HOW U/S CAN HELP GUIDE MEDICAL MANAGEMENT OF MENOPAUSE AND PERIMENOPAUSE

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DISCLOSURE SLIDE

- Gynecologic Advisory Boards: Eli Lilly, Glaxo Smith Kline, Merck, Pfizer, Beringer Ingelheim, Amgen, Novo Nordisk, Wyeth, Watson
- Consultant: Cook Ob/Gyn, Philips U/S
- Director, Sonosite, Inc
ENDOMETRIAL CANCER

- American cancer society (2008): 41,520 new cases, 8,145 deaths
- Vaginal bleeding will be the presenting sign in almost all
- Most women with PM bleeding actually bleed secondary to atrophic changes of vagina or EM
- Incidence of EM cancer in women with PMB ranges from 1-14%
POSTMENOPAUSAL BLEEDING
NOT SO EASILY DEFINED

- Menopause “The Final Menstrual Period”
- Retrospective diagnosis
- Classic definition: “No bleeding for 12 months due to a depletion of ovarian follicles”
- Serum measurements of FSH and estradiol notoriously unreliable – snapshot of ovarian function at that time.
Erratic function of the ovaries in late perimenopause often makes it difficult to label bleeding as definitively postmenopausal.
Postmenopausal bleeding is “endometrial cancer until proven otherwise” mandates evaluation.

ACOG Practice Bulletin #14 (2000) “endometrial assessment to exclude cancer is indicated in any woman older than 35 years who is suspected of having anovulatory uterine bleeding.”
THE GREAT DIVIDE

- Abnormal uterine bleeding that is dysfunctional..oligo or anovulatory
  (pts often told “hormone imbalance”)

vs.

Anatomic organic pathology (e.g. polyps, myomas, hyperplasia, carcinoma)
PERIMENOPAUSAL UTERINE BLEEDING

• AN ULTRASOUND BASED APPROACH TO DIAGNOSIS
PERIMENOPAUSAL PATIENTS WITH ABNORMAL UTERINE BLEEDING

VAGINAL ULTRASOUND (day 4-6)

- THIN DISTINCT ENDOMETRIAL ECHO < 5mm (BILAYER)
  - Dx: Dysfunctional Uterine Bleeding

- CENTRAL UTERINE ECHOS THICKENED (> 5mm) or ENDOMETRIAL ECHO NOT ADEQUATELY VISUALIZED

SALINE INFUSION SONOHYSTEROGRAPHY (SIS)

- THIN ENDOMETRIUM (< 3mm LAYER) WITH NO FOCAL ABNORMALITIES DETECTED
  - Dx: Dysfunctional Uterine Bleeding No Further Diagnostic Procedures Necessary

- SYMMETRICALLY THICKENED EM (> 3mm SINGLE LAYER)
  - Office Endometrial Biopsy

- FOCAL LESION OR ASYMMETRIC THICKENING
  - D&C Hysteroscopy (Resectoscopic Surgery if Necessary)
HOW DID WE ARRIVE AT THIS?
Use of ultrasonohysterography for triage of perimenopausal patients with unexplained uterine bleeding

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OBJECTIVE: Concerns about pathologic anatomy in perimenopausal women with irregular vaginal bleeding have made invasive diagnostic procedures commonplace. This study evaluated the use of fluid instillation to enhance vaginal probe ultrasonographic examination of the endometrium in such patients.

STUDY DESIGN: This was a prospective study of 21 women between 40 and 52 years old with irregular vaginal bleeding. On day 4 to 6 of the menstrual cycle a 5.5F Storah Intrauterine Injection catheter (Cook ObGyn, Spencer, Ind.) was inserted, and under direct ultrasonographic examination sterile saline solution was slowly infused. If present, any polyp or submucous myoma was noted and the endometrial thickness surrounding the fluid was measured. Invasive endometrial sampling was then carried out.

RESULTS: Of the 21 patients, 8 had obvious polypoid lesions and underwent triage for operative hysteroscopic removal. The pathology report confirmed benign polyps in all 8. Three patients had submucous myomas. Two had wire loop hysteroscopic excision. The third, with a submucous myoma that extended to the serosal edge of the uterus, received expectant management. Nine patients had no obvious anatomic lesion and endometrial thickness of ≤ 4 mm. Biopsy in all 9 of these patients revealed early proliferative endometrium. One patient had endometrial thickness of 8 mm; fractional curettage with hysterection revealed simple hyperplasia without atypia.

CONCLUSIONS: Endometrial fluid instillation to enhance vaginal ultrasonography in perimenopausal women can reliably distinguish between patients with minimal tissue whose bleeding may be of anovulatory origin and best treated with hormonal therapy and those patients with significant amounts and type of tissue in need of formal curettage. Furthermore, polyps may be distinguished from submucous myomas, which allows appropriate preoperative triage for operative hysteroscopy when indicated and eliminates the need for diagnostic hysteroscopy. (Am J Obstet Gynecol 1994;170:565-70.)

Key words: Perimenopause, uterine bleeding, ultrasonography, sonohysterogram
Pilot Study

- 21 perimenopausal women (age range 40-52)
- Clinical history of irregular vaginal bleeding
- Studied on day 4-6
- 5.3Fr Soules IUI catheter inserted
- Sterile saline infused under real-time vaginal ultrasound video taping
Results

- 8 patients with obvious polyps, triaged for hysteroscopic removal
- 3 patients with submucous myomas (2 offered wire loop resectoscopic surgery, 1 with extension to serosa treated expectantly)
- 9 patients with no anatomic lesion and surrounding endometrium < 3.2mm, all showed proliferative endometrium on biopsy. DX: DUB. Subsequently treated with progestin
- 1 patient with 8mm endometrium, path revealed simple hyperplasia without atypia: subsequently treated with progestin
Of note 9/21 patients had clinical and sonographic evidence of myomas but only 3/21 had a submucous component on sonohysterogram. Thus 6/21 had dysfunctional uterine bleeding co-existing with intramural/subserosal myomas.
CONCLUSION

- Endometrial fluid instillation to enhance vaginal ultrasonography in perimenopausal women can reliably distinguish between patients with minimal tissue (\(< 3\text{mm}\)) whose bleeding is annovulatory (best treated hormonally) from patients with significant tissue (\(> 3\text{mm}\)) in need of tissue sampling.
CONCLUSION

- Broad based endometrial masses can be distinguished from those on a stalk or pedunculated
- Allows appropriate triage for operative hysteroscopy when needed
- Eliminates the need for diagnostic hysteroscopy in patients whose bleeding is dysfunctional
Ultrasonography-based triage for perimenopausal patients with abnormal uterine bleeding

Ultrasound based triage uses vaginal ultrasound screening of all patients and selected SIS when the unenhanced TV U/S is not thin or reliable.
MATERIALS AND METHODS

- 433 patients
- Perimenopausal
  (average age 47.4, range 37-54 years)
- Abnormal uterine bleeding
  (menorrhagia, metrorrhagia, or both)
ABNORMAL PERIMENOPAUSAL BLEEDING:

433 PATIENTS
Unenhanced Vaginal Ultrasound
280 patients \( \leq 5\text{mm} \) (day 4-6)
153 patients \( > 5\text{mm} \) or nonvisualization of EM
153 patients
44 (29%) for nonvisualization of EM
109 (71%) for EM > 5mm
THUS OF 433 PATIENTS:

- 342 (78.9%) had dysfunctional bleeding
- 23 (5.3%) had submucous myomas
- 58 (13.4%) had polyps of which 3 were endocervical
- 15 (3.5%) had hyperplasia (of which 5 were symmetrical, 4 were focal, and 6 were in polyps)
OF 15 PATIENTS WITH HYPERPLASIA

- 5 were symmetrically thick (4 simple, 1 complex)
- 4 were focally thick (1 simple, 3 complex)
- 6 were in polyps (3 simple, 3 complex)
THE STUDY ALGORITHM ALLOWS

65% to have ultrasound exam done
17% to have ultrasound and SIS only
2.3% to have U/S, SIS pipelle bx only
15.9% to have U/S, SIS D&C hysteroscopy
PITFALLS AND PEARLS FOR SONOHYSTEROGRAPHY
**PITFALL**  
- Inability to thread catheter

**SOLUTION**  
- Change position of speculum, use a “cervical stabilizer” (a fine toothed tenaculum). Small dilator (#13 Pratt) as last resort.
PITFALL
- anesthesia/analgesic

SOLUTION
- not required; now 3 cases (in over 1000 performed) of vaso-vagal response similar to days of IUD insertion into nulliparas.
PITFALL
- infection? GC, chlamydia cultures??, antibiotics???

SOLUTION
- similar to traditional HSG, depends on your patient population, protocol
IMPORTANT CAVEAT

- procedure is VERY time sensitive. It must be done on the last days of staining or the first days after the bleeding cycle ends when the endometrium will be as thin and uniform as possible.
- as endometrium proliferates and thickens it is not always perfectly symmetrical (BEWARE “moguls” or small irregularities)
...ANOTHER EXAMPLE
WHILE WE’RE AT IT...
AVOID SONOHYSTEROGRAPHY WITH ACTIVE BLEEDING !!!
IN FACT...

...If the patient is bleeding so much or so often and cannot really tell what is a menses...

Consider an empiric course of a progestin “medical curette” and then time the sonographic evaluation to the withdrawal bleed.
AVOID GETTING AIR INTO THE CATHETER OR THE SYRINGE (AIR IS VERY ECHOGENIC !!)
PITFALL
- concern about spreading adenocarcinoma

SOLUTION
- does the benefit outweigh theoretical risk.

-- 14 SIS in OR (known cancers) prior to TAH…one (7%) had identifiable cells in washings (Alcazar 2000)
- 32 SIS in OR (also known cancers) prior to TAH…two (6%) had malignant cells (Dessole 2006 AJOG)
IN MY OPINION…

No longer appropriate to do a blind office biopsy procedure unless you first verify that whatever the endometrial process it is indeed global and not focal.
I ACKNOWLEDGE...

- Ultrasound does NOT give you
  a tissue diagnosis

- The value of U/S and Sonohysterography
  is to TRIAGE patients to...
  - NO anatomic pathology
  - GLOBAL EM process (blind biopsy)
  - FOCAL process (direct vision)
WHAT ABOUT PATIENTS BEYOND PERIMENOPAUSE

• POST MENOPAUSAL BLEEDING
• HORMONE THERAPY (HT…previously HRT)
TV U/S IN PMB: HISTORICAL PERSPECTIVE
ENDOMETRIUM IN MENOPAUSE

- Becomes thin and atrophic
- No epithelial stimulation by estrogen
- Atrophic mucosa prone to superficial punctate ulceration
- Such “senile endometritis” is most common cause of PMB. Must be distinguished from hyperplasia or adenocarcinoma
ULTRASOUND APPEARANCE:

- Thin “pencil line” echogenicity
- Intact hypoechoic “halo” surrounds
TRANSVAGINAL ULTRASOUND

- In the early 1990’s, it was utilized in women with postmenopausal bleeding to see if it could predict which patients lacked significant tissue and could avoid D&C or endometrial biopsy and its discomfort, expense, and risk.

Consistently, the finding of a thin distinct endometrial echo ≤ 4 to 5mm was shown to effectively exclude significant tissue in postmenopausal women with bleeding.
<table>
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<th>AUTHOR</th>
<th>YEAR</th>
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TRANSVAGINAL U/S VALIDATION OF EARLY STUDIES
## Endometrial Thickness and Cancer Findings in Postmenopausal Women With Bleeding

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endometrial thickness*</th>
<th>Number of women</th>
<th>Number of cancers</th>
<th>Negative Predictive Value</th>
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<td>Karlsson 1995</td>
<td>≤ 4 mm</td>
<td>1,168</td>
<td>0</td>
<td>100%</td>
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<tr>
<td>Ferrazzi 1996</td>
<td>≤ 4 mm</td>
<td>930</td>
<td>2</td>
<td>99.8%</td>
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<td></td>
<td>&lt; 5 mm</td>
<td></td>
<td>4</td>
<td>99.6%</td>
</tr>
<tr>
<td>Gull 2000</td>
<td>≤ 4 mm</td>
<td>163</td>
<td>1</td>
<td>99.4%</td>
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<tr>
<td>Epstein 2001</td>
<td>≤ 5 mm</td>
<td>97</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Gull 2003</td>
<td>≤ 4 mm</td>
<td>394</td>
<td>0</td>
<td>100%</td>
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</table>
TRANSGAVINAL U/S VALIDATION OF EARLY STUDIES

• For EM ≤ 4mm incidence of malignancy 1 in 917
IS ENDOMETRIAL BIOPSY STILL NECESSARY?

- False negative rate of TV U/S \( \leq 4\text{mm} \) significantly less than a negative suction piston biopsy
- EM biopsy on patients with EM \(< 5\text{mm}\): only 82% successfully performed, and of those only 27% gave a sample adequate for diagnosis
IS ENDOMETRIAL BIOPSY STILL NECESSARY? (Con’t)

• ACOG Committee Opinion (2/09) “When transvaginal ultrasound is performed for patients with postmenopausal bleeding and an EM thickness $\leq 4$mm is found EM sampling is not required”
POST MENOPAUSAL BLEEDING...

- "CANCER UNTIL PROVEN OTHERWISE"
- ROLE OF HIGH NEGATIVE PREDICTIVE VALUE OF A THIN DISTINCT EM ECHO
- PERFORM TV U/S FIRST, SONOHYSTEROGRAPHY IF NECESSARY, TO TRIAGE PTS TO 1) NO PATHOLOGY 2) GLOBAL PROCESS (BLIND BX) 3) FOCAL PROCESS (DIRECT VISION)
HORMONE THERAPY: A NEW ROLE FOR ULTRASOUND
HORMONE THERAPY (HT) NEW NOMENCLATURE (POST WHI)

- No longer appropriate to use indefinitely to promote long term health
- Continues to be appropriate for short term use in treatment of disruptive transitional symptoms
SEQUENTIAL PROGESTIN
(Pedwick, Pryse-Davis, Whitehead NEJM, 1986;315:930)

- 102 women - continuous estrogen
  progestin 12 days

- Bleeding ≤ Day 10: 100% proliferative
  or hyperplastic EM

- Bleeding ≥ Day 11: 100% Secretory or
  Absent EM
CONTINUOUS PROGESTIN

- No scheduled bleeding
- After 3 months, 75% have no further bleeding
- Less progestin related side effects
- Method utilized in HERS and WHI
THE CASE FOR LESS THAN MONTHLY PROGESTOGEN IN HT: IS TV U/S THE KEY?

- Unopposed ET increases a patient’s risk of EM cancer
- Addition of a progestogen to estrogen (HT) decreases but does not eliminate that risk
- Initially this was done sequentially. More recently continuous combined regimen attempting to eliminate bleeding became popular
THE CASE FOR LESS THAN MONTHLY PROGESTOGEN IN HT: IS TV U/S THE KEY?

- Published data point to E+P increasing the risk of breast cancer 2-3X above that of E alone
- In the past, less than monthly P has been attempted. It results in less bleeding, but some hyperplasia (7 per 100 women at 6 months)
- TV U/S has a very POOR Positive predictive value (4% for serious EM disease) but a very HIGH Negative Predictive value (99% for EM echo <5mm)
THE CASE FOR LESS THAN MONTHLY PROGESTOGEN IN HT: IS TV U/S THE KEY?

- Patients with an initial thin distinct EM echo (<5mm) can begin with unopposed E.
- At 3 months they get a progesterone withdrawal for 12 days and the EM echo is again measured after withdrawal bleed.
- If thin and distinct the interval between withdrawals can be further increased and in some women (those who do not bleed) potentially eliminated.
THE CASE FOR LESS THAN MONTHLY PROGESTOGEN IN HT: IS TV U/S THE KEY?

CAVEATS:

- Not all uteri will lend themselves to a reliable initial U/S exam (Axial uterus, coexisting fibroids, marked obesity, previous ablation)

- Since the majority will bleed, women need to accept 2-4 withdrawal bleeds per year that she can plan and control the timing of

- If the EM echo does not thin after withdrawal, the patient should be triaged with SIS and resume a conventional regimen
THE CASE FOR LESS THAN MONTHLY PROGESTOGEN IN HT: IS TV U/S THE KEY?

- The advantage of such a regimen is that the successful patient may sharply reduce and possibly eliminate her progesterone exposure.
- Currently we treat 100% of women with a uterus to protect the 7% who will develop simple hyperplasia at 6 months.
PUTTING IT ALL TOGETHER
A thin distinct homogenous EM echo ≤ 4-5mm with a hypoechoic zone surrounding it reliably predicts lack of significant tissue.
In all other scenarios fluid instillation coupled with high resolution endovaginal probes can offer tremendous diagnostic enhancement as a simple inexpensive well tolerated office procedure.
An algorithm of U/S as the first step in the evaluation of AUB works in ALL CASES – as long as you understand the difference between patients who cycle vs. those who do not.
CYCLING VS. NON CYCLING

- In NON CYCLING patients – everyday is the same.
- In patients WHO ARE CYCLING, timing is crucial.
- Ultrasound evaluation should be performed at a time when the EM will be as thin as it will all month long (just as the bleeding ends).
- This prevents misinterpretation of EM “moguls” later in the cycle as being pathologic.
IN SUMMARY

- EM Pathology NOT ALWAYS Global
- Pitfalls of random blind EM sampling
- Reliability of “thin” EM in excluding pathology (High Negative Predictive Value)
- Role of Fluid enhancement (sonohysteroscopy) in all other scenarios