Learning Objectives:
- Review and debate data on breast cancer overdiagnosis
- Compare sensitivity and specificity of current imaging techniques
- Develop strategies for discussing benefits and harms of mammography with patients

Case Presentation

56 year old black women with no family history of breast cancer presents for her annual exam. Past mammograms have been BIRADS1, with some dense breast tissue reported. She is asking for a mammography requisition slip, because it is 11 months since her last mammogram, and she doesn’t want to be late this year. She has also talked to a number of friends. One tells her she should repeat the test, but at a location with a 3D mammogram. Another friend, a physician, suggested she obtain an MRI “just to be sure”

a. Will you write out the mammogram requisition, or engage her in a discussion of the new controversies?

b. What information would you provide for the patient if you decide to engage her in shared decision making?

c. Given past dense breast tissue, what are the advantages to “3D” breast tomosynthesis or MRI?

Evidence and Discussion

1. Screening RCTs did show benefit of screening mammography between the ages of 40 – 69 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>Trials Included, n</th>
<th>RR for Breast Cancer Mortality (95% Crl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39–49 y</td>
<td>8*</td>
<td>0.85 (0.75–0.96)</td>
</tr>
<tr>
<td>50–59 y</td>
<td>6†</td>
<td>0.86 (0.75–0.99)</td>
</tr>
<tr>
<td>60–69 y</td>
<td>2‡</td>
<td>0.68 (0.54–0.87)</td>
</tr>
<tr>
<td>70–74 y</td>
<td>1§</td>
<td>1.12 (0.73–1.72)</td>
</tr>
</tbody>
</table>

Most metanalyses found a significant benefit of screening in terms of breast cancer mortality. The benefits were greater for women ages 60 – 69 than 40 – 49 and 50 – 59 years.
2. Despite these benefits we have seen a persistent increase in incidence, relatively small decrease in mortality, especially when compared with other screening modalities.

Breast Cancer and Colorectal Cancer Incidence (solid) and Mortality (dashed) in White and Black Women SEER 1975-2010

Breast cancer screening (on the left) has shown a persistent increase in incidence, with minimal decreases in mortality, especially in comparison with colorectal cancer screening benefits. European data (Autier, 2010) has shown no mortality benefits when comparing countries that began screening earlier compared to countries with similar populations and demographic characteristics. These observations have led many to question whether most of our mortality benefits are from advances in treatment, and whether the persistent increased incidence represents overdiagnosis (Esserman L, 2010, Bleyer, Welch, 2010, 2012, 2014).

3. The recent Canadian Screening Study provided further evidence that screening may be resulting in overdiagnosis, that is detecting cancers that would never become clinically relevant in the patient’s lifetime.

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Mammography arm (n=44,925)</th>
<th>Control arm (n=44,910)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of cancers detected</td>
<td>Mean size (cm)</td>
</tr>
<tr>
<td>Screening 1-5</td>
<td>666</td>
<td>1.91</td>
</tr>
<tr>
<td>6-10</td>
<td>514</td>
<td>1.93</td>
</tr>
<tr>
<td>Subtotal 1-10</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>11-25</td>
<td>2070</td>
<td>—</td>
</tr>
<tr>
<td>Total 1-25</td>
<td>3250</td>
<td>—</td>
</tr>
</tbody>
</table>

Review of the Canadian data demonstrates increased detection of ~140 cancers during the 5 screening years. If screening is only detecting cancers earlier, then in later years those 140 cancers should be present in the control arm, but at a later stage of disease. The control group did have 40 additional cancers in years 6 – 10. However, there are 100 additional cancers never found in the control arm, suggesting that overdiagnosis is present.

4. New imaging modalities are unlikely to address this problem.

We currently have no data that the increased sensitivity will decrease overdiagnosis, and may increase the rates of overdiagnosis. Digital mammography provided relatively small benefits in sensitivity to women less than 50 years, and had decreased sensitivity for women over age 50.
The benefits of digital mammography have been promoted, especially for women under age 50, premenopausal women, and women with dense breasts. The largest trial included 42,760 women who were followed 15 months after receiving simultaneous digital and film mammography, each read independently. 335 Breast Cancers were found:

29% of the breast cancers found within 15 months were not detected by either method at 15 months.

Based upon the recommendation for workup for either result, the sensitivity for each test was as follows:

<table>
<thead>
<tr>
<th>Sensitivity by group of breast cancer within 15 months</th>
<th>Film Mammography</th>
<th>Digital Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>.52</td>
<td>.55</td>
</tr>
<tr>
<td>Women under 50</td>
<td>.44</td>
<td>.67</td>
</tr>
<tr>
<td>Women over 50</td>
<td>.54</td>
<td>.52</td>
</tr>
<tr>
<td>Women with Dense Breasts</td>
<td>.44</td>
<td>.57</td>
</tr>
<tr>
<td>Women without Dense Breasts</td>
<td>.59</td>
<td>.53</td>
</tr>
</tbody>
</table>

The data on breast tomosynthesis is still evolving, and the current trials are continuing to modify their imaging techniques (Ciatto 2013, Skaane 2013). The current head-to-head comparisons demonstrate increased sensitivity. We do not know if this will identify the interval cancers, or whether this will only increase overdiagnosis. The new imaging in clinical trials has resulted in fewer call backs, but we do not yet know if this will increase specificity and BIRADS 3 readings in real practice. Data suggest possible fewer false positives with dense breast tissue, but requires further study.

This new imaging requires new equipment investment, doubles reading times and doubles radiation exposure. It is not covered by insurers and sites are charging an additional $40-70 out of pocket costs.

Neither ultrasound nor MRI has been studied as screening modalities for dense breast tissue in average risk women. With high risk women these modalities have had higher sensitivity for breast cancer, but with high rates of false positives (Berg, 2012)

5. **2009 US Preventive Task Force Guidelines**

- The USPSTF recommends biennial screening mammography for women aged 50 to 74 years.
  Grade: B recommendation.
- 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.
- The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older.
  Grade: I Statement.
• The USPSTF recommends against teaching breast self-examination (BSE).
  Grade: D recommendation.

• The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older.
  Grade: I

• The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging (MRI) instead of film mammography as screening modalities for breast cancer.
  Grade: I

6. Information to patients

Data indicates that there has been little change in screening practices or in screening intervals since release of the 2009 USPSTF guidelines. A qualitative study of white, black and Hispanic women demonstrated considerable skepticism in the rationale for the guideline changes, especially in the emphasis of the harms of anxiety from false positives, and that guideline changes were motivated by cost containment, and not benefits and harms to women (Allen 2012). The prevalent messaging has been “mammography saves lives” for the past two decades. Changing this message will require a greater consensus of the scientific community (eg. American Cancer Society and the National Comprehensive Cancer Network), and significant public health education. Shared decision making between patients and their primary care physicians alone will be insufficient to change screening behavior.

A recent review by Pace and Keating (2014) suggested a number of statements to provide an update to women on overdiagnosis. They recommend separate information for women in their 40s, 50s, and 60s. This information would include:

1. Statement about benefit of breast cancer screening
2. Statement that some women will die with screening.
3. Statement that most women will live even without screening
4. Statement that some cancers are overdiagnosed, and meaning of this concept.

Any discussion of benefits and harms of mammography should include:

5. For high risk women, especially those with positive family histories before age 40, those with BRCA gene mutations, the benefits of mammography are likely much greater, and additional screening with MRI, as well as other preventive strategies may be recommended
6. While data is insufficient on Clinical breast examination, would recommend annual examination if women opt against annual screening.
7. If women stop screening mammography, or extend the interval from 1 to 2 years, recommendation to seek care for any signs of breast cancer – diagnostic mammography recommended in context of new clinical findings.
References


Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. BMJ. 2011 Jul 28;343:d4411.


What you should know about Mammography and Breast Cancer Screening

Women in the 40s

- Mammography is a good test but it is not perfect.
- Mammography does detect cancer early in your age group, and can save lives
- Some cancers are missed by mammography and some women will die from breast cancer even with mammography
- Most women diagnosed with breast cancer will be cured whether or not the cancer was found by mammography
- Some cancers and some DCIS found by mammography would never cause problems, we call this “overdiagnosis”. Since we don’t know which cancers these are, they are treated like all other cancers.
- If you have a mother, sister, aunt with breast cancer before age 50, you benefit the most from mammography, and are recommended to have this yearly. You may also benefit from other testing.

Breast Cancer by the Numbers

If 100,000 women like you have mammography every 1 -2 years for 10 years:

- 190 will develop breast cancer
- 30 will die from breast cancer, even with mammography
- 5 will be saved because of mammography
- 36 will be told they have breast cancer that would never have caused a problem (overdiagnosis)
- 50,000 or more will be called back for further tests
- 20,000 will need a biopsy

What Should I Do?

- If you are higher risk for breast cancer due to a family history, or dense breast tissue, mammography is probably more helpful for you.
- Whether or not you are getting mammograms, call our office if you notice:
  - A new lump in your breast
  - New redness of the skin of the breast
  - Changes in the nipple, including scaly skin or new inversion
  - Breast pain that persists beyond one menstrual cycle
What you should know about Mammography and Breast Cancer Screening

Women in the 50s

- Mammography is a good test but it is not perfect.
- Mammography does detect cancer early in your age group, and can save lives.
- Some cancers are missed by mammography and some women will die from breast cancer even with mammography.
- Most women diagnosed with breast cancer will be cured whether or not the cancer was found by mammography.
- Some cancers and some DCIS found by mammography would never cause problems, we call this “overdiagnosis”. Since we don’t know which cancers these are, they are treated like all other cancers.

Breast Cancer by the Numbers

If 100,000 women like you have mammography every 1 -2 year for 10 years, approximately:

- 300 will develop breast cancer
- 60 will die from breast cancer, even with mammography
- 10 will be saved because of mammography
- 57 will be told they have breast cancer that would never have caused a problem (overdiagnosis)
- 50,000 or more will be called back for further tests
- 20,000 will need a biopsy

What Should I Do?

- If you are higher risk for breast cancer due to a family history, or dense breast tissue, mammography is probably more helpful for you.
- Whether or not you are getting mammograms, call our office if you notice:
  - A new lump in your breast
  - New redness of the skin of the breast
  - Changes in the nipple, including scaly skin or new inversion
  - Breast pain that persists beyond one menstrual cycle
What you should know about Mammography and Breast Cancer Screening

Women in the 60s

- Mammography is a good test but it is not perfect.
- Mammography does detect cancer early in your age group, and can save lives
- Some cancers are missed by mammography and some women will die from breast cancer even with mammography
- Most women diagnosed with breast cancer will be cured whether or not the cancer was found by mammography
- Some cancers and some DCIS found by mammography would never cause problems, we call this “overdiagnosis”. Since we don’t know which cancers these are, they are treated like all other cancers.

Breast Cancer by the Numbers

If 100,000 women like you have mammography every 1 -2 year for 10 years, approximately:

- 440 will develop breast cancer
- 95 will die from breast cancer, even with mammography
- 42 will be saved because of mammography
- 83 will be told they have breast cancer that would never have caused a problem (overdiagnosis)
- 50,000 or more will be called back for further tests
- 20,000 will need a biopsy

What Should I Do?

- If you are higher risk for breast cancer due to a family history, or dense breast tissue, mammography is probably more helpful for you.
- Whether or not you are getting mammograms, call our office if you notice:
  - A new lump in your breast
  - New redness of the skin of the breast
  - Changes in the nipple, including scaly skin or new inversion
  - Breast pain that persists
Clinical Dilemmas in Women’s Health: Partnering With Patients To Answer Questions Asked Frequently in the Middle Years

Who should be screened for gynecologic cancers and with what test/s?

Teacher’s Guide

Amy Weil, MD FACP

Learning Objectives – At the end of this session learners should be able to

1) Understand the rationale for the type of examination, testing and intervals suggested in various circumstances for cervical cancer screening and be able to communicate this to patients.
2) Communicate regarding future directions for cervical cancer prevention and diagnosis at home and abroad
3) Know when to recommend endometrial sampling for endometrial cancer diagnosis and communicate about risk factors for endometrial cancer
4) Be familiar with older and newer screening modalities available for ovarian cancer screening and their efficacy based on state of the art ideas about this cancer’s pathophysiology.
5) Be able to communicate effectively the evidence, risk and benefits of pursuing ovarian cancer screening.

Introduction

As women ourselves we are often not just physician actors but interested participants with a stake in the answers to questions about gynecological screening. Thus, the ever shifting recommendations can leave even knowledgeable people confused about when what is needed and why some screens are no longer recommended. Additionally, effective screening tests are not available for the majority of gynecologic cancers. In the face of limited screening options is there anything on the horizon to protect us from disease and/or to detect it sooner?

Vignettes

1. A 50 year old woman presents to your clinic for routine care. She says according to her records she hasn’t had a Pap smear in 3 years and that she is ‘late’ for her annual exam. How do you respond?
You look back in the record and see that she has had 3 normal annual exams prior to the one in 2011 and respond that she is just on time according to USPSTF guidelines.

2. You ask her if she feels safe in her current relationship and if she has any sexual issues she would like to discuss relating to the menopause transition. When she says things are fine you perform a Pap for cytology and an HPV test, but do not do a bimanual exam. After the exam she asks how come you didn’t do a complete exam like her old doctor used to but asked her those weird questions and that, if she comes back, she will see you next year for the ‘whole exam’ like her prior provider used to do.

You tell her that you are following current ACOG recommendations regarding both the violence screening and the Pap and HPV interval, and USPSTF guidelines regarding the lack of efficacy of the bimanual exam, and that in fact if her HPV test comes back negative she won’t need cervical screening for 5 years. The rationale here is that cervical cancer is predominantly caused by the HPV virus and in the absence of the virus she is not at risk for cancer. You read up on this in the NEJM last year. There is even some very recent suggestion from the FDA that she may receive HPV without Pap testing in the future. You express solidarity with her that the ever shifting recommendations regarding gyn screening are frustrating but that you are doing your best to review the evidence, keep up with it and offer her state of the art care. You remind her that her 24 year old daughter is still in the window to be immunized for HPV. Remembering that her partner is from India you mention that HPV immunization and screening, if effective alone, may help narrow the gap worldwide in cervical cancer prevention and screening by being more cost effective. For example, a randomized controlled trial in India showed even a single lifetime screening test significantly decreased the risk of mortality from and incidence of advanced cervical cancer compared to no screening (mortality: risk ratio 0.65, 95% confidence interval 0.47, 0.90; incidence: relative risk 0.56, 95% confidence interval 0.42, 0.75).

3. Your same patient, somewhat mollified by your answers re the cervical screening, wants to know what you are doing these days to screen for/prevent endometrial cancer.

Regarding endometrial cancer you tell her that there is no screening test currently. If she is no longer menstruating then bleeding after 6 months with no period would warrant an endometrial biopsy for diagnosis. If she had intolerable symptoms of menopause and chose to be on hormonal replacement this should always contain a progestin art. Any bleeding after 6 months on this regimen would again be cause for a biopsy.

There is some potential advice on the behavioral front for prevention. There are some known risk factors for endometrial cancer including parity, oral contraceptive use, cigarette smoking, young age at menarche, and diabetes. Of these, smoking and risks for diabetes are modifiable. We would love to help her quit if she is smoking. Regarding diabetes, recently we have learned that in a long and big study
looking at cancer risk (the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) that even prediabetic conditions such as overweight and obesity, high carbohydrate intake and high glycemic load have been associated with increased endometrial cancer risk (though there had been a contradictory study prior and endometrial cancer was not a direct target of the study). You feel confident that encouraging her to lose weight through exercise and most likely low carb diet would possibly assist her in preventing endometrial cancer and benefit her overall health. You also encourage her that of the female cancers, endometrial cancers have the best prognosis.

4. This same patient is hoping you will repeat her every 6 month CA 125 and transvaginal ultrasound like her old doctor used to do. She is Ashkenazi Jewish and while her mom did not have the BRCA 1 or 2 gene, she did die from ovarian cancer at age 78.

You agree with the patient that ovarian cancer is a difficult cancer to diagnose and that it has the worst outcomes compared to cervical and endometrial cancer.

Specifically

- Fifth most common malignancy in the US
- with 22,430 new cases diagnosed each year, 15,280 women dying each year
- 1 in 55 women will develop ovarian cancer in their lifetime
- 20% of ovarian cancers are detected at Stage 1, where the 5 year survival exceeds 90%.
- Majority at later stages where survival is much poorer, 30-55%
- Leading cause of gynecologic malignancy death the Western world.
- Median age of diagnosis is 63

You tell the patient that the USPSTF does not recommend ovarian cancer screening due to its lack of efficacy in detecting disease in both specificity and sensitivity. The CA 125 has a high false positive and false negative rate (abnormal falsely alarming, normal values falsely reassuring) so does not have the characteristics of a useful screening test, unfortunately. There have been many groups working on single and groups of biomarkers that have offered promise, but none have been universally endorsed as effective. There is some promise through a technique called proteomics research to find better biomarkers, but a panel of biomarker proteins has not been approved yet for use clinically.

You tell her that you have been keeping up with the literature and remain hopeful.
There is discussion about using genetic testing with BRCA 1 and 2 as a way to stratify patients for screening. Additionally, there have been attempts to incorporate a scoring system searching for symptoms of ovarian cancer to enhance detection rates, which would include bloating, urinary frequency, rectal bleeding, postmenopausal bleeding, loss of appetite, abdominal pain, abdominal distension and age greater than 50. Unfortunately, none of these are early signs of an asymptomatic phase but are rather diagnostic signs. Fortunately, she doesn’t have any of these.

A new marker (HTATIP2/TIP30) seems to distinguish patients with other gyn complaints from those with ovarian cancer, but this is very early information.

You reassure her that she doesn’t have too many of the risk factors for ovarian cancer, which include (those she has are underlined):

- Older age
- Nulliparity
- Infertility
- Endometriosis
- North American/European ancestry
- Personal history of breast, endometrial or colon cancer
- Family history of ovarian cancer
- Prolonged oral contraceptive use
- Hormone replacement therapy (dose response in recent meta analysis)
- Alcohol
- Talcum powder use in the genital area
- Higher SES
- Tobacco smoking.

Her biggest risk would come from her family history

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td></td>
</tr>
<tr>
<td>Hereditary syndrome (HBOC/HNPCC)</td>
<td>25-30</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>2 or more relatives c OC</td>
<td>4.6</td>
</tr>
<tr>
<td>First degree relative c OC</td>
<td>3.1-3.6</td>
</tr>
<tr>
<td><strong>Other Risks</strong></td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td>2.0-5.0</td>
</tr>
<tr>
<td>From North America/Europe</td>
<td>2.0-5.0</td>
</tr>
<tr>
<td>Older age</td>
<td>3.0</td>
</tr>
<tr>
<td>No pregnancies</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Socially advantaged</td>
<td>1.5-3.0</td>
</tr>
<tr>
<td>Talc exposure</td>
<td>1.0-2.5</td>
</tr>
<tr>
<td>Late menopause</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Nutrition (animals, galactose)</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.5</td>
</tr>
<tr>
<td>Early menarche</td>
<td>1.5</td>
</tr>
</tbody>
</table>


Additionally, she has several of the protective factors or is working towards them:

- Higher parity
- Use of oral contraceptive pills
  - Data from a large cohort study showed a 40% reduction for ever use of OCP’s, 50% for 5 years of use (Byler), 90% reduction for greater than 15 years of use
• Tubal ligation
• Hysterectomy
• Late menarche
• Early menopause
• Late first and last births
• Breast feeding
• Physical activity
• Nutrition

5. As your hand is on the doorknob, your patient reminds you that she did take hormones (clomiphene) in order to become pregnant with her daughter and wonders if this places her in a high risk group as it is in the table above. It seems a lot of her friends who took those fertility drugs have come down with breast cancer, and she always wondered about Elizabeth Edwards...

You can tell her that the Cochrane Collaboration shared her concern regarding risk and did an extensive review of existing literature. While there is a suggestion of possible increased risk with more than 12 cycles of clomiphene overall the group could not conclude that this or other fertility drugs used (including growth hormone, tamoxifen and clomiphene) caused an increase in ovarian cancer. You remind her that Ms Edwards died from breast, not ovarian cancer, so that is a different topic.

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USPSTF Screening for Ovarian Cancer, September, 2012.
Controversies in Prescribing Combined Oral Contraceptive Pills  
Abby Spencer MD, MS, FACP  
Cleveland Clinic Foundation, Cleveland, Ohio  
April, 2014  
Clinical Dilemmas in Women's Health: Using the current evidence to answer questions asked frequently in the middle years  
2014 National meeting of the Society of General Internal Medicine

Introduction: 
Primary care physicians frequently provide contraceptive counseling to women who have medical conditions that may be exacerbated by pregnancy or who have medical comorbidities that necessitate the use of potentially teratogenic medications. In women in the middle years, combined hormonal contraception offers many unique contraceptive and non-contraceptive benefits which must be weighed against potential risks. Effective counseling requires up-to-date knowledge about hormonal contraceptive methods that differ in hormonal exposure, dose, and method of delivery. Effective counseling also requires an understanding of a woman’s preferences and medical history, as well as the risks, benefits, side effects, and contraindications of each contraceptive method.

Objectives: 
1) Outline the risks and benefits of combined-hormonal contraception (OCPs) in women in the middle years  
2) Identify key risk factors that would preclude the safe use of OCPs  
3) Balance the risk and benefits of OCP exposure in women with specific comorbidities  
4) Discuss VTE risk in patients based on type of progestin

Case 1 
A 38 year-old woman presents to you to request “the pill”. She is sexually-active with her fiancée and they are still discussing whether or not they will try to conceive. She had been on depo-provera in the past, but couldn’t tolerate the abnormal bleeding that she experienced. She is much more comfortable when “things are regular”. She denies dysmenorrhea or particularly heavy menses. She is fairly healthy, quit smoking about 3 years ago, and has a family history of breast cancer in her mother (diagnosed at 60, still living). Her blood pressure is 125/85 on 12.5 mg of HCTZ and her BMI is 25.

1) Is it safe to prescribe an oral contraceptive pill to this woman given her age and comorbidities?  
2) How does her smoking history affect your decision?  
3) Does her family history of breast cancer preclude her from OCPs?  
4) Given that her cycles are already regular and she denies dysmenorrhea, are there any non-contraceptive benefits for her in selecting OCPs over an alternative form of birth control?
Case 2

A 33 year old woman requests a prescription for oral contraceptive pills. She reports terrible pre-menstrual symptoms with cramping and heavy bleeding. Her friend told her that taking “the pill” helped her symptoms and the type she took eliminated her acne and excess chin hair, so your patient is very interested in learning more about OCPs that can help her with these issues. She is generally quite healthy, active, does not smoke, and takes no other medications than prn Motrin for her migraines. Her migraines are associated with nausea, photophobia and phonophobia. Headaches are usually preceded by a flush of nausea. She denies any weakness, blurry vision, or focal deficits. She has migraines about 8 to 10 times per year.

1) Would you provide her with OCPs? Why or why not?

2) Which type of pill did her friend likely take and how would you counsel your patient on risks and benefits of this OCP?

3) How do her migraines affect your decision?

4) Provided you decide to prescribe her OCPs, would you suggest she take them only for a limited time period? Would you recommend a “stop date”?

References


2) Parkin, Sharples, Hernandez, Jick. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ. 2011;342:d2139.


Prescribing combined oral contraceptive pills to healthy, non-smoking women older than 35 years old is generally safe provided that other contraindications to taking the pill do not exist. In particular, stroke and myocardial infarction risks for OCP users compared with nonusers appear similar in younger and older non-smoking women in large US trials. The risks of ischemic and hemorrhagic strokes and myocardial infarction clearly increase with age, but are more strongly influenced by smoking and the presence of other cardiovascular risks factors such as hypertension and diabetes mellitus. OCPs have been shown to elevate systolic and diastolic blood pressure by about 8 and 6 mm Hg respectively and caution should be used in starting OCPs in women who already have elevated blood pressures, especially women older than 35. Both the WHO and ACOG guidelines suggest that the risks outweigh the benefits if blood pressure is uncontrolled. The WHO suggests specifically that at a blood pressure above 140/90, risks likely outweigh benefits. The risks of myocardial infarction and stroke among users of OCPs who have medication-controlled hypertension are not known.

Progestin-only contraceptives (Depo, IUD, POP) may provide a lower cardiovascular risk for women with HTN older than 35 years, Migraine headaches with focal neurologic signs, Cigarette smoking or obesity in women older than 35 years, History of thromboembolic disease, Systemic lupus erythematosus with vascular disease, nephritis, or antiphospholipid antibodies, hypertriglyceridemia, CAD, CHF, or cerebrovascular disease.

Indeed, while hypertension may increase the relative risk of MI or stroke, the absolute risks in otherwise healthy reproductive-aged women remain fairly low, especially in younger women. These risks should be balanced with the risk of pregnancy and pregnancy-related complications. Table 2 outlines the estimated number of excess cases of ischemic stroke or myocardial infarction attributable to oral-contraceptive use among nonsmokers, smokers, and women with hypertension according to age. Table 3 outlines recommendations from the WHO and ACOG regarding acceptable risks. A large population-based case control study suggests that using a third-generation OCP instead of a first- or second-generation OCP may provide less of a risk for MI, but risks remain high regardless of OCP preparation among users who smoke, have diabetes mellitus, or have hypercholesterolemia.

It is well-established that providing OCPs to smokers older than 35 years provides substantial and unacceptable risks for MI and stroke and is ill-advised. The relative risk of stroke or MI in OCP users who smoke and are over 35 years-old is 20 times greater than smoking OCP-users less than 25 years old and the risk is 10-times greater than aged-matched non-smokers on OCPs (Table 2). Cardiovascular risks for former smokers who subsequently take OCPs are not known, regardless of age. However, the cardiac risks associated with cigarette smoking are thought to diminish relatively soon after smoking cessation in those with and without cardiovascular disease, and continue to fall with increasing length of time since quitting. These risks would have to be taken into account along with her other cardiovascular risk factors and weighed against the benefits of OCPs and the risks of unintended pregnancy.

Although her family history of breast cancer does increase her risk for developing breast cancer, OCPs are not likely to further increase that risk. The Women’s Care study, a large case-control study of >7000 women aged 35-64 years, found no increased risk of breast cancer with current or past OCP use compared with never using OCPs, including those with a family history of breast cancer. Data regarding breast cancer risk for BRCA carriers taking OCPs is more controversial and must be balanced with the known risk reduction for ovarian cancer in mutation carriers on OCPs. Family history of breast cancer is not a contraindication for prescribing OCPs in our patient, and according to the ACOG Practice Bulletin,
family history of BRCA 1 or 2 mutations should not preclude provision of OCPs either. Use of OCPs may offer substantial benefit to women with BRCA mutations. Personal history of benign breast disease or a positive family history of breast cancer are not contraindications to OCP use.

Women older than 35, including peri-menopausal women, may have additional non-contraceptive benefit from OCP use even if preventing acne or minimizing dysmenorrhea or menorrhagia are not goals of care. Older reproductive age women may experience a positive effect on bone mineral density and reduced fracture rate, a reduction in perimenopausal symptoms, and well-established risk reductions for endometrial, colorectal, and ovarian cancer. Our patient will also benefit from cycle regularity which is important to her and is likely to worsen in the peri-menopausal time without treatment. The contraceptive benefit in older reproductive aged women deserves mention as these women are more likely than younger women to have adverse consequences if they do conceive. One study of pregnant women in various age groups identified an increased risk of death for women 35 years and older regardless of parity, time of entry into prenatal care, and level of education. This data underscores the importance of effective contraception for women in this age group and contraceptive risks must be balanced with risks of pregnancy and non-contraceptive health benefits. Use of FSH to determine menopausal status may be expensive and misleading, ACOG suggests that until a well-validated tool to confirm menopause is available, it is appropriate for healthy, nonsmoking women doing well on OCPS continue them until age 50–55 years.

Case 2 Answers

OCPs containing the progestin drospirenone have antiandrogen and antimineralocorticoid activity that may result in less weight gain and less water retention, and may also offer even greater reduction in acne and hirsutism. Drosperinone has been associated with higher rates of venous thromboembolism (VTE) than levonorgestral-containing OCPs in two large trials published in 2011, however, a more recent prospective cohort study suggests that 21- or 24-day regimens of drosperinone-containing ocp's have similar risks to other ocp's including non-drosperinone and levonorgestral-containing pills. Patients with PCOS or symptoms of hyperandrogenisms often request and respond well to drosperinone-containing ocp's.

Migraine headaches are common among reproductive age women and while “menstrual” migraines often improve on OCPs, other women experience worsening of their symptoms on OCPs. Understanding the timing of the headaches in women on OCPs is critical, as often headaches occur during the hormone-free intervals and improve with extended-cycling and reduction of hormonal fluctuations. However, migraine headaches with aura have been associated with an increased risk of stroke in otherwise healthy women on OCPS. One large case-control study in the US found that OCP use in women with migraines was associated with twice the risk of stroke as women on OCPs without migraines; they did not distinguish between women with and without aura. Another study found that OCP users with migraine headaches with aura had an increased risk of stroke while those without aura did not. Smoking further increased the risk of stroke in OCP users with aura.

Did our patient’s symptoms constitute an aura? Nausea, vomiting, photophobia, phonophobia, visual blurring or spots do not constitute an aura according to the International Headache Society. Rather, auras are characterized by reversible neurologic symptoms which last 5–60 minutes. Auras most commonly involve visual disturbances such as a flickering uncolored zigzag lines or scotomas (area of depressed vision within a visual field, surrounded by an area of normal vision), but can also involve disturbances in sensory, motor, or speech centers. Asking the question “Have you ever had visual disturbances lasting 5-60 minutes followed by headache?” may help to determine whether a true aura was present or not. The risk for ischemic stroke associated with migraine without aura is probably low enough that it is not a major consideration in prescribing OCPs unless the patient has other major risk factors (smoking, hypertension, diabetes) or unless the patient's headaches become substantially exacerbated when OCPs are started. Therefore women who report a history of migraines without associated neurological deficits should not be considered to have a contraindication to the use of oral contraceptives. Recommendations for OCP provision in women with migraines is listed below in Table A.
Taken together, OCPs should be considered for women with migraines if they do not have focal neurologic signs, do not smoke, are younger than 35 years, and are otherwise healthy. Although stroke is rare among women with migraines who use OCPs, the impact is so devastating that alternative birth control methods such as progestin-only IUD, depo provera, or barrier methods should be considered first. Whether non-smoking young women with migraines who are already taking OCPS should stop taking them at age 35 is not known.

The contraceptive benefit in older reproductive aged women deserves mention as these women are more likely than younger women to have adverse consequences if they do conceive. One study of pregnant women in various age groups identified an increased risk of death for women 35 years and older regardless of parity, time of entry into prenatal care, and level of education. This data underscores the importance of effective contraception for women in this age group and contraceptive risks must be balanced with risks of pregnancy and non-contraceptive health benefits. Use of FSH to determine menopausal status may be expensive and misleading, ACOG suggests that until a well-validated tool to confirm menopause is available, it is appropriate for healthy, nonsmoking women doing well on OCPS continue them until age 50–55 years.

Table A. Adapted from Becker. Neurology 53(4) 1999.

<table>
<thead>
<tr>
<th>Recommendations for OCP use in patients with Migraines</th>
</tr>
</thead>
<tbody>
<tr>
<td>When patients with migraine are prescribed OCPs, they should be carefully monitored for increasing headache frequency and severity, for the development of new focal neurologic symptoms, and for significant change in aura symptoms if they already experience aura.</td>
</tr>
<tr>
<td><strong>Specific recommendations</strong></td>
</tr>
<tr>
<td>1. Women who have migraine without aura can probably use OCPs with relative safety, unless other significant stroke risk factors are present (e.g., smoking, hypertension), although caution should be exercised over age 40.</td>
</tr>
<tr>
<td>2. For women who have significant worsening of migraine without aura while taking the pill, discontinuation should be considered, especially if the worsening is dramatic.</td>
</tr>
<tr>
<td>3. Women who have migraine with a relatively brief common aura type (e.g., visual aura under 30 minutes) probably have significantly increased ischemic stroke risk if OCs are used. This risk probably increases with age as baseline stroke rates increase, so that the increased risk may be acceptable to the younger patient but not to the older patient (&gt; age 30).</td>
</tr>
<tr>
<td>4. Women who have prolonged migraine auras (beyond 60 minutes) or multiple or less common aura symptoms (e.g., dysphasia, hemiparesis) should be strongly discouraged from using OCs.</td>
</tr>
<tr>
<td>5. Patients who develop a migraine aura for the first time while taking OCs, or whose previous typical migraine aura becomes more prolonged or complex, should discontinue OCs.</td>
</tr>
<tr>
<td>6. OCs should be discontinued in women with migraine of any type who develop transient ischemic attacks, stroke, or ischemic vascular disease elsewhere.</td>
</tr>
</tbody>
</table>
### Table 2. Age-Specific Estimates of the Excess Rates of Myocardial Infarction, Ischemic Stroke, and Venous Thromboembolism Attributable to the Use of Low-Estrogen Oral Contraceptives and Pregnancy-Related Mortality.a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20–24 Yr</td>
</tr>
<tr>
<td>No. of excess cases of myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>and ischemic stroke attributable to oral contraceptive use (per 100,000 woman-yr of use)†</td>
<td>0.4</td>
</tr>
<tr>
<td>Among nonsmokers</td>
<td></td>
</tr>
<tr>
<td>Among smokers</td>
<td>1</td>
</tr>
<tr>
<td>Among women with hypertension</td>
<td>4</td>
</tr>
<tr>
<td>No. of pregnancy-related deaths (per 100,000 live births)</td>
<td>10</td>
</tr>
<tr>
<td>No. of excess cases of venous thromboembolism attributable to oral-contraceptive use (per 100,000 woman-yr of use)</td>
<td>6</td>
</tr>
<tr>
<td>With norethindrone, norethindrone acetate, levonorgestrel, or ethynodiol diacetate</td>
<td></td>
</tr>
<tr>
<td>With desogestrel or gestodene</td>
<td>16</td>
</tr>
</tbody>
</table>

a Low estrogen was defined as less than 50 μg.
† Data are from Farley et al.24

### Table 3. Summary of Guidelines for the Use of Combination Estrogen–Progestin Oral Contraceptives in Women with Characteristics That Might Increase the Risk of Adverse Effects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACOG Guidelines</th>
<th>WHO Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker, &gt;35 yr of age</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>&lt;15 cigarettes/day</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>≥15 cigarettes/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure controlled</td>
<td>Risk acceptable; no definition of blood-pressure control</td>
<td>Risk usually outweighs benefit if systolic blood pressure is 140–159 mm Hg and diastolic blood pressure is 90–99 mm Hg</td>
</tr>
<tr>
<td>Blood pressure uncontrolled</td>
<td>Risk unacceptable; no definition of uncontrolled blood pressure</td>
<td>Risk unacceptable if systolic blood pressure is ≥160 mm Hg or diastolic blood pressure is ≥100 mm Hg</td>
</tr>
<tr>
<td>Migraine headache</td>
<td>Risk usually outweighs benefit</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Age ≥35 yr</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Focal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Risk unacceptable</td>
<td>Risk unacceptable</td>
</tr>
<tr>
<td>Current disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past disease, no active disease for 5 yr</td>
<td>Risk unacceptable</td>
<td>Risk usually outweighs benefit</td>
</tr>
<tr>
<td>Family history of breast or ovarian cancer</td>
<td>Risk acceptable</td>
<td>Risk acceptable</td>
</tr>
</tbody>
</table>

From: Petitti, D. Combination Estrogen–Progestin Oral Contraceptives NEJM. 349;15: 1443-1450
References


Treatment of Menopausal Symptoms
Carol Bates, MD
Workshop WE10, Friday, Apr 25, 2014 3:30 – 5:00 PM
Clinical Dilemmas in Women’s Health: Using the current evidence to answer questions asked frequently in the middle years
2014 National Meeting of the Society of General Internal Medicine

Learning Objectives:
1. Review constructs on natural history of menopause
2. Understand options to treat vasomotor symptoms and atrophic vaginitis
3. Review risks of HRT

Introduction:
Menopause affects every woman who lives beyond the age of the menopause transition, so one’s positions on treatment recommendations have enormous consequences. The medical community’s consensus position on HRT has been a swinging pendulum over the past 20 years. Many recommended that most women should be encouraged to take HRT in order to prevent myocardial infarction irrespective of symptoms in the 1990s; this position was based on a roughly 50% relative risk reduction for heart disease seen in many largely concordant cohort studies. We swung to the opposite extreme of fear of HRT in any women following publication of the Women’s Health Initiative in 2002. In 2014, our position should be patient centered and focused on quality of life.

CASE 1:
EW is a 46 year old woman with hot flashes. When symptoms are at their worst, she wakes up 3 times a night and has to change her nightgown twice a week. She wonders if she has made it through the worst period since her symptoms have improved dramatically over the last 3 weeks. She isn’t sure that she can tolerate the fatigue from her sleep disturbance if her symptoms return. She has had ~6 hot flashes during the day and at times has felt very embarrassed when these occur during important work meetings. Her periods historically came every 28 days like clockwork; they are now variable every 24-26 days. She missed one period in the last 6 months with a 50 day intermenstrual interval. She uses condoms for contraception and wonders if she can stop worrying about birth control now that she is entering the menopause transition.

Questions:
1. What might we predict about her vasomotor symptoms; could the worst be over?

Freeman, Obstetrics & Gynecology. 2011
2. What are her treatment options?

<table>
<thead>
<tr>
<th>Hot Flash Symptom Reduction</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>95%</td>
<td>20-40%</td>
</tr>
<tr>
<td>Progesterone</td>
<td>80-90%</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine 75-150 mg qd</td>
<td>61%</td>
<td>27%</td>
</tr>
<tr>
<td>Desvenlafaxine 100 mg qd</td>
<td>64%</td>
<td>51%</td>
</tr>
<tr>
<td>Fluoxetine 20 mg qd</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td>Paroxetine 12.5 – 25 mg qd *</td>
<td>65%</td>
<td>38%</td>
</tr>
<tr>
<td>Citalopram 20 mg qd</td>
<td>55%</td>
<td>23%</td>
</tr>
<tr>
<td>Escitalopram 10-20 mg qd</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>Gabapentin 300 mg tid</td>
<td>54%</td>
<td>31%</td>
</tr>
<tr>
<td>Clonidine 0.1-0.2 mg qd</td>
<td>30-40%</td>
<td></td>
</tr>
<tr>
<td>Methyldopa 250-1000 mg qd</td>
<td>65%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Only FDA approved non-hormonal treatment Paroxetine 7.5 mg qhs (Brisdelle)

A new treatment option in 2014 is a “Tissue selective estrogen complex” combining premarin 0.45 mg with the SERM badoxifene. It behaves as an agonist in bone, an antagonist in the uterus, and is perhaps neutral for vaginal epithelium and breast tissue. It is being marketed both for osteoporosis prevention and to treat vasomotor symptoms in women with a uterus as it does not cause endometrial hyperplasia.

3. How should we approach the HRT option?

Safety of HRT: WHI used premarin 0.625 mg and medroxyprogesterone acetate 2.5 mg in women with an average age of 60. It was a prevention trial and not a trial of treatments for hot flashes. Post-hoc analysis of WHI suggests lower risks of MI and CVA in women who were closer in age to the menopause transition. We will never know if estradiol rather than premarin would have resulted in different outcomes or if some of the adverse effects were dose related.

Dose: Premarin 0.625 mg is roughly equivalent to estradiol 1.0 mg. Many women will have good symptom control with 0.5 mg estradiol.

Progestin: Only needed to protect endometrium; does increase risk of breast cancer

Route: Transdermal may be safer than oral for VTE.

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI) (1)</th>
<th>OR (95% CI) (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>4.2 (1.5-11.6)</td>
<td>2.5 (1.9-3.4)</td>
</tr>
<tr>
<td>Transdermal</td>
<td>0.9 (0.4-2.1)</td>
<td>1.2 (0.9-1.7)</td>
</tr>
</tbody>
</table>

(1) Case control study Circulation 2007;115:840-845
(2) Meta Analysis BMJ 2008;336(7665)
Duration: It is common for symptoms to recur after HRT is discontinued. Though there is no evidence to support gradual taper, many providers do this, and introduce the notion of working towards lower doses when they first prescribe HRT. It is probably easiest to have women reduce their doses by skipping days of treatment (i.e. 6 days for at least 2 months, followed by 5 days, 4 days, 3 days, 2 days, stop.

Gordon, ObGyn, 2004

4. When can she stop contraception?

She should continue contraception until she is truly at menopause (1 year after final menstrual period). There is no definite maximal age for contraceptives like OCP, though many would stop at ~51. Progestin releasing IUD (Mirena) is a great alternative.

Case 2: MW is 60 years old. Her LMP was at age 53. She has not been sexually active for several years, but she has a new partner. She is afraid she will have pain with intercourse.

1. How might you assess her for likelihood of dyspareunia?

If a pelvic examination is indicated, findings of atrophic vaginitis include narrow introitus, loss of rugae, pale, smooth and shiny mucosa,
possible petechiae.

Is a 2 finger internal exam uncomfortable? Consider using an ultrathin speculum.

2. What are her treatment options?

Most women first try lubricants and over the counter vaginal bioadhesive moisturizers (i.e. Replens). Topical vaginal estrogen is very effective and prompts return towards premenopausal vaginal epithelium increasing superficial and intermediate cells, and normalizing (lowering) vaginal pH.

Systemic estrogen will treat atrophic vaginitis but should be used only if there are other indications.

Vaginal Estrogens:

<table>
<thead>
<tr>
<th>Brand</th>
<th>Type</th>
<th>Ingredient</th>
<th>Dose</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarin</td>
<td>Cream</td>
<td>0.625 mg CEE/gram</td>
<td>0.5-2 g/d</td>
<td>$189/30 g</td>
</tr>
<tr>
<td>Estrace</td>
<td>Cream</td>
<td>Estradiol</td>
<td>1 gram 1-3 times/wk</td>
<td>$158/42 g</td>
</tr>
<tr>
<td>Estring</td>
<td>Ring</td>
<td>Estradiol</td>
<td>1 ring q 90 days</td>
<td>$239/3 months</td>
</tr>
<tr>
<td>Vagifem</td>
<td>Vaginal tablet</td>
<td>Estradiol 10 mcg</td>
<td>Twice/week</td>
<td>$78/month</td>
</tr>
</tbody>
</table>

One additional new option released in spring 2013 is Ospemifene (Brand name Osphena) which is a SERM (Selective Estrogen Receptor Modulator) marketed purely for atrophic vaginitis. It is an agonist to vaginal epithelium, endometrium, and bone; its properties with respect to breast tissue are less clear. It has an FDA warning for risk of DVT and CVA, and costs ~$160/month.

Conclusions:
Most would recommend against HRT for prevention of CAD, but for short term use in the lowest effective dose, HRT remains the most effective treatment for vasomotor symptoms. While there are no RCTs yet available to demonstrate relative safety of oral vs. transdermal HRT, many have moved to transdermal therapy because of the case control data suggesting a reduced risk of VTE. There are also many non-hormonal options for vasomotor symptom management including a variety of anti-depressants and gabapentin.

While vasomotor symptoms do improve over time for most women, atrophic vaginitis worsens over time. Increasing frequency of intercourse has actually been shown to be helpful. Lubricants and vaginal moisturizers may also be helpful. Vaginal estrogen appears to be safe with no proven evidence of systemic harm and is available in a wide range of preparations.

New SERMS are being marketed both for vasomotor symptoms and atrophic vaginitis. As best we understand, they are associated with risk of DVT, and they are currently expensive.
References:

North American Menopause Society www.menopause.org


Col NF et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA* 1997;277:1140-47.


Case Vignette: Osteopenia
Shobhina G. Chheda MD MPH, Deborah Kwolek MD
Clinical Dilemmas in Women's Health: Partnering with Patients to Answer Questions asked frequently in the Middle Years
2014 National Meeting of the Society of General Internal Medicine

Learning Objectives:
1. Discuss options for deciding whether or not to use bone mineral density to screen postmenopausal women less than age 65 for osteoporosis.
2. Highlight important factors to discuss with women with osteopenia as they are considering treatment.
3. Debate intervals for using bone mineral density testing/vertebral fracture assessment in following women with osteopenia.

Introduction

The dilemma of osteopenia management is that it is a “pre-condition” as are pre-hypertension, impaired fasting glucose and borderline high cholesterol (1). The relation between bone mineral density and risk of fracture is continuous, with no absolute cut-off to define a disease state. Osteopenia has been defined by the World Health Organization working group as a T-score of higher than -2.5 but less than -1.0 for postmenopausal women. Using this criterion almost 26.9 million American women have osteopenia. This label identifies a group of women with intermediate risk, in which management is unclear. At a population level, the significantly greater number of women with osteopenia compared to the number of women with osteoporosis compounds the issue as the absolute number of fractures observed is greater among those with osteopenia (2). This case will allow us to examine the evidence and share our current clinical practices, in particular in areas where evidence is lacking.

JW is a 54 year old postmenopausal female of south-Asian descent who comes in to see you as a new patient as she has recently moved from a different city. Prior to her move she had slipped on ice and fractured her left arm. She wonders if she should have a bone mineral density test done. Her height is 65 inches (165.1cm) and weight 137 lbs (62.14 kg). Her mother had a hip fracture at age 70 and she currently smokes. Her LMP was at age 51

1. How would decide with the patient whether or not she get a dual-energy x-ray absorptiometry (DEXA) bone mineral density (BMD) test?

Screening for risk of fracture prior to ordering the test allows identification of a population of women whose risk of fracture is great enough that therapy is cost-effective (3). According to the USPSTF, women between ages 50-65 who have a 10-year risk of fracture equivalent to that of a 65 year old woman (ie. 9.3% or greater 10-year risk for major osteoporotic fracture is an indication for bone mineral density screening (4). This assumes that screening is in alignment with a woman’s decision to treat/engage in
behavior change. The WHO Fracture Risk Algorithm - **FRAX**[^5] tool, can be used for this purpose (ie. without already having the BMD result). The FRAX[^5] tool has limitations in that it may underestimate risk if the patient herself has had multiple fractures, diabetes, a hip fracture or a silent vertebral fracture that was picked up incidentally. Women with hip or vertebral fractures could be considered for therapy regardless of their bone mineral density result.

### Table: Relative risk of Hip fractures according to key clinical risk factors after adjustment for age and bone mineral density

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior fracture after age 50</td>
<td>1.62 (1.30-2.01)</td>
</tr>
<tr>
<td>Body mass index (20 vs. 25)</td>
<td>1.42 (1.23-1.65)</td>
</tr>
<tr>
<td>Previous or current use of systemic glucocorticoids*</td>
<td>2.25 (1.60-3.15)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.73 (0.94-3.20)</td>
</tr>
<tr>
<td>Parental history of hip fracture</td>
<td>2.28 (1.48-3.51)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.60 (1.27-2.02)</td>
</tr>
<tr>
<td>Alcohol intake &gt;2 drinks daily</td>
<td>1.70 (1.20-2.42)</td>
</tr>
</tbody>
</table>

* use of oral corticosteroid therapy (daily dose equivalent ≥ 5 mg prednisone) for more than 3 months. (From Kholsa and Melton [1]-Based on data from Kanis et al. [6])

No controlled studies have evaluated the effect of screening for osteoporosis on fracture rates or fracture related morbidity or mortality. There is, however, data that pharmacologic treatment of postmenopausal women with no prior osteoporotic fractures can reduce the risk of fractures [4].

Using **FRAX**[^5] calculator you find that her 10 year risk for a major osteoporotic fracture is 12%, which is greater than that of a 65 year old without other risks and decide together to move ahead with a dual-energy x-ray absorptiometry (DEXA) bone mineral density (BMD). Her results indicate that her T-score at her spine is -1.5 and at her femoral neck is -1.6. Because of her prior history of fracture you decide to order vertebral imaging study at the time of her DEXA. The study shows no vertebral fractures.

2. **Why did you do the vertebral imaging? What other additional testing could be considered? What if there was a vertebral fracture seen on VFA?**

The use of vertebral imaging is controversial. The single best predictor of future fractures is prior osteoporotic fractures. Though this can be often elicited by history, vertebral fractures may be asymptomatic. Only 25-35% of vertebral fractures present with acute symptoms. Once a vertebral fracture is present it increases the risk of another fracture 5-fold and of a hip fracture 2-3 fold. [7]. Silent vertebral fractures can be detected by using a newer type of dual-energy x-ray absorptiometry (VFA imaging using central DXA densitometers) which allows for lateral views and includes special software to allow for detection of vertebral fractures while obtaining bone density measurements. This has benefit of being done at time of DEXA BMD, with lower cost and less radiation...
than x-ray and with greater patient convenience. This is in alignment with 2014 NOF guidelines (7), but different than ISCD guidelines (8). In this patient’s situation the presence of vertebral fractures would have likely changed the conversation regarding medication for her osteopenia.

Indications for Vertebral Imaging (2014 National Osteoporosis Foundation)
Consider vertebral imaging tests in the following individuals:
- In all women age 70 and older and all men age 80 and older if BMD T-score at the spine, total hip or femoral neck is < -1.0
- In women age 65 to 69 and men age 75 to 79 if BMD T-score at the spine, total hip or femoral neck is < -1.5
- In postmenopausal women age 50 to 64 and men age 50 to 69 with specific risk factors:
  - Low trauma fracture
  - Historical height loss of 1.5 inches or more (4 cm)
  - Prospective height loss of 0.8 inches or more (2 cm)
  - Recent or ongoing long term glucocorticoid treatment

Secondary causes of osteoporosis should be considered in patients with osteopenia (especially if the Z score is less than -2.0). Most of these will be identified on history and exam. Given the challenges of clinically diagnosing hyperparathyroidism, subclinical hyperthyroidism and vitamin D deficiency, especially in areas of high prevalence, clinicians may consider checking calcium, TSH and vitamin-D 1, 25 OH levels. Based on clinical judgment, renal and hepatic function may be assessed.

Biochemical markers of bone turnover are considered as one approach to identify women with accelerated bone turnover. Markers of resorption include urinary or serum C-terminal and N-terminal cross-linked telopeptides of type I collagen; markers of formation include bon-specific alkaline phosphatase, osteocalcin and N-terminal propeptide of type I collagen. In large cohort studies, increased bone turnover is associated with increased risk of fracture, independent of bone mineral density (8). However, routine use of these tests is not recommended as they have significant biological and assay variability (1). The use of these tests is primarily in research, though they may be indicated to assess absorption of bisphosphonates in patients with gastrointestinal disorders, to evaluate patients who lose bone on anti-resorptive therapy, and to assess compliance with therapy. Biochemical markers can cost more than a DEXA BMD.

You use the FRAX® calculator to assess JW’s 10-year hip and major osteoporotic fracture risk. It is 2.6% and 12% respectively. You engage with JW in discussion regarding this data. She is committed to life-style modification.
3. How would you advise her? What factors would influence your decision about whether to recommend treatment?

The 2013 National Osteoporosis Foundation guidelines recommends drug treatment for T score between -1.0 and -2.5 when FRAX® calculator indicates a 10-year risk for hip fracture is ≥ 3% or risk for major osteoporotic fracture is ≥ 20%. This recommendation is based on economic modeling to determine fracture risk above which it is cost-effective from a societal perspective to use pharmaceutical therapy (specifically, generic alendronate). The benefits of treatment and the risks to JW need to be discussed with her so that she may be able to make a decision that is best for her.

Clearly smoking cessation would be beneficial to not only her bone health but also her general health.

Regarding calcium and vitamin D intake, it is recommended that women in this age group have a total intake of 1200 mg/day of calcium and 400-800 IU/day of vitamin D (1). National Osteoporosis Foundation recommends a higher dose of vitamin D, 800-1000 IU/day (x). In general, it is agreed upon that the serum 25 (OH) vitamin D level should be above 30 ng/ml (1).

Weight bearing exercise and muscle-strengthening exercise is important in maintaining and improving agility, strength, posture and balance that may reduce the risk of falls. Additionally, there seems to be a modest benefit in increasing bone density.

You and JW decide against the use of medication at this time.

4. When would you repeat her BMD testing? What would change your recommendations concerning treatment?

The main objective of serial BMD measurements is to identify patients with significant loss in BMD so consideration can be given to change in management. To compare follow-up BMD results with baseline, one must determine whether change over time represents true biologic change. The serially measured BMD change must exceed the least significant change (LSC) to be reported as significant. The LSC is impacted by the specific instrument being used, patient population being assessed, measurement site, technologist’s skill with patient positioning, test analysis, and confidence intervals used. For patients measured on that device, if change in BMD (not T-score) at follow-up exceeds the LSC, that change is considered real. Changes of lower magnitude than the LSC are considered within the measurement variation of the instrument. In general, changes less that 3-6% at the hip and 2-4% at the spine may be due to the precision error of testing itself.
**New Data (Gourlay et al, 2012)**

<table>
<thead>
<tr>
<th></th>
<th>Time to Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal bone density</td>
<td>15 years</td>
</tr>
<tr>
<td>Mild Osteopenia T&gt; -1.5</td>
<td>15 years</td>
</tr>
<tr>
<td>Moderate Osteopenia T -1.5 to -2.0</td>
<td>5 years</td>
</tr>
<tr>
<td>Severe Osteopenia T-2.0 to -2.5</td>
<td>1 year</td>
</tr>
<tr>
<td>Monitoring Treatment</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**New Recommendations (Yu and Finkelstein, 2012)**

<table>
<thead>
<tr>
<th>Normal Bone Density</th>
<th>Rescreen 10-15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia Low Risk by FRAX</td>
<td>Rescreen 5-10 years</td>
</tr>
<tr>
<td>Osteopenia borderline risk by FRAX</td>
<td>Rescreen 2-3 years</td>
</tr>
<tr>
<td>Osteopenia High Risk by FRAX</td>
<td>Treat empirically</td>
</tr>
<tr>
<td>Osteoporotic Bone Density and/or history of fragility fracture</td>
<td>Treat empirically</td>
</tr>
</tbody>
</table>

- More frequent testing may be warranted in certain clinical situations. (advanced age, height loss, DM, expected rapid bone loss, frequent falls, prednisone use, and changes in other risk factors)
- Re-evaluate patient clinically every year for changes in status. Perform BMD testing as indicated above.
- Once therapy is initiated, repeat BMD 1-2 years after initiating every two years thereafter.

**Take Home points**

1. Frax may be used to help decide when to first screen a postmenopausal woman for Osteoporosis.
2. Vertebral fracture assessment at the time of DEXA can aid decision-making.
3. Individualize treatment and rescreening decisions with the woman based on FRAX score, additional risk factors and patient preferences.
4. Treatment is recommended when there is a history of hip or spinal fracture, or when FRAX indicates a 10 year risk of hip fracture ≥ 3% or a risk of major osteoporotic fracture is ≥ 20%.
References


