SPECIAL GYN ULTRASOUND
CONSIDERATIONS FOR THE
BREAST CANCER PATIENT

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BREAST CANCER USA: THE SCOPE OF
THE PROBLEM

• 2nd most common cancer in women
  (only recently surpassed by lung cancer)
• 212,000 new cases diagnosed annually
• 45,000 deaths annually

Tamoxifen

• First clinically available SERM
• Originally called an “anti-estrogen”
• Developed 1966, FDA approved 1978
• Most widely prescribed antineoplastic drug worldwide
• More than 20 million women years of use
• Significant improvement in recurrence free survival and overall survival in postmenopausal women with breast cancer
PROBLEMS WITH TAMOXIFEN

- THROMBOEMBOLIC EVENTS
  - Deep vein thrombosis
  - Pulmonary emboli
  - Retinal vein thrombosis

- UTERINE CHANGES
  - Endometrial carcinoma
  - Endometrial hyperplasias
  - Endometrial polyps
  - Sarcomas

TAMOXIFEN’S EFFECTS ON ENDOMETRIAL CANCER

In the mid to late 1980’s, a series of letters and case reports suggested an association between Tamoxifen and Endometrial Neoplasia
Tamoxifen Induced Endometrial Changes

- 16 Patients followed prospectively with hysteroscopy for 36 months:
  - 8 Atrophic/inactive endometrium
  - 7 Proliferative (including 4 polyps)
  - 1 Adenocarcinoma

WHERE DOES GYN U/S FIT IN??

Unusual ultrasonographic appearance of the uterus in patients receiving tamoxifen

Steven R. Goldstein, MD
New York, New York
Tamoxifen

Some patients will display bizarre heterogenous echoes centrally located in the uterus which represents a loss of the normal junctional zone. This has often been misinterpreted as “endometrial” thickening.

When viewed with Saline Infusion Sonohysterography (SIS) these changes are often “microcysts” which are dilated cystic atrophic glands and can be located in the endometrium, the proximal myometrium, or even in polyps.

Tamoxifen in Asymptomatic Postmenopausal Women
Schwartz, Goldstein, et al. (Ultrasound Obstet Gynecol 1998;114:48)

- 27% polyp
- 4% carcinoma
- 9% proliferation/hyperplasia
- 25% maintained thin EM≤5mm
- 59% ultimately demonstrated inactive/atrophic EM (often by sonohysterography)
Tamoxifen and Endometrial Cancer
ACOG Committee Opinion # 169, 2/96

- Women with breast cancer should have annual gynecologic examinations, including Pap tests and bimanual and rectovaginal examinations.
- Any abnormal bleeding, including bloody discharge, spotting, or any other gynecologic symptoms, should be evaluated thoroughly. Any bleeding or spotting should be investigated.
- Practitioners should be alert to the increased incidence of endometrial malignancy. Screening procedures or diagnostic tests should be performed at the discretion of the individual gynecologist.

Tamoxifen and Endometrial Cancer
ACOG Committee Opinion # 232, 4/2000

- Women taking tamoxifen should be monitored closely for symptoms of endometrial hyperplasia or cancer and should have a gynecologic examination at least once every year.
- Any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting should be investigated.
- Because screening tests have not been effective in increasing the early detection of endometrial cancer in women using tamoxifen and may lead to more invasive and costly diagnostic procedures, they are not recommended.

Tamoxifen: Pretreatment Screening

- 264 postmenopausal women with breast cancer
- Baseline transvaginal ultrasound. If EM > 4mm hysteroscopy and biopsy
- 17% had baseline lesions (mostly polyps, 2 atypical hyperplasias
- All polyps were removed and everyone treated
- Incidence of atypical hyperplasia was significantly higher in the group that was abnormal initially and then treated (P= .009)
Tamoxifen: Pretreatment Screening


- 575 patients with breast cancer studied up to 5 years
- 16.6% had endometrial polyps prior to tamoxifen therapy
- In the group with no initial polyps ("Squeaky clean")
  - 12.9% developed benign polypos
  - 0.7% developed atypical hyperplasia
- In the group with initial polyps
  - 17.6% developed polypos
  - 11.7% developed atypical hyperplasia (18 fold increase)

Tamoxifen: Pretreatment Screening

Conclusion

- There appears to be two distinct groups of women (initial polyps vs no polyps lesions)
- The high risk group can be identified by systematic pretreatment screening. These patients may require ongoing surveillance while low risk group may not.

Tamoxifen and Endometrial Cancer
ACOG Committee Opinion # 336, 6/2006

- "Emerging evidence suggests the presence of high and low risk groups...based on the presence or absence of benign EM polyps before therapy. Thus there may be a role for pretreatment screening of PM women with TV U/S, and sonohysterography when needed, or office hysterography, before initiation of Tamoxifen therapy"
TAMOXIFEN: UPDATED DATA FROM BCPT (May, 2002)

- 8306 women with intact uterus
- Median F/U 6.9 years (all users > 2 years)
- Adenocarcinoma of EM
  - 53 cases Tamoxifen (52 FIGO Stage 1, 1 FIGO Stage III)
  - 17 cases Placebo (16 FIGO Stage 1, 1 FIGO Stage IV)
- Uterine Sarcoma
  - 4 cases Tamoxifen (2 FIGO Stage I, 1 Stage II, 1 Stage III)
  - 0 cases Placebo

UTERINE SARCOMAS

- In 2002 FDA required “black box” warning be added to the label of tamoxifen
- Directed at use for breast cancer PREVENTION not treatment

NEW TAMOXIFEN LABELING: HEALTHY PATIENTS

### ADVERSE EVENTS

<table>
<thead>
<tr>
<th></th>
<th>TAMOXIFEN</th>
<th>PLACEBO</th>
<th>RR</th>
<th>C.I.</th>
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</thead>
<tbody>
<tr>
<td>Endometrial Adenocarcinoma</td>
<td>2.2/1000 pt years</td>
<td>0.71/1000 pt years</td>
<td>Not given</td>
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<tr>
<td>Uterine Sarcoma</td>
<td>0.17/1000 pt years</td>
<td>0.00/1000 pt years</td>
<td>Not given</td>
<td></td>
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<tr>
<td>Stroke</td>
<td>1.43/1000 pt years</td>
<td>1.00/1000 pt years</td>
<td>1.42 (0.82-2.51)</td>
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<tr>
<td>Pulmonary Embolism</td>
<td>0.75/1000 pt years</td>
<td>0.25/1000 pt years</td>
<td>3.01 (1.15-9.27)</td>
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### BENEFICIAL EFFECTS

<table>
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<tr>
<th></th>
<th>TAMOXIFEN</th>
<th>PLACEBO</th>
<th>RR</th>
<th>p-Value</th>
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<tr>
<td>Breast Cancer</td>
<td>6.49/1000 pt years</td>
<td>3.38/1000 pt years</td>
<td>0.49</td>
<td>p=0.00001</td>
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</table>
WHAT ABOUT OVARIAN CANCER?

OVARIAN CANCER IN THE GENERAL POPULATION

- Leading cause of death from gynecologic malignancy in U.S.
- 2012 estimates
  - 20,180 new cases
  - 15,310 deaths
- Lifetime probability of developing ovarian cancer 1.8% (1 in 55)
- Incidence increases with age
- Highest proportion of cases of women 50-59

WHAT ABOUT THE BREAST CANCER PATIENT AND HER OVARIES?
• IN THE BREAST CANCER PATIENT WHO IS NOT BRCA1 OR BRCA2 POSITIVE HER LIFETIME RISK OF OVARIAN CANCER DOUBLES (3.6% vs 1.8%)

• WE MUST BE CAREFUL IN COUNSELING
• MANY PATIENTS DO NOT UNDERSTAND THE DIFFERENCE BETWEEN RELATIVE RISK AND ABSOLUTE RISK

• A “DOUBLING” OF A SMALL RISK MAY STILL BE A SMALL RISK (1.8% vs 3.6%)
• STILL 3.6% IS NOT INSIGNIFICANT
FOR INSTANCE, WE USED TO DO AMNIOCENTESIS ROUTINELY ON WOMEN AT 35 YEARS OF AGE.
THEIR RISK OF A POSITIVE FETUS IS 1 IN 305 OR 0.3%!

A 3% RISK OF SOMETHING IN MEDICINE IS NOT AN INSIGNIFICANT RISK.
PMB ... A 3-7% RISK OF EM CANCER.
WE TREAT FOR FRACTURE RISK REDUCTION WHEN THE 10 YEAR RISK OF HIP FX IS 3% OR MORE (MORE ON THAT TOMORROW).

OVARIAN CANCER

Early stage ovarian cancer is highly curable when treated by conventional therapy.
Thus the obvious desire to detect ovarian cancer at an earlier stage.
RISK FACTORS: GENETICS

- Family history (only 10% of cases)
- Lifetime probability in a 35 y/o woman:
  - No relatives = 1.8%
  - One relative = 5%
  - Two relatives = 7%
- Familial ovarian cancer syndromes (5-10% of cases)
  - BRCA 1 and BRCA 2
  - Lynch II (Colon, Breast, EM, Ovary)

RISK FACTORS

- Age (rate in 50-75 y/o 2x younger women)
- OCP use, ↑number of pregnancies, breast feeding: decreases risk
- Infertility treatments: ? Increased risk
- Long term HRT increased risk in case control studies, were not RCTs

BRCA GENE MUTATIONS

- Suspected in women with a family member with ovarian cancer prior to age 50 or ovarian and breast cancers in multiple members
- Higher in Ashkenazi Jews; suspect when a single family member has ovarian or breast prior to age 50
- Any male breast cancer
### Estimated cancer risks associated with BRCA1 and BRCA2 mutations

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Estimated lifetime risk in BRCA1 mutation carriers</th>
<th>Estimated lifetime risk in BRCA2 mutation carriers</th>
<th>Lifetime risk in general population</th>
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<tbody>
<tr>
<td>Breast cancer</td>
<td>55 to 88 percent</td>
<td>50 to 85 percent</td>
<td>12.5 percent</td>
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<tr>
<td>Ovarian cancer</td>
<td>40 to 50 percent</td>
<td>15 to 25 percent</td>
<td>1.8 percent</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Not increased, or increased very slightly</td>
<td>Not increased, or increased very slightly</td>
<td>5 percent</td>
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### POTENTIAL PITFALLS

- LEAD TIME VS LENGTH TIME BIAS
  - WE WILL COVER THIS TOMORROW
  - AS SCIENTISTS WE REALIZE THE POTENTIAL PROBLEMS, BUT AS CLINICIANS WE BELIEVE EARLIER DETECTION MATTERS AND IS IMPORTANT
IT IS ALSO IMPORTANT TO UNDERSTAND...

It appears that epithelial ovarian neoplasms are benign or malignant from the beginning... in other words cystadonomas do not become cystadenocarcinomas

...Which is unlike breast, cervix, endometrium, where I spend most of my day looking for “pre cancers” before they “cross the line...”
• WHEN to do TV U/S in breast cancer patients?

• In PREMENOPAUSAL patients TV U/S is best done in the early proliferative phase BEFORE ovulation as the Corpus Luteum can be variable in appearance and SOMETIMES difficult to distinguish from small suspicious complex cysts.

• However the typical “ring of fire” on Color Doppler morphology helps to solidify the diagnosis.
In POSTMENOPAUSAL patients there is no “cycle” and timing of the study is NOT relevant

ANATOMY OF A POSTMENOPAUSAL OVARY
- Folliculogenesis ceases
- Tunica albuginea becomes very dense causing the surface of the ovary to become scarred and shrunken
- Eventually ovary is inert, consisting mainly of connective tissue, clings to posterior leaf of the broad ligament
- Can no longer be palpated on bimanual exam (basis for Barber’s original thesis)

OVARIAN ANATOMY AND ULTRASOUND: PREMENOPAUSE
- Sonolucencies of follicles make visualization relatively simple
- When a woman assumes lithotomy, freely mobile premenopausal ovary is lateral to uterus and easily seen on vaginal probe ultrasound immediately adjacent to the pelvic side wall (iliac artery and iliac vein)
OVARIAN ANATOMY AND ULTRASOUND POSTMENOPAUSE

- Lack of normal folliculogenesis (no sonolucencies)
- Does not reach pelvic sidewall, therefore iliac vessels not so helpful in identification
- Loops of bowel everywhere

LINGERING QUESTION:

WILL THE LACK OF A NORMAL OVARY ON ULTRASOUND BE AS REASSURING AS DEFINITIVELY LOCATING IT AND SEEING IT TO BE ATROPHIC?

Postmenopausal ovaries: Detection and Diagnosis

- 82% of ovaries seen; all abnormal ones were seen
- Mean surgical diameter of non-visualized ovaries: 7.3mm (5-12mm)
- No ovaries with normal ultrasound were abnormal at surgery
- One microscopic Brenner tumor; ovary appeared grossly normal at TVU and to the eye

“ANATOMIC IMAGING”
- “Sonomicroscopy”
- Further ultrasound refinement ???

“PHYSIOLOGIC IMAGING”
- Doppler
- Color flow

COLOR FLOW DOPPLER: PRINCIPLE
- Tumors are rich in neovascularization
- Bizarre vessels rich in AV anastomoses
- This results in diminished resistance to flow across these vessels as measured by Doppler
- Color flow mapping allows easy, rapid assessment of where to place Doppler gate to perform spectral analysis (i.e., obtain resistive indices)
Will physiologic assessment compliment or eventually replace anatomic assessment in order to distinguish benign from malignant?

IN OTHER WORDS...

Will color flow Doppler allow us to diagnose stage IA cancer in an ovary that appears morphologically normal?

Very exciting concept but… the verdict is not yet in.
ANALOGY ?!?  
Fetal heart rate monitoring vs. continuous fetal pH

HOW OFTEN SHOULD BREAST CANCER PATIENTS HAVE THEIR OVARIES EVALUATED?

OVARIAN CANCER SCREENING UPDATE (2)  

- 25,327 women screened  
- 364 surgeries (1.4%) yielding 35 primary invasive cancers, 9 serous LMP tumors, and 7 metastatic to ovary  
- 64% Stage I, 18% Stage II, 18% Stage III  
- 9 women developed ovarian cancer within 12 months of a negative screen
UPDATE ON PLCO STUDY

- 9% of all cancers picked up at baseline
- 25% picked up at annual screen
- 17% picked up in < 1 year after annual screen (similar to Univ. of Ken.)
- 37% picked up after screening phase was over!!

UKCTOCS: Sharma, A. Ultrasound Obstet Gynecol 2012;40 338-334

- Of 11,982 women with normal scans for 3 years, none developed type I EOC but 8 were diagnosed with Type II EOC before the next screen. (range 6-13 months)

WHAT IS THE TAKE HOME MESSAGE?

- If you are going to screen …This data calls into question if 12 months is just too long a screening interval!!
IN SUMMARY

- Invasive Breast cancer is a VERY prevalent disease
- Tamoxifen is the most widely prescribed cancer drug worldwide

IN SUMMARY

- Tamoxifen causes various benign and malignant changes in the uterus
- TV U/S and Sonohysterography are the most appropriate means to evaluate GYN pts receiving tamoxifen

IN SUMMARY

- Non BRCA positive breast cancer pts have DOUBLE the lifetime risk of ovarian cancer (3.6% vs 1.8%)
- We hope that early detection with TV U/S (not exactly the same as screening) will lead to better outcomes.
IN SUMMARY

- PM ovaries are not always seen on TV U/S
- Color Doppler has NOT been a useful screening tool
- If one DOES do TV U/S surveillance of ovaries in Breast cancer patients 6 month intervals will be more appropriate than 12 months