Top Things You Should Know This Year

Prevalence of Sexual Dysfunction after Risk-Reducing Salping-oophorectomy. *Gynecology Oncology*, 140, 95-100


Background and Significance

- Current recommendation for women at high risk for ovarian cancer is risk-reducing salpingo-oopherectomy (RRSO)
- Several studies have shown a reduction in quality of life including a decline in sexual function for women who undergo RRSO
- Sexual dysfunction following RRSO appears to be multifactorial (psychosexual issues in families with breast-ovarian cancer hx; body image; relationship satisfaction; serum testosterone levels)
Specific Aims

- To date, a comprehensive, quantitative study evaluating the rate and associated factors associated with RRSO has not been completed.
- Therefore, the primary aim was (1) to determine the prevalence of female sexual dysfunction (FSD) and hypoactive sexual desire disorder (HSDD) after RRSO and (2) to assess factors which may influence FSD and HSDD.

Design

- Cross sectional study of women who has RRSO; women completed questionnaires and serum testing for androgen levels.
- Primary outcome (FSD and HSDD) was measured by the Female Sexual Function Index (FSFI-six domains of sexual function measured; arousal, desire, pain, orgasm, lubrication, and satisfaction).

Characteristics of Participants

- Total participants: 119
- Mean age ± SD (range): 52 years ± 8 (34–71 years)
- Mean time since operation ± SD (range): 24 months ± 16 (6–72 months)
- Menopause status: Pre-menopausal 51 (43%) Post-menopausal 68 (57%)
- History of breast cancer: 60 (50%)
- Estrogen use: None 85 (72%), Systemic HT 24 (20%), Vaginal 9 (8%)
- Mastectomy: Unilateral 9 (8%), Bilateral 43 (36%), Prophylactic 16 (13%)
- Hysterectomy: 106 (89%)
- At the time of RRSO 92 (77%), Before RRSO 14 (12%)
- Current estrogen blocking therapy: Selective estrogen receptor modulator 7 (6%), Aromatase inhibitor 21 (18%), Both 2 (2%)

Results

Prevalence:
- 74% high likelihood of FSD
- 73% high likelihood of HSDD

Influencing Factors/Higher Sexual Functioning: (Multivariate Logistical Regression)
- Higher relationship satisfaction (p=.0006), lower bodily pain (p=.0008) and use of local vaginal estrogen (p=.036)
- Low serum testosterone was not associated with lower FSD or HSDD
Importance
• First study to address sexual function for women with hx of RRSO
• Prevalence of FSD 74% (Gen pop 40-45%)
• Prevalence of HSDD 73% (Gen pop 9-22%)
• Relationship satisfaction has not been assessed prior to this study using a validated measure
• Role of local estrogen therapy
• Lack of support regarding serum testosterone levels

Predicting the Risk of Malignancy in Adnexal Masses Based on the Simple Rules from the International Ovarian Tumor Analysis Group


Introduction
• In 2008 the IOTA Group (International Ovarian Tumor Analysis) described “Simple Rules” to use ultrasound features to characterize adnexal masses as malignant, benign or indeterminate.
• These were based on 5 ultrasound features indicative of a benign tumor and 5 ultrasound features indicative of malignancy.
• This paper utilized “Simple Rules” to prospectively analyze data on 4848 patients with adnexal masses who underwent surgery.

• This was an international study conducted at 22 centers including both oncology centers and general hospitals.

• The RCOG (Royal College of Obstetrics and Gynecology) in the U.K. has included the Simple Rules in their Green Top Guideline for the assessment and management of ovarian masses

• Utilizing Simple Rules, this paper resulted in 2.3 surgeries for every malignancy in specialized centers and 5.4 surgeries in all other centers.
Why did I pick this paper?

• In the U.S. there are 9.1 surgeries for every ovarian malignancy.

Why is the U.S. rate so high?

• The ACOG Practice Bulletin #83 (reaffirmed 2015) still states, “With the exception of simple cysts on a transvaginal ultrasound finding, most pelvic masses in postmenopausal women will require surgical intervention.”

Why is the U.S. rate so high?

• Is it inferior ultrasound ability or equipment?

• Is the ultrasound training inadequate?

• Is it fear of medico-legal liability?

Today’s take home points:

1. Unlike cervix (dysplasia), breast (LCIS, DCIS) and endometrium (hyperplasia), BENIGN ovarian tumors do not BECOME malignant.

2. There is too much surgery for what many experts in ultrasound clearly recognize as benign disease.

3. The ABOG and RRC should require better and more formal training in gynecologic ultrasound.

4. Adoption of techniques like Simple Rules (as in Europe and Britain) might be a reasonable first step to reduce unnecessary surgery.
Aim

• To investigate the association between OC use during later reproductive life and risk of fracture across the menopausal transition

Methods

• Population-based case-control study of 1,204 case women between the age of 45 and 59, with incident adjudicated fractures, and 2,275 comparable control women selected from the same defined population

• Study variables examined by case-control status.
• Logistic regression to analyze the association between incident adjudicated fracture and oral contraceptive exposure.
Results

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 1,204)</th>
<th>Controls (n = 2,275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>54.1</td>
<td>54.0</td>
</tr>
<tr>
<td>Age at menopause – years</td>
<td>51.0</td>
<td>52.0</td>
</tr>
<tr>
<td>FRAX – major fracture 10 year risk</td>
<td>9.03%</td>
<td>8.24%</td>
</tr>
<tr>
<td>FRAX – hip fracture 10 year risk</td>
<td>1.04%</td>
<td>0.91%</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ever</td>
<td>76.7%</td>
<td>75.4%</td>
</tr>
<tr>
<td>within 10 years of menopause</td>
<td>15.1%</td>
<td>15.3%</td>
</tr>
<tr>
<td>at age 38 years or later</td>
<td>16.6%</td>
<td>17.5%</td>
</tr>
<tr>
<td>began before age 20 years</td>
<td>52.4%</td>
<td>53.6%</td>
</tr>
</tbody>
</table>

No difference: BMI, calcium or vitamin D supplements, physical activity, self reported health

Cases: more prior fracture, parental history of fracture, postmenopausal estrogen use (26.5% vs 20.4%), smoking, alcohol intake, falls, history of diabetes and hyperthyroidism

Controls: more Hispanic (3.9% vs 3.1%)


Why This Information is Important

• Oral contraceptive use
  • in adolescents results in lower peak bone mass1
  • in perimenopausal women has beneficial effect on BMD2
• Effect on peri- postmenopausal fracture risk is uncertain3,4
• These results substantially dispel concern about negative effect
• They do not exclude a benefit – since
  • a) case control study
  • b) ankle fractures accounted for 25% of incident fractures


No association between fracture risk and history of oral contraceptive use, use within 10 years of menopause, use at age 38 or later, duration of use or age at first use
Metabolic Syndrome and Menopause: Pathophysiology, Clinical and Diagnostic Significance

Anna Stefanska, Bergman K, and Sypniewska Advances in Clinical Chemistry Vol 72 Elsevier 2015
http://dx.doi.org/10.1016/bs.acc2015.07.001

Presented by Lila Nachtigall, MD NCMP professor of Ob/Gyn NYU School of Medicine

Aims

• Define Insulin Resistance (IR) and Metabolic Syndrome (MetS)
• Prove the high prevalence of both in postmenopausal women
• Separate age and estrogen deficiency as causative of IR & MetS
• Explain why menopause leads to IR and MetS
• Show how IR and MetS effect lipid metabolism and biologically active substances (i.e. TNF-a & adipocytocines)
• Demonstrate that those changes can cause both cardiovascular disease and breast cancer
• Express the effect of hormone replacement on C/V events
• Determine the prevention and treatment of IR, MetS and type 2 diabetes.

Method

• Review of 301 studies of:
  • Insulin Resistance
  • Menopause and Metabolic Syndrome
  • Metabolic Syndrome and Cardiovascular Disease
  • Lipid Metabolism and the role of Sex Hormones
  • Exercise effects on metabolism and fat distribution
  • Biomarkers related to Metabolic Syndrome

Metabolic Syndrome in Menopause

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
<th>Estrogen Metabolic Effects</th>
<th>Estrogen Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Obesity</td>
<td>Waist circumference &gt;35”</td>
<td>Dec appetite increased energy</td>
<td>Abdominal Obesity</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt; 150 mg/dl</td>
<td>Lowers insulin</td>
<td>Raises insulin with visceral obesity</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>&lt;50 mg/dl</td>
<td>Increases HDL Cholesterol</td>
<td>Decreases HDL Cholesterol</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>&gt;130/85</td>
<td>Decreases insulin levels, decreases BP</td>
<td>Increases insulin levels, increases BP</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>&gt;100 mg/dl</td>
<td>Insulin Sensitivity decreases glucose</td>
<td>Insulin Resistance increases glucose</td>
</tr>
</tbody>
</table>

Any three of above ≥ Metabolic Syndrome

Dasgupta S J Midlife Health 2012
**Results**

- Menopause
  - Estrogen withdrawal
    - Decreased peripheral fat
      - Reduced lean body mass
  - Androgen:Estrogen ratio increase
    - Increased abdominal fat
    - Leads to MetS T2 Diabetes

**Significance**

- Prevalence of MetS in postmenopausal women=65%
- Greater change toward IR is at menopause transition(1)
- A balanced diet and increased physical activity has insulin sensitizing effects as does estrogen therapy
- Resistance training reduces the risk of MetS and decreases insulin levels(2)
- 45 minutes/day of aerobic activity 5 days/week decreases body fat as well as insulin levels and can reverse MetS (3)
- Reversing MetS early can significantly decrease the major long term disorders in older women

2. Macedo MF et al 2013
3. Frank LI et al Obes Res 2005
Wen Shen, MD, MPH, FACOG
Assistant Professor of Gynecology and Obstetrics
Johns Hopkins University School of Medicine
Baltimore, MD

Goal
To study the impact of menopause and estrogen therapy on lymphocyte frequency and the immune response to seasonal influenza vaccine.

Study population
1. Young adult women with regular menses, not on hormonal contraception. N=15. 19-38 y/o
2. Post menopausal women not on hormone therapy for > 4 years. N=15. 55-63 y/o
3. Surgically postmenopausal women on ET only. N=15. 47-64 y/o.

Method
• Day 0 – seasonal trivalent inactivated influenza vaccine Fluzone.
• Blood samples obtained on days 0, 7-10, and 30-35.
• Measurements: serum E2 and P4, CD4 and CD8 Tcells, Bcells, inflammatory cytokines IL-6.

Results
• Inflammatory cytokines IL-6 and CRP on day 0, significantly higher in Group 2 > Group 3 > Group 1.
• Naïve CD8 Tcells Group 1 > Group 3 > Group 2.
• Increased CD4 and CD8 Tcells on days 7 and 30 for all 3 groups.
• Further increase in CD4 Tcell response on day 30 in Group 1 and Group 3.
**Why this is important**

Public Health
Importance of vaccination for prevention of disease in older adults.

Inflammatory Diseases
Osteoporosis and cardiovascular diseases.

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**What are the needs**

Uncertain effect of MHT on lymphocyte homeostasis and immune response

Need studies on optimal estrogen therapy dose, delivery method and serum levels of estrogen

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**What we know**

Immune senescence
- Decreased ability to respond to infection and vaccination
- Prior to menopause, females have more reactions to vaccines and autoimmune diseases.
- Immune systems age the same, but males experience them earlier and more dramatically than females.
Association of Age at Menopause with Incident Heart Failure: a Prospective Cohort Study and Meta-Analysis

Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, Folsom AR.
*J Am Heart Assoc*, 2016

**Background and Aims**

- Heart failure accounts for 35% of CVD mortality in women
- Early age (<45 y) at menopause has been postulated to be associated with increased CVD risk
- Evidence of the relationship of early menopause with heart failure incidence is limited
- To examine whether the age at menopause is associated inversely with heart failure incidence in the Atherosclerosis Risk in Communities (ARIC) study
- To summarize all existing data in a meta-analysis

**Methods**

- In ARIC, data were obtained from 5629 postmenopausal women
  - Mean age 56 years
  - 26% with bilateral oophorectomy
  - Median follow-up of 21.4 years
  - Cox regression model adjusted for reproductive health and heart failure risk factors
- Meta-analysis (included 3 prospective studies)
Results: ARIC
Early Age at Menopause Associated with Modestly Greater Risk of Heart Failure

Results: Meta-Analysis
Early Menopause Associated with Incident Heart Failure Risk

### Results: Meta-Analysis

Early Menopause Associated with Incident Heart Failure Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebong et al. 2014</td>
<td>1.66</td>
<td>(1.01–2.73)</td>
</tr>
<tr>
<td>Rahman et al. 2015</td>
<td>1.40</td>
<td>(1.20–1.65)</td>
</tr>
<tr>
<td>Appiah et al. 2016</td>
<td>1.20</td>
<td>(1.01–1.43)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.33</td>
<td>(1.15–1.53)</td>
</tr>
</tbody>
</table>

*33% increase in risk in women who experienced early menopause (< 45 years)*

Appiah D, et al. *J Am Heart Assoc* 2016; 5:e003769; *No evidence of heterogeneity*

### Why is this work significant?

- Heart failure affects about 2.4 million American women\(^1\)
- Prevalence projected to increase by 46% by 2030\(^2\)
- Identification of women with early menopause as a population at high risk of heart failure provides a window of opportunity for intervention to prevent the onset of heart failure\(^3\)


### Characterizing the Trajectories of Vasomotor Symptoms Across the Menopause Transition.

*Menopause, 2016* [epub ahead of print]

Rebecca C. Thurston, PhD
- Professor of Psychiatry and Clinical and Translational Science
- Director, Women’s Biobehavioral Health Laboratory
- Director, Midlife Women’s Behavioral Health Clinic
- University of Pittsburgh
- Pittsburgh, PA

Tepper, Brooks, Randolph, Crawford, El Khoudary, Gold, Lasley, Jones, Joffe, Hess, Avis, Harlow, McConnell, Bromberger, Zheng, Ruppert & Thurston
Aims

• Investigate the heterogeneity of temporal patterns of vasomotor symptoms (VMS) over the menopause transition
• Identify factors associated with these patterns in a diverse sample of women

Methods

• Study of Women’s Health Across the Nation
• 1455 women followed up to 15.4 years
  • 5 Racial/ethnic groups
  • Uterus and ≥1 ovary
  • Visits taking hormone therapy dropped
• VMS (hot flashes, night sweats) reported yearly, past two weeks
• Group based trajectory modeling

Results

Four Distinct Trajectories of VMS

Years around final menstrual period

Probability of Hot Flashes

- Low, 27.0%
- Early onset, 18.4%
- Late onset, 29.0%
- High, 25.6%

Factors Associated with Trajectories*

<table>
<thead>
<tr>
<th>Early Onset</th>
<th>Late Onset</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorer health</td>
<td>Current Smoker</td>
<td>African American</td>
</tr>
<tr>
<td>Depression &amp; Anxiety</td>
<td>Leaner</td>
<td>Poorer health</td>
</tr>
<tr>
<td>Later age at final menstrual period</td>
<td>~Higher E2</td>
<td>Depression &amp; Anxiety</td>
</tr>
</tbody>
</table>

*Relative to Low Trajectory

Tepper et al. Menopause. 2016;23(10)
Why this work is significant

- Natural history of VMS not well understood
- Extends other key work showing VMS last longer than thought:
  - Frequent VMS persist 7.4 years¹
  - 33% of women severe VMS 10+ years after menopause²
  - VMS prevalent (42%) in 60-65 year old women³
- Challenge idea VMS follow universal pattern
- Factors that predict patterns: Demographic, biological & psychological/behavioral

1. Avis et al. JAMA Internal Medicine. 2015;175(4):531-39
2. Freeman et al. Menopause. 2014;21(9):924-32