EVALUATION OF POSTMENOPAUSAL BLEEDING: WHAT IS THE STANDARD OF CARE?

Steven R. Goldstein, M.D., FACOG, NCMP, CCD, FRCOG (H)
Professor of Obstetrics & Gynecology
New York University School of Medicine
Director of Gynecologic Ultrasound
Co-Director of Bone Densitometry
New York University Medical Center

RELEVANT DISCLOSURES

- EQUIPMENT LOAN: PHILIPS ULTRASOUND
- CONSULTANT: COOK OBGYN, COOPER SURGICAL

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

TRANSVAGINAL ULTRASOUND

- Introduced in the mid 1980's, the vaginal probe utilizes higher frequency transducers in close proximity to the structure being studied.
SONOMICROSCOPY

Vaginal sonography provides a degree of image magnification that is as if we were doing ultrasound through a low power microscope.


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.


TRANSVAGINAL ULTRASOUND

Consistently, the finding of a thin distinct endometrial echo < 4 to 5mm was shown to effectively exclude significant tissue in postmenopausal women with bleeding.
Goldstein  90  7  6
Varner  91  5  5
Granberg  91  9  15

**TRANSVAGINAL U/S VALIDATION OF EARLY STUDIES**
Endometrial Thickness and Cancer Findings in Postmenopausal Women With Bleeding (ACOG 2009)

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Karlsson 1995</td>
<td>≤ 4 mm</td>
<td>1,168</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Ferrazzi 1996</td>
<td>≤ 4 mm</td>
<td>930</td>
<td>2</td>
<td>99.8%</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Gull 2003</td>
<td>≤ 4 mm</td>
<td>394</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Gull 2003</td>
<td>&lt; 5 mm</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TRANSVAGINAL U/S VALIDATION OF EARLY STUDIES (ACOG 2009)

- For EM ≤ 4mm incidence of malignancy 1 in 917

IS ENDOMETRIAL BIOPSY STILL NECESSARY?

- ACOG Committee Opinion (2/09) “When transvaginal ultrasound is performed for patients with postmenopausal bleeding and an EM thickness ≤ 4mm is found EM sampling is not required”

IN FACT...

- False negative rate of TV U/S < 4mm significantly less than a negative suction piston biopsy (more on that later)
- EM biopsy on patients with EM < 5mm: only 82% successfully performed, and of those only 27% gave a sample adequate for diagnosis

Elsandabese D, Obstet Gynecol 2005;25:32-4
UPDATED DATA...

Endometrial Thickness and Incidence of Cancer in Postmenopausal Women with Bleeding

<table>
<thead>
<tr>
<th>Reference</th>
<th>Endometrial Thickness on TVUS</th>
<th>Number of Women</th>
<th>Total Sample of Bleeding Women</th>
<th>Number of Cases of Cancers</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurken 1995</td>
<td>≤ 4 mm</td>
<td>518</td>
<td>1138</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Ferrari 1996</td>
<td>≤ 4 mm</td>
<td>336</td>
<td>930</td>
<td>2</td>
<td>99.6%</td>
</tr>
<tr>
<td></td>
<td>≤ 5 mm</td>
<td>456</td>
<td>930</td>
<td>4</td>
<td>99.1%</td>
</tr>
<tr>
<td>Gull 2003</td>
<td>≤ 4 mm</td>
<td>394</td>
<td>394</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Wong 2016</td>
<td>≤ 3 mm</td>
<td>1915</td>
<td>4383</td>
<td>5</td>
<td>99.7%</td>
</tr>
<tr>
<td></td>
<td>≤ 4 mm</td>
<td>2025</td>
<td>4383</td>
<td>10</td>
<td>99.6%</td>
</tr>
<tr>
<td></td>
<td>≤ 5 mm</td>
<td>3131</td>
<td>4383</td>
<td>11</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

THUS...

- For average risk women the current standard of ≤ or equal to 4mm as a “cut-off” beneath which no further evaluation is necessary is still acceptable
HOWEVER…

- For high risk women (obese, hypertensive, diabetic, h/o PCOS, etc) OR patients who “re-bleed”, then further evaluation in spite of an initial thin ultrasound echo may be warranted.

ULTRASOUND ENDOMETRIAL EVALUATION

SO WHAT ELSE IS ESSENTIAL?

GENERAL PRINCIPLES FOR TRANSVAGINAL U/S

- Use the highest frequency transducer that still yields adequate penetration.
- Once EM echo well visualized use as much magnification as feasible.
- Obtain multiple images in the Long Axis plane... midline as well as to the right and left of midline.
- Measurements should be on a long axis view of the thickest point.
Not all uteri lend themselves to a meaningful U/S examination (Axial uterus, marked obesity, coexisting fibroids, adenomyosis, previous surgery, etc.).

Just because you can produce something that is “linear and white” DOESN’T mean you should!!!

When an EM echo is not TOTALLY distinct, do NOT be afraid to indicate “EM echo not well visualized.”
EXAMPLES OF “GOOD” EM ECHOS SEEN ORIGINATING FROM CERVICAL OS

ENDOMETRIAL ABNORMALITIES ARE NOT ALWAYS GLOBAL
IMPORTANCE OF 3D RECONSTRUCTION

Realize that any single frozen ultrasound image is a two dimensional “snapshot” e.g. a single long axis view of a seemingly normal endometrium does not rule out pathology. The entire structure must be observed and three dimensional anatomy reconstructed.
THE STANDARD OF CARE HAS CHANGED!!!!

BUT HOW MANY CLINICIANS ARE AWARE OF IT?

ACOG PRACTICE BULLETIN ON ABNORAMAL UTERINE BLEEDING (JULY 2012)

“One third of outpatient visits to the gynecologist are for AUB and it accounts for more than 70% of GYN consults in the perimenopausal and postmenopausal years”
WHAT IS THE PROPER USE OF THE ENDOMETRIAL ECHO CLINICALLY?

ENDOMETRIAL CANCER
- American Cancer Society (2016): 60,050 cases, 10,470 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%

ANSWER
- THE HIGH NEGATIVE PREDICTIVE VALUE OF A THIN DISTINCT ECHO IN PATIENTS WITH BLEEDING

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 July 2012 mandates that endometrial assessment to exclude cancer is indicated in any woman older than 40 years who is suspected of having abnormal uterine bleeding.

The reliability (and liability) of Pipelle has radically changed.

So why is there an issue with Pipelle?
SUCTION PISTON BIOPSY INSTRUMENTS

- Smaller, cheaper, disposable plastic catheters with an internal piston to generate suction
- Marketing success of Pipelle brand ("Xerox, Kleenex")
- Similar efficacy but better patient acceptance when compared to Vabra

PIPELLE SUCTION PISTON BIOPSY

- 1st described by Cornier in an article in the Gray Journal in 1984
- Of next 8 papers (1988-1991) 7 dealt with EM dating as part of infertility W/U (no longer utilized)
- One paper dealt with AMOUNT of tissue obtained with Pipelle compared to Vabra
- Next paper (1991) was WIDELY publicized

PIPELLE AND EM CARCINOMA

Stovall (1991)
- 40 women with known carcinoma
- Pipelle prior to TAH
- Cancer diagnosed in 39/40 patients
- "Accuracy" = 97.5%
- Widely publicized

PIPELLE

- Rodriguez (1993) did prehysterectomy sampling with both. Pipelle sampled an average of 4% of EM lining (range 0-12%) vs. 41% for Vabra
- Pipelle agreed with post hysterectomy diagnosis in only 84% of cases
**PIPELLE ENDOMETRIAL SAMPLING**

65 pts with known carcinoma of EM
Pipelle under anesthesia prior to TAH
- missed 11/65 cancers of which
  3 were < 5% EM area
  4 were 5-25% EM area
  4 were 25-50% EM area
- 5/11 had tumor in polyps that were missed

Concluded “Pipelle is excellent for detecting global processes in the endometrium”

---

**False Negative Rate of Blind Endometrial Sampling in Patients with Known Carcinoma**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Device</th>
<th>Number of patients</th>
<th>Cancers missed</th>
<th>False negative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stovall 1991</td>
<td>Pipelle</td>
<td>40</td>
<td>1</td>
<td>2.5%</td>
</tr>
<tr>
<td>Ferry 1993</td>
<td>Pipelle</td>
<td>37</td>
<td>12</td>
<td>32.4%</td>
</tr>
<tr>
<td>Larson 1994</td>
<td>Z sampler</td>
<td>80</td>
<td>14</td>
<td>17.5%</td>
</tr>
<tr>
<td>Guido 1995</td>
<td>Pipelle</td>
<td>65</td>
<td>11</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

---

**The ACOG Practice Guideline #128 (7/12) states:**

The primary imaging test of the uterus for the evaluation of AUB is transvaginal ultrasonography.

---

“If transvaginal ultrasonographic images are not adequate or further evaluation of the cavity is necessary, then sonohysterography (also called saline infusion sonohysterography) or hysteroscopy (preferably in the office setting) is recommended.”
SALINE INFUSION 
SONOHYSTEROGRAPHY

• REMEMBER FLUID ENHANCES SOUND TRANSMISSION

GOLDSTEIN’S 1ST AXIOM OF ULTRASOUND

FLUID IS YOUR FRIEND
SONOHYSTEROGRAM

- Fluid instillation to enhance U/S detail of the endometrium
- Among the easiest TV U/S scans you will ever perform!
- Technical aspects simple for gyns, slightly more daunting for radiologists
SONOHYSTEROGRApH: TECHNIQUE
- Pelvic scan, unenhanced (baseline appearance)
- Palpatory bimanual (anteverted, retroverted)
- Insert speculum
- Cleanse cervix
- Thread catheter (flush air first)

SONOHYSTEROGRApH: TECHNIQUE
- Remove speculum (carefully)
- Insert vaginal probe
- Instill sterile saline (10cc syringe), slowly, watch the screen
- Scan from cornua to cornua
- “reload”, turn 90° and scan from fundus to cervix
Endometrial fluid instillation to enhance vaginal ultrasonography can reliably distinguish between patients with no anatomic abnormality (best treated expectantly) from patients with significant tissue in need of tissue sampling (done blindly for a global process and under direct vision for a focal process).
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 WROTE THAT SLIDE 21 YEARS AGO!!!!!!

SO WHAT ABOUT OFFICE HYSTEROscopy?
I have not previously done office hysteroscopy because of the space needed for the equipment, need to be able to sterilize the equipment, time involved as well as patient comfort/discomfort.

Thus, office hysteroscopy has not been a satisfactory option in my hands and definitely not “point of care.”

A new device, Endosee, while technically a form of office hysteroscopy, is truly revolutionary because it is absolutely a point of care option – it can and should be done with a patient up in stirrups just as one has done a Pipelle endometrial biopsy in the past.
The entire visualization procedure takes a maximum of about 90 seconds to get total and adequate visualization. If there is no focal pathology, I will perform an endometrial biopsy and the patient can be treated expectantly or hormonally. If there is focal pathology (polyps, myoma, focal tissue), I will schedule operative hysteroscopy with anesthesia.
ANOTHER TAMOXIFEN PT
ENDOMETRIAL HYPERPLASIA
Once again with no focal abnormality I can do a blind endometrial sampling with confidence.
Path revealed a recurrence of her complex hyperplasia.
In spite of no atypia she opted for a hysterectomy instead of another prolonged course of progestin.

SO BACK TO THE ACOG PRACTICE BULLETIN OF JULY 2012...

"An office endometrial biopsy is the first-line procedure of tissue sampling in the evaluation of patients with AUB."

"Endometrial biopsy has high overall accuracy in diagnosing endometrial cancer when an adequate specimen is obtained and when the endometrial process is global."
“If the cancer occupies less than 50% of the surface area of the endometrial cavity, the cancer can be missed by a blind endometrial biopsy sample.”

“A positive test result is more accurate for ruling in disease than a negative test result is for ruling it out.”

“These tests are only an endpoint when they reveal cancer or atypical complex hyperplasia.”

“Now the standard of care corroborates that a negative blind biopsy is not a stopping point. Clinicians can still begin with a bx but unless it is malignant (or complex atypical hyperplasia) the endometrial evaluation is not complete!”
ONE MORE IMPORTANT POINT...

- WHAT ABOUT NON-BLEEDING PATIENTS WHO HAVE AN INCIDENTAL FINDING OF A THICK ENDOMETRIAL ECHO ON TRANSVAGINAL ULTRASOUND?

What have health care practitioners HEARD and DONE?!?

If <4mm is good then >4mm must be bad.
But remember this was all done in women WITH BLEEDING

So without any validation women with EM > 4mm ABSENT BLEEDING have been and often still are routinely biopsied.

1) how common is a thick EM echo in non bleeding patients?
   2) when present what is its significance?

There is an increasing body of data worth reviewing…
10% of postmenopausal women trying to enroll in the Raloxifene uterine safety studies had asymptomatic endometrial polyps on sonohysterography

A. Parsons (verbal communication)

17% of 550 newly diagnosed postmenopausal breast cancer patients in Brussels had unsuspected asymptomatic polyps prior to initiating tamoxifen therapy


- A randomly selected Danish population aged 20-74 underwent TV U/S and SIS
- Prevalence of uterine polyps overall = 7.8%
- Prevalence increased with age
- In PM women (n=169) prevalence of Asx polyps was 13.0% (n=22)

Dreisler et al Ultrasound Obstet Gyencol 2009:33-102

WHAT IS THE RISK OF MALIGNANCY IN SUCH POLYPS?

- Removed 117 polyps in PM women without bleeding
- NONE were malignant
- Discussed importance of distinguishing EM carcinoma with polypoid growth from carcinoma arising in a polyp (base and surrounding EM must be benign)


- 1152 Asx PM women diagnosed with a polyp by SIS underwent hysteroscopic removal
- 1 EM cancer in a polyp (<0.1%), Mean diameter 40 mm
- 3 perforations, 7 cervical tears, 3 false passages
- 3 cancers (0.3%) occurred in Asx PM women that were not in polyps but were polypoid appearing on imaging and not global

Lev-Sagie A et al, BJOG 2005; 112:379-382

- 82 postmenopausal women with incidental sonographic findings of EM “thickening”
- Operative hysteroscopy
- 67 (82%) inactive polyps, 7 submucosal myomas, 6 atrophic EM, 1 proliferative EM, 1 polyp with simple hyperplasia
- NO complex hyperplasia or carcinoma
- 3.6% total complication rate (2 perforations, 1 difficult intubation)


- 190 women with EM cancer dx AFTER bleeding (symptomatic)
- 123 PM women with “suspicious” U/S on screening…of which 16 (13%) were ultimately dx with EM cancer
- Through 55 months of follow-up overall survival and disease free survival were the same when treatment was undertaken within 8 weeks of bleeding episode

U/S detection of Asx EM cancer in PM women offers no prognostic advantage over Sx disease discovered by uterine bleeding
Thus for the negligible risk that an Asx polyp MIGHT harbor a cancer (<1 in a 1000), or < 4 in a 1000 if you include “polypoid growth”, there is no therapeutic or prognostic advantage over waiting until it results in bleeding; and such an approach would spare the other 996 out of a 1000 any intervention and its risks, discomfort and expense.

SO …IN 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 OR OFFICE HYSTEROSCOPY, IF NECESSARY, TO TRIAGE PTS TO 1) NO PATHOLOGY 2) GLOBAL PROCESS (BLIND BX) 3) FOCAL PROCESS (DIRECT VISION)

BUT…FOR AN INCIDENTAL FINDING OF EM THICKENING…

- There is NO validation whatsoever that these patients need AUTOMATIC EM sampling
- The incidence of thick EM echo is probably 10-17% and is much like “simple” cyst of the post menopausal ovary was 20 years ago (which is something we NOW know is common and benign)
- Still appropriate (and always was) to use clinical JUDGEMENT if high risk (obese, diabetic, hypertensive, nulliparous)

In Summary

- THE MAIN USE OF ENDOMETRIAL THICKNESS MEASURED ON TV U/S IS THE HIGH NEGATIVE PREDICTIVE VALUE OF A THIN DISTINCT ECHO (LOSE THE WORD “STRIPE”)
In Summary

- **IN AVERAGE RISK WOMEN WITH POSTMENOPAUSAL BLEEDING EM< 4 MM HAS A LOW RISK OF MALIGNANCY AND DOES NOT REQUIRE ENDOMETRIAL SAMPLING**

In Summary

- **IN HIGH RISK WOMEN OR IF AN ENDOMETRIAL ECHO IS NOT WELL VISUALIZED OR RE-BLEEDING OCCURS FURTHER EVALUATION IS INDICATED**

In Summary

- **SALINE INFUSION SONOHYSTEROGRAPHY (SIS) OR NEWER EASIER FORMS OF OFFICE HYSTEROscopy WILL DISTINGUISH GLOBAL FROM FOCAL PROCESSES AND ALLOW APPROPRIATE TRIAGE**

In Summary

- **IN POSTMENOPAUSAL WOMEN WITHOUT BLEEDING THE INCIDENCE OF “THICK” ENDOMETRIAL ECHO (MOSTLY POLYPS ) IS 10-17% AND NO ROUTINE INTERVENTION IN SUCH NON BLEEDING PATIENTS IS INDICATED**