Update in Women’s Health

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Disclosure of Financial Relationships

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Have no relationships with any proprietary entity producing health care goods or services consumed by or used on patients.
<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Problem</th>
<th>Nursing Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>48</td>
<td>F/U breast CA, ? stop tamoxifen</td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>47</td>
<td>? about mammo, dense breasts</td>
<td></td>
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<tr>
<td>AL</td>
<td>75</td>
<td>F/U osteopenia</td>
<td>?DXA</td>
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<tr>
<td>LM</td>
<td>69</td>
<td>F/U breast biopsy</td>
<td></td>
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<tr>
<td>CS</td>
<td>30</td>
<td>Well woman ex. w. Pap</td>
<td>? HPV</td>
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<tr>
<td>RQ</td>
<td>40</td>
<td>Anemia, heavy periods</td>
<td></td>
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<tr>
<td>BD</td>
<td>27</td>
<td>Well woman ex., breast cancer gene test, wants OCPs</td>
<td></td>
</tr>
<tr>
<td>LP</td>
<td>53</td>
<td>Hot flashes, pain with intercourse, wants rx, to discuss new med</td>
<td></td>
</tr>
<tr>
<td>LL</td>
<td>37</td>
<td>F/U migraine headaches, missed period</td>
<td>Pregnancy test by protocol</td>
</tr>
<tr>
<td>BR</td>
<td>28</td>
<td>Discuss weight loss surgery</td>
<td></td>
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</tbody>
</table>
AG is a 48 year old woman with a history of stage 2 ER/PR positive breast cancer s/p lumpectomy, XRT and chemotherapy who is completing 5 years of tamoxifen. Should asks if she needs to see her oncologist again or have additional treatment.
Continuing adjuvant tamoxifen treatment for 10 years reduced recurrence and increased survival in women with estrogen receptor positive breast cancer.

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, randomised trial

Background: Adjuvant Treatment of Breast Cancer with Tamoxifen

- Tamoxifen is a selective estrogen receptor modulator that decreases recurrence and increases survival in women with estrogen receptor positive tumors.

- Based on data from previous trials, 5 years of treatment has been standard.

- The American Society of Clinical Oncology recommends adjuvant treatment with tamoxifen for premenopausal women with estrogen receptor positive tumors, and postmenopausal women with estrogen receptor positive tumors who are unable to tolerate aromatase inhibitors.

- Recognized significant risks are increased incidence of pulmonary embolism and endometrial cancer.

Barstein J Clin Oncol 2010
ATLAS: Effect of Continuing Adjuvant Tamoxifen for 10 years
Davies Lancet 2013

N= 6846
aTTom: Effect of Continuing Adjuvant Tamoxifen for 10 years
Gray J Clin Oncol (suppl, abstr 5) 2013

N= 6953

Recurrence | Breast Cancer Mortality | Overall Mortality
---|---|---
Tamoxifen x 5 yrs | Tamoxifen x 10 yrs
*Statistically significant difference
Aromatase Inhibitors Should Be Used When Possible in Postmenopausal Women: Effect of Switching from Tamoxifen to Exemestane on Disease-Free Survival

![Graph showing relative and absolute risk reduction](image-url)

- Relative Risk Reduction: -32%
- Absolute Risk Reduction: -4.7%

Events:
- Local or metastatic recurrence
- Contralateral breast cancer
- Death

Source: Coombes NEJM 2004
AG is a 48 year old woman with a history of stage 2 ER/PR positive breast cancer \(\text{s/p lumpectomy, XRT and chemotherapy} \) who is completing 5 years of tamoxifen. Should asks if she needs to see her oncologist again or have additional treatment.
Implications: Two Large Trials Reported in 2013 Showed Benefit for Continuing Adjuvant Tamoxifen for 10 Years

- Continuing tamoxifen for 10 years should be considered for women who have completed 5 years of adjuvant therapy for breast cancer

- Aromatase inhibitors, with or without sequential tamoxifen, remain the preferred adjuvant treatment for postmenopausal women

- Many women who begin adjuvant tamoxifen prior to menopause will become menopausal over the course of the first five years of treatment. The optimal approach to such women is not clear. Continued care or reconsultation with an oncologist is recommended.

- Internists should remain alert for signs and symptoms of uterine cancer (vaginal bleeding) and venous thromboembolism in women taking tamoxifen

Barstein J Clin Oncol 2010
DD is a 47 year old woman who received a letter from the radiologist after her screening mammogram. It informed her that she has “extremely dense breasts”. She asks if further mammograms will be useful, how often she should have mammograms, and if she should have other tests, like ultrasound or MRI.
Annual mammography was associated with lower risk of advanced cancer and large tumors in women aged 40-49 with extremely dense breasts

Outcomes of screening mammography by frequency, breast density, and post-menopausal therapy
The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms.

Grade: C recommendation There is moderate or high certainty the benefit is small.

"So, what does this mean if you are a woman in your 40s? You should talk to your doctor and make an informed decision about whether mammography is right for you based on your family history, general health, and personal values."

Diana Petitti, MD, MPH
Vice Chair, U.S. Preventive Services Task Force
November 19, 2009
Change in Recommendations for Women Aged 40-49 years--what changed in 2009?

Summary of rationale

- USPSTF finds CONVINCING EVIDENCE that screening with film mammography REDUCES breast cancer mortality for women aged 40-49 years. There is a greater absolute risk reduction for women aged 50-74 years. Strongest evidence is for women aged 60-69 years.

- Harms are moderate for every age group considered, including psychological harms, unnecessary imaging tests and biopsies in women without cancer, inconvenience from false positive results, treatment of cancer that would not have been clinically apparent during a woman’s life, and radiation exposure (a minor concern for mammography)

- False positive results are more common for women aged 40-49 years, whereas overdiagnosis is a greater concern for women in older age groups

USPSTF 2009
Type 1
Almost entirely fat

Type 2
Scattered fibroglandular densities

Type 3
Heterogeneously dense

Type 4
Extremely dense

Source: Larry Bassett M.D., Iris Cantor Center for Breast Imaging
Contribution of Various Factors to Individual Breast Cancer Risk

Relative risk > 4.0

- Age (≥ 65 y/o, risk ↑’s with age until age 80)
- BRCA1 and/or BRCA2 inherited genetic mutations
- ≥ 2 first-degree relatives with breast cancer diagnosed at an early age
- Personal history of breast cancer < 40 years
- High breast density
- Biopsy-confirmed atypical hyperplasia
- Lobular carcinoma in situ

Relative risk 1.1-2.0

- Alcohol consumption
- Diethylstilbestrol exposure
- Late age at 1st full-term pregnancy (>30 yrs)
- Early menarche (<12 yrs)
- Late menopause (>55 yrs)
- No full-term pregnancies
- Recent OCP use
- Recent and long-term use of estrogen and progestin
- Obesity (postmenopausal)
- High socioeconomic status

American Cancer Society Breast Cancer Facts and Figures 2013-2014
Kerlikowske JAMA Intern Med 2013

Odds Ratio

* Statistically Significant
DD is a 47 year old woman who received a letter from the radiologist after her screening mammogram. It informed her that she has “extremely dense breasts”. She asks if further mammograms will be useful, how often she should have mammograms, and if she should have other tests, like ultrasound or MRI.
Annual Mammography in Women Aged 40-49 with Extremely Dense Breasts

- Diagnosis of statistically significantly less advanced breast cancers and large tumors compared to biennial mammography. **This difference was not found among women aged 50-74 years.**

- More false positive recalls (65.5% vs. 43.2% of women over 10 years of mammography) and false positive biopsies (12.3% vs. 6.6% over 10 years of mammography)

Like all women, women with extremely dense breasts should undergo breast cancer risk evaluation. Screening MRI and/or genetic testing for BRCA should be considered based on calculation of lifetime risk of cancer and family history

Kerlikowske JAMA 2013
Current Screening Recommendations of Other Major Groups Regarding Women Aged 40-49

• Current recommendations that call for starting annual screening mammography at age 40:
  • American Cancer Society (2003)
  • American College of Obstetricians and Gynecologists (2011)

• Current recommendations similar to USPSTF 2009, discussion of biennial screening age 40-49 based on risk and personal preferences:
  • American College of Physicians (2007)
  • Canadian Task Force on Preventive Health Care (2011)

LM is a 69 year old African American woman who had infiltrating intraductal carcinoma diagnosed on core biopsy of the breast performed because of an abnormal mammogram. She presents for discussion of results. You plan to refer her for treatment.
Shorter survival among black Medicare beneficiaries with breast cancer were mainly attributable to differences in presentation and co-morbidities

Characteristics associated with differences in survival among black and white women with breast cancer

5-year Survival after Breast Cancer Diagnosis in White vs. Black Medicare Beneficiaries 1991-2005
Silber JAMA 2013

*Statistically significant difference, median survival 34 months less for demographics-matched black compared to white patients
Analysis of Disparities in Breast Cancer Survival Between Black and White Medicare Beneficiaries

• After adjusting for socioeconomic status, the hazard ratio for breast cancer mortality was no longer significant
• Black women waited longer for treatment, and were more likely to receive no treatment or no treatment except breast-conserving surgery. Analysis found they had less frequent mammograms, and less evidence of receiving continuity primary care
• Most of the difference in 5-year survival was attributed to differences in breast cancer presentation and co-morbidities
  • Black women were diagnosed with more advanced stage disease with more adverse biological features
  • Black women had more comorbid conditions and poorer health

Potentially important data elements, including use of endocrine therapies, and characteristics to identify triple negative tumors were not available

Silber JAMA 2013
Analysis of Disparities in Breast Cancer Survival Between Black and White Medicare Beneficiaries

• Black Medicare beneficiaries had significantly shorter survival after breast cancer diagnosis. This disparity was not longer present after adjustment for socioeconomic status.

• In this study, most of the disparity was explained by differences in presentation and co-morbidities.
  • Black women were diagnosed with more advanced stage disease with more adverse biological features. This was not fully explained by differences in mammography rates. Some have suggested that differences in exposure to environmental toxins might explain poorer health outcomes in women of lower socioeconomic status. More research is needed.

• Black women waited longer for treatment, and received less aggressive treatment.

Silber JAMA 2013
LM is a 69 year old African American woman who had infiltrating intraductal carcinoma diagnosed on core biopsy of the breast performed because of an abnormal mammogram. She presents for discussion of results. You plan to refer her for treatment.
Analysis of Disparities in Breast Cancer Survival Between Black and White Medicare Beneficiaries

- Public health strategies to reduce disparities must address treatment and prevention of comorbid conditions, as well as breast cancer screening and treatment.

- Internists should be aware that black women are at risk for worse breast cancer outcomes, and strive to ensure they receive optimal care.
AL is a 75 year old woman who presents for follow up of chronic conditions. Two years ago, DXA revealed a femoral neck T-score of -1.5. She received a letter from her secondary insurance company advising her that bone densitometry is recommended for her every two years. She asks if she should have another bone density test now.
Repeating bone mineral density testing after 4 years in older adults did not improve prediction of hip or major osteoporotic fracture

Repeat bone mineral density screening and prevention of hip and major osteoporotic fracture
Guidelines on Diagnosis of Osteoporosis: Background

• Women aged 65 years and older should undergo screening for osteoporosis with bone mineral density testing.

• Targeted testing for younger women is also recommended, but who to test and at what age is controversial.

• The appropriate interval for follow up testing for women with low bone density who do not meet criteria for treatment is unclear.

USPSTF Ann Intern Med 2011
ACP Guidelines: Pharmacologic Treatment of Low Bone Density or Osteoporosis

- Women with the following conditions should receive pharmacological treatment for known osteoporosis:
  - Fragility fracture
  - Fractures occurring spontaneously
  - Fractures arising from trauma that would not have resulted in fracture in a healthy individual
  - BMD 2.5 SD or more below the mean for young adult females (ie T score –2.5 or lower)

Qaseem Ann Intern Med 2008
According to the NOF, the following women who do not meet criteria for osteoporosis should receive pharmacologic treatment:

- 10-year probability of hip fracture $\geq 3\%$
- 10-year probability of major osteoporotic fracture $\geq 20\%$
- These probabilities can be calculated at http://www.shef.ac.uk/FRAX/

These cutoffs were developed by the World Health Organization based on economic modeling using treatment efficacies based on published randomized trials.
Figure Legend:
Receiver Operating Characteristic Curves for Models Investigating Fracture in Older Adults From the Framingham Osteoporosis Study.

BMD indicates bone mineral density. All models are adjusted for age, sex, body mass index, weight loss (per pound), and history of fracture measured at the time of the second BMD test. Models are defined in the Methods section.
Figure Legend:

Scatterplot Showing the Distribution of Risk Scores of Hip Fracture With Baseline BMD vs Risk Scores of Hip Fracture and the Second BMD Measure. BMD indicates bone mineral density. Risk scores of hip fracture are calculated with updated clinical characteristics. The dotted line indicates no change between the 2 risk assessment estimates (ie, BMD is unchanged).
AL is a 75 year old woman who presents for follow up of chronic conditions. Two years ago, DXA revealed a femoral neck T-score of -1.5. She received a letter from her secondary insurance company advising her that bone densitometry is recommended for her every two years. She asks if she should have another bone density test now.
Serial Testing in Untreated Women

Study of Osteoporotic Fractures:
Postmenopausal women ≥65 years old

If baseline T-score is.... | then the interval capturing 90% of women developing osteoporosis during f/u is...
---|---
-1.01 to -1.49 | 15 years
-1.50 to -1.99 | 5 years
-2.00 to -2.49 | 1 year

Gourlay NEJM 2012
CS is a 30 year old woman who presents for a well woman exam. She has no complaints. Her last Pap test was 3 years ago, and was normal. When she was 22 she had an abnormal Pap test that did not require subsequent treatment. The nurse asks if you want an HPV test ordered with the Pap.
Screening for high risk HPV reduced the incidence of cervical carcinoma compared to screening with cytology alone

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow up of four European randomized controlled trials
UPSTF Guidelines: Screening for Cervical Cancer 2012

• The USPSTF recommends screening for cervical cancer in women ages 21 to 65 years with cytology every 3 years or, for women ages 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years: Grade A recommendation

• The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years: Grade D recommendation

• Excludes high risk women: history high grade precancer or cervical cancer, DES daughters, immunocompromised women, eg. HIV positive

ACOG and ACS guidelines agree, except combination testing for women 30 to 65 years is preferred.

Human papillomavirus infection and cervical cytology in women screened for cervical cancer
Datta Ann Intern Med 2008

% High-risk HPV detected for patients with normal Pap results

<table>
<thead>
<tr>
<th>Age Group</th>
<th>%</th>
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<tbody>
<tr>
<td>14-24 yrs</td>
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<tr>
<td>25-29 yrs</td>
<td>17</td>
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<tr>
<td>30-34 yrs</td>
<td>11</td>
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<tr>
<td>35-54 yrs</td>
<td>9</td>
</tr>
<tr>
<td>55-59 yrs</td>
<td>4</td>
</tr>
<tr>
<td>60-65 yrs</td>
<td>0</td>
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</tbody>
</table>
Risk of Invasive Cervical Cancer: HPV +/- Cytology Screening vs. Conventional Cytology
Ronco Lancet 2013

N= 176 464, follow up median 6.5 yrs from 4 European trials
CS is a 30 year old woman who presents for a well woman exam. She has no complaints. Her last Pap test was 3 years ago, and was normal. When she was 22 she had an abnormal Pap test that did not require subsequent treatment. The nurse asks if you want an HPV test ordered with the Pap.
Co-screening women aged 30 years and over with cervical cytology and HPV

Reduces the risk of invasive cancer, most likely by identifying more cervical adenocarcinomas in the precancerous stage

Results in more cervical biopsies (but maybe not if current guidelines for management of HPV (+) results are followed)

Is supported by USPSTF, and preferred by ACS, ACOG, and other groups

• Note: Cytology alone is currently also considered acceptable in this age group. For women under 30, HPV testing is used to triage women with atypical squamous cells of undetermined significance.

RQ is a 40 year old woman who presents for follow up of iron deficiency anemia associated with heavy periods. She finds it difficult to take iron because it causes constipation. Her husband has had a vasectomy. She tried birth control pills before, but felt bloated. Her mother had a hysterectomy for heavy bleeding, and she wonders if she needs surgery or if there are other options.
Levonorgestrel IUD was more effective than other commonly used medical treatments to improve quality of life in women with menorrhagia, but did not reduce surgical interventions

Levonorgestrel intruterine system versus medical therapy for menorrhagia
Menorrhagia

- Accounts for 18.5% of visits to the gynecologist in the US
- Is a major cause of surgical procedures (endometrial ablation and hysterectomy)
- Affects quality of life
- Common medical interventions include:
  - NSAIDs (inhibit prostaglandin synthase)
  - Antifibrinolytics (tranexamic acid (Lysteda ® up to 650 mg x 2 tid for 5 days during menses))
  - OCPs
  - Depo-provera (long-term use carries osteoporosis risk)

Gupta NEJM 2013
Levonorgestrel IUD vs. Usual Care for Menorrhagia

- 571 women in the UK randomized to levonorgestrel IUD or usual medical treatment
- 64% of women with levonorgestrel IUD were still using it at 2 yrs compared to 38% in the usual care group
- Improvement in Menorrhagia Multi-Attribute Score statistically greater in all domains for levonorgestrel IUD
  - Practical difficulties
  - Social Life
  - Family Life
  - Work and daily routine
  - Psychological Well Being
  - Physical Health
- No statistical difference in sexual activity scores, surgical intervention

Gupta NEJM 2013
RQ is a 40 year old woman who presents for follow up of iron deficiency anemia associated with heavy periods. She finds it difficult to take iron because it causes constipation. Her husband has had a vasectomy. She tried birth control pills before, but felt bloated. Her mother had a hysterectomy for heavy bleeding, and she wonders if she needs surgery or if there are other options.
Levonorgestrel IUD for Menorrhagia

• Improves quality of life
• Does not change likelihood of need for surgery
• Minimally invasive procedure
• Cost a barrier for some women
• Two levonorgestrel IUDs currently available in the US
  • Mirena ®: Approved for 5 years of use, including for treatment of menorrhagia in women desiring contraception
  • Skyla ®: Approved for 3 years of use as contraceptive
• Commonly used “off label” in women not needing contraception for menorrhagia

Gupta NEJM 2013; FDA.gov
BD is a 27 year old Ashkenazi Jewish woman who presents for genetic testing. Her 53 year old mother was recently diagnosed with ovarian cancer. She brings a copy of her mother’s gene testing report, which indicates the 185delAG BRCA1 mutation. She currently uses condoms for contraception with her fiance, but asks, based on what she has read, whether she should take OCPs.
Use of oral contraceptives is associated with a lower risk of ovarian cancer in BRCA 1/2 carriers

Oral contraceptives and risk of ovarian cancer and breast cancer among high risk women: a systematic review and meta-analysis

- Known family member with BRCA1 or BRCA2 mutation
- Known Ashkenazi Jewish heritage:
  - One first degree or two second degree relatives with breast or ovarian cancer
- All other women:
  - Two first degree relatives with breast cancer, of whom one received the diagnosis at the age of 50 years or younger
  - One first degree relative with bilateral breast cancer, regardless of age of diagnosis
  - A combination of three first or second degree relatives with breast cancer regardless of age of diagnosis
  - Breast cancer in a male relative
  - A combination of breast and ovarian cancer among first and second degree relatives, or 2 or more first or second degree relatives with ovarian cancer
Care for Women with BRCA1/BRCA2

- Prophylactic bilateral salpingo-oophorectomy to prevent ovarian and breast cancer
- Screening MRI- recommended by the American Cancer Society, WITH screening mammography
- Prophylactic mastectomy
- ? Risk reducing medication

Saslow CA Cancer J Clin 2007, image courtesy of Lawrence Bassett, M.D.
Ovarian Cancer Risk in Ashkenazi Jewish Women with Family Histories of Breast Cancer and BRCA 1/2 Mutations
King Science 2003
Association of Salpingo-Oophorectomy with Mortality Outcomes in BRCA patients

All comparisons statistically significant

Domchek JAMA 2010
Meta-analysis of case control and cohort studies of the effect of OCP use on ovarian cancer risk in BRCA 1/2 carriers
Moorman J Clin Onc 2013

N = 6 ovarian cancer and 8 breast cancer studies
BD is a 27 year old Ashkenazi Jewish woman who presents for genetic testing. Her 53 year old mother was recently diagnosed with ovarian cancer. She brings a copy of her mother’s gene testing report, which indicates the 185delAG BRCA1 mutation. She currently uses condoms for contraception with her fiance, but asks, based on what she has read, whether she should take OCPs.
OCPs in Women with BRCA 1 /2

- All patients with a family history of breast and/or ovarian cancer who are BRCA positive should be offered risk reducing surgery. Given high rates of ovarian cancer mortality after diagnosis, 2% risk for premenopausal BRCA2 patients is clinically important.

- For women who elect to delay surgery, some experts recommend OCPs for contraception.
  - Association of reduction in risk of ovarian cancer, longer duration of use generally associated with greater protection.
  - Some experts still have concern about possible effects of OCPs on breast cancer risk in BRCA 1/2 patients, there was no statistically significant association in this meta-analysis.

- OCPs should not be considered an alternative to risk reducing surgery.
LP is a 53 year old woman with no significant past medical history who presents for treatment of hot flashes and vaginal dryness causing painful sexual intercourse. Her periods stopped six months ago. She currently wakes several times nightly with hot flashes. Several of her friends are currently taking hormone therapy, and recommended it to her. She brings copies of 2 magazine ads for new treatments for menopause symptoms she wants to discuss.
Menopausal hormone therapy should not be used for chronic disease prevention, but is appropriate for symptom management in some women.

Menopause hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women’s Health Initiative randomized trials

Global Events per 10,000 Women Per Year:
CHD, Invasive Breast, Colon, and Endometrial Cancer,
Hip Fracture, PE, All Cause Mortality
Manson  JAMA 2013

Note: In WHI, all women assigned to CEE alone were s/p hysterectomy
Estrogen + Progestin
Risk-Benefit Balance 2014
Major Chronic Disease Outcomes

Risks

Stroke
Breast Cancer (includes increased breast cancer mortality, risk persisted after discontinuation of treatment)
CHD (at initiation, older women/existing CHD)
Venous thrombosis
Dementia (women over 65 years)
Pancreatitis
?Ovarian Cancer

Benefits

Osteoporosis
Diabetes (taking therapy)

ACOG Task Force for Hormone Therapy Obstet Gynecol 2004; Chlebowski JAMA 2008; Chlebowski JAMA 2010; Manson JAMA 2013; Grady JAMA 2002
Estrogen Alone
Risk-Benefit Balance 2014
Major Chronic Disease Outcomes

Risks (while on therapy)

Stroke
Dementia (women over 65 years- trend, trial stopped early)
Venous thrombosis
Endometrial Hyperplasia/Cancer
Pancreatitis
?Ovarian Cancer

Benefits

Breast Cancer Incidence (5-6 yrs of therapy, 13 yrs of follow-up)
Osteoporosis (taking therapy)
Diabetes (taking therapy)

ACOG Task Force for Hormone Therapy, Obstet Gynecol 2004; Chlebowski JAMA 2011; Manson JAMA 2013; U.S. FDA
Newly FDA approved for Treatment of Vasomotor Symptoms

- Conjugated equine estrogens/bazedoxifene (Duavee®)
  - Estrogen with new SERM, approved by FDA in 2013 for treatment of vasomotor symptoms and prevention of osteoporosis in women with a uterus
  - Boxed warning: risk of endometrial cancer, stroke, DVT, dementia, do not use for prevention of dementia OR CHD. Also, do not use if breast or other estrogen-dependent cancer, pregnancy.
    - 24 months of endometrial safety data, over 24 months increased hip and spine BMD, effect on hot flashes similar range to estrogen
    - Studies lacked power (6200 patients over max 2 years) to adequately assess stroke and DVT, but increased risk known for HT and other SERMS; breast cancer effects unknown
    - About 15% of patients spotting at one year
  - Dose CEE 0.45 mg/bazedoxifene 20 mg, one po daily; given limited data, an alternative to traditional estrogen plus progestin therapy for hot flashes, but not proven to be safer/better than estrogen plus progestin although it might be

FDA 2013
Newly FDA Approved for Treatment of Vaginal Atrophy

- Ospemifene (Osphena ®)
  - SERM approved in 2013 by the FDA for treatment of moderate to severe dyspareunia
  - Boxed warning: risk of endometrial cancer, stroke, DVT, contraindicated in pregnancy, MI, known or suspected estrogen-dependent neoplasia, use of estrogen, another SERM; fluconazole, ketoconazole coadministration may increase risks
    - 52 week study of endometrial safety showed RR 3 for endometrial thickening and polyps and RR 6 for proliferative endometrium; ? need for progestin if used longer term (not studied)
    - Studies lacked power to adequately assess stroke and DVT, but increased risk known for HT and other SERMS (only 409 women studied for one year or more)
    - Breast cancer, osteoporosis effects unknown
  - Dose 60 mg daily with food, based on limited safety data, would possibly consider in refractory cases, significant concerns for longer term use in women with a uterus

FDA 2013
Ospemifene FDA Warning Regarding Risk of Endometrial Cancer:
Approval based on 12-15 months of follow up in 409 women

![Graph showing endometrial thickness and uterine polyps](image)
LP is a 53 year old woman with no significant past medical history who presents for treatment of hot flashes and vaginal dryness causing painful sexual intercourse. Her periods stopped six months ago. She currently wakes several times nightly with hot flashes. Several of her friends are currently taking hormone therapy, and recommended it to her. She brings copies of 2 magazine ads for new treatments for menopause symptoms she wants to discuss.
What the Experts Are Saying about Hormone Therapy

• American College of Obstetricians and Gynecologists (ACOG)
  • “Menopausal HT should not be used for the primary or secondary prevention of CHD at the present time.”
  • “Recent evidence suggests that women in early menopause who are in good cardiovascular health are at low risk of adverse cardiac outcomes and should be considered candidates (for HT) for relief of menopausal symptoms.”

• U.S. Preventative Services Task Force (USPSTF)
  • The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women (Grade D: Evidence of Harm)
  • The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade D: Evidence of Harm)
Treatment of Vaginal Atrophy

- Lubricants
  - Eg, KY Jelly®, Astroglide®, etc, as needed or on a regular basis
  - Replens® on a regular basis
- Local hormone therapies- more effective/good safety data
  - Estring® insert one q 12 weeks
  - Vagifem® 10 ug nightly x 14 d then biw
  - “Low dose” topical estrogen
    - Cochrane review found ? more risk of endometrial hyperplasia,
      Premarin® vaginal cream .5 gm biw studied for one year
- Systemic dose therapies- use only if other treatments fail or if using systemic
dose estrogen for vasomotor symptoms
  - Systemic dose estrogen delivered vaginally (cream or Femring®), use
    progestin if patient has a uterus
  - Ospemiphene (SERM): If patient has a uterus, concern for endometrial
    hyperplasia/cancer with longer use
  - Other systemic dose hormones

Cochrane Database Syst Rev. 2006, 2010; FDA 2013
LL is a 37 year old woman with a history of severe migraine headaches who has takes valproic acid for migraine prophylaxis. She uses condoms for contraception. She was recently under stress because of the illness and death of her mother. Her period is 2 weeks late. Her pregnancy test in the office is negative. She and her new husband are planning to try to conceive. She asks for advice planning for pregnancy.
Maternal use of valproic acid during pregnancy was associated with an increased risk of autism in offspring

Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism
Risk of Autism Among Offspring of Women Who Took Valproic Acid During Pregnancy in Denmark, 1996-2006
Christensen JAMA 2013

% of Offspring With Diagnosis

* statistically significant difference

Total N= 655615; 508 exposed to valproic acid
LL is a 37 year old woman with a history of severe migraine headaches who has takes valproic acid for migraine prophylaxis. She uses condoms for contraception. She was recently under stress because of the illness and death of her mother. Her period is 2 weeks late. Her pregnancy test in the office is negative. She and her new husband are planning to try to conceive. She asks for advice planning for pregnancy.
In 2013 the FDA Changed Designation of Valproic Acid to Category “X” for Migraine Headache Prophylaxis

- Findings which contributed to the strength of the finding
  - Odds ratio for autism spectrum disorder for women who took valproic acid:
    - Women with epilepsy 1.7 (CI 0.9-3.2)
    - Women without epilepsy 4.4 (1.4-13.6)

- Most valproic acid prescriptions in the US are for treatment of migraine headache (category X) or bipolar disorder (category D), not epilepsy (category D)

- Half of pregnancies are unplanned; women of reproductive potential should be treated with medications other than valproic acid when possible, and counseled about possible teratogenic effects if valproic acid is prescribed

Meador JAMA 2013
BR is a 28 year old woman with a impaired glucose tolerance, chronic back pain, and a strong family history of morbid obesity and type 2 diabetes who presents to discuss referral for bariatric surgery. Her BMI is 41. She has participated in multiple structured weight loss programs, and has been able to lose up to 30 pounds, but she has always gained it back. She wants to have children in the next 5 years.
History of bariatric surgery is associated with increased risk of preterm and small for gestational age birth

Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study
Maternal Obesity Increases the Risk of Extremely Preterm (22-27 weeks) Birth
Cnattingius JAMA 2013
Roos BMJ 2013

% of births

Preterm birth differences only significant for BMI <35

All findings statistically significant

Controls matched for prepregnancy BMI, smoking, age, parity, education, year of delivery

N=2562
BR is a 28 year old woman with a impaired glucose tolerance, chronic back pain, and a strong family history of morbid obesity and type 2 diabetes who presents to discuss referral for bariatric surgery. Her BMI is 41. She has participated in multiple structured weight loss programs, and has been able to lose up to 30 pounds, but she has always gained it back. She wants to have children in the next 5 years.
Preconception Counseling for Women with a History of Bariatric Surgery

- Bariatric surgery confers both risks and benefits for pregnancy outcomes
  - Risks are seen for both gastric banding and gastric bypass procedures, other studies suggest higher risk of small for gestational age birth for gastric bypass patients
  - Although mechanisms affecting the fetus are unknown, it is prudent to be sure to maintain micronutrient intake before conception and during pregnancy; malabsorption and malnutrition are known risks with bariatric procedures
  - Complications requiring surgical intervention appear to be rare, but can include bowel obstructions, ulcers, band events, and staple line strictures, studies have shown delay before diagnosis, and high rates of maternal and fetal death
  - Preconception planning is very important, and pregnancies should be managed by a team including individuals familiar with issues related to bariatric surgery

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Problem</th>
<th>Nursing Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>48</td>
<td>F/U breast CA, ? stop tamoxifen</td>
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<tr>
<td>DD</td>
<td>47</td>
<td>? about mammo, dense breasts</td>
<td></td>
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<tr>
<td>AL</td>
<td>75</td>
<td>F/U osteopenia</td>
<td>?DXA</td>
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<td>LM</td>
<td>69</td>
<td>F/U breast biopsy</td>
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<td>CS</td>
<td>30</td>
<td>Well woman ex. w. Pap</td>
<td>? HPV</td>
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<tr>
<td>RQ</td>
<td>40</td>
<td>Anemia, heavy periods</td>
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<tr>
<td>BD</td>
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<td>Well woman ex., breast cancer gene test, wants OCPs</td>
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<tr>
<td>LP</td>
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<td>Hot flashes, pain with intercourse, wants rx, to discuss new med</td>
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<tr>
<td>LL</td>
<td>37</td>
<td>F/U migraine headaches, missed period</td>
<td>Pregnancy test by protocol</td>
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<tr>
<td>BR</td>
<td>28</td>
<td>Discuss weight loss surgery</td>
<td></td>
</tr>
</tbody>
</table>
Iris Cantor-UCLA Women's Health Center

Education and Resource Center