ADVANCES IN WOMEN’S HEALTH

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OVERVIEW

• Update in Women’s Health for SGIM
  – Drs. Eleanor Schwartz, Redonda Miller and Meg McNamara
• Review of literature from March, 2009 through February, 2010
• Journals, Cochrane
• Criteria
  – Scientific rigor
  – Potential to impact clinical practice

BUT NOT....

• Osteoporosis Prevention
• Menopause
• Colorectal, breast, or ovarian cancer screening
• Contraception
• Other topics covered at this course
TOPICS
• Migraines and Cardiovascular Disease
• Hormone Therapy and Ovarian Cancer
• Cervical Cancer Screening and HPV Vaccine
• Vitamin D
• Treatment of Osteoporotic Compression Fractures

MIGRAINES AND CARDIOVASCULAR DISEASE

Question
• Ms. M.G. is a 37 year old woman with a 5 year history of migraines. She always has an aura before her migraines and typically gets relief with a triptan. She is concerned about whether these headaches increase her risk of future disease. What do you tell her?
QUESTION

• She has an increased risk of heart disease
• She has an increased risk of cardiovascular death
• She has an increased risk of stroke
• Her risk for all these diseases is increased

Migraines and Cardiovascular Disease

• Migraines affect 10-20% of the population
  – Women affected 4 times as often as men
• Headaches and GI/autonomic symptoms
• About 1/3 of individuals have aura
  – Most commonly visual

Migraines and Cardiovascular Disease

• AIM: To assess the current evidence on the association between migraine and cardiovascular disease
Migraines and Cardiovascular Disease

- 25 case control or cohort studies
- All assessed clearly defined cardiovascular outcomes occurring after migraine
- Two investigators assessed eligibility and all studies

Results

- Migraine was associated with an increased risk of ischemic stroke
  - RR 1.73 (95% C.I.: 1.31, 2.29)
- Risk of ischemic stroke higher among individuals with aura
  - 2.16 (95% C.I.: 1.53, 3.03)
- Risk higher in women, age <45, smokers and OCP use

Impact for Practice

- Individuals with migraine are at increased risk for ischemic stroke
  - Migraine with aura
- Young women who have migraine with aura should be strongly encouraged to quit smoking and birth control methods should be carefully considered
- Cardiovascular risk factor identification and modification
  - Consider earlier risk factor modification
Ovarian Cancer Risk

Question

- Ms. O. is a 50 year old woman who is having significant hot flashes and is not sleeping well. She is considering taking estrogen but is worried about her risk for ovarian cancer on estrogen. What do you tell her?

- Her risk for ovarian cancer is not affected
- Her ovarian cancer risk is increased while she takes hormone therapy and remains elevated when she stops
- Her risk of ovarian cancer is increased on hormone therapy but decreases when she stops
Hormone Therapy and Ovarian Cancer

- AIM: To assess the risk of ovarian cancer in perimenopausal and postmenopausal women receiving different hormone therapies.

Hormone Therapy and Ovarian Cancer

- Prospective cohort study
  - Over 900,000 Danish women
  - 8 year follow-up
- Prescription data
- 3068 incident cancers

Results

- Increased risk of ovarian cancer in current users
  - RR 1.38 (1.26-1.51)
- Risk declined with years since past use
- Risk did not differ by type of hormone therapy or duration of use
- 1 ovarian cancer per 8,300 women taking hormone therapy each year
Impact for practice

- Hormone therapy is associated with a small increase in ovarian cancer risk and the risk declines after HT is discontinued
- No effect of type or dose of estrogen or progestin or route of administration
- Additional factor to consider in decision making about hormone therapy

Cervical Cancer Screening and Prevention

Which of the following do you most commonly use for routine cervical cancer screening?
- Conventional cytology
- Liquid based cytology
- HPV testing
- Liquid based cytology and HPV testing
Cervical Cancer

- Cervical cancer mortality has dramatically decreased with routine Papanicolau smear screening
- Pap smear is the most commonly used method for cervical cancer screening
- Cervical cytology is used to predict abnormal histology

Classification of Cervical Cancer Histology

<table>
<thead>
<tr>
<th>Histology (Biopsy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Cervical intra-epithelial level, grade 1 (CIN 1)</td>
</tr>
<tr>
<td>Cervical intra-epithelial level, grade 2 (CIN 2)</td>
</tr>
<tr>
<td>Carcinoma in situ (CIN 3), Invasive carcinoma</td>
</tr>
</tbody>
</table>

Classification of Cervical Squamous Cell Pathology

<table>
<thead>
<tr>
<th>Cytology (Papanicolau test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Atypical squamous cells-undetermined significance (ASC-US)</td>
</tr>
<tr>
<td>Atypical squamous cells-cannot exclude HSIL (ASC-H)</td>
</tr>
<tr>
<td>Low-grade squamous intra-epithelial lesion (LSIL)</td>
</tr>
<tr>
<td>High-grade squamous intra-epithelial lesion (HSIL)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
</tbody>
</table>
NATURAL HISTORY OF CERVICAL CANCER

- Human Papilloma Virus is the causative agent
- HSIL (High-grade squamous intraepithelial lesion) is a significant precancerous lesion
- LSIL (Low-grade SIL) is much more benign
  - 65% will regress spontaneously in 3 years in women aged 15-34
  - Regression rates lower in older women
- Many HPV infections will regress
  - 50-70% regress in young women
  - Regression rates lower in older women

LIQUID BASED CYTOLOGY

- The use of liquid based cytology for primary cervical cancer screening is widespread
  - Limited data on diagnostic accuracy

LIQUID BASED CYTOLOGY

- AIM: To compare the accuracy of liquid based and conventional cytology for detection of histologically confirmed cervical intraepithelial neoplasia.
METHODS

• Cluster randomized controlled trial within 246 family practices in the Netherlands
• 89,784 women aged 30-60
• 122 practices assigned to liquid based cytology and 124 practices assigned to conventional screening
• Detection rates of and positive predictive values for histologically verified CIN
• Blind verification of all test positive outcomes

RESULTS

• Primary outcome was ratio of detection rate of histologically confirmed CIN or cervical carcinoma between the two tests
  – Absolute sensitivity could not be calculated
• Detection Rate Ratio
  – CIN 1+ : 1.01 (95% C.I. 0.85, 1.19)
  – CIN 2+ : 1.00 (95% C.I. 0.84, 1.20)
  – CIN 3+: 1.05 (95% C.I. 0.86, 1.29)
  – Carcinoma: 1.69 (95% C.I. 0.96, 2.99)
• Positive predictive value ratios also did not differ
  – Specificity

CONCLUSIONS/IMPACT

• Liquid based cytology is not superior to conventional Pap tests when used in a well organized cervical cancer screening program
• Main advantage is a reduction in unsatisfactory smears
  – Potential to do HPV testing for ASCUS smears
• Keep using conventional cytology
HPV Testing

- Currently HPV testing is recommended for the triage of abnormal Pap smears
  - Women with ASC-US are tested for high risk HPV types
- Use for routine screening?
  - FDA approved

HPV testing and clinical outcomes

<table>
<thead>
<tr>
<th>Name</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>POBASCAM</td>
<td>Pap plus HPV vs Pap alone</td>
<td>CIN 3 or greater</td>
<td>More CIN3+ detected during round 1 in HPV group (0.8% vs 0.5%); Less CIN3+ during round two (0.3% vs 0.6%); Number of CIN3+ lesions in the two rounds did not differ between groups (1.1% vs 1.1%)</td>
</tr>
<tr>
<td>Naucler, 2007</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SWEDE-SCAN</td>
<td>Pap plus HPV vs Pap alone</td>
<td>CIN 2 or invasive cancer</td>
<td>More CIN2+ at baseline in HPV group (1.8% vs 1.2%); Less CIN 2+ in subsequent exams (0.4% vs 0.7%)</td>
</tr>
<tr>
<td>Bulkmans, 2007</td>
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</tbody>
</table>

HPV Testing and Clinical Outcomes

- Does earlier detection of lesions lead to improved outcomes?
- Many CIN2 lesions will regress on their own anyway
HPV Trials and Test Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>HPV followed by Pap or HPV followed by HPV</th>
<th>Sensitivity and specificity for detecting CIN 2 or higher</th>
<th>HPV</th>
<th>Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayrand, 2007</td>
<td>94.6% 55.4%</td>
<td>94.9% 96.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTCC, 2006</td>
<td>97.3% 82.3%</td>
<td>97.1% 97.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTCC, 2006</td>
<td>98.2% 84.8%</td>
<td>97.1% 97.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test Characteristics

- HPV testing is consistently more sensitive but less specific than Pap smears
- Higher false positive rates

HPV vs Cytology?

- What to do about women who are positive for HPV but have negative cytology?
HPV and Pap Cotesting

- AIM: To estimate the prevalence of positive carcinogenic HPV test results in cytologically-normal women

HPV and Pap Cotesting

- Analysis of all cotesting results in women aged 30 and older collected at KP Northern California Jan 2003-April 2008
- 580,289 women had 812,598 cotests
- Testing for carcinogenic HPV using hybrid capture 2 (hc2) assay

Results

- Overall 6.27% of cotests were hc2 positive
  - Likelihood of positive test most common in women aged 30-34 and decreased with age
- 5.18% of cotests has AS-CUS or greater cytology
- 2.87% of cotests in women aged 30 and older had ≥AS-CUS cytology and tested hc2 negative
Impact

- In a program where cotesting is routine for women aged 30 and older, concerns about excessive positive HPV results are not borne out.
- What should we do about women who are positive for carcinogenic HPV but cytology negative?

HPV TESTING: POTENTIAL HARMS

- More false positives lead to additional testing
- Increased anxiety
- Stigma and labeling
- Partner discord
- Potential undermining of cytological screening which is known to be effective
- Economic costs

HPV Testing: Potential Benefit

- Main potential benefit is decreased screening interval
- Women with negative Pap smears and negative HPV tests can increase the interval between screening tests
HPV TESTING: ACS RECOMMENDATIONS

- Consider for women aged 30 and older HPV testing in conjunction with conventional cytology or liquid based cytology
  - Combined screening should NOT be more often than every three years
- Women who are negative for HPV could be screened less often
- What to do about women who have a normal smear but a high risk HPV type?
  - Repeat screening tests in 1 year?
  - Colposcopy if either abnormal
- www.asccp.org

USPSTF RECOMMENDATION: HPV

- Evidence is insufficient to recommend for or against the routine use of HPV testing as a primary screening test for cervical cancer
  - Grade "I" recommendation

New ACOG Cervical Cancer Screening Guidelines

- Cervical cancer screening should begin at age 21 regardless of the age at onset of sexual activity
- Screening should occur every 2 years in women aged 21-29
  - More frequent if HIV, immunosuppression, DES exposure or history of CIN
New ACOG Cervical Cancer Screening Guidelines

• Women ≥ age 30 who have had at least 3 negative smears can be screened every 3 years
  – Cotesting with cervical cytology and high risk HPV typing is also appropriate
  – Re-screen in 3 years if cotesting negative

New ACOG Cervical Cancer Screening Guidelines

• Women who have had a hysterectomy do not need cervical cancer screening
• After age 65 or 70, screening can cease in women who have had at least 3 previous negative tests and no abnormalities in the past 10 years
• Those with CIN2, CIN3 or cancer should undergo annual screening for 20 years
• HPV vaccine does not change these recommendations

ACOG vs USPSTF

• Guidelines very similar
• ACOG addresses screening intervals if there is a history of previous abnormal tests
• ACOG and cotesting
SUMMARY

• The vast majority of cervical cancer cases occur in women who have never been screened or who have not been screened in the past 5 years.

What do you think is the most appropriate recommendation for HPV vaccination?

• Routinely vaccinate all girls/women aged 11-12 to 26 years
• Routinely vaccinate all girls/women aged 11-12 to 18 years
• Routinely vaccinate virginal girls/women aged 11 to 26
• No vaccination at this time

HPV VACCINE

• Several studies have shown safety and efficacy of vaccines against the most common cancer-causing HPV types
• Who should be vaccinated?
VACCINE

- Vaccine does not contain DNA and is not live or attenuated virus
- Two vaccines
  - Quadrivalent (Gardisil)
    - HPV 6, 11, 16, 18
  - Bivalent (Cervarix)
    - HPV 16, 18

VACCINE

- 3 dose series
  - 0, 2, 6 months
- Cost is approximately $360
- Duration of protection
  - Recent study showed safety and efficacy in prevention of incident cervical infection with HPV 16/18 up to 6.4 years
  - More studies needed

ACS VACCINE RECOMMENDATIONS

- Routine HPV vaccination is recommended for girls aged 11 to 12
  - Girls as young as 9 years may be vaccinated
- Vaccination for girls aged 13-18 to catch up on missed vaccine or to complete the series
- Insufficient data to recommend for or against routine vaccination of women aged 19-26
  - ACIP/CDC recommends vaccination of this age group
HPV VACCINE: ISSUES

- Highest efficacy in virginal women
  - Should guidelines be based on number of sexual partners or age?
- Final results of the phase III trials have not yet been reported

VITAMIN D

Violet D. is a 69 year old woman who comes in for a health care maintenance exam. You order a bone mineral density. She tells you she also wants a Vitamin D level checked. What do you do?
Question: Vitamin D

- Order a Vitamin D level
- Don’t order a Vitamin D level because you are not sure to do with the results
- Don’t order it but start her on a calcium/Vitamin D supplement

BACKGROUND

- Vitamin D deficiency is common in older adults, homebound individuals and women admitted with hip fracture
- Association between Vitamin D level and fracture risk is inconsistent
- Association could be influenced by renal function, muscle strength and estrogen receptors

DEFINITIONS

- Vitamin D optimum minimal level: ~25(OH)D concentration >30 ng/ml
- Vitamin D insufficiency: ~25(OH)D concentration 20-30 ng/ml
- Vitamin D deficiency: ~25(OH)D concentration <20 ng/ml
CLINICAL QUESTIONS

- What is the association between Vitamin D level and fracture?
- Does Vitamin D prevent fracture?
- When should Vitamin D levels be checked?
- When and how should Vitamin D supplementation be given?

VITAMIN D AND HIP FRACTURE RISK

Odds Ratios of Risk for Hip Fracture*

<table>
<thead>
<tr>
<th>25-hydroxyvitamin D Level</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per 2.5-nmol/L decrease‡</td>
<td>1.03 (1.01-1.05)</td>
<td>1.03 (1.01-1.05)†</td>
</tr>
<tr>
<td>Per 25-nmol/L decrease</td>
<td>1.30 (1.07-1.58)</td>
<td>1.33 (1.06-1.68)</td>
</tr>
<tr>
<td>Quartile (according to control group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First (9.2-47.5 nmol/L)</td>
<td>1.73 (1.13-2.66)</td>
<td>1.71 (1.05-2.79)</td>
</tr>
<tr>
<td>Second (47.6-60.1 nmol/L)</td>
<td>1.08 (0.72-1.63)</td>
<td>1.09 (0.70-1.71)</td>
</tr>
<tr>
<td>Third (60.2-70.6 nmol/L)</td>
<td>0.78 (0.50-1.20)</td>
<td>0.82 (0.51-1.33)</td>
</tr>
<tr>
<td>Fourth (70.7-121.5 nmol/L)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
</tbody>
</table>

P for trend 0.009 for unadjusted and 0.015 for adjusted models


Vitamin D and Fracture

- Linear association suggests dose-response effect
  - No difference by age or geographic region
- Low serum 25 (OH) vitamin D concentrations can help identify women at high risk for hip fracture
- Perhaps we should consider Vitamin D level in decision making about anti-resorptive therapies
Vitamin D and Fractures


- AIN: To determine whether oral Vitamin D can prevent non-vertebral and hip fractures

Vitamin D and Fractures

- Included studies evaluated Vitamin D supplementation and reported at least one fracture
  - Studies had to be double blind with at least one year of follow-up and include adherence
  - Participants took cholecalciferol (D₃) or ergocalciferol (D₂)

Results

- 12 included trials
- Vitamin D doses >400 IU per day reduced nonvertebral and hip fractures but lower doses did not
  - Overall reduction was relatively small
    - RR 0.86 (0.77, 0.96) for nonvertebral fractures
- Addition of calcium did not appear to enhance the effect of Vitamin D
- Antifracture efficacy was higher with higher achieved 25-hydroxyvitamin D serum levels
Impact for Practice

- Vitamin D supplementation can reduce fracture risk
- What is the added value of other therapies with Vitamin D?
  - Calcium
  - Bisphosphonates
  - At what age should supplementation start?

Vitamin D Evidence

- AHRQ Systematic Review of the efficacy and safety of Vitamin D in relation to bone health
- BMD-fair
- Fractures- inconsistent
  - Included open label study designs
  - Did not account for adherence
- Performance measures (body sway, gait speed)- inconsistent
- Falls- fair, but few studies
- Harms- check levels
  - www.ahrq.gov

TRENDS OF VITAMIN D INSUFFICIENCY

- Mean serum 25(OH)D level is decreasing
  - 30 vs 24 ng/mL
- Prevalence of Vitamin D deficiency is increasing
  - Ethnic differences persist
  - Majority of non-Hispanic Blacks and most Mexican Americans have vitamin D insufficiency
  - Ginde Arch Intern Med 2009
Measuring 25(OH)D

- Should we measure it or encourage adequate intake/exposure?
- For those without regular sun exposure, consumption of 800 IU per day necessary to keep 25 (OH) D levels >30 ng/ml
- Measure in homebound, malabsorption, individuals with osteoporosis

TREATMENT

- Nutritional Deficiency
  - 50,000 IU of Vitamin D₂ or D₃ per week for 6-8 weeks and then 800-1000 IU per day
- Nutritional Insufficiency
  - 800-1000 IU per day
  - Goal will be reached in 3 months
- Serum levels may increase more quickly with cholecalciferol (D₃)

TREATMENT

- Monitor at 3 months
- Safe upper limit for Vitamin D
  - 2000 units per day
    - National Academy of Sciences
- Higher doses appear to be safe for several months
Compression fracture: treatment

- Bea Brittle is a 76 year old woman who was driving over a speed bump last week and had sudden onset of severe back pain. You saw her, diagnosed a compression fracture and started her on NSAIDs and tylenol with codeine. Today she is continuing to have severe pain, is having problems doing her usual activities and wants to know if there is anything else that can be done.

What do you recommend?

- Add a long acting opiate and continue the tylenol with codeine for breakthrough pain
- Increase the dose of tylenol with codeine
- Refer her for vertebroplasty
- Refer her for kyphoplasty

Background

- Vertebral compression fractures can be asymptomatic or can cause substantial morbidity and mortality
- Traditional treatment includes bed rest, analgesics and bracing
Treatment alternatives

• Vertebroplasty: Augment vertebral compression fractures with polymethylmethacrylate (PMMA)
• Kyphoplasty: Inflatable balloon to restore the vertebral body to original height while creating a cavity into which PMMA can be injected under low pressure
  – Stabilization of the spine
  – Prevent kyphosis?

Use of Vertebroplasty and Kyphoplasty

• Use of both procedures has been increasing despite little evidence
• Reports of repeat procedures at previously treated levels
• Reports of prophylactic use of vertebroplasty despite no evidence
• May increase the risk of subsequent vertebral fracture at adjacent levels

Vertebroplasty

• AIM: To determine the short term efficacy and safety of vertebroplasty for alleviating pain and improving function in persons with painful osteoporotic vertebral fractures
Methods

- 78 Individuals with one or two painful osteoporotic compression fractures of <12 months duration
- Vertebroplasty vs sham
- Overall pain at 1 week, 1, 3 and 6 months

Results

- Overall pain was reduced in both groups at each point of follow-up
  - No significant difference
- Similar improvements in nocturnal pain, pain at rest, physical functioning, quality of life
- Similar rate of incident fractures in both groups
  - 3 vertebroplasty vs 4 placebo

INVEST Trial

- Similar trial done in the United Kingdom
  - Vertebroplasty vs sham
- Both groups had improvement in disability and pain after the intervention
- Trend toward a clinically significant reduction in pain at one month
  - 30% decrease from baseline
  - 64% vs 48%; (p=0.06)
- Overall no significant differences between groups
- Similar rate of adverse events
Vertebroplasty: Conclusions

- Vertebroplasty does not lead to improved outcomes compared with a sham treatment
- What if fractures were more acute?
- High rate of crossover
- Placebo involves injection of short acting analgesic into the periosteum

Kyphoplasty

- AIM: To assess the efficacy and safety of balloon kyphoplasty in the treatment of painful vertebral compression fracture

Methods

- Kyphoplasty was compared to nonsurgical care in 300 participants in 18 countries
  - Nonsurgical care: back brace, walking aids, analgesics, physical therapy
- Patients with acute fractures (<3 months)
Results

- At 1 month, improvement in SF-36 physical component survey
  - 5.2 points greater in kyphoplasty group (95% C.I. 2.9, 7.4)
  - By 12 months, no differences
- No difference in adverse events
- High rate of subsequent fractures in both groups
  - 33 % kyphoplasty vs 25% control: NS

Kyphoplasty: Impact

- In patients with acute fractures, kyphoplasty improves pain and function at 1 month
  - After 12 months, no difference compared with usual care
- Kyphoplasty appears to be safe in the short term

Kyphoplasty vs Vertebroplasty

- No direct comparisons
- Age of the fracture may make a difference
- Is there an effect of injection into the periosteum?
- What are the long term risks?
- Consider in individuals with acute fracture who have failed nonsurgical therapy
CONCLUSIONS

- Migraine with aura is associated with an increased risk of ischemic stroke
- Hormone therapy is associated with a small but real increase in ovarian cancer
- Cervical cancer screening can occur less often
  - Role of HPV testing is debated
  - Receipt of HPV vaccine does not affect screening recommendations

CONCLUSIONS

- Low vitamin D levels can help identify women at high risk for hip fracture
- Vitamin D supplementation can reduce fracture risk
- Vertebroplasty and kyphoplasty have not been directly compared
  - Some women with acute compression fractures may achieve short term benefit