Menopause

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Defining Menopause

- Defined as the point in time after 12 consecutive months of amenorrhea with no obvious pathologic cause (avg. 52)
- Peri-menopause/menopause transition – span of time when cycle and endocrine changes occur a few years before and 12 months after final menses resulting from natural menopause
- Premature menopause is less than or equal to age 40, whether natural or induced; ~1% of women
- Induced menopause is permanent cessation of menses after BSO or iatrogenic ablation of ovarian function
- 1/3 of a woman’s life
STRAW + 10

<table>
<thead>
<tr>
<th>Stage</th>
<th>-5</th>
<th>-4</th>
<th>-3b</th>
<th>-3a</th>
<th>-2</th>
<th>-1</th>
<th>+1a</th>
<th>+1b</th>
<th>+1c</th>
<th>+2</th>
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<tbody>
<tr>
<td>Terminology</td>
<td>REPRODUCTIVE</td>
<td>MENOPAUSAL TRANSITION</td>
<td>POSTMENOPAUSE</td>
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<td>Duration</td>
<td>variable</td>
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<td>1-3 years</td>
<td>2 years (1+1)</td>
<td>3-6 years</td>
<td>Remaining lifespan</td>
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<td>PRINCIPAL CRITERIA</td>
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<tr>
<td>Menstrual Cycle</td>
<td>Variable to regular</td>
<td>Regular</td>
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<td>Subtle changes in Flow/Length</td>
<td>Variable Length Persistent ≥7-day difference in length of consecutive cycles</td>
<td>Interval of amenorrhea of &gt;=60 days</td>
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<td>SUPPORTIVE CRITERIA</td>
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<td>FSH</td>
<td>Low</td>
<td>Variable</td>
<td>↑ Variable</td>
<td>↑ Variable &gt;25 IU/L**</td>
<td>Variable</td>
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<td>AMH</td>
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<td>Very Low</td>
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<td>Inhibin B</td>
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<td>Very Low</td>
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<td>Antral Follicle Count</td>
<td>Low</td>
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<td>Very Low</td>
<td>Very Low</td>
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<tr>
<td>DESCRIPTIVE CHARACTERISTICS</td>
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<td>Symptoms</td>
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<tr>
<td>Vasomotor symptoms</td>
<td>Likely</td>
<td>Vasomotor symptoms Most Likely</td>
<td>Increasing symptoms of urogenital atrophy</td>
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* Blood draw on cycle days 2-5 ↑ = elevated
** Approximate expected level based on assays using current international pituitary standard

Source: Menopause © 2012 The North American Menopause Society
Menopause physiology

- Loss of follicles, most from atresia, accelerated in our late 30’s
- Elevated FSH and LH
- Ovarian estrogen and inhibin production/feedback decreases
- Androgen availability increases with age
- Adrenals decrease DHEA/DHEAS and ovaries decrease androstenedione
Midlife Changes

- Changes in bleeding patterns
- Vasomotor/hot flushes
- Sleep disturbances
- Vulvovaginal dryness and discomfort
- Urinary changes
- Sexual/decreased libido
- Cognition concerns
- Weight gain
- Skin and hair changes
Routine evaluations
Office exam

- Measured height and weight; BMI or hip/waist ratio
- BP
- Pelvic and indicated pap smear
- Breast exam?
- Lifestyle concerns
Breast Screening

- ACS - annual mammograms at 40
- NCI - annual mammograms at 50, every 1-2 years 40-50
- NAMS - annual mammograms at 40
- USPSTF - mammograms every 2 years at 50-74; no SBE
- WHO - mammograms every 2 years at 50-69; no SBE
- ACOG – 1-2 year interval age 40-50 and annual after 50
Breast changes

- Breasts decrease in size due to less estrogen stimulation
- Supportive connective tissue decreases
- Ratio of fat to fibrous tissue increases which makes breasts less firm but easier to evaluate with mammography
Colon cancer screening

- Colonoscopy every 10 years beginning at 50
- Fecal occult blood testing (FIT, guaiac) yearly
- Sigmoidoscopy every 5 years; this can be done in combination with FOBT every 5-10 years as an alternative to colonoscopy
- Barium enema with air contrast every 5 years
- CT
Laboratory screenings to consider

- Lipids
- Chemistry/HbA1c
- TSH
- Vitamin D
- STI, HIV and Hep C as indicated
Clinical issues
Irregular bleeding

- 90% of women experience 4-8 years of menstrual cycle changes before menopause
- Main cause is irregular ovulation especially in early perimenopause; lack of ovulation in late perimenopause
- Must consider and evaluate for numerous causes, assess risk factors (reproductive tract, systemic, meds)
- EMB, ultrasound for endometrial thickness, hysteroscopy, labs, STD screening
HOT FLASH!

YOU HAVE NO IDEA HOW FREAKY IT IS TO LIVE WITH MENOPAUSE!

DON'T I?
Why Flash??

- Etiology is unclear but could be related to estrogen withdraw, other diseases and medications; also a more narrow thermoneutral zone.

- Average lasts 1-5 minutes; occurs over months to years especially right before and after the LMP.

- Affects up to 75% of women.


- Increased in obesity.
SO YOU CAN BE JUST SITTING THERE AND HAVE A HOT FLASH FOR NO REASON?

THAT'S RIGHT.

AND YOU NEVER KNOW WHEN IT'S GOING TO HAPPEN?

NEVER.
**Vasomotor symptom treatment**

- Treatment of moderate to severe vasomotor symptoms (VMS) remains the primary indication for systemic hormone therapy.

- Hormone therapy is the most successful treatment (a complete list of products available in the US and Canada is on the NAMS website at menopause.org).

- 75% successful.

- 50% recurrence with discontinuation.

- Brisdelle 7.5 mg paroxetine approved 2013 for VMS; off label use of other SSRIs.

- Duavee is CE/bazedoxifene approved for VMS.
Alternative treatments for hot flashes

- Cooler environment
- Weight loss/exercise
- Acupuncture
- Phytoestrogens/soy/isoflavone
- black cohosh
- Decrease smoking
- Vitamin E, omega-3
- Progesterone
- Medications used off-label such as Gabapentin, Lyrica, Clonidine
Alternative treatments for hot flashes con’t

- Cognitive behavioral treatment and hypnotherapy have evidence of benefit to decrease bothersome level of symptoms
- Weight loss and s-equol of soy have evidence of benefit also, though less
"Taking estrogen has been very effective, although sometimes I do miss the hot flashes."
Genitourinary syndrome of menopause (GSM) & VVA

- Up to 75% of women have atrophic symptoms
- Lack of estrogen leads to decrease lactobacilli, increased pH, epithelial thinning
- Ulcerations, petechiae, trauma, pain and dyspareunia can result
- Rule out other etiologies such as infection and vulvar dystrophy
- Urinary changes include urgency and increased urinary tract infections
**Vaginal estrogen therapy**

- Estrogen is the most effective treatment for moderate to severe symptoms of vulvar and vaginal atrophy; topical recommended if this is the only indication for estrogen.
- Up to 90% improve vaginal symptoms.
- Treatment increases blood flow, epithelial maturity, decreases pH, and increases secretions; urethral benefits of decreased UTIs and urgency.
- Progesterone not needed but no safety data beyond one year of treatment; serum estrogen remains in postmenopausal range.
FDA approved vaginal estrogens:

- estradiol cream (Estrace)
- conjugated estrogen cream (Premarin)
- estradiol ring (Estring)
- estradiol hemihydrate tablet (Vagifem)

All equally effective and choice based on patient preference
Ospemifene

- estrogen agonist/antagonist (SERM)
- FDA approved to treat dyspareunia related to vaginal atrophy
- 60 mg oral tablet
- may cause vasomotor symptoms
Non prescription treatment

- lubricants - usually water-based and used with sexual activity
- vaginal moisturizers - used at any time to provide comfort to vaginal tissues
- sex
Menopause and sexual function

- Treatment of moderate to severe vaginal atrophy with systemic HT or local ET can relieve dyspareunia which is a common cause of intercourse avoidance.
- Hormonal therapy not recommended as sole treatment of other sexual function problems (such as decreased libido).
- Testosterone does not continue to decline at menopause and limited benefit to supplements.
- Flibanserin (Addyi) for treatment of HSDD in premenopausal women.
Disease Risks
Breast Cancer

- 1 out of 8 risk in US; 2% of women by age 50
- Most important risk factors are age and gender
- SBE, mammogram, MRI, ultrasound, ductal lavage are all screening tools
- Potential risks include BRCA gene, personal cancer hx, first degree relative with breast cancer, menarche <12, menopause >55, nulliparity or first child after age 30, obesity after menopause, alcohol > 2 drinks/day, lack of exercise, low vitamin D, poor diet, radiation exposure
Breast cancer risk reduction

- Lifestyle changes – decrease weight, decrease alcohol
- Chemoprevention – women at increased risk benefit from SERM treatment to prevent primary breast cancer (ex. tamoxifen and raloxifene)
- Aromatase inhibitors reduce breast cancer recurrence
- Prophylactic mastectomy
HT and Breast cancer

- Breast cancer risk increases with estrogen-progestin use beyond 3-5 years
- Estrogen only therapy for up to 7 years had no increase on cancer risk
- No increased risk if wait for 5 years after menopause to start HRT
- Unclear if HT risk differs between continuous and sequential progestogen therapy or choice of progestogen; low dose HT has not been evaluated long term
<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio (95% CI)</th>
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<tbody>
<tr>
<td>WHI: combined HRT</td>
<td></td>
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<tr>
<td>Total study population (n=16 608)</td>
<td>1.26 (1.00–1.59)</td>
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<tr>
<td>No previous HRT use</td>
<td>1.06 (0.81–1.38)</td>
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<tr>
<td>5 years’ previous HRT use</td>
<td>2.13 (1.15–3.94)</td>
</tr>
<tr>
<td>5–10 years’ previous HRT use</td>
<td>4.61 (1.01–21.02)</td>
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<tr>
<td>WHI: oestrogen-only HRT</td>
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<tr>
<td>Total study population (n=10 739)</td>
<td>0.77 (0.59–1.01)</td>
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<tr>
<td>Million women study (n=1 084 110)</td>
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<tr>
<td>All HRT users</td>
<td>1.70 (1.56–1.86)</td>
</tr>
<tr>
<td>Oestrogen-only HRT users</td>
<td>1.30 (1.21–1.40)</td>
</tr>
<tr>
<td>Ross et al (n=3534)</td>
<td></td>
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<tr>
<td>Any HRT</td>
<td>1.10 (1.02–1.28)</td>
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<tr>
<td>Oestrogen-only HRT</td>
<td>1.06 (0.97–1.15)</td>
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<tr>
<td>Schairer et al (n=46 355)</td>
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<tr>
<td>Combined HRT</td>
<td>1.3 (1.06–1.6)</td>
</tr>
<tr>
<td>Oestrogen-only HRT</td>
<td>1.1 (1.0–1.3)</td>
</tr>
</tbody>
</table>

Table: Risk of invasive breast cancer after treatment with HRT in different studies
B-B-B-B-B-B-B-BAD!

BAD TO THE BONE!

THEY HAVE SONGS ABOUT OSTEOPOROSIS?

YOU GOTTA ADMIRE THE POSITIVE ATTITUDE.
Osteoporosis

- most common bone disorder affecting humans
- peak bone mass achieved in third decade
- 80% of osteoporosis diagnoses are women
- 12th leading cause of death in women; average age of hip fracture is 82 with 25% increase mortality in the next year
- Frailty fracture allows the diagnosis clinically
- >50 years old - DXA measurements include total hip, femoral neck and posterior-anterior lumbar spine and can define the diagnosis with T-score 2.5 SD below the mean
- T score is comparison of patient to normal young adult female
<table>
<thead>
<tr>
<th>Classification</th>
<th>BMD Criteria</th>
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<tr>
<td>Normal</td>
<td>$BMD \geq -1.0$</td>
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<tr>
<td>Low bone mass (osteopenia)</td>
<td>$BMD &gt; -2.5$ and $\leq -1.0$</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>$BMD \leq -2.5$</td>
</tr>
<tr>
<td>Severe (established) osteoporosis</td>
<td>$BMD \leq -2.5$ with history of fragility fracture</td>
</tr>
</tbody>
</table>
All fractures are Associated With Morbidity

One year after an hip fracture:

- Unable to walk independently: 40%
- Unable to carry out at least one independent activity of daily living: 80%
- Permanent disability: 30%
- Death within one year: 20%

Patients (%)

Cooper C, Am J Med, 1997;103(2A):12S-17S
Osteoporosis Risks

- Age – increases with age
- Genetics – affects peak bone mass
- Lifestyle – poor nutrition, smoking, alcohol, decreased activity
- Thinness – BMI < 21
- Menopausal status – decreases 2% per year during perimenopause
Bone Mineral Density testing indications:

- All women > 65 years old
- Postmenopausal with fragility fracture
- Postmenopausal <65 years old with one or more risk factor: previous fracture after menopause, thinness or BMI <21, parental hip fracture or family hx of osteoporosis, smoker, rheumatoid arthritis, excessive alcohol intake, long term high risk medications
Vertebral Fractures

- Most common fracture type
- Often silent
- Insidious, progressive nature
- Associated with significant morbidity
- Predict future spine and hip fractures
- Associated with 2-fold increase in risk of death
FRAX

- Uses risk factors identified by WHO
- Uses g/cm² measurement of BMD at femoral neck
- Calculates 10 year risk of major osteoporotic fracture and risk of hip fracture
- Used to guide appropriate patients for therapy
Prescriptive treatment

NAMS recommends tx if postmenopausal:

- with vertebral or hip fracture
- with BMD diagnosis of osteoporosis
- with osteopenia and FRAX calculator fracture risk of major osteoporotic fx of at least 20% and hip fx of at least 3%
Osteoporosis treatment Rx

- Systemic estrogen therapy is approved for prevention, not treatment of osteoporosis; this includes Estrogen, E+P regimens and BZA-CE
- Bisphosphonate medications are approved for prevention and treatment with a diagnosis of osteoporosis
- Estrogen agonist/antagonist (SERM) raloxifene approved for prevention and treatment
- Teriparatide (Forteo) - PTH - stimulates osteoblasts; approved for treatment; daily SQ
- Denosumab-(Prolia) - inhibits osteoclasts; approved for treatment; q 6 month SQ
- Calcitonin approved for treatment
Bisphosphonates

- first line drugs for treatment
- reduces risk of vertebral > non-vertebral fractures
- uncertain if vary in protection from fracture risk
- Dosing available as oral or intravenous
- includes alendronate, risedronate, ibandronate and zoledronic acid
Selective Estrogen-receptor modulators (SERMs)

- raloxifene (Evista) approved as prevention and treatment
- reduces vertebral osteoporotic fracture and decreases bone turnover
- also reduces risk of invasive breast cancer
- available as oral tablet
- bazedoxifene+conjugated equine estrogen (Duavee) approved 10/13 for prevention
"You’re not getting enough calcium."
Calcium

- Institute of Medicine recommends 1200 mg daily total from food and supplements for women over 50 to maintain bone health
- Absorption affected by estrogen, Vitamin D, foods
- Works with exercise to improve BMD
- Women >60 had decreased hip fractures with calcium/vitamin D when supplement initiated
- Dietary calcium does not appear to increase kidney stones or risk for CVD
Vitamin D

- Approximately 50% of the population is thought to be deficient
- Active form mediates the absorption of calcium in the intestines
- Must be metabolized to be active so does not have to be taken with calcium
- Definition of low level not always agreed upon; 20 ng/ml to 50 ng/ml should be adequate; above this does not show continued improvement
- Recommended dose ~600-1000 IU daily for women
Vitamin D

Risk factors for decreased D levels:

* increased age
* northern climate
* limited sun exposure
* obesity
* poor dietary intake
* dark skin
* various medical conditions (poor absorption)
Cardiovascular Disease

- #1 killer of women
- ET does not increase the risk of CHD when initiated in women recently menopausal (within 10 years) and may even reduce the risk (age 50-59)
- CVD prevention is not an indication for estrogen treatment
- Menopause related rise in LDL-C occurs
- Long term HRT use associated with less accumulation of coronary artery calcium and reduced CHD risk and mortality
- Risk factors (HTN, DM) and lifestyle choices play a role
Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial

Conclusion

- After 10 years of randomized treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.

Schierbeck et al BMJ 2012;345.
GI Diseases

- Colon cancer associated with other GI diseases (polyps, IBS) and high fat/low fiber diet
- Decreased risk of colon cancer in E+P treated patients
- Offer routine screenings

- Gallbladder disease 2x as frequent in women
- HRT and OCs increase risk for gallstones with E+P more risk than Estrogen alone and oral HRT has greater risk than transdermal
Diabetes Mellitus

- Glucose metabolism worsens with weight gain and aging
- Hormonal changes at menopause may contribute to worsening glucose metabolism (relative increase in cortisol) and HT may reduce new onset DM though not approved as prevention
- More risk of CVD in women with DM; statin tx recommended for age 40-75
- Screening for DM in women age 45 or older (HbA1c, fasting glucose)
HT and Cognition

- evidence mixed on effect of HT on cognition at time of menopause but overall no negative effects.
- not recommended at any age for prevention or treatment.
- may increase dementia if begun after age 65.
Hormonal Therapy
HRT guidelines

- Therapeutic goal is lowest effective estrogen dose consistent with individual treatment goals, benefits, and risks plus corresponding low progestogen dose for women with a uterus.
- Lower doses may be better tolerated and have a more favorable benefit-risk ratio than standard doses.
HT Benefits

- May reduce total mortality when initiated soon after menopause (<10 years); ET and EPT may reduce mortality by 30% in those <60
- Women > 60 who had natural menopause at the median age and never used HT should not start without compelling indication/counseling
- No clear indication that longer HT duration improves or worsens the benefit-risk ratio in postmenopausal women
HT in premature/surgical menopause patients

- Use of HT or COC’s for hormone replacement recommended until median age of menopause
- Women under age 50 likely have smaller risks and greater benefits than women over 50 for same estrogen replacement
HT and Venous Thromboembolism

- Oral E+P increases risk 2-5 times and ET up to 1.5 times in postmenopausal women.
- Risk emerges soon after therapy began (1-2 years) and decreases over time.
- Possible lower risk with transdermal than oral and lower doses may be safer but no randomized controlled evidence for either.
- Synthetic progestins may increase risk compared to natural progesterone.
Venous Thromboembolism risk

- baseline risk increases with age
- BMI >30 increases risk 3 fold
- other risk factors include immobilization, CVD, thrombophilic disorders, prothrombotic mutations, etc
- this is a coagulation event
Rx Hormone therapy options

- oral contraceptives
- estrogen
- progesterone
- estrogen/progesterone
- agonists/antagonists
- androgens
E/P Contraceptives

- safe option for healthy, lean, non-smoking women in midlife
- include OC’s, patch and ring
- all other usual contraindications apply to patient selection
- have non-contraceptive benefits which can be important at peri-menopause
Progesterone contraceptives

- DepoProvera - may be used to treat irregular bleeding; has concerns for BMD
- Levonorgestrel IUD’s may also be used for contraception, menorrhagia or off label use when taking estrogen
- Progesterone only oral contraceptive may be used when combined estrogen/progesterone pills are contraindicated.
Estrogen

- approved treatment for menopause related symptoms
- estrogen alone appropriate for women with a hysterectomy
- can be prescribed for those with intolerance to progesterone and still have a uterus with close surveillance
- all routes of administration equally treat symptoms (pill, patch, topical, vaginal)
Progesterone

- Primary menopause related indication for progesterone is endometrial protection from systemic estrogen with multiple regimens approved
- Cyclic oral progesterone to create regular withdraw cycles or daily for continuous suppression
- Micronized progesterone may help with symptoms and can benefit sleep
- Over the counter not adequate for endometrial protection
Estrogen/Progestogen

- Individualization of therapy for each patient is key incorporating quality of life and risk factors (pills and patches)
- Duration of therapy more limited with EPT (5 years) than ET (7 years)
- Women with premature/early menopause can use until average age of menopause then apply risks/benefits to consider extended therapy
- ACOG does not recommend routine discontinuation based on age
Discontinuation of ET/EPT

- 50% chance of vasomotor symptoms returning when therapy is stopped
- no difference if stops abruptly or tapers
- individualize decision
Estrogen agonists/antagonists

- raloxifene/Evista - prevention and treatment of osteoporosis
- Conjugated estrogen/bazedoxifene (Duavee) for hot flashes and prevention of bone loss
- Tamoxifen – approved as treatment for breast cancer and prevention of breast cancer in high risk women
Testosterone

- Ovaries account for a small portion of circulating testosterone and the post-menopausal ovary continues to produce testosterone.
- The level declines as a function of age and in our 40’s is half of what it was in our 20’s.
- After menopause there is no continued decline from the ovary!
- Endogenous levels are not directly linked to sexual function; no normal physiologic range or threshold for insufficiency is established in postmenopausal women.
- No recommended testing of levels for treatment guidance.
Testosterone therapy

- In post-menopausal women replacement has been shown to improve desire, responsiveness and frequency in those with sexual dysfunction.
- May be considered when patient has sexual concerns not improved with estrogen.
- Only US approved product for women is Estratest (generic); not testosterone alone.
- Injections, compounded topical and subcutaneous implants available for off label use.
- Blood levels should be kept in physiologic range for reproductive age women and patient monitored for side effects.
Bioidentical hormone therapy

- Defined as “compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body”
- There are prescriptive and compounded bioidenticals
- There is no data for a difference in safety
- Compounded not FDA approved
- No reliable testing of levels (including salivary)
Resources

- **www.menopause.org** - the north american menopause society website has information for providers and patients, including updated position statements on the prominent topics in menopause management
- **www.fda.gov/womens** - free information and publications
- **www.nof.org** – information on osteoporosis and link to FRAX calculator (also at **www.shef.ac.ok/frax**)
- **ACOG.org**