Advances in Women’s Health: A Critical Review of This Year’s Most Important Papers

Mary S. Beattie, MD, MAS
Professor of Medicine
UCSF Women’s Health, Primary Care

Advances in Women’s Health

- Not cancer screening, osteoporosis, menopause
- Human Papilloma Virus
- Contraception
- Dysfunctional Uterine Bleeding
- Breast Cancer Risk and Prevention

Case 1: Maria’s HPV vaccine

- 20 year old college student
- Received 2 doses of the HPV vaccines years ago
- Never got the third dose
- Virgin in high school
- Three lifetime partners
- Using condoms
- Has never had a pap

Which do you think is most important for Maria?

- HPV #3
- Pap #1
- Chlamydia screen
- Birth control discussion
**Is Less More with HPV Vaccine?**

- Over 7000 women in Costa Rica studied in a RCT of bivalent HPV vaccine
- 83%—3 doses; 11%—2 doses; 6%—1 dose
- Efficacy was not diminished
  - 81%—3 doses; 84%—2 doses; 100%—1 dose
- ↓ doses may save money, time, resources
- Also consider disparities in HPV and paps
- Goal is to ↓ cervical cancer
  
  \[\text{Kreimer AR, JNCI 2011}\]
  \[\text{Goldie S J, JNCI 2011}\]

**New Pap Guidelines**

- Agreement between ACS, ACOG, and USPSTF
  - ACS and USPSTF drafts in 2011, ACOG in 2009
- Start at 21 and screen every 3 years
- HPV testing has no role in adolescents
- HPV testing should be done in women 21-30
  
  \[\text{ONLY if pap shows ASCUS}\]
- Stop screening at age 65 (if well-screened, ↓ risk)
- After hysterectomy, D/C pap if no cancer or dysplasia

  \[\text{Feldman NEJM 2011}\]

**Chlamydia Screening—USPSTF**

- Screen in all sexually active women under 25
- Grade A Recommendation
- Nucleic acid amplification tests (NAATs) have high specificity—vaginal swab or urine
- In low-prevalence populations (<5%), more likely to be false positive than true positive
- Population prevalence is 5% in women <25

  \[\text{USPSTF, Annals of IM, 2007}\]
Cervical cancer risk and IUD use

- Pooled analysis of 26 studies
- Adjusted for cervical HPV DNA and number of prior paps
- Strong inverse association between IUD use and cervical cancer (OR 0.55)
- IUD ↓ uterine cancer and may trigger cellular immunity to ↓ cervical cancer

Maria wants OCP instead of IUD

3 months later, Maria is pregnant

- She wasn’t 100% adherent with OCP
- She got a UTI and was concerned that antibiotics would decrease efficacy of OCP
- Changed to condoms, but it broke last month and she didn’t know about “morning after” pill

Despite over-the-counter availability of EC, few women receive counseling; however EC use is ↑

Preventing unintended pregnancy New Evidence

- Counseling for emergency contraception
  - Over-the-counter since 8/2006
  - National Survey of Family Growth, > 7000 US ♂
  - 3% of ♂ received EC counseling in last year
  - 10% of those surveyed reported ever using EC
  - Most got EC OTC and used it only once
- Texting for contraception
  - RCT of 962 women
  - Continuation at 6 months- 64% text, 54% control p = .005

What’s new on OCP’s?

- No evidence of increased risk of breast cancer
- Levonorgestrel-containing OC’s are among the safest of the safe
- Some health care providers have fixed ideas about monthly cycles and medical amenorrhea
- Women who were given 12 packs of OCP’s were less apt to have an unplanned pregnancy (OR = 0.70) or abortion (OR = 0.54) compared with those given 3 packs or less

Lu Y, CEBP 2011
Lidegaard, BMJ 2011
Jick SS, BMJ 2011
Foster D, Ob Gyn 2011

Toh S, Contraception 2011
Kavanaugh ML Fertil Steril 2011
Castano ObGyn 2012
Which of the following are true?

- Rates of unintended pregnancy in the US have not significantly changed in a decade
- The proportion of unintended pregnancies ending in abortion has ↓ slightly
- IUD use in the US has ↑ slowly
- Emergency contraception use in the US has ↑ slightly
- All of the above are true

If Maria terminates, are there mental health consequences?

- First-trimester induced abortion was studied in multiple Danish registries (n = 84,620)
- Psychiatric contact was study outcome and childbirth was comparison group
- In the 9 months before or 12 months after abortion, no evidence of ↑ psychiatric contact
- Psychiatric contact ↑ after childbirth (p < 0.001) for 6-9 months; RR = 3.8 in first postpartum month

Maria’s Case Conclusion

- Maria chose to terminate her pregnancy and wanted to change to longer-acting birth control
- She got a depo-provera (D-MPA) injection in clinic and will return every 3 months for these
- In 2004, FDA “black box” notification regarding bone loss and cautioning against long-term use (>2 years)
- New data suggests that benefits of D-MPA over 2 years outweigh bone loss risks

Case 2: Sarah’s Bothersome Menorrhagia

- 44 year old G2P2
- Heavier and more frequent menses
- Cycles every 22-24 days
- Last cycle was on time
- but her bleeding lasted 3 days > usual and she’s still spotting.
What would you do next?

- Transvaginal ultrasound
- Endometrial biopsy
- Progestin-containing medication
- Hematocrit
- Pregnancy Test

Sarah’s Menorrhagia

- Sarah is not pregnant
- She has a 3 cm posterior fibroid
- Her hematocrit is 34%
- Her symptoms are interfering with her life
- She has no desire for more children
- What are her options?
  - Medications (PO and SQ)
  - IUD
  - Other procedures: Ablation, Embolization, Surgery

Which do you recommend?

1. Progestin-containing PO medication
2. Transexamic Acid (SQ injection)
3. Uterine Artery Embolization
4. Surgery (Myoectomy/Hysterectomy)
5. Progestin-containing IUD

Transexamic Acid for Menorrhagia

- Inhibits activation of plasminogen, increasing clot formation
- Injectable approved in 1986; oral used safely in Europe for 40 yrs and approved in US in 2009
- RCT (n = 196) for 5 days/month had ↓ blood loss q month x 6 and ↓ social and physical limitations with menses
- Could provide short-term relief, but prior study of levonorgestrel IUD had more long-term efficacy

Lukes AS, Ob Gyn 2010
RCT of Hysterectomy vs. Embolization and Cost-Effectiveness

- RCT (n = 157) began in 2000 in UK
- Uterine artery embolization (n = 106) vs. surgery (n = 42 hysterectomies + 9 myomectomies)
- 5 year outcomes were QoL, recommend procedure, adverse events, and re-intervention
- AE in UAE -- 19%; AE in surgery -- 25% (NS)
- Re-intervention in UAE -- 32%; in surgery -- 4%* 
- UAE had cost benefit at 1 year, but this was negated by 5 years

Minimally invasive laparoscopic hysterectomy had no difference in safety, lower morbidity, shorter hospital stays, and decreased costs.

Oophrectomy was not associated with long-term adverse events.

Both were observational studies, difficult to study these questions with RCT

Moss JG, BJOG 2011
Roberts TE, BMJ 2011
Munfo MG, Menopause 2011
Jonsdottir GM, Ob Gyn 2011
Jacoby VT, Archives 2011

Advances in Hysterectomy and New Data on Oophrectomy

Sarah Chose IUD

- Progestin-containing IUD provides birth control and ↓ menorrhagia
- Recommended for 5 years for birth control efficacy—up to 7 years for menorrhagia
- Efficacy comparable to tubal ligation (0.1% failure/year)

Worldwide Use of IUD
Sarah and mammography

- She’s 44 and now that her menorrhagia is under control, she’d like to discuss mammography
- No prior mammogram
- Normal clinical breast exam
- No family history of breast cancer
- No significant breast cancer risk factors
- No strong opinions about mammograms in the 40’s
- Her community mammography center has digital and computer-aided mammography

What do you recommend for Sarah regarding mammography?

1. Annual mammography
2. Mammography every 2 years
3. Wait till 50 years old
4. Have a personalized discussion about pros/cons

Digital mammography and computer-aided detection

- Observational studies of community practice
  - 70% of mammography machines in US are digital
  - Overall detection rates are similar with digital and film mammography
  - Digital mammography had better sensitivity when breast tissue was dense
- Multicenter study results suggest that computer-assisted detection lowers specificity with little potential to improve breast cancer outcomes.

Ivana’s Breast Cancer Prevention

- Ivana tested positive for a BRCA2 family mutation
- What lifestyle changes can she make to lower risk?
- What is the latest on risk-reduction medications?
Lifestyle advice for Ivana?

- She is 25, doesn’t smoke, and exercises 3 days/week
- BMI is 23
- She drinks wine most nights, about 2 glasses 7 nights a week
- She is sexually active, has never been pregnant, and always uses condoms

Which lifestyle change would most ↓ breast cancer risk?

1. ↑ exercise to 6-7 days a week for at least 30 min
2. ↓ alcohol to 0-1/week
3. ↓ 10 pounds
4. Start OCP

Even moderate alcohol ↑ risk

- Low levels of alcohol consumption are associated with moderately elevated risk
- In the general population, benefits of alcohol should also be considered
- New model predicts the effects of modifying alcohol consumption, physical activity, and body-mass index.
- Predicting risk is risky business, differences in framing absolute and relative risk
Exercise and risk of breast cancer

- Overall 25-30% decreased risk
- Greatest in thinner women
- Lifetime exercise matters
- Modest amounts: 1-3 hours brisk walking/week

WHI Observational Cohort (n=74,171; 1780 cancers)

If Ivana was interested in “chemoprevention”

Would you recommend….
1. Tamoxifen
2. Raloxifen
3. Exemestane
4. None of the above

New data on exemestane

- RCT of 4560 postmenopausal women, either
  - > 60, 5 year risk > 1.66, prior neoplasia
- During mean follow up of 3 years, invasive breast cancer diagnosed in 11 exemestane recipients and 32 placebo recipients
  - Annual incidence 0.19% vs. 0.55%* 
  - NNT of about 100 to prevent 1 case during 3 years
- Hot flashes and joint pain main side effects

Goss PE, NEJM 2011

Ivana’s Case Conclusion

- Ivana will decrease her alcohol intake and increase her exercise
- She will focus on lifestyle changes in her 20’s and early 30’s
- She will consider oophrectomy after having children
- She will consider chemoprevention in her 30’s or 40’s
**Advances in Women’s Health**

- HPV vaccine may be effective without all 3 doses, but this deserves dedicated study.
- Long-term contraceptives are most effective; IUD use in the US is slowly increasing.
- Multiple options and new data exists for menorrhagia.
- Reducing the risk of breast cancer can involve lifestyle, “chemoprevention,” and surgery—match intervention to risk.
- Mammography in the 40’s is still a hot topic!!

---

**Summary of Recommendations for Cervical Cancer Screening**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACS-ASCP-ASCO 2012</th>
<th>ASCC 2009</th>
<th>USPST 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age to start</td>
<td>21 yr</td>
<td>21 yr</td>
<td>21 yr</td>
</tr>
<tr>
<td>Testing Frequency</td>
<td>Every 3 yr</td>
<td>Every 3 yr</td>
<td>Every 3 yr</td>
</tr>
<tr>
<td>Age to stop</td>
<td>65 yr</td>
<td>65 yr</td>
<td>65 yr</td>
</tr>
<tr>
<td>Pap and HPV testing</td>
<td>Recommended at intervals up to every 5 yr</td>
<td>Every 3 yr</td>
<td>In sufficient data recommended</td>
</tr>
<tr>
<td>Age to stop</td>
<td>65 yr after three negative tests or two negative HPV tests or Pap 27020203</td>
<td>65 yr after three negative tests or Pap 27020203</td>
<td>65 yr after adequate screening</td>
</tr>
<tr>
<td>Abnormality detection</td>
<td>Determined by physician or cancer</td>
<td>Determined by physician or cancer</td>
<td>Determined by physician or cancer</td>
</tr>
<tr>
<td>Screening after HPV vaccine</td>
<td>Same as when unvaccinated</td>
<td>Same as when unvaccinated</td>
<td>Same as when unvaccinated</td>
</tr>
</tbody>
</table>

ACS-ASCP-ASCO, American College of Obstetricians and Gynecologists, ASCC, American Cancer Society; ASCO, American Society for Clinical Oncology; and USPSTF, US Preventive Services Task Force.
Recent Publications in Women’s Health


32. Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis. Guiliano A et al. JAMA 2011; 305: 569-575.