dosage showed be titrated to lowest EFFECTIVE dose. Patients with POI generally require higher doses.

PROGESTERONE AND THE PROGESTOGENS : THE VILLAINS ?

DR. JAMES H. LIU

Progestin therapy should be guided by three principles, which include: preventing endometrial hyperplasia and cancer; reducing the frequency of withdrawal bleeding and side effects, and reducing the overall progestin exposure on accessory target tissues in order to improve patient's compliance. Irregular bleeding, dysmenorrhea, breast tenderness, increased breast density and mood changes are some of the side effects that may lead to poor compliance with hormone therapy. Progestins are structurally related molecules but form distinct agents. They are classified according to their carbon template and induce systemic response through their interaction with either Progesterone Receptor A (PR-A) or Progesterone Receptor B (PR-B). After oral intake, only 15% of the initial dose is available in the bloodstream following first pass effect in the intestines and liver. Oral progesterone is metabolized into different components such as 20αDHP causing brain sedation or 5αP acting mainly on breast tissue. An alternative and efficient way to deliver progesterone is by vaginal application. Progestins induce secretory changes in estrogen-primed endometrium, limit endometrial growth, and reduce the concentration of estrogen receptors. Progestin can be added to estrogen therapy either cyclically or in a continuous-combined way. When given cyclically, a simple method for determining if the optimal dosage of progestin is administered is to monitor withdrawal bleeding which should occur on day 11 or later. An alternative to previous regimens is the long-cycle progestin administration given every 3 to 6 months. However, there is a risk of endometrial hyperplasia ranging between 1,5% to 6,7%. Finally, some authors showed a reduction in daily symptom score and number of hot flushes with progestins alone.

SERMS—A NEW APPROACH TO MENOPAUSAL HEALTH
DR. DONALD MCDONNELL

New research suggests that post-menopausal women have an important biological role, as grandmothering appears to promote fitness of the species. If menopause is natural and good for the species, why are vasomotor symptoms and other discomforts still present at the time of menopause?

Many peri and post-menopausal women seek medical advice about management of menopausal symptoms. One of the most effective therapies, estrogens, are not widely used because of the association with breast cancer. The question also exists as to why some HT regimes are less likely associated with breast cancer: in the WHI study, women using conjugated equine estrogen (CE) alone had a REDUCED breast cancer risk.

One potential explanation is that all pharmacologically available estrogens are not the same. 17 B estradiol is pure estradiol: CEE is a combination of various estrogens, some of which may have selective tissue effects depending on the target tissue.

Selective Estrogen Receptor Modulators (SERMs) are compounds which have differential effects on estrogen receptors. They may act as an agonist at the the receptor and have estrogenic effects in the tissues, or they may act as an antagonist and have no estrogenic effect. SERMs are an area of intense interest in the management of menopausal symptoms.

In obstetrics and gynecology, many SERMs are familiar. Tamoxifen has been used for breast cancer treatment and prevention. Raloxifene is used for treatment of osteoporosis, and clomiphene has been used for years as an ovulation induction therapy. But all SERMs are not the same: we can use the knowledge of differential tissue selectivity to choose the best SERMs to create a new concept in menopausal HT.

New to menopausal HT is the concept of a Tissue Selective Estrogen Complex (TSEC), which is the combination of a different, well characterized mixture of estrogens with a SERM. The hope is that this complex will reduce the risks associated with HT (breast and endometrial cancers) while maintaining maximal benefit for treatment of menopausal symptoms.

There is one TSEC in North America, which has received FDA and Health Canada approval. It is a combination of CE and the SERM bazedoxifene. Bazedoxifene has shown to have very little stimulatory effect on the endometrium, and a positive effect on the breast, inhibiting tumour growth in both tamoxifen sensitive and tamoxifen resistant breast cancer in animal models. As CE has already shown a reduced breast cancer risk compared to 17 B estradiol, it is reasonable to assume that this TSEC will have protective effects in the breast.

TSECS—EXPLORING THE CLINICAL UTILITIES IN MENOPAUSE MANAGEMENT

DR. JOANNE PINKERTON

In post menopausal women with a uterus, estrogen alone therapy increases the risk of uterine cancer. Estrogen and progestogen in this population has been the gold standard, but 60-70% of women on these therapies will discontinue use during the first year. One reason for this is bleeding, which can result in an increased number of uterine procedures such as biopsy. A second reason is breast pain and tenderness, with a fear of breast cancer. This may result in an increased number of breast investigations and interventions. Clearly, there is a need for an alternative to conventional estrogen-progestogen therapy.

Tissue Selective Estrogen Complexes (TSECs) may be that alternative. A currently FDA and Health Canada approved thereapy includes conjugated equine estrogen (CE) and bazedoxifene (BZA), a selective estrogen receptor modulator (SERM). Unlike many other SERMs, BZA possesses sufficient antagonistic effect on uterine tissue to be safely paired with an estrogen.

This TSEC was evaluated in clinical trials, the SMART trials (Selective Estrogens, Menopause, and Response to Therapy). These were multiple trials which looked at different efficacy and safety aspects of this therapy. They were conducted in healthy, mostly younger post menopausal women with a uterus. The osteoporosis arm had a slightly older population studied.

In the vasomotor symptoms (VMS) study, compared to placebo, CE/BZA resulted in a 74% reduction in hot flush frequency, and 52% reduction in hot flush severity. Treatment effect was seen early, 2-3 weeks after onset of therapy, and was sustained for the duration of the trial.

The vulvovaginal atrophy study demonstrated a reduction in severity of vulvovaginal symptoms by 56%. There was restoration of normal vaginal histology and vaginal pH.

The prevention of osteoporosis study showed CE/BZA to be significantly better than placebo with respect to bone density, comparable or superior to raloxifene, and comparable or slightly inferior to CE/MPA (medroxyprogesterone acetate). This study was one year in duration.

The endometrial safety study showed a frequency of endometrial hyperplasia of <1% after 12 months, with a low incidence of asymptomatic endometrial polyps on ultrasound. There was a <0.5 mm increase in endometrial thickness over the study period. Amenorrhea rates were similar to placebo, with 94% of subjects reporting amenorrhea at one year.

Breast data was collected. The amount of breast tenderness seen in users of CE/BZA was comparable to placebo, and significantly less than users of traditional EPT. Breast density on CE/BZA was comparable to placebo, as opposed to the increased breast density seen with CE/MPA. Increased breast density is an independent risk factor for breast cancer. In the SMART trials, breast cancer incidence was similar to placebo, but the maximum duration of the trials was only two years.

In summary, the TSEC CE/BZA may offer another choice in the management of menopausal symptoms, with evidence of early efficacy for hot flushes, improvement in vulvovaginal symptoms, a positive effect on bone, endometrial safety, and high rate of amenorrhea. Early breast data is encouraging, with no evidence of increased breast density. Long term data on breast cancer with this therapy is currently not available, but data out to two years does not show an increased risk over placebo.

HORMONES AND THROMBOSIS
DR. SHANNON BATES

- VTE is one of the most harmful effects of HT
- Risk of VTE varies throughout lifespan
    - Main exogenous factor is hormone exposure
    - One of greatest risk factors for VTE is age
    - <20y = 1/100,000
    - 20-40y = 1/10,000
    - 40-80y = 1/1000 (**age 40 is the turning point)
    - >80y = 1/100
- Mechanism for increasing VTE risk with HT is not well known
    - Procoagulant: decreasing Favor VIII/fibrinogen, increasing Protein C resistance, increasing thrombin generation
    - Anticoagulant activity: decreasing ATT activity, decreasing protein S activity, decreasing tissue factor pathway inhibitor
    - Fibrinolytic activity (increasing TAFI and PAI-1)
- Data isn't consistent between studies
- More hemostatic effect with CEE < Oral E2 <Transdermal (? As a result of reduced first pass effect)
- Various studies of oral combined HT and risk of VTE
    - Generally positive OR 2-3x risk of VTE
    - HERS 2.7
    - WHI 2.1
    - WISDOM 7.4 (very wide CI)
- Therefore, absolute risk is likely an additional 1-2/1000/year
- CEE adjusted OR of VTE = 2.08 vs. Oral estradiol = 1 (reference)
    - Smith 2014 (but not RCT; observational and small numbers)

- Systematic review by Olie et al, 2010 – Current opinion in hematology
  - Oral estrogen OR 1.9 vs. TD estrogen (1.0)
  - But all data from observational studies, so can't be called definitive data
- Progestogen contribution to risk of VTE
  - Canonico et al, Maturitas 2011
  - E + P = increased risk of VTE OR 2.3
  - E alone = increased risk of VTE 1.7

    But difference wasn't statistically significant
- WHI: E alone 1.32 vs. 2.09
- WISDOM: results were not statistically significant
- Thus, we don't really know the impact of progesterone on VTE
- ? lower risk with micronized progesterone and pregnane derivatives vs. non-pregnane derivatives (but again, all based on observational data)
- VTE risk in Tibolone: Pooled risk 0.5 (but CI are very broad)
- Women with prior VTE:
  - Olie et al, 2010
  - Rx of HT was associated with a marked increased risk of VTE (7.8x) in women with a prior clot
  - Same study showed likely no increased risk in TD therapy show an increased risk over placebo.
- Hereditary Thrombophilia:
  - Group I = inhibitor deficiencies (AT, Protein C/S)

    Very rare; often lethal if homozygous; VTE risk by 60 years >50%

- Group II = gain of function (single gene defects; ie. FVL)
  - More common; heterozygote FVL ~5% of population
  - Heterozygote FVL almost approximates risk of normal population
- Combined oral HT:
  - On average, associated with 5x risk of VTE
  - HT increased the risk by 3-4x from baseline
  - If FVL and HT risk is multiplied ~15
  - Prothrombin gene mutation and HRT = very small risk increase (not statistically significant); 2.4-2.9
- ESTHER Study Subgroup analysis
  - FVL and PT gene mutation = 2.6 and 6.4 x increase at baseline
  - Reduction in risk with TD seen in PT gene mutation

Risk of Combined Oral HT-related VTE Risk

Patient characteristic	%/yr
No family history	0.3
Positive family history	0.6
AT deficiency	7.5
PC or PS deficiency	3.0
FVL homoygote	15.0
FVL heterozygote	1.5
PT gene mutation	0.6

- For women on HT pre-op; more important to prophylax them pre-op than to worry about withdrawing HT long in advance
- If they develop a VTE on HT
    - Stop HT and anticoagulate for 3-6 months
    - If ongoing HT is warranted; good quality anticoagulation must be continued for duration for hormonal therapy

Recommendations:

- Combined > Oral estrogen > TD
- Comparatively lower risk with micronized progesterone and pregnane derivatives
- Avoid oral HT in:
    - Women with a personal history of VTE
    - High risk thrombophilia and family history of VTE
- Proceed with caution
    - VTE in 1st degree relative with or without lower risk thrombophilia
    - Multiple clinical risk factors
- Transdermal HT could be considered in women at risk of VTE, if quality of life is severely affected
- All women who are on HT pre-op receive prophylaxis
- SLE + antiphospholipid antibodies (APLA); no HT

DIABETES AND MENOPAUSE
DR. CYNTHIA STUENKEL

1) DIABETES MELLITUS

a) Classification: Diabetes Mellitus (DM) is a disease that affects glucose processing. It can be further classified into Type 1 and 2 DM. Type 1 DM, also known as insulin-dependent diabetes mellitus (IDDM), is usually diagnosed in childhood/early adulthood. In this condition, there is little or no production of insulin from the beta cells of the pancreas. In comparison, Type 2 DM is non-insulin dependent diabetes mellitus (NIDDM), characterized by insulin resistance, with the average age of onset later on in life.

b) Pre-Diabetes: Pre-diabetes represents another category where a patient's glucose level is above the normal range, but not high enough to be in the diabetic range. This can be further divided into impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) which are measured when the patient is fasting vs non-fasting respectively.

c) Diagnosis: The diagnosis of pre-diabetes and diabetes can be summarized in the table below, taken from the Canadian Diabetes Association (CDA) Guidelines.

d) Prevalence and Impact of Disease: The prevalence of Diabetes is high and continues to increase linearly with time. This disease also has significant health impacts including increased cardiovascular risk, hospitalizations, depression and even death.

e) Screening: Patients ≥40 should be screened every 3 years or more frequently (ie: every year) for those patients who have pre-diabetes or multiple risk factors.

DIAGNOSIS OF PREDIABETES & DIABETES

Test	Result	Dysglycemia category
FPG (mmol/L) No caloric intake for at least 8 hours	6.1 – 6.9	IFG
	≥7.0	Diabetes
2hPG in a 75 g OGTT (mmol/L)	7.8 – 11.0	IGT
	≥11.1	Diabetes
A1C (%) Standardized, validated assay, in the absence of factors that affect the accuracy of A1C and not for suspected type 1 diabetes	6.0 – 6.4	Prediabetes
	≥6.5	Diabetes
Random PG (mmol/L)	≥11.1	Diabetes

If asymptomatic, a repeat confirmatory test (FPG, A1C, or a 2hrPG in a 75 g OGTT) must be done. If symptomatic, diagnosis made, and begin treatment.

2) THE LINK BETWEEN DIABETES AND MENOPAUSE

a) Recent Studies: The objective of the EPIC-InterAct study was to examine the relationship between menopausal age and diabetes risk. This was a prospective study with 3,691 post-menopausal women with type 2 DM and 4,408 subcohort patients. The median follow-up was 11 years and several risk factors for type 2 DM were assessed. The conclusions of this study illustrated that early menopause was associated with a greater risk of developing Type 2 DM. However, other risk factors such as smoking, body mass index (BMI) and waist circumference did not have an impact on the findings.

Further studies assessed the link between having surgical menopause (ie: hysterectomy with bilateral oophorectomy (BSO)) with diabetes risk. An earlier age of menopause (natural or surgical) and a shorter reproductive lifespan had a linear relationship with the development of Type 2 DM.

In patients with Type 1 DM, some initial research did suggest a possible association with earlier menopause, but newer trials do not support this conclusion.

In the Diabetes Control and Complications Trial (DCCT), rigorous versus conventional treatment of Type 1 DM patients was studied. The purpose of the study was to determine the potential impact of diabetes treatment on menopause. There were 657 women included in this randomized controlled trial with an average 28 years of follow-up. At that point, 240 (38%) of women had experienced natural menopause and 115 (18%) had surgical menopause. There was no difference in menopausal risk between the intensive versus conventional treatment group.

b) Distinguishing Diabetes from Menopausal symptoms:
Menopausal related vasomotor symptoms can often be mistaken as a symptom of low blood glucose. As a result, regular glucose monitoring is important for diabetic women to distinguish between menopausal symptoms and low glucose levels.

c) Effect of Hormone Replacement Therapy on DM: The HERS trial demonstrated that women on Hormone Replacement Therapy (HRT) had overall lower Glucose levels then those not on hormone therapy. HbA1C appeared lower on those with oral hormone replacement; however, the reduction was not seen in those on transdermal therapy. The Postmenopausal Estrogen/Progestin Interventions (PEPI) study found that women on HRT have lower fasting glucose levels but elevated post prandial glucose levels. The WHI study showed a 15% to 20 % reduction in diabetes in women on HRT, a decrease in glucose levels in diabetics as well as preventative effects on the age appropriate rise in glucose levels. Despite the findings of these studies, the safety of HRT treatment to help with glucose levels is unknown, and therefore, overall insufficient evidence to justify HRT use for diabetes prevention. Instead, prevention of DM should include weight loss, exercise and the use of metformin.

D) DM and cancer: Women with diabetes are at increased risk of developing breast, colon and endometrial cancers. Awareness of the increased risk is essential for appropriate management and screening.

HPV INFECTIONS AND MID-ADULT WOMEN
DR. NANCY DURAND

When looking at oncogenic types of HPV (type 16 and 18), the bivalent vaccine offers 93% efficacy, compared with the 98% efficacy offered by the quadrivalent vaccine. This data comes from a comparison of patients who had normal or low-grade cytology at baseline, received all three doses of the vaccines, and were assessed on the first day after the third dose. The reported efficacy is based on the development of CIN2 or higher grades of dysplasia. [1,2]

The data is also favourable for the quadrivalent vaccine when comparing efficacy for preventing genital warts. The vaccine is overall 99% effective in preventing genital warts. [3]

According to Health Canada the HPV vaccine approved indications prior to Feb 2015 were are follows:

1. Bivalent vaccine (covers type 16 and 18) – for females 10-45 years old with CIN, AIS cervix, or cervical cancer
2. Quadrivalent vaccine (covers type 6, 11, 16 and 18) – for females 9-45 years old with CIN, AIS cervix, cervical cancer, VIN, VAIN, vulvar and vaginal cancer, AIN and anal cancer, external genital warts. It is also approved for males 9-26 years old with external genital warts, and AIN or anal cancer

According to the National Advisory Committee on Immunization (NACI), as of December 2014, all females age 10-13 should be offered routine vaccination against HPV, with a catch up range of 14-26 year old women. They acknowledge that the vaccine can be given to women over the age of 26 with no upper limit. They do recommend it for any women with a current or past history of abnormalities on pap, cervical cancer, or external genital warts.

With respect to men, they recommend the quadrivalent vaccine for the prevention of external genital warts, AIN, anal cancer, PIN, and penile cancer. There is no upper age limit for administration to males

The reason for heavily targeting women is that they remain at high risk throughout their lifetimes. The highest risk is in the younger cohorts; however, the cumulative risk of HPV infection remains above 10% over the course of 5 years for women above the age of 40. In one study of on-line dating females age 25-65, the prevalence of HPV DNA was 35.9% and it was unrelated to age[4]. Therefore, middle age women remain at high risk of HPV infection.

In the future III trial women age 24-45 were randomized either to the quadrivalent vaccine group or placebo. There were all free of a history of LEEP, hysterectomy, HPV disease or genital warts in the past 5 years. They received pap testing every 6 months for 48 months and colposcopy if they developed ASCUS or a higher grade lesion. The quadrivalent vaccine was 89% effective at protecting against persistent infections, 83.3% effective against CIN2/3 or higher grade lesions, and 100% effective against external genital lesions.[5,6] Of note is the point that women over 25 years of age have more persistent HPV infections and higher chance of progression of infection thus leading to a higher risk of cervical cancer, compared to women under 25 years old, 80% of whom clear HPV infections

In the Future I and II trials of the quadrivalent vaccine, two groups of women were studied: those who were HPV negative and those who were HPV positive. Both groups of women were healthy, age 15-64 years old, had a lifetime of 4 sexual partners at most. They were followed for an average of 3.6 years. 15% of these women were

HPV sero-postive but HPV –DNA negative, meaning that they had cleared past disease. These women were followed for the development of disease due to the same type of HPV that they were previously infected for. The immunized group showed no cases of reinfection/reactivation with the same HPV type compared to the placebo.[7] Furthermore, in the larger group there was a 65% reduction of CIN2/3 lesions in the immunized group regardless of the HPV type.[8] Even vaccination after LEEP for CIN 2/3 lesions reduced the recurrence in the vaccinated group to 2-5% compared to 7-10% in the placebo group.[9] Therefore it is worthwhile to offer the quadrivalent vaccine to women who have had HPV infection in the past.

The availability of the new nonavalent HPV vaccine has opened the door for the next generation in HPV prevention. The new vaccine covers types 6,11,16,18 as well as five new types: 31, 33, 45,52, and 58 (all of which are oncogenic types of HPV). It has the potential to prevent 90% of cervical cancers and 75-80% of HSIL. It follows the same dosing schedule as the quadrivalent vaccine at 0, 2, and 6 months. Of interest is the fact that the previously covered oncogenic types (16 and 18) had their highest prevalence in the younger age groups (typically less than 35 years old for HSIl and 30 years old for cervical cancer). The five new oncogenic types, have the highest prevalence in the older group of women, with prevalence increasing with age.[10,11]

When comparing the nonavalent versus the quadravalent vaccine in randomized trials, the nonavalent vaccine results in a 96.7% efficacy of reducing high grade lesions due to the five additional HPV types, as well a 97.1% efficacy of any grade lesion due to these HPV types, and 96.0% efficacy in reduction of persistent infections with these HPV types after 6 months.[12] With regard to its immunogenicity, the nonavalent vaccine is non-inferior to the quadrivalent vaccine, and there is no decrease in the efficacy of the original four types by the addition of the other five types of HPV. The adverse effect profile of

the two vaccines are also very similar with the exception of increased local-site reactions with the nonavalent vaccine on days 1-15 after immunization. These, however, are generally mild to moderate in intensity. Finally, the nonavalent vaccine is endorsed by Health Canada for the same indications as the quadrivalent vaccine.

IN SUMMARY, the message is simple. There are clear benefits to offering women HPV immunization including women who are over the age of 26 and those who have had pap abnormalities or tested positive for HPV in the past. It can simply be stated that the vaccines are effective, safe and recommended.

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ADULT IMMUNIZATION UPDATE
DR. JAY KEYSTONE

Vaccines have varying impact on the immune system response of body depending on age. Immunosenescence, referring to the gradual deterioration of the immune system brought on by natural age advancement, explains why childhood vaccines are able to prevent illness in children, but not in adults. Most adult vaccines do not prevent infection, but can reduce morbidity and mortality.

As a woman ages and reaches menopause, the deprivation of estrogen increases the pro-inflammatory serum markers within the body, decreasing CD4 T- and B-lymphocyte counts and decreasing the cytotoxic activity of Natural Killer Cells. This implies that post-menopausal woman have a higher susceptibility to infection.

Taking on a stance of preventative medicine, and not curative medicine, Dr. Jay Keystone discussed three different immunization topics:

1) INFLUENZA

Influenza vaccine is especially important in elderly patients, and those with increased morbidity and mortality from influenza: obesity, pregnancy, immunosuppression, metabolic disease (eg. diabetes), chronic lung disease and heart disease. However, from a epidemiological standpoint, it is important that we also encourage younger patients (who have better immune responses) to immunize themselves, in order to protect the older patients, who's response to immunization may be less effective.

There are two available types of vaccines: trivalent (two A-serotypes, one B-serotypes) and quadrivalent (two A-serotypes, two B-serotypes). The National Advisory Council on Immunization (NACI) does not currently recommend giving the quadrivalent vaccine to adults. However, there are no specific recommendations for trivalent or quadrivalent vaccines for adults.

The influenza vaccine also appears to reduce the incidence of myocardial infarction and strokes for patients at risk. Recent studies suggest that the influenza vaccine is able to reduce the incidences of serious sequelae from influenza infection.

2) PNEUMOCOCCAL INFECTION

Streptococcal pneumonia is a major cause of death in individuals greater than 65 years old and immunocompromised. There are two available vaccines: Pneumovax23, a polysaccharide vaccine; and Prevnar13, a conjugate vaccine. The former, when interacted with B-cells leads to plasma cell multiplication and antibody production, but do not stimulate memory cells. Future exposures following the immunization may potentially result in a decreased response depending when the vaccine is given again. The later vaccine, conjugated Prevnar13 vaccine, has a carrier protein added to the polysaccharide vaccine, which stimulates antibody production and memory cells, and also leads to carriage reduction.

Pneumovax23 (Polysaccharide vaccine) is effective in preventing invasive disease (pneumonia with bacteremia), which only occurs in approximately 20-25% of pneumococcal pneumonia infections. It does not stop non-invasive bacteria pneumonia, nor does it prevent mortality.

Prevnar13 (conjugated vaccine) has recently been approved for use in patients over 18 years old. When possible, it is always recommended to give Prevnar13 before Pneumovax23. Usually, the doses are separated by 2 months for patients who are immunocompromised, and up to 1 year for healthy individuals. However, if Pneumovax23 has already been given first, the next vaccine of Prevnar13 would need to be administered at least 1 year later (in order for B-cells to repopulate). The immune response is not nearly as good if the subsequent vaccine is given too early.

Highest risk individuals (over 2 years of age) include:

- functional or anatomic asplenia
- sickle cell disease
- SC or organ transplant
- lymphoproliferative malignancy
- HIV infection
- liver, lung, kidney and DM
- Immunosuppression related to disease or therapy

They should receive Pneumovax23, followed by another Pneumovax23 booster 5 years later. They would also be eligible to receive Prevnar13 as well.

High risk individuals include:

- alcohol
- smoker
- homelessness
- illicit drug use
- asthma

They require one dose of Pneumovax23. But should also be considered for PCV13 + PPV23

Lowest risk individuals (healthy), should be considered for PCV13 + PPV23 for healthy individuals greater than 65 years old.

Ontario funding of vaccine for those greater than 50 years old include:

- immunosuppression, HIV infection
- sickle cell disease
- asplenia / coelia disease
- HSC or SO transplant
- lymphoproliferative malignancy

3) SHINGLES

Shingles confers a 30% lifetime risk (Brisson M, CIC 2004). This risk reaches 50% by the time a person reaches 80 years of age. Among those who have shingles, 15% have post-herpetic neuralgia (defined as chronic pain lasting greater or equal to 3 months), among which 70% suffer a moderate to severe degree of pain. Immunosuppression also leads to a greater risk of susceptibility to shingles from baseline, with autoimmune rheumatic disease resulting in a two-fold increase, diabetes > 65 years of age leading

to three-fold increase, and with 17x increase if multiple family members have experienced it.

Vaccination against shingles should be considered for patients greater than 50 years old because it may prevent morbidity. According to The Shingles Prevention Study, severity is reduced by 65.5% for individuals between 60-69 years of age, 55.4% for those greater than 70 years old.

The vaccine may last for at least 5 years with full benefit from The Shingles Prevention Study. However, after those 5 years, there will be a slow decrease in efficacy up to one decade. By 10-11 years, there will be nearly 50% decrease in the efficacy of the vaccine.

It is approved for those greater than 50 years of age, and recommended to those greater than 60 years old. If an individual has had shingles before, administration of the vaccine is still advised because recurrence risk is still approximately 8% over 10 years. However, it should be done at least 1 to 3 years after the shingles infection.

The vaccine is contraindicated for lymphoproliferative disorders, such as lymphoma, leukaemia and multiple myeloma. But it still can be administered to patients with solid tumour cancer, on low dose of immunosuppressants or biologics. It can also be administered concurrently with Pneumovax23 or Prevnar13.

There is also a new vaccine, manufactured by GlaxoSmithKline (NEJM 2015;372:2087-96). It shows promising efficacy rates of 97%. However, this 2 dosed vaccine is still not available in Canada and has significantly higher adverse events ranging between moderate to severe symptoms (17% for experimental group versus 3% for control group). It is still advisable to still leave the choice up to the patient.

Dr. Keystone concluded his talk by advising clinicians to make immunization counselling a part of each of our encounters.

MEMORY AND ATTENTION IN MIDLIFE WOMEN
DR. PAULINE MAKI

Dr. Maki began her talk outlining the clinical importance of memory and attention for women in midlife and beyond. It was explained that women show a lifelong advantage in verbal memory compared to men and that this is thought to be related to organizational effects of sex steroid hormones on the brain systems underlying memory.

New and emerging data show that women can mask changes related to dementia. Neural systems that support memory are laid down in utero. Declines in verbal memory are the earliest signs of Alzheimer's dementia and are central to its diagnosis. New findings suggest that women are able to maintain their verbal memory early in the course of Alzheimer's dementia and then rapidly decline.

How does this relate to the role of memory and attention in midlife women? In the menopausal transition there are increased complaints of "forgetfulness". This starts in early perimenopause and can be associated with less education, lacking employment and being older than 44 years old. If women have more severe memory complaints this is associated with worse performance on memory tasks such as the California Verbal Learning Test (CVLT). Subjective memory complaints have also been shown to correlate with scores on tests of attention in midlife women. Delayed memory performance is tied to menopausal status - women perform worse in perimenopause and then once they are post-menopause demonstrate the ability to learn again. This ability to "bounce back" post-menopause was shown in the Penn Ovairan Aging Study. Concurrent depression and anxiety symptoms are associated with lower processing speed but no symptom was able to account for the lower performance in late perimenopause as compared to early perimenopause.

Objective memory performance also depends on menopausal status. Women's fine motor skills are affected and they perform worse in early postmenopause. Women begin to experience these changes in memory as FSH begins rising and estrogen is declining. This is also seen in causes of surgical induced menopause following oophorectomy where verbal memory shows a decline post surgery. Interestingly adding estrogen back in these women demonstrates a rebound effect in memory. The Mayo Clinic Cohort Study of Oophorectomy and Aging showed that the removal of ovaries before age 48 increased the risk of Alzheimer's dementia by 70% and that using estrogen removed that risk.

Interestingly memory performance is unrelated to reported vasomotor symptoms. However increased objective vasomotor symptoms are associated with worse verbal memory. Using biological skin conductance monitors showed that women underreport vasomotor symptoms by about 40%. The placebo effect is not evident when vasomotor symptoms are measured objectively. The number of hours of sleep obtained independently predicts worse memory. A greater number of objective vasomotor symptoms are associated with greater connectivity between brain regions when the brain is in "default mode". There is hyperconnectivity in the hippocampus and prefrontal cortex. This is also seen in depression where there is greater functional connectivity. More vasomotor symptoms are associated with greater white matter hyper intensity. White matter hyper intensity serves as a marker for stroke and dementia. There are adverse effects on brain function and structure with an increase in objectively measured vasomotor symptoms. Dr. Maki concluded her discussion with indicating that more study is needed in this area.

HOT FLASHES: MORE THAN A MINOR NUISANCE
DR. JOANNE PINKERTON

PATHOPHYSIOLOGY OF HOT FLASHES:

Hot flashes, sleep, and depression are all inter-related. Thus, treating one of the above will in fact equate to improvement in all three domains. If you are one of the 25% of women who have bothersome symptomatic hot flashes, you have a narrower window for temperature fluctuations and more easily get hot or cold.

PREVALENCE OF VASOMOTOR SYMPTOMS:

We now know that hot flashes can persist beyond the 3-5 years we previously thought. The recent Penn Ovarian Aging study looked at the overall duration of menopausal symptoms. This study found that the median duration of vasomotor symptoms was 10.2 years and up to 11 years when they included those women in the peri-menopausal transition. A study published in JAMA in February of 2015 reported that 80% of menopausal women had hot flashes and these symptoms lasted anywhere from 7-15 years. They also emphasized that the duration of vasomotor symptoms was longer if the women were of lower socioeconomic status, had lower education, were under greater stress, or were suffering from depression or anxiety. They also concluded that African American women had a mean duration of symptoms of 10 years while Asian women were symptomatic for an average of 5 years. Overall, we have learned that vasomotor symptoms can last much longer than we initially realized.

MENOPAUSE AND SLEEP:

Women in the menopausal transition have increased sleep disruption secondary to hot flashes. Insomnia, then, leads to increased stress, anxiety, depression, and tension. Sleep disruption tends to occur in the first half of the night. It is unclear whether the problems experienced are age-related changes in the brain, hormone levels with hot flashes, or secondary to life stressors.

HEALTH RISKS OF HOT FLASHES:

Emerging evidence has demonstrated a link between hot flashes and cardiovascular disease. This was discussed at length in another conference session. Research has also shown that there is greater white matter disease in women who experience hot flashes which is believed to result from less blood flow to the brain. It is reasonable to imagine that the patients we see on a daily basis who are having 6-10 hot flashes per day, drenching night sweats, emotional lability, fatigue and mental fatigue, vaginal dryness, urinary symptoms are subjected to higher health risks overall.

MENOPAUSE HORMONE THERAPY:

Menopause hormone therapy is the most effective treatment for hot flashes and in women under age 60 the overall benefits are more likely to outweigh the risks. Multiple studies have shown that hormone therapy reduces the frequency of hot flashes by approximately 77%. It can take up to 4-6 weeks to see the full effect, especially at lower doses. If you start a patient on estrogen and see significant improvement in symptoms within 3 months and then discontinue estrogen and switch over to placebo, hot flashes are likely to come back, but can take up to 8 weeks to return.

NON-HORMONAL TREATMENT FOR MILD HOT FLASHES:

Common non-hormonal treatments for hot flashes include black cohosh, dong quai, ginseng, evening primrose oil, red clover, and homeopathy. These therapies are often considered in patients who cannot take estrogen. Overall, studies of these treatments have not demonstrated significant improvements in vasomotor symptoms compared to placebo. Hypnosis may have some benefit. Yoga improves overall quality of life and thus can help with hot flashes. Acupuncture may be a reliable and safe option with benefits lasting up to 6 months in duration, but requires additional study. Further studies on acupuncture, though, are difficult as the very nature of the therapy makes creation of reliable study designs difficult to achieve.

ALTERNATIVE NON-HORMONAL TREATMENT MEDICATIONS FOR HOT FLASHES:

Antidepressant SSRIs can decrease the frequency of hot flashes from 35-50% from baseline while SNRIs are even more effective with reductions in hot flashes from 60-70% from baseline. It is important to keep in mind that higher doses of antidepressants are not necessarily better. Higher doses can actually increase that medication's side effect profile and potentially reduce quality of life in our patients.

Low-dose Paroxetine salt 7.5 mg po daily is the only non-hormone FDA-approved treatment for vasomotor symptoms in the United States. This treatment has been shown to reduce severity and frequency of hot flashes, improve sleep and sleep duration while also remaining neutral in terms of weight gain or sexual dysfunction.

Escitalopram 5-10-20 mg po daily has been shown to decrease the severity of hot flashes while reducing the number of hot flashes by 4.5 hot flashes per day over a period of 8 weeks. This is an effective treatment option for women with breast cancer and can significantly improve quality of life.

Desvenlafaxine 100 mg po daily also decreases the number and severity of hot flashes. Its effects can be seen within 1 week of therapy and can significantly decrease night-time awakenings. It is important to monitor for elevated blood pressures while using this medication. Patients should be warned that they may experience nausea and sedation for 1-2 weeks every time the dose is increased. Desvenlafaxine is also a good choice for patients with breast cancer and has an additional benefit of reducing anxiety.

Gabapentin can decrease both the frequency and severity of hot flashes. Initially start dosing at 300 mg at night then after 2 weeks increase to 600mg at night and then after an additional 2 weeks add an extra 300 mg dose during the day for a total daily dose of 900 mg which has been found to be the most effective dose to manage hot flashes. It is important to warn patients about sedation and drowsiness prior to initiation of gabapentin.

CONCLUSIONS:

We now know that hot flashes can last a lot longer than we initially thought; up to 15 years! Additionally, a small group of people will still experience hot flashes into their 70s and 80s. While hot flashes are a nuisance, it is also important to consider the health risks and implications that these symptoms can have on women.

Consider hormone therapy or alternative non-hormonal therapies to maximize quality of life. In women who have been on hormone therapy for long durations, it is reasonable to try to reduce or eliminate hormone therapy for a 3 month period; if the hot flashes return, resume hormone therapies at a low dose as needed. If a patient is not a candidate for hormone therapy, consider one of the non-hormonal treatment options. There are many off-label medication choices to manage vasomotor symptoms and in complicated situations, combining therapies can also be an effective strategy to manage symptoms. Finally, with persistent symptoms and failed medication trials, it is always important to consider other potential causes of night sweats such as tuberculosis and mycobacteria avium. Overall, we do have an extensive repertoire of therapeutic options to help women who are struggling with hot flashes.

GETTING TO THE HEART OF THE MATTER: CARDIOVASCULAR HEALTH AND WOMEN

DR. MARTHA GULATI

Although the overall cardiovascular death rate is declining, women are still more likely than men to die from cardiovascular disease (CVD), and those women who survive cardiovascular events are likely to have a poorer outcome. Although there is the popular perception that breast cancer is the leading killer of women, in the USA in 2011, there were 10X more deaths due to CVD than breast cancer. A woman's lifetime risk of CVD at age 40 is 1 in 2, compared to a lifetime breast cancer risk of 1 in 8.

In spite of these numbers, "women's health" has always had a bikini approach to care. Women's health is traditionally thought to encompass only the breasts and reproductive organs, which were the only things thought to distinguish women from men. It may be time to consider that women are much more than just small men, and that a gender-centric approach to cardiovascular care is indicated.

Women who present with symptoms of angina or EKG abnormalities are less likely than men to have exercise EKG testing, less likely to get coronary angiography, are less likely to be placed on statin and antiplatelet therapy, and are more likely to die from a CV event. Among younger women presenting with STEMI, their overall quality of life is significantly lower after the episode compared with similar aged men with STEMI. There is underutilization of evidence based treatments in women, including both medical and procedural treatments. This has been shown in a Canadian registry of acute coronary syndromes to result in a statistically significant increased death rate in women compared to men.

Women report more anginal symptoms than men, despite lower rates of obstructive coronary artery disease (CAD). One out of three women with unstable angina will have no visible obstruction on angiography. Much of the focus on management is on obstructive CAD, as most early studies of CAD were done on men. It appears that the pathophysiology of CAD differs in women. The male pattern of CAD is obstruction. The female pattern appears to be more due to microvascular disease and subendocardial ischemia.

The current working model of ischemic heart disease in women surmises that an inflammatory milieu is the inciting factor for clinical disease. Some of the causes of this inflammation may be hypertension, obesity, hyperlipidemia, autoimmune disease and hypoestrogenemia. This inflammatory milieu then causes abnormal vascular reactivity. This may be due to endothelial dysfunction caused by the inflammation, or microvascular dysfunction such as hyperreactivity. This in turn causes some coronary remodeling, which may result in CV symptoms. This subendocardial ischemia may be responsible for the higher incidence of heart failure seen in women.

The optimal diagnosis and management of heart disease in women is still evolving, but it is important to approach heart disease in women with a different mindset than heart disease in men.

CARDIOVASCULAR HEALTH AND MENOPAUSE HORMONE THERAPY
DR. HOWARD HODIS

We know that best practices in primary prevention and treatment of coronary disease is different for women than for men. Concern was raised by the results Women's Health Initiative, which studied women who were older and had increased body mass indices. Over 60 years of observational studies have shown that heart disease and stroke risk decreases with use of menopause hormone therapy when it is started early to treat vasomotor symptoms. More specifically, evidence shows that when HT is initiated less than 10 years from menopause in women who are less than 60 years old a protective effect occurs.

Further observational studies have shown that risk of coronary disease decreases with early initiation and longer duration of HT. Mortality rates worsened in women who stopped HT following the release of the WHI. Recently, the ELITE trial examined women taking HT consisting of oral estrogen plus vaginal micronized progesterone vs. placebo. Those women who initiated HT less than 6 years post menopause (median time 4 years) had a significant beneficial treatment effect on carotid artery intima-media thickness. The study duration was average 6 years, with some participants longer than 6 years. Women who started HT more than 10 years since menopause (median 15 years) showed no treatment effect.

When we compare HT to other forms of primary and secondary prevention of cardiovascular disease, it is important to look at studies with female participants as opposed to extrapolating data from studies examining men. Lipid lowering statins have been shown to have no effect on cardiac events or mortality when used as primary prevention in women. When used-post event as secondary prevention we see a decreased number of events but no change in mortality. Daily ASA has been shown to have no effect on heart disease, ischemic events or mortality in women; however it does decrease rates of ischemic stroke. ACE-inhibitors in women as primary prevention have not been shown to have any beneficial effect on heart disease or mortality.

Compare this to HT, which deceases rates of heart disease and mortality by 30-40%. If we think beyond the current paradigm, we're going to extend life and improve primary prevention of heart disease in women.

WHAT HAPPENS DOWN THERE?
DR MARGERY GASS

Dr Gass' presentation discussed the postmenopausal anatomic and physiologic changes in the genitourinary system as well as the symptoms associated with genitourinary syndrome of menopause (GSM).

Estrogen levels in the vulvovaginal area varies during a woman's lifespan. It goes from a low estrogen level in the pre pubertal years, to a high estrogen level during the reproductive years and back down to a low estrogen level during the postmenopausal years. These changes affect susceptibility to yeast infection and bacterial vaginosis, which will be much more common during the reproductive years. The incidence of these infections together with the normal amount of vaginal discharge decrease as the amount of estrogen decreases. Therefore, menopausal women treated with hormonal therapy will be more susceptible to yeast infections and bacterial vaginosis.

Menopause is a normal phase of a woman's life. Medical terminology such as kraurosis vulvae, atrophic vaginitis and vulvovaginal atrophy were thought to be too pejorative when describing the genitourinary changes of menopause. The term genitourinary syndrome of menopause was created to describe the collection of signs and symptoms associated with the decreased level of estrogen. These signs and symptoms are wide and included genital dryness, pain with intercourse, dysuria and urinary frequency, decreased elasticity of the vagina, labia minora resorption, tissue fragility and the list goes on. Treatment is indicated when the symptoms are bothersome and should be individualized for each patients.

There is some evidence to support changes in the vaginal flora after menopause, more specifically with the lactobacilus species. Furthermore, there seems to be various types of vaginal microbiome.

Patients with a prevalence of certain types of bacterias in their microbiome were more likely to have clinical signs of vaginal atrophy. These are very recent findings and caution was advised to wait before recommending using probiotic until the topic is better understood.

The decreased estrogen state also brings changes to the epithelium in the bladder and urethra. This is associated with an increased prevalence in bacteriuria, going from 5% in younger women up to 15-20% in women from 65-70 years and 20-50% in women older than 80.

All women with GSM should be counselled on the available hormonal and non hormonal treatment options. The non hormonal treatments consist of vaginal lubricants and moisturizers. Dysuria and urgency symptoms may be treated with a low dose vaginal estrogen, as use of non-hormonal therapies will not help these symptoms. For recurrent urinary tract infections vaginal estrogens, DHEA, testosterone and probiotics could be considered. Progestogen is not routinely recommended with the use of low dose vaginal estrogen, although safety studies do not extend beyond one year. Any bleeding in a postmenopausal women should be investigated, and women with higher risk of endometrial cancer may required additional monitoring, such as transvaginal ultrasound or progestogen test, when treated with a vaginal estrogen. Finally, increased sexual activity greater then 3 times per month (including both coital activity and masturbation) has shown to help decrease signs of vaginal atrophy.

Unfortunately, studies shows that the discussion of GSM and its symptoms is initiated by the health care provider less then 10% of the time. Therefore it is important to become confortable with the term genitourinary symptoms of menopause and to initiate the conversation with our patients.

"MANAGING URINARY INCONTINENCE: WHAT WORKS?"

DR. LINDA CARDOZO

Urinary incontinence is defined as the complaint of any involuntary loss of urine. It is a common problem in women with an estimated prevalence of 12-46% and although not life threatening it has a significant negative impact on quality of life. By the age of 80 years 11% of women will have undergone surgery for pelvic organ prolapse or urinary incontinence and almost a third will require re-operation during their lifetime. As age increases so does the prevalence of urinary incontinence with a slight peak at the time of menopause due to stress urinary incontinence but in older women mixed urinary incontinence and urgency incontinence predominate.

This presentation covers the two most prevalent types of urinary incontinence: stress urinary incontinence and overactive bladder which together account for more than 90% of cases of urinary incontinence in women.

The initial management of urinary incontinence in women is based on symptoms and clinical examination. Those who complain predominantly of stress urinary incontinence are likely to have urethral sphincter incompetence whereas those who complain mainly of urgency, frequency and nocturia are more likely to have an overactive bladder. It is important to consider other symptoms including bowel and sexual function. Examination should include the abdomen, genitalia and pelvic organs. It is important to exclude other causes of urinary incontinence such as urinary tract infections and other "red flag" symptoms and signs which may require referral to a specialist.

For women with predominantly stress or mixed urinary incontinence, it is appropriate to offer lifestyle advice followed by supervised pelvic floor muscle training for at least three months duration. The only medication for stress urinary incontinence is Duloxetine which has been shown to decrease urinary incontinence episodes by 60% but has a poor side effect profile. Systemic oestrogen therapy is not effective in the management of urinary incontinence but low dose local vaginal oestrogen should be recommended for those women with symptoms or signs of urogenital atrophy.

Surgery is appropriate for women with stress incontinence who have failed conservative or medical therapy. Urodynamic studies should be

carried out to enable appropriate counselling regarding the various surgical techniques, their success rates and the risk of surgical intervention. The most popular procedures nowadays are the mid-urethral slings both retropubic and trans obturator but there is still a place for the retropubic Burch colposuspension, autologous fascial slings and urethral bulking agents. Surgery for stress incontinence has become less invasive and "mini slings" which can be undertaken under local anaesthesia in the out patients setting are becoming more popular. Current research includes the use of stem cells as a potential bulking agent and laser therapy is also being studied. There is still no consensus regarding the appropriate surgery to undertake when mid-urethral tapes fail or are inappropriate.

The overactive bladder syndrome is a symptom complex defined as urgency usually accompanied by frequency and nocturia with or without urgency urinary incontinence in the absence of urinary tract infection or other obvious pathology. It is a common condition with the prevalence of approximately 12-17% in adults over the age of 40 years. Once again it is appropriate to offer conservative therapy in the first instance including lifestyle advice. By reducing excessive fluid intake, symptoms of an overactive bladder can be improved and advice should also be given regarding the consumption of caffeine, artificial sweeteners and alcohol. Bladder retraining should be advised for at least six weeks. Should these simple measures fail, then drug therapy with an anti muscarinic agent e.g. Oxybutynin, Tolterodine, Solifenacin, Fesoterodine or Trospium can be offered but these drugs all have side effects including dry mouth and constipation. There is also the risk of contributing to the anti cholinergic load which may increase the risk of dementia in the elderly. An alternative medication is the β3 adrenoreceptor agonist Mirabegron which does not have anti muscarinic side effects. Should drug therapy fail then Botulinum Toxin A can be injected into the bladder. This can be repeated every six to 12 months but carries the risk of voiding difficulties and urinary retention which may require clean intermittent self catheterisation and also an increased risk of urinary tract infections. Neuromodulation both percutaneous tibial nerve stimulation and sacral neuromodulation are available but the former is time consuming and the latter expensive and may require revision. Reconstructive surgery or a long term suprapubic catheter may be used as a last resort.

PREMATURE OVARIAN INSUFFICIENCY (POI)
DR. NICK PANAY

Incidence: Thought to be 1%, although increase with childhood cancer (can be up to 6-8%)

ETIOLOGY:

- Genetic: Turner's, fragile X, dysgenetic gonads
- Autoimmune: MEN 1 and 2
- Infection: oophritis
- Iatrogenic: cancer, rads, chemo
- Idiopathic

SYMPTOMS:

- VMS
- Tiredness
- Vaginal dryness
- Decreased Mood
- Decreased libido and arousal
- Cognitive issues
- Higher incidence of symptoms if etiology of POI is secondary to malignancy

DIAGNOSIS:

- FSH >40 on 2 occasions (minimum 4-6 weeks apart) in women <40 y.o.
- ESHRE recommends FSH >25 (however this is controversial)

Note: FSH is most reflective of ovarian function when drawn on day 2-5

RECOMMENDED INVESTIGATIONS:

- Hx, and family hx of menopause
- Repeat FSH (2nd value >40 is required for diagnosis)
- Karyotype and Fragile X testing (Especially if <30y.o. or family Hx)
- Anti-Thyroid Ab
- Anti-Adrenal Ab
- Baseline BMD
- TVUS (to assess AFC)
- +/- RF, ANA, HgA1c, TSH, T4
- +/- AMH (for research purposes)

CAN WE USE AMH, AFC AND OTHER BIOMARKERS TO PRECISELY PREDICT THE COURSE/TIMING OF OVARIAN INSUFFICIENCY?

Research demonstrates that once AMH levels become undetectable the final menses will occur within 5 yrs. However, in general biomarkers have not been well evaluated in regards to onset of menopause and are therefore not recommended in clinical practice.

RISKS ASSOCIATED WITH POI

- Increased coronary heart disease and associated mortality
- Increased osteoporosis
    - Note: Bone mineral density is lower when time to diagnosis is delayed
- Decreased libido and arousal
- Increased mental health concerns
- Decreased life expectancy
- Cognitive impairment (including an increase risk in Parkinson's Disease)

TREATMENT OPTIONS – IS NOT STRAIGHTFORWARD!

Recommended until the average age of menopause

1. HRT (combined or sequential) +/- testosterone

HRT has demonstrated superiority in regards to maintenance of bone mineral density (lumbar spine density); metabolic effects; and improved sexual function and satisfaction scores

Higher doses of estrogen and Progesterone are required in POI than in postmenopausal women

- Estrogen:
  - 17 β Estradiol (Estradot) 75-100ug Patch
  - Estrogel 3-4 pumps daily
  - Estrace 2-4mg PO daily
  - Optimal estradiol levels are lacking but aim for 300-500pmol/l to protect BMD
- Progesterone:
  - Prometrium 100mg for continuous combined or 200mg for sequential combined
  - Mirena IUD
- Testosterone is recommended for decreased libido and energy
  - 0.5-1.0mL of androgel per day (no beard growth seen with this dose)

2. OCP

- More practical and simple for patients
- Consider in women who do not want to fall pregnant (5% per year risk)
  - Recommend using <5 yrs
- Women will have supra-therapeutic doses of Estrogen
- Can do continuous use or give short hormone free interval (HFI)

3. E2/SERM

- not available in Canada

How do you treat a patient with POI and a cancer?

- If a curative procedure is expected than start POI Rx immediately
- Delay treatment initiation if worried about hormone sensitive cancer
- Women who have chemo/rads for cancer may benefit from hormone holiday to see if re-establish menses (spontaneous return of ovarian function)

FERTILITY AND POI:

- up to 5% may conceive spontaneously
- 50% have intermittent ovarian function
- need to consider contraception if pregnancy not desired
- IVF with donor oocytes has the highest chance of pregnancy (60-70% per cycle)
- On the horizon – research currently evaluating the effectiveness of ovarian stem cell reactivation

RESOURCES:

1. ***POI registry worldwide - https//:poiregistry.net***

- Limited definitive research, therefore this database will allow for collaboration and collection of data
- Global availability

2. ***DAISY NETWORK – http://daisynetwork.org.uk***

- designed for patient support

3. ***ESHRE* POI Guidelines 2015***

http://www.eshre.eu/Guidelines-and-Legal/Guidelines/Guidelines-in-development/Ovarian-insufficiency.aspx

- will be available later this year

*ESHRE – European Society of Human Reproduction and Embryology

FIBROID MANAGEMENT IN MIDLIFE
DR. ALLY MURJI

Fibroids are benign intrauterine growths that increase in prevalence as women age up until menopause. Of note, fibroids are more prevalent in Black women in comparison to their Caucasian counterparts across every age group. While they may be asymptomatic, nearly half of women with fibroids experience bothersome symptoms such as vaginal bleeding, bulk symptoms (urinary urgency or pressure symptoms) or impact on fertility; all of these have been shown to diminish women's quality of life.

Vaginal bleeding secondary to fibroids may be cyclical and predictable as is the case with heavier menses, may result in intermenstrual bleeding or may be entirely irregular and unpredictable. An endometrial biopsy is performed as part of the investigation for abnormal uterine bleeding. Indications for a biopsy include: a) age over 40, b) risk factor for endometrial cancer (obesity, nulliparity, PCOS, diabetes, HNPCC), c) unusual bleeding pattern i.e. intermenstrual or irregular or d) failure of medical treatment.

While fibroids are usually considered a benign entity, the risk of occult sarcoma in symptomatic patients is 1/769 in ages ≤ 49. However, this rises to 1/172 in 50-59 year olds and 1/65 (1.5%) in those ≥ 60. According to a retrospective review over ten years of three cancer centres in Ontario, 25% of uterine sarcomas were diagnosed by endometrial sampling.

Hysterectomy is the fourth most common surgical procedure performed nation-wide as per data from the Canadian Institute for Health Information (2012-2013.) However this should not be the reflex for symptomatic fibroids, as several effective medical options exist for their management. Oral contraceptives, levonorgestrel-releasing IUDs, danazol and tranexamic acid may be used for bleeding-predominant symptomology.

In cases of predominantly bulk symptoms, fibroid shrinkage can be achieved via GnRH-agonists (i.e. Lupron) or Selective Progesterone Receptor Modulator such as ulipristal acetate (UPA i.e. Fibristal.) The latter works via fibroid shrinkage, stopping bleeding at level of endometrium as well as inducing amenorrhea at the level of the pituitary. PEARL III and its extension trial studied UPA 10 mg daily up to four sequential 12 week courses. It proved effective in its primary endpoint of amenorrhea (79.5%, 88.5% 88.2% and 89.7% in 1st, 2nd, 3rd and 4th UPA courses) with a rapid control of bleeding (median 5 days.) It was also efficacious in fibroid volume reduction, with a reduction of 49.9%, 63.2%, 67.0% and 72.1% in the 1st, 2nd, 3rd and 4th UPA courses. This study was limited by its 10 mg dose (higher than the 5 mg usual dosing), low proportion of ethnic African Americans (5-9%), BMI 25, fibroid size restricted to 10 cm and that one third of patients did not enroll in the extension phase of the study. UPA use in this manner remains off-label.

In summary, fibroids are a common problem in midlife. Appropriate workup in abnormal uterine bleeding is necessary to rule out cancer and other etiologies that may co-exist with fibroids. Symptoms should be treated; several effective medical options exist and should be tried prior to hysterectomy if appropriate.

VULVAR DERMATOLOGY - "ITCHY & SCRATCHY"
DR. LYNNE MARGESSON

WHAT MAKES DIAGNOSIS DIFFICULT:

- Pathology inconclusive
- Patients are often partially treated when they arrive to a specialist's office

ACUTE CAUSES OF VULVAR PRURITIS

Infections:

- Candida, dermatophytosis
- Pinworms, scabies, pediculosis
- Herpes simplex virus, human papillomavirus, molluscum contagiosum
- Staphylococcus aureus, Streptococcus

Dermatoses:

- Contact dermatitis
- Atopic dermatitis/eczema
- Drug eruptions
- Psoriasis

CHRONIC CAUSES OF VULVAR PRURITIS

- Dermatoses:
- Contact dermatitis
- Lichen planus
- Hailey-Hailey
- Squamous cell carcinoma
- Neuropathy
- Lichen simplex chronicus
- Lichen sclerosus
- Psoriasis
- Malignancy:
- Extramammary Paget's disease
- VIN

OTHER CAUSES OF VULVAR PRURITIS

- Vaginitis
- Sarcoidosis
- Urticaria
- Bullous diseases (pemphigoid)
- Tumours (syringomas, angiokeratomas)
- Itching, generalized with disease (pregnancy, diabetes, renal or liver disease)

COMMONEST CAUSES OF VULVAR ITCHING POSTMENOPAUSAL

- Atrophic vulvovaginitis
- Irritant contact
- Lichen Sclerosus
- Lichen Planus
- Squamous cell carcinoma

ESTROGEN DEFICIENCY

- 50% postmenopausal women have atrophic vaginitis and less than 25% are treated
- Decrease in barrier function
- Thus, increased irritation from soap, creams, urine, faces, friction
- Squamous cell carcinoma remains part of differential

GENITOURINARY SYNDROME OF MENOPAUSE (GSM)

Clinical Presentation

- Thin, pale skin
- Hair loss
- Tissue loss
- Cliteromegaly
- Introital narrowing
- Loss of prepuce
- Flabby labia majora, shrunken labia minora
- Loss of vaginal rugae with narrowing and shortening of vagina
- Fissures, watery discharge with itch, burn, dysuria, dyspareunia

Treatment

- Despite systemic estrogen, 25% still need local estrogen
- Avoid irritants
- Local or systemic estrogen: for vulva and vagina
- Topical conjugated estrogens (Premarin®) cream
- Estrone 0.1% cream
- Estradiol tab 10 mcg (Vagifem) or ring (Estring®)

CANDIDIASIS

•75% Candida albicans •25% Candida tropicalis, etc.

•Flares with Estrogen – topical and systemic

Eczematous candidiasis - chronic with secondary ezcematous change

- redness
- swellling
- little discharge
- fissures
- thickening
- lichen simplex chronicus

Diagnosis

- KOH & culture (determine species)
- biopsy

Treatment

Topical

- Imidazole cream or vag tabs– 1, 3, 7d
- Nystatin cream or ointment

Oral

- Imidazole - fluconazole 150 mg on day 1, 3, 7

Suppression

- clotrimazole 500g vag tab weekly or 200 mg twice a wk
- fluconazole 150 - 200 mg orally weekly
- itraconazole 100 mg orally daily

Resistant Candida

- Boric acid vag suppositories 600mg X 14 d (for resistant Candidiasis e.g.. C. glabrata)

CONTACT DERMATITIS

Primary irritant : common, erosive or ulcerative

- Variably itchy – may be sore

Causes:

- Hygiene habits – sponges, soap, wipes, pads
- Moisture - urine, feces, sweat
- Topicals – lotions, antifungals

LICHEN SIMPLEX CHRONICUS

Characteristics

- Relentless pruritus
- Loss of pigmentation
- Excoriations, crusts
- Lichenification
- Unilateral or bilateral hair loss

Management

- Immediate therapy: Tap water soaks in tepid water
- Control infection (cefadroxil, fluconazole)
- Reduce heat, sweat, irritation
- Stop irritants - Stop excessive hygiene
- Medications
    - START WITH topical superpotent steroids
    - Clobetasol 0.05% oint BID x 2 wks, then OD x2 wks then MWF x 2 wks
    - IF NOT BETTER (or if severe) use systemic therapy:
    - Oral prednisone: 40 mg qAM X 5; then 20 mg qAM X 10 days
    - IM Triamcinolone (Kenalog-40): 1mg/kg up to 80 mg/dose, repeat in 1- 2 months if necessary
    - To help with scratching
    - Recognize and manage psychological factors
    - Psychotropic agents work well
    - Non-sedating antihistamines work poorly
    - Night: hydroxyzine (Atarax) or doxepin 10 or 25 mg 2-3 hours before bedtime; Increase by 10 or 25 mg increments slowly
    - Day: scratching is a form of OCD so use an SSRI - citalopram (Celexa) 20 to 40 mg q AM

TIPS

- For recurrent infection: Swab skin folds and nose for C&S to identify organisms R/O MRSA, Candida
- To prevent recurrent infection
    - Bleach Baths – 2-3 times a week for 5-7 min
    - Tub -½ cup bleach in 10" water
    - Sitz bath -1 ¼ teaspoons of bleach per gallon of water (4 liters)
- For recurrent Vulvar LSC
    - Review treatment plan – make sure no irritants
    - Patch test
    - Use a daily topical – tacrolimus 0.03 or 0.1% to alternate with steroid
    - Stop scratching

VULVAR PSORIASIS

- In genital area – often atypical
- Moist, thin red patches in skin folds, gluteal cleft
- In hairy areas – red, scaly papules, plaques
- Secondary changes with infection, common: fissuring, pustules

LICHEN SCLEROSIS

- Commonest cause of white vulvar scarring
- Itch – 90%; Severe itch – 30-50%
- Onset - perimenopausal women, 40-50 yrs
- Management
    - Confirm diagnosis – biopsy, photograph
    - Use topical steroid ointment 1 X or 2 X a day until skin is as normal as possible - not just symptom control
    - Severity will indicate strength of topical steroid
    - Lifelong treatment 1 - 7 days a week

- Estrogen:
    - Use estrogen cream on vulva for lichen sclerosis and lichen planus to improve barrier function
    - Consider compounded cream in bland base if sensitive

LICHEN PLANUS

- Itchy in 60%
- On skin, scalp, nails, vulva, vagina, mouth, esophagus
- On vulva typically nondescript erosions with itching, burning, irritation and sexual dysfunction; white ring, lacey change

INTRAEPITHELIAL AND INVASIVE SCC

- High grade intraepithelial lesion HSIL (HPV related intraepithelial SCC) and dVIN III (differentiated Vulvar intraepithelial neoplasia/SCC in situ) can present with intolerable pruritus resistant to treatment
- Biopsy and re biopsy if not convinced
    - Differentiated SCC looks just like LSC on pathology

NEUROPATHIC PRURITUS

- R/O all other causes of vulvar pruritus
- May be a history of trauma or biomechanical problems - back, hip or pelvis
- Treatment:
    - Tricyclics – doxepin 50 – 100 mg/qhs
    - Amitriptyline 10–150 mg qhs
    - Gabapentin up to 3600 mg per day (100-900 TID)
    - Pregabalin 75 mg to 400 mg per day
    - Mirtazapine 7.5 mg to 15 mg qhs
- Investigate & Rx for underlying cause of neuropathy

TREATMENT OF THE ITCHY VULVA

Nonspecific Measures

- Patient support and education
- Stop all irritants
    - over washing - strong soaps, detergents, pads, wash cloths
    - scratching, unnecessary topical preparations
- Topical anesthetics
    - 5% lidocaine ointment bid to qid (may sting); No benzocaine
- Cool compresses, soaks, gel packs (not frozen)
    - keep in refrigerator in self-sealed plastic bag
- Bland emollients (plain petrolatum or zinc oxide ointment) to soothe open fissured or eroded

Specific Measures

- Treat secondary bacterial and yeast infection
- Stop scratching by using sedation -
    - hydroxyzine or doxepin 10–100 mg / citalopram 20–40 mg AM
- Use topical estrogen, if indicated, to improve barrier function
- Use topical corticosteroid ointments
- As steroid sparer, consider calcineurin inhibitors
    - 1% pimecrolimus cream or
    - 0.03%–1% tacrolimus ointment
- Manage anxiety and depression.
- Manage urinary incontinence and contributory menstrual flow
- Find allergen - Patch test

Miscellaneous:

- Control sweating
- Topical antiperspirant – 0.18% glycopyrrolate compounded in cream base
- Oral oxybutynin ½ of 5 mg tab am and increase 2.5 mg noon very slowly increase to 5 mg tid if needed
- Assess bowel function and manage fecal soiling, and incontinence
- Manage menstrual flow – continuous BCP, progesterone IUD
- For Nonresponsive Pruritus Treatment
    - Naltrexone 50 mg/d for 3 weeks
    - Reported successful in 5 cases chronic vulvovaginal pruritus ages 24-54 years that had failed other treatment

COMMONEST MISSED CONCURRENT VULVAR DISEASES

- Candidiasis
- Contact Dermatitis
- HSV
- Atrophy
- Cancer

DIAGNOSIS AND EVALUATION OF OSTEOPOROSIS IN PREMENOPAUSAL WOMEN

DR. ALIYA KHAN

The World Health Organization's definition of osteoporosis, which is based on the relationship between Bone Mineral Density (BMD) and fracture risk, was developed on a population basis for post-menopausal caucasian women. The precise relationship between BMD and fracture risk in younger patients is thus more difficult to define as the fracture data has been obtained mostly from women older than 65 years of age. We would require different criteria to be established for women less than 50 years of age, however there is insufficient data to do so at this time. It is to be noted that, independent of age & menopausal status, low BMD is a major risk factor for osteoporotic fractures. (Smith 2014 but not RCT; observational and small numbers)

The diagnosis of osteoporosis in postmenopausal women can made both by a fracture history and a low BMD, via a Z-score of less than -2. In premenopausal women, however, we cannot use T-score or BMD alone. We can only diagnose osteoporosis in the presence of fragility fractures. A clinically significant fracture history in children and adolescents is defined as either : two or more long bone fractures by age ten, three or more by age 19, or a vertebral compression fracture.

Low BMD in an adult population may be secondary to either a low peak bone mass attained in the second to third decade of life, or a subsequent BMD loss post peak bone mass. DNA mutations and polymorphism affects BMD, quality, geometry and impact fracture risk. Environmental factors, such as calcium ingestion and

vitamin D production, also interact with genetic susceptibility and determine BMD and fracture risk. When presented with low BMD in premenopause, clinical and subclinical estrogen deficiency needs to be excluded, such as the following:

- Hypogonadism in young women (either primary or secondary)
- Anorexia nervosa
- Excessive exercise
- Hyperprolactinemia
- Iatrogenic: GnRH agonists & Depo-Provera
- Premature menopause, either spontaneous or secondary to surgery, chemotherapy or radiation.

Ovulatory disturbances are the most common cause for low BMD in premenopausal women. Subclinical decreases in sex steroids may impair the attainment and/or maintenance of bone mass in otherwise reproductively normal women. In various studies subclinical estrogen deficiency was associated with a greater bone loss at menopause. When FSH is consistently less than 20, a smaller decrease in BMD was observed. Inversely, higher FSH equalled greater decrease in BMD. Postmenopausal weight gain is associated with a higher BMD. This is attributed to the aromatase activity in adipose tissues which creates higher levels of E1 and E2. Urinary sex steroid levels was evaluated in premenstrual females with low BMD versus normal BMD. Those with lower BMD had lower urinary estrogen and progesterone metabolites than those with a high BMD and had a less pronounced LH response. The actions of FSH are estrogen dependent and osteoclast specific. The majority of FSH receptors causes osteoclast genesis, bone resorption, osteoclast survival in vitro. FSH directly up regulates Tumour Necrosis Factor production from bone marrow macrophages, stimulating osteoclast

and osteoblast formation. FSH levels over 26 lowers BMD more in pre and early perimenopausal women than those with an FSH less than 10. This suggests that serial FSH is a useful predictor of bone loss in transitional period, better than single E2. Correlation on bone loss and turnover with FSH and not estradiol suggests that FSH reflects serum estrogen levels better than single estradiol and is better predictor of BMD than menstrual pattern in defining menopausal status.

In women suffering from anorexia nervosa, there in a rise in the level of the gut derived anorexigenic hormone, PPY. This hormone is normally released in response to food intake. Inverse correlation between PYY and BMD have been observed and PYY levels predicted whole body BMD. BMD loss is reversed by regain of weight & return of menses. Oral estrogen supplementation did not increase BMD but one study showed that transdermal E with cyclic progesterone increased BMD in adolescents with Anorexia Nervosa. Estrogen decreases sclerostin from osteocytes, thus decreasing their function and enhances osteoblast function. Estrogen deficiency decreases bone cortical thickness due to increased endosteal bone resorption.

Depot medoxyprogesterone acetate (DMPA) users have lower BMD in comparison to premenopausal controls. Bone loss is more rapid in the first few years of use and then the rate of loss declines. Discontinuation of therapy is associated with some recovery. It is also to be noted that DMPA use is associated with reductions in long term BMD when used before peak bone mass achieved. In contrast, in premenopausal women, BMD in controls on combined oral contraceptive pills are not different from those using non hormonal contraceptives.

Biphosphonates may be of value in delaying the rate of loss of BMD, and may help preserve micro architecture and prevent bone loss in peri menopause, however further studies are required. The need for further prospective data to evaluate estrogen replete perimenopausal women for antiresorptive therapy for prevention of bone loss may be possible to decrease current and lifetime fracture risk.

Diagnosis and evaluation of osteoporosis in premenopausal women should guided by clinical presentation and BMD studies should be restricted to those who have an identifiable cause for bone loss: glucocorticoid therapy, primary or secondary ovarian failure, diseases associated with bone loss and/or presence of fragility fractures. High FSH correlates with high bone turnover in perimenopause as well as premenopause. Currently management consists of treating the underlying cause of bone loss, if identified, and addressing patients' nutrition and lifestyle. Further studies concerning biphosphonate and estrogen replacement therapy are required but may some day prove to be useful in the prevention of bone loss and decreasing fracture risk.

UPDATES IN OSTEOPOROSIS THERAPY

DR. ALIYA KHAN

INTRODUCTION

In women of reproductive age, peak bone mass is generally achieved by the third decade of life. During these years while estrogen levels are adequate, bone quality and quantity remains generally stable due to a balance of bone formation and resorption. Osteoblasts promote bone formation and mineralization by creating a collagen matrix while osteoclasts promote bone resorption by dissolving bone mineral and proteins.

At time of menopause, the process of bone loss has already begun 2-3 years prior to the final menstrual period and accelerates for another 3-4 years after menopause. On average, there is a 1% to 2% loss of bone annually in the first few years. With a decrease in circulating levels of estrogen, there is an increase in RANK ligand on the surface of osteoblasts causing a two fold increase in bone resorption. This leads to demineralization of bone and thus bone strength decreases while fracture risk increases. This common skeletal disorder is defined as osteoporosis and a major cause of both morbidity and mortality in postmenopausal women.

Bone quality is most commonly measured using bone mineral density (BMD) which assesses both bone quality and quantity. In a pre-menopausal female, BMD results are reported in Zscores (a discussion of this is not done here). In a post-menopausal female, a T-score is used and is calculated by comparing current BMD to the mean peak BMD of a normal white young adult female.

Osteoporosis in a post-menopausal female greater than fifty years of age is defined as (a) a BMD T-score of -2.5 or less at any of the total hip, femoral neck, or lumbar spine or (b) the presence of a fragility fracture regardless of the T-score (a fragility fracture is a

fracture from standing height of ANY bone other than hand, feet, ankles, tarsal bones). Osteopenia is defined by a T-score between -1.0 and -2.5. Normal BMD has a T-score >-1.0.

CLINICAL ASSESSMENT OF OSTEOPOROSIS

Clinical risk factors to assess for osteoporosis include age, genetics (parental history of osteoporosis and/or hip fracture), lifestyle factors (smoking, <1200 mg/day Calcium, <1000 IU/day Vitamin D), BMI less than 21, menopausal status, fracture history (prior osteoporotic fracture increases risk for future fractures), a height loss of >1.5 inches (or 3.8 cm), and glucocorticoid use >3 months.

BONE MINERAL DENSITY TESTING:

All women 65 years of age or older should have a screening bone mineral density. In addition, women between 50 and 65 years of age with any clinical risk factors should be tested. BMD testing is done at the hip (femoral neck, total hip), spine or radius. When interpreting the results, the lowest of the T-scores is used to make the diagnosis. If the patient does not require treatment, BMD testing is not requiring until 2-5 years later. If however therapy is started, retesting should be repeated in 1-2 years later to assess improvement or stability of bone loss.

Laboratory Evaluation

Once a diagnosis has been made, it is important to complete lab investigations to rule out secondary causes of osteoporosis such as hyperparathyroidism, a malabsorption syndrome, etc . This includes CBC, creatinine, calcium, albumin, alkaline phosphatase (ALP), serum protein electrophoresis, vitamin D level, TSH, and a celiac screen.

TREATMENT OF OSTEOPOROSIS

The goal of osteoporosis treatment is to minimize fracture risk. Osteoporotic fractures, particularly hip fractures, are a major cause of decreased quality of life, disability, a loss of independence often requiring long term care admissions, and eventual mortality.

The 2010 CAROC 10-Year Fracture Risk Tool and the FRAX tool from the World Health Organization are validated tools using Canadian data which guide decision-making about pharmacotherapy for osteoporosis in post-menopausal women. The risk system takes into account age, gender, and BMD T-score at the femoral neck. In addition, the FRAX system also includes BMI, parental hip fracture, rheumatoid arthritis, smoking status, and alcohol intake.

A patient at low risk for osteoporotic fracture is defined as <10% risk of having a fracture over the next ten years, with moderate and high risk being 10-20% and >20%, respectively.

In low risk post-menopausal women, management involves encouragement of adequate bone health with >1200 mg/day of calcium and >1000-2000 IU/day Vitamin D. For moderate risk post-menopausal women, the recommendation often involves pharmacotherapy with consideration of a drug holiday after 5 years due to side effects with prolonged use. High risk post-menopausal women are those that have a history of (a) an osteoporotic or hip fracture regardless of BMD T-score, (b) a BMD T-score of -2.5 or less at any of the lumbar spine, femoral neck, or total hip or (c) a BMD T-score of -1.0 to -2.5 and FRAX/CAROC calculation of >20% risk of osteoporotic fracture. These women should always be treated and drug holidays are not recommended.

PHARMACOLOGIC TREATMENTS AVAILABLE:

Osteoporosis therapies can be divided into anti-resportive therapy and bone formation therapy.

1) Bisphosphonates:

This class of medication decreases fracture risk by inhibiting osteoclast-mediated bone resorption and thus normalizing bone remodeling to a pre-menopausal state by. Clinical trials demonstrate a decrease of 40-70% for both vertebral and non-vertebral fractures. Approved formulations in Canada include oral alendronate, risedronate and IV zoledronic acid. Etidronate is no longer available. Adherence can be a challenge due to poor absorption and the requirement for it to be taken first thing in the morning on an empty stomach. Common side effects include esophagitis and dysphagia. In 2005, atypical femoral fractures were first identified as a risk factor for long-term bisphosphonate therapy (over five years). These are transverse femoral shaft fractures that appear to be associated with cortical thickening and often present with groin or thigh pain. Diagnosis can be made with bilateral xrays, MRI, or bone scan. Due to this risk warning, it is now recommended to reassess need for continued bisphosphonate therapy at 5 years. For those patients at moderate risk of fracture, a drug holiday should be considered. For those at high risk of fracture, considering another class of drug such is recommended.

2) Selective estrogen receptor agonists (SERMs):

This class of drug is a weak estrogen agonist. The only approved medication in this class is raloxifene. 60 mg daily reduces the risk of osteoporotic vertebral fractures only, with no benefit to hip or nonvertebral fracture.

3) ESTROGEN THERAPY (ALONG WITH PROGESTERONE FOR WOMEN WITH A UTERUS):

There is a dose dependent response with estrogen therapy on improved bone density and also subsequent bone loss occurring after discontinuation. In Canada, systemic estrogen therapy is approved for the prevention, but not treatment, of osteoporosis.

4) DENOSUMAB:

Denosumab is a RANK ligand inhibitor and thus blocks the interaction of RANK receptor and RANK ligand. Normally, the RANK receptor on the surface of osteoclasts binds to the RANK ligand on the surface of osteoblasts. When bound, it causes osteoclast proliferation and thus bone resorption. Through its action however, Denosumab increases bone density and reduces the risk of vertebral and non-vertebral fractures. Women on Denosumab have been studied now for over 10 years and it is considered safe when used for ongoing prolonged treatment.

5) PARATHYROID HORMONE:

Teraperatide is recombinant human parathyroid hormone and the only approved bone-forming therapy available in Canada currently. It is an anabolic agent that allows osteoblasts to lay down new bone there by increasing cortical thickness and trabecular connectivity. The dose of 20 microgram subcutaneous once daily is reserved for those who have not responded to or have contraindications to first line therapy with bisphosphonates.

IN SUMMARY, there are numerous pharmacotherapy options available in Canada for the treatment of post-menopausal osteoporosis. Studies are now assessing combination therapy and other formulations of parathyroid hormone, however data is still not available.

SACRCOPENIA: DR. N. PINKLEY

Menopause consists of many physiological, psychological, and biochemical changes. During menopause, due to steady decline of estrogen and age related decline of GH and IGF-1, loss of muscle mass is noted. This age related loss of muscle mass is known as sarcopenia.

Muscle continues to grow stronger and bigger in size until the 3rd decade of life and loss of muscle mass begins there after. As women enter perimenopause, a steady decline of estrogen, age related decrease of GH and IGF-1 (also known as somatomedin C) causes decrease in lean body mass. Inadequate calories and protein intake, and changes in metabolism which interfere with protein synthesis also contributes to sarcopenia.

Although a strong correlation has yet to be made, frequent falls and fractures in older age appears to have some correlation with loss of muscle mass and decreased strength.

There are no diagnostic tests for sarcopenia, however loss of muscle mass and loss of strength is a strong indication of sarcopenia.

As for treatment option, resistance, strength training exercise and endurance with weights or resistance bands can be helpful in treatment of sarcopenia and may be helpful in prevention. As for pharmacotherapy, there are no approved treatment options, however HRT did show some increase in body mass, and bone loss prevention. The other treatment options like testosterone and growth hormone supplements are currently under investigation.

Thus far, exercise remains the safest management option for both treatment and prevention of sarcopenia. Any new medication in future can work synergistically with exercise.

In the world of mature women and menopause, sarcopenia is relatively young topic. Therefore there is a great need of more research and investigation to understand, diagnose and properly manage sarcopenia.

IMAGING PEARLS IN THE MIDLIFE WOMAN
DR. STEVE GOLDSTEIN

The vaginal probe has revolutionized gynecology. It is like a low power microscope. Where once we could only assess by feel in the clinic, or with our eyes in the operating room, we can now see prior to surgery. The trouble is knowing what to do with the new things that we see.

PALPABLE POST-MENOPAUSAL OVARY SYNDROME

In 1971, any palpable post-menopausal ovary was immediately removed via laparotomy. The concern was malignancy because an ovary in this age group, should not be palpable. With the advent of ultrasound, the idea of expectant management in this setting began to arise.

1989	Goldstein followed women with simple ovarian cysts and showed that follow-up with serial ultrasounds can work
1992	Another study of 184 woman showed that 17% had simple cysts, very few which worsened or progressed to cancer
1998	A review of 7705 women showed that 3.3% had simple cysts.
2003	Over 15,000 women were evaluated. 18% had simple cysts. Of those 2763 women with cysts, 0.3% had cancer. None of the cancers originated from the cysts.
2010	Another study of greater than 15,000 women. 14% had cysts and 1/3 of the cysts resolved. The cysts seen did not predict a higher risk of malignancy. Also removing the cyst did not protect a woman from developing cancer subsequently.

In summary, there is a growing body of evidence which refutes the old adage that any palpable post-menopausal ovary requires surgery. In concert with the radiologists, a less than 1 cm cyst is insignificant and often not even reported. There is no follow-up needed. A cyst that is 1-7 cm which is simple can be managed with yearly ultrasound follow-up. A simple cyst greater than 7 cm in size should be offered surgery or MRI.

THICKENED POST-MENOPAUSAL ENDOMETRIUM

Dr. Goldstein presented a case where a healthy 65 year-old woman had a CT scan for diverticular disease. It incidentally showed a thickened endometrium of 11.2 mm and heterogenous. She is in excellent health, asymptomatic, a does not have risk factors for endometrial cancer. The endometrium could not be sampled in the office, so she was booked for a hysteroscopy D&C. The surgeon could not get into the endometrium in the operating room. The patient was subsequently had a total abdominal hysterectomy, because the endometrium could not be assessed. The final pathology showed inactive endometrium and a submucous myoma.

An incidental finding of a thickened endometrium without bleeding in a post-menopausal women is also a challenging situation. It can be difficult to get a sample of the endometrial lining due to pain, stenotic cervix, insufficient sampling. Investigating this can often take women into the OR, where they have the risk of general anesthetic. This begs the question, should we be investigating everyone in this circumstance?

According the ACOG guidelines if a lining is 4 mm or less with no bleeding, then no endometrial biopsy is necessary. Other studies show that if the endometrium is 4 mm or less, the incidence of cancer is 1 in 917. In general, endometrial biopsies are only successfully achieved 82% of the time and only 27% of them will show a sufficient sample.

A study evaluated healthy post-menopausal women with a thickened endometrium. 10% had asymptomatic endometrial polyps. 17% of women with breast cancer on tamoxifen have asymptomatic polyps. So if a woman has a polyp, what is her risk of malignancy? Anywhere between 0.1 -0.3%. Gerber suggests that for asymptomatic women with thickened endometrium, you can wait until they have bleeding before you assess. If there is bleeding, then a sonohysterogram may be helpful.

What about the management of women with an endometrial fluid collection? The main point is to 'look at the donut rather than the hole'. Fluid collections in the endometrium are often reported, but whether that fluid is sinister truly depends on the thickness of the endometrium (donut) surrounding the fluid (hole). If the endometrium is thin, the perhaps its simply a stenotic cervix which is not allowing the fluid to leave the uterus. If this endometrial thickness is very thick, this is worrisome and requires investigation.

In summary, good quality ultrasound studies can help us better understand how to manage women in a less invasive fashion.

ABOUT SIGMA CMS

SIGMA Canadian Menopause Society
is a multidisciplinary society consisting of family physicians, specialists and healthcare professionals who are devoted to menopausal health. Our mission is to advance the health of midlife women at and beyond the menopause transition through research, education and knowledge transfer.

To this end, we have published the following **patient/physician brochures:**
"Because I am Unique"
"Vaginal Atrophy: When Sex Hurts"
"12 Myths"
"Menopause: Frequently Asked Questions"
"Menopause: Times Have Changed, Let's Talk"
"Menopause: Managing Symptoms, Improving Health"
"Treating Osteoporosis with Bisphosphonates"
"Osteoporosis and Denosumab Therapy"
"Bone Anabolic Therapy"
"Herpes Vaccination: Frequently Asked Questions"

We have also created the following **distinguished lecture series** for physicians
"Round Table Discussion: Bone Quality Issues"
"A Systems Approach to Post-Fracture Assessment and Treatment"
"Vulvovaginal Atrophy: Current Diagnosis and Treatment"
"A Global Consensus Statement on Menopausal Hormone Therapy by the World's Leading Experts; a View from the Inside"

Our Society is a member of the International Menopause Society (IMS), a member of the European Menopause and Andropause Society (EMAS) and is a member of the Committee of National Societies (CNS) of the International Osteoporosis Foundation (IOF).

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GRAPHIC & LAYOUT: Dr. Chui Kin Yuen

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CONTRIBUTORS:
Debra Evaniuk (Winnipeg) **Radomir Jarcevic (Montreal)**
Kelsey Mills (Toronto) **Ardelle Stauffer (Ottawa)**
Zechlin Itzelt Madrid Lugo (Mexico)

Tessa Bergeron (Quebec City) **Chantel Braun (Winnipeg)**
Marie Coroneos (Toronto) **Pierre de Moissac (St. Anne)**
Kheira Jolin-Dahel (St. Anne) **Nihal ElKhouly (Bolton)**
Zein Faraj (Toronto) **Kelly Goodwin (Ottwa)**
Vered Kakzanov (Toronto) **Sadia A Khan (Winnipeg)**
Eva Knifed (Toronto) **Victoria Kornelsen (Winnipeg)**
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Erin Olivier (East St. Paul) **Carrie Palatnick (Winnipeg)**
Shafeena Premji (Calgary) **Sarah Ramzan (Toronto)**
Rebecca Renkas (Winnipeg) **Parisa Rezaiefar (Ottawa)**
Liane Tan (Toronto) **Flora Teng (Vancouver)**
Keith Wong (Toronto) **Amel Zaki (Winnipeg)**

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ABBREVIATIONS

MHT- Menopausal Hormone Therapy
Beers List - A consensus list of potentially inappropriate medicatiions for older persons
POI - Premature Ovarian Insufficiency
KEEPS - Kronos Early Estrogen Prevention Study
CIMT - Carotid Intima Media Thickness
ELITE - Early vs Late Intervention Trial with Estradiol
VMS - Vasomotor Symptoms
VTE - Venous Thromboembolic Events (DVT and PE)
WHI - Women's Health Initiative
GSM - Genitourinary Syndrome of Menopause
TSEC - Tissue Selective Estrogen Complex
OR - Odds Ratio
STEMI - ST Elevation Myocardial Infarction
MEN - Multiple Endocrine Neoplasia
AFC - Atral Follicle Count
AMH - Anti-Mullerian Hormone
HNPCC - Hereditary Nonpolyposis Colorectal Cancer (also known as Lynch Syndrome)
GH - Growth Hormone
IGF-1 - Insulin-like Growth Factor 1