

ULTRASOUND LECTURE SERIES

– Presented by –

AIUM • CREOG • ACOG • ACOOG



SONOGRAPHIC EVALUATION OF POSTMENOPAUSAL BLEEDING

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ENDOMETRIAL CANCER

- American cancer society (2008): 41,520 new cases, 8145 deaths.
- Vaginal bleeding will be the presenting sign in almost all.
- Most women with postmenopausal bleeding (PMB) bleed secondary to atrophic changes of the vagina or endometrium (EM).
- The 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 follicle-stimulating hormone 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.

CLINICAL REALITY

- Postmenopausal bleeding is “endometrial cancer until proven otherwise,” mandates evaluation.
- American College of Obstetricians and Gynecologists (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.”

ENDOMETRIAL ASSESSMENT

HISTORICAL BACKGROUND

- Dilatation and curettage (D&C):
 - First described in 1843.
 - Most common operation performed on women in the hospital through much of the 20th century.
 - Prehysterectomy studies showed that when done blindly, much of the uterine cavity goes unsampled.

HISTORICAL BACKGROUND

Vabra aspirator:

- Reusable metal cannula attached to suction machine for in-office EM sampling with little or no anesthesia.
- High level of patient discomfort.
- 86% accurate in diagnosing cancer.

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

- First described by Cornier in an article in the Gray Journal in 1984.
- Of the next 8 papers (1988-1991), 7 dealt with EM dating as part of infertility workup (no longer utilized).
- One paper dealt with the *amount* of tissue obtained with Pipelle compared to Vabra.
- Next paper (1991) was widely publicized.

PIPELLE AND EM CARCINOMA

Stovall et al (1991):

- 40 women with known carcinoma.**
- Pipelle prior to total abdominal hysterectomy.**
- Cancer diagnosed in 39/40 patients.**
- Accuracy = 97.5%.**
- Widely publicized.**

PIPELLE

- Rodriguez et al (1993) did prehisterectomy sampling with both. Pipelle sampled an average of 4% of the EM lining (range, 0%-12%) vs 41% for Vabra.
- Pipelle agreed with posthisterectomy diagnosis in only 84% of cases.

PIPELLE ENDOMETRIAL SAMPLING

Guido et al (1995):

- **65 patients with known carcinoma of the EM.**
- **Pipelle under anesthesia prior to total abdominal hysterectomy.**
 - **Missed 11/65 cancers, of which**
 - 3 were <5% EM area.**
 - 4 were 6%-25% EM area.**
 - 4 were 26%-50% EM area.**
 - **5/11 had tumors in polyps that were missed.**
- **Concluded “Pipelle is excellent for detecting global processes in the endometrium.”**

PIPELLE ENDOMETRIAL SAMPLING

- Performed in 135 premenopausal patients before curettage.
- 13 patients (10%) had different histologic results compared with curettage.
- 5 of these patients had polyps, of which Pipelle sampling missed 3.
- 18 patients had hyperplasia, of which Pipelle sampling missed the diagnosis in 7 (39%), thus underscoring the often focal nature of that pathologic process.

Goldschmidt et al (1993).

SENSITIVITY OF PIPELLE IN PATIENTS WITH KNOWN CARCINOMA (OTHER STUDIES)

- 93% (missed 2/26).
- 83% (missed 14/80).
- 67% (missed 12/37).
- Not nearly as reliable as the original work by Stovall et al.

TRANSVAGINAL ULTRASOUND IN PMB: HISTORICAL PERSPECTIVE

ENDOMETRIUM IN MENOPAUSE

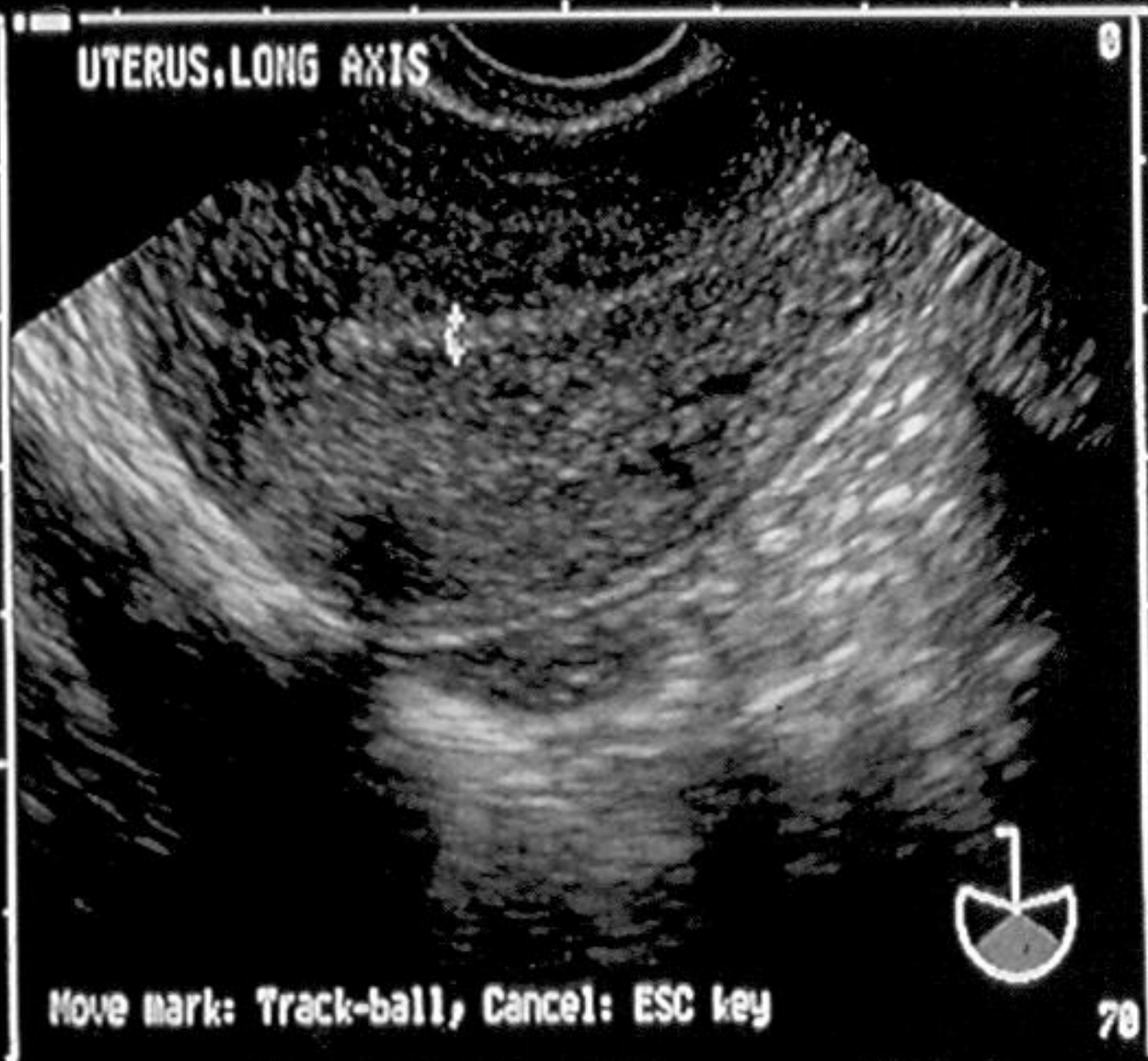
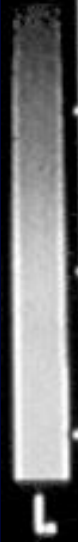
- Becomes thin and atrophic.
- No epithelial stimulation by estrogen.
- Atrophic mucosa prone to superficial punctate ulceration.
- Such “senile endometritis” is most common cause of PMB; must be distinguished from hyperplasia or adenocarcinoma.

ULTRASOUND APPEARANCE

- Thin “pencil line” echogenicity.
- Intact hypoechoic “halo” surrounds.

UTERUS, LONG AXIS

- Gyn
- 75/6/5EV 7.5
- 1 Uterus
- 2 L Ovary
- 3 R Ovary
- 4 L Fol#
- 5 R Fol#
- 6 Cervix
- 7 Endome



01= 2.1mm



Move mark: Track-ball, Cancel: ESC key

70

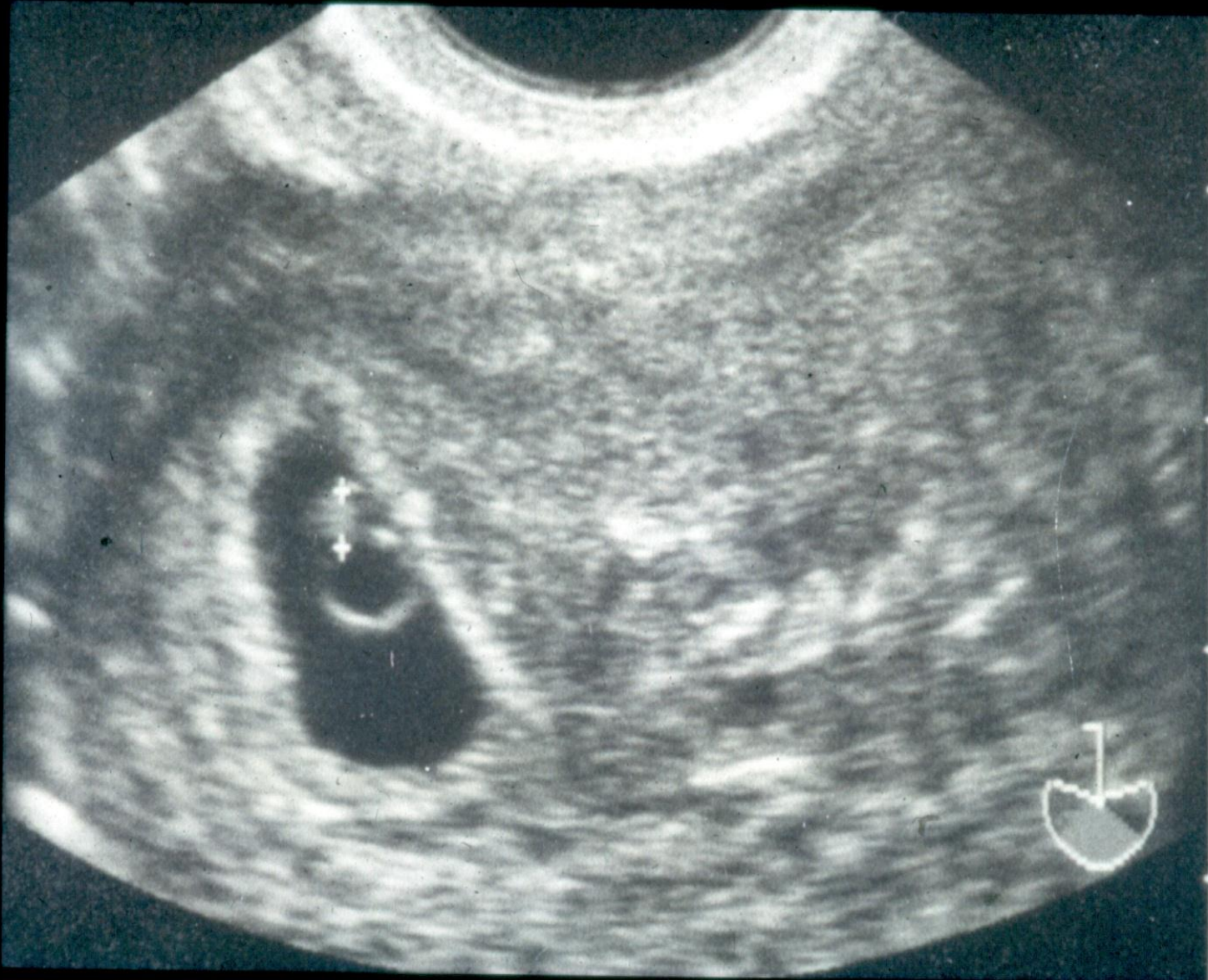
TR:GALF

R:60/3/0/30/ 50 0071V

M120.4

TRANSVAGINAL ULTRASOUND

- Introduced in the mid-1980s, the vaginal probe utilizes higher-frequency transducers in close proximity to the structure being studied. It yields a degree of image magnification that has been dubbed “sonomicroscopy.”



007 511
GA
1 GSD
2 CRL
3 BPD
4 OFD
5 HC
6 FL
7 TAD
8 APAD
9 AC
0 CHD
P Report
D=2.5 mm

TRANSVAGINAL ULTRASOUND

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

Goldstein SR, Nachtigall M, Snyder JR, et al. Am J Obstet Gynecol 1990; 163:119-123.

Granberg S, Wikland M, Karlsson B, et al. Am J Obstet Gynecol 1991; 164:47-52. ©AIUM

TRANSVAGINAL ULTRASOUND

- Consistently, the finding of a thin, distinct EM echo ≤ 4 to 5 mm was shown to effectively exclude significant tissue in postmenopausal women with bleeding.

HDI
4000

NYU MEDICAL CTR | #1
Gynecology

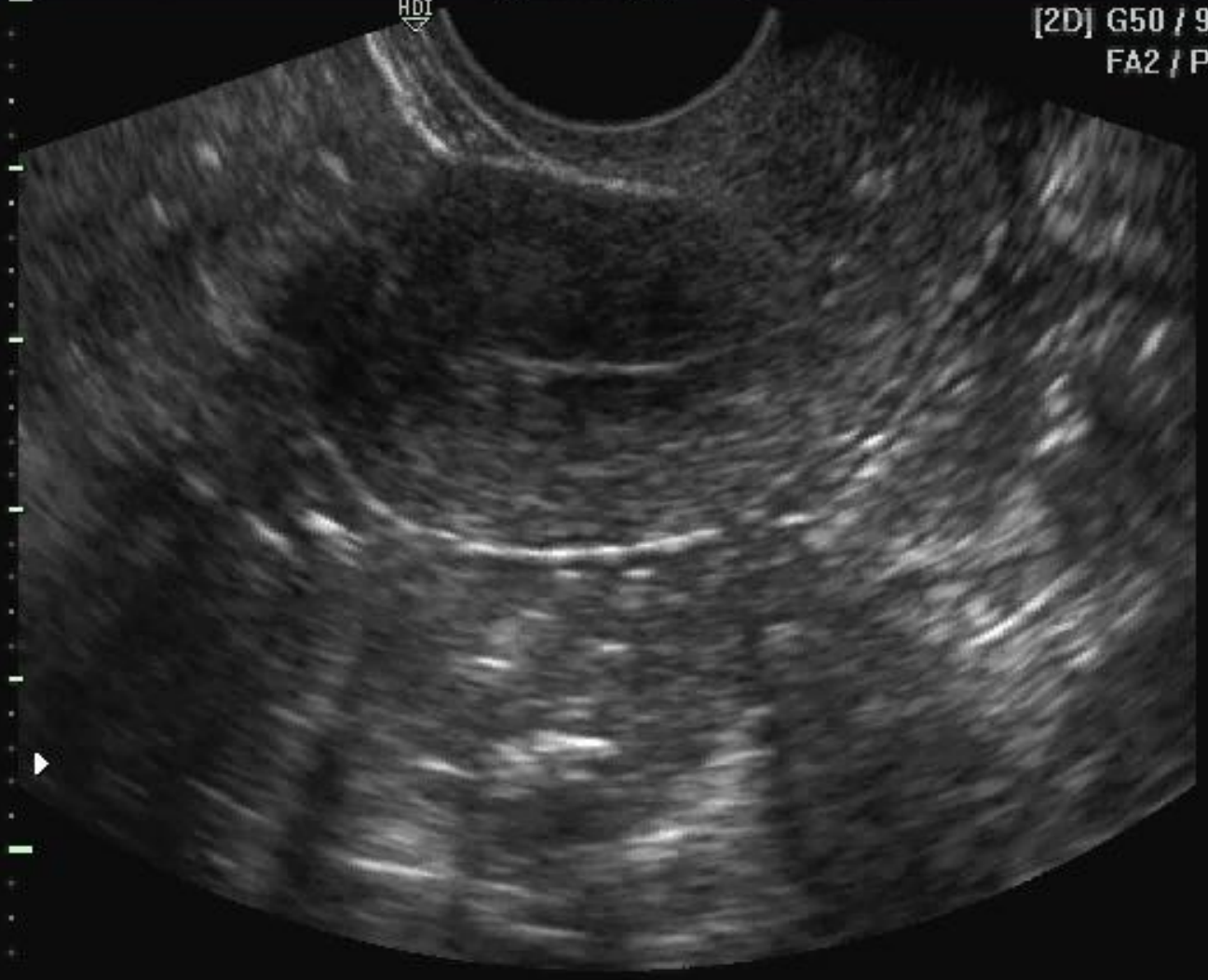
15.0cm MI 0.5
P3D8-5v /

Gen Tls 0.7

05-24-2005
03:39:28 am

HDI

[2D] G50 / 95dB
FA2 / P90





J95

RIC 5-9H/Gynecology MI 0.9 NYU Medical Center

5.4cm / 68Hz

Tis 0.1

11/21/2005

11:38:15 AM

COMP

Uterus 1
10.00 - 2.90
Pwr 100 %
Gn 1
C5 / M5
E3
CRI 3



3.0 sec

GOLDSTEIN (Am J Obstet Gynecol 1990)

30 women with PMB:

- 1 cancer (7 mm).
- Inactive EM 6 mm or less.
- No curettage for EM ≤ 5 mm reduces D&C 37% and misses no cancer.

VARNER (Obstet Gynecol 1991)

80 women (65 asymptomatic, 15 bleeding):

- 60 of 60 (100%) with EM \leq 4 mm had inactive EM on biopsy.
- 5 women with 5-mm EM (2 inactive, 1 proliferative, 1 hyperplasia, 1 carcinoma).
- Thickest EM associated with inactive was 5 mm.
- 2 cancers: EM measured 5 and 9 mm.

GRANBERG (Am J Obstet Gynecol 1991)

205 women with PMB:

- EM cancer ranged from 9 to 25 mm.
- Atrophic EM ranged from 1 to 15 mm, although 150/157 were ≤ 5 mm (? polyps).
- No curettage for EM ≤ 5 mm would reduce D&C 70% and not miss any cancer.

| <u>AUTHOR</u> | <u>YEAR</u> | THINNEST EM IN A CASE OF <u>CANCER</u> | THICKEST EM ASSOCIATED WITH INACTIVE <u>HISTOLOGY</u> |
|---------------|-------------|---|---|
| Nasri | 89 | 8 | 8 |
| Goldstein | 90 | 7 | 6 |
| Varner | 91 | 5 | 5 |
| Granberg | 91 | 9 | 15 |

TRANSVAGINAL ULTRASOUND: VALIDATION OF EARLY STUDIES

Endometrial Thickness and Cancer Findings in Postmenopausal Women With Bleeding

| Reference | Endometrial thickness* | Number of women | Number of cancers | Negative predictive value |
|---------------|------------------------|-----------------|-------------------|---------------------------|
| Karlsson 1995 | ≤4 mm | 1,168 | 0 | 100% |
| Ferrazzi 1996 | ≤4 mm | 930 | 2 | 99.8% |
| | ≤5 mm | | 4 | 99.6% |
| Gull 2000 | ≤4 mm | 163 | 1 | 99.4% |
| Epstein 2001 | ≤5 mm | 97 | 0 | 100% |
| Gull 2003 | ≤4 mm | 394 | 0 | 100% |

TRANSVAGINAL ULTRASOUND: VALIDATION OF EARLY STUDIES

- For EM \leq 4 mm, incidence of malignancy 1 in 917.

IS ENDOMETRIAL BIOPSY STILL NECESSARY?

- False-negative rate of transvaginal ultrasound ≤ 4 mm significantly less than a negative suction piston biopsy.
- EM biopsy on patients with EM < 5 mm: only 82% successfully performed, and of those, only 27% gave a sample adequate for diagnosis.

IS ENDOMETRIAL BIOPSY STILL NECESSARY? (Cont)

- ACOG committee opinion (2/09):
“When transvaginal ultrasound is performed for patients with PMB and an EM thickness ≤ 4 mm is found, EM sampling is not required.”

TRANSVAGINAL ULTRASOUND

GENERAL PRINCIPLES

- Use the highest frequency transducer that still yields adequate penetration.
- Once the EM echo is 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.

IMPORTANCE OF “EM NOT WELL VISUALIZED”

- Not all uteri lend themselves to a meaningful ultrasound examination (axial uterus, marked obesity, coexisting fibroids, 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.”

UTERUS, LONG AXIS



OB/GYN
6.0MHz E-U
Depth 60
Offset 0
Focus
FPS 10
Edge 0
Dyn Rng 60
Fr Avg 3
Out -3dB
Gain 28dB



UTERUS, LONG AXIS

UB/DTN
7.5MHz E-4
Depth 60
Offset 0
Focus
FPS d10
Edge 0
Dyn Rng 60
Fr Avg 3
Out -3dB
Gain 43dB



**EXAMPLES OF “GOOD” EM
ECHOS SEEN ORIGINATING
FROM THE CERVICAL OS**

NYU MEDICAL CENTER

B11*

GE

LONG UTERUS_

CN0

7cm

DR72

G 54

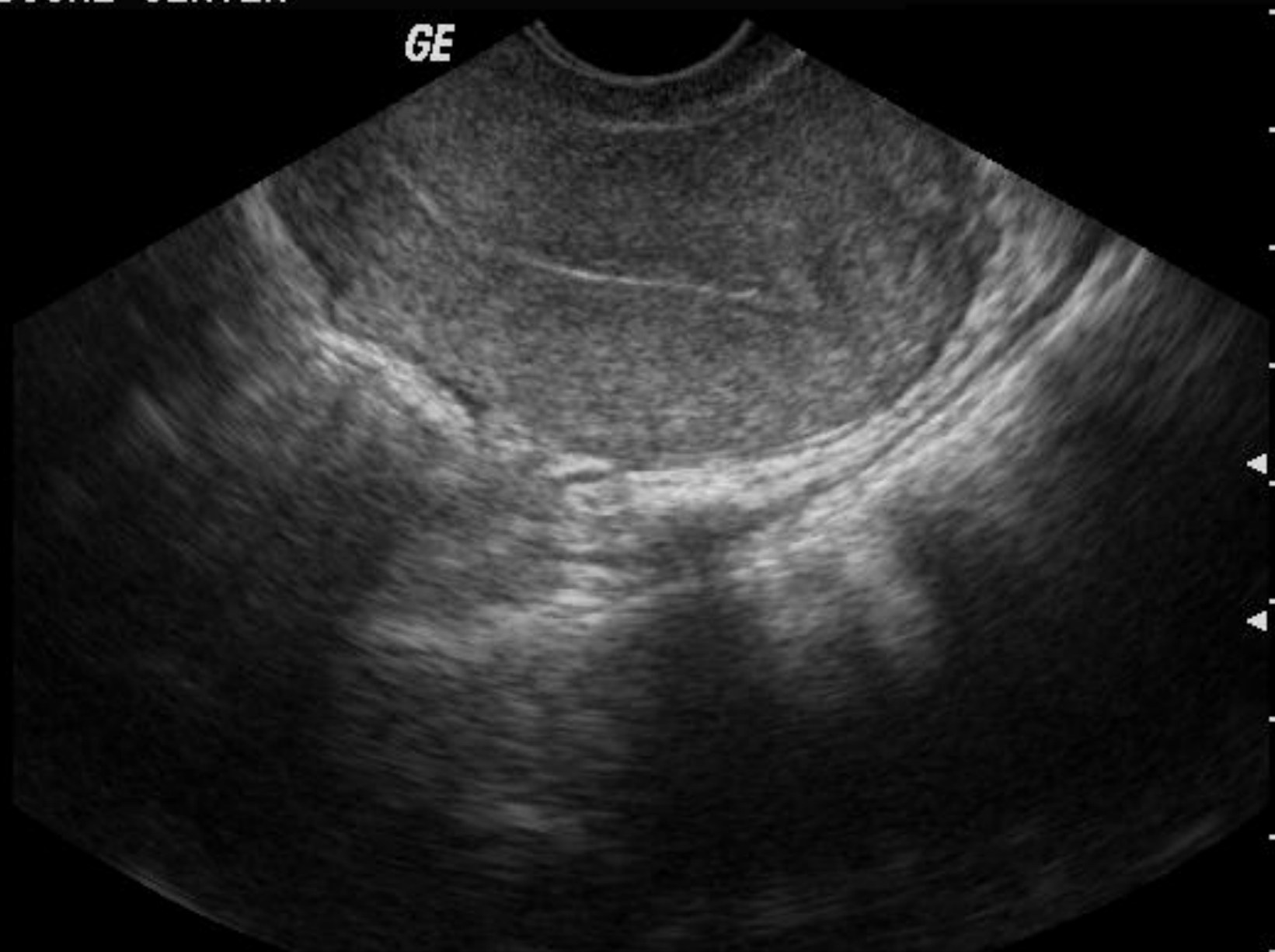


NYU MEDICAL CENTER

B11

GE

CN0
8cm
DR72
G 54



MI 0 4

EM ECHO

- If you angle the transducer long enough, you can probably find something linear and white (echogenic).
- If you freeze the frame and put on calipers, the image is not necessarily the EM echo.

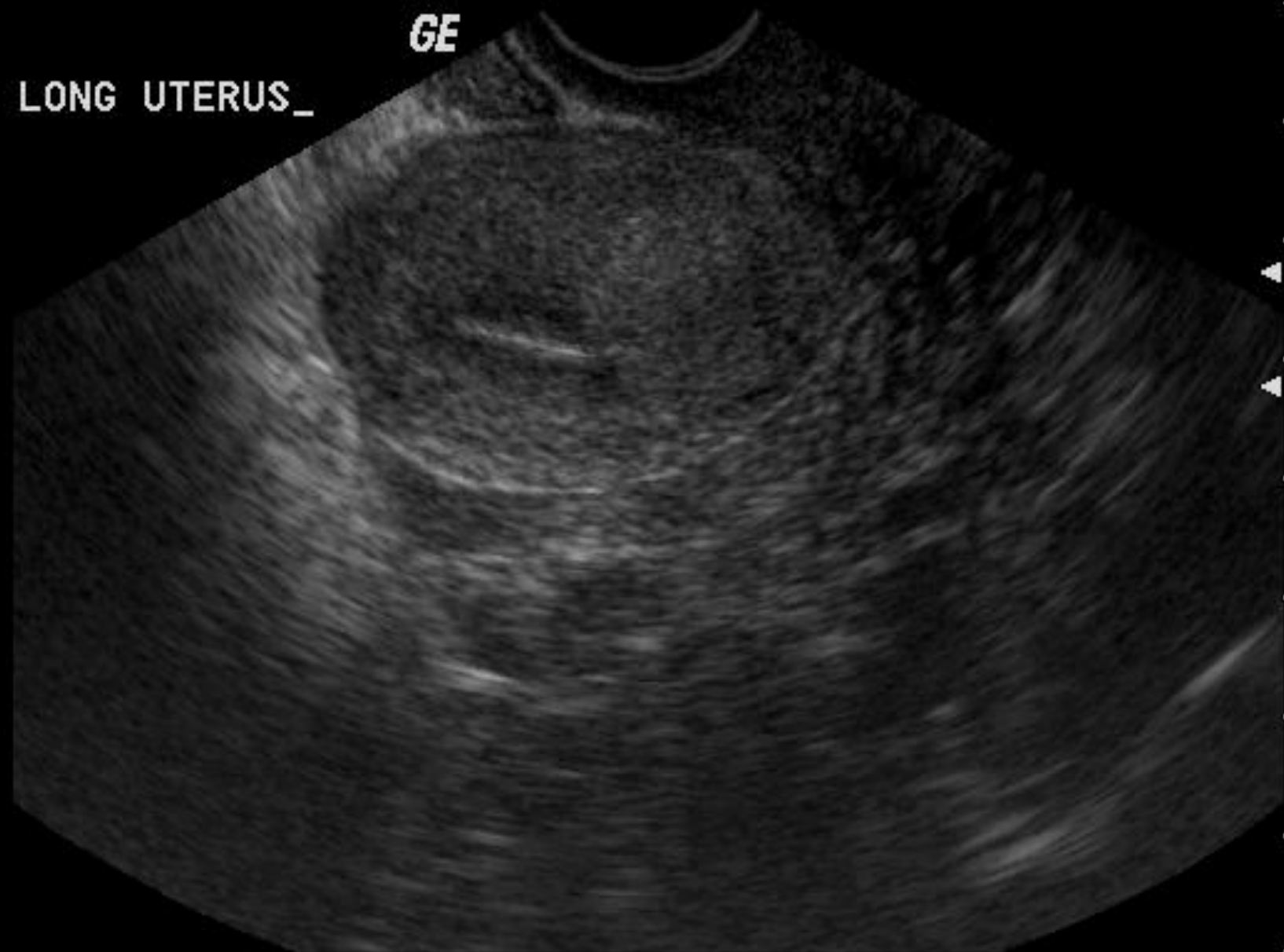
NYU MEDICAL CENTER

B11*

GE

LONG UTERUS_

CN0
8cm
DR72
G 54



MI 0 4

ENDOMETRIAL TEXTURE

- Heterogeneity or irregularity may be important in addition to simply measured thickness.

ENDOMETRIAL ABNORMALITIES ARE NOT ALWAYS GLOBAL

IMPORTANCE OF 3-DIMENSIONAL RECONSTRUCTION

Realize that any single frozen ultrasound image is a 2-dimensional “snapshot”; eg, a single long-axis view of a seemingly normal EM does not rule out pathology. The entire structure must be observed and 3-dimensional anatomy reconstructed.

UTERUS, LONG AXIS
LEFT OF CENTER

OB/GYN
7.5MHz E-U
Depth 60
Offset 0
Focus
FPS d10
Edge 0
Dyn Rng 60
Fr Avg 3
Out -0dB
Gain 29dB



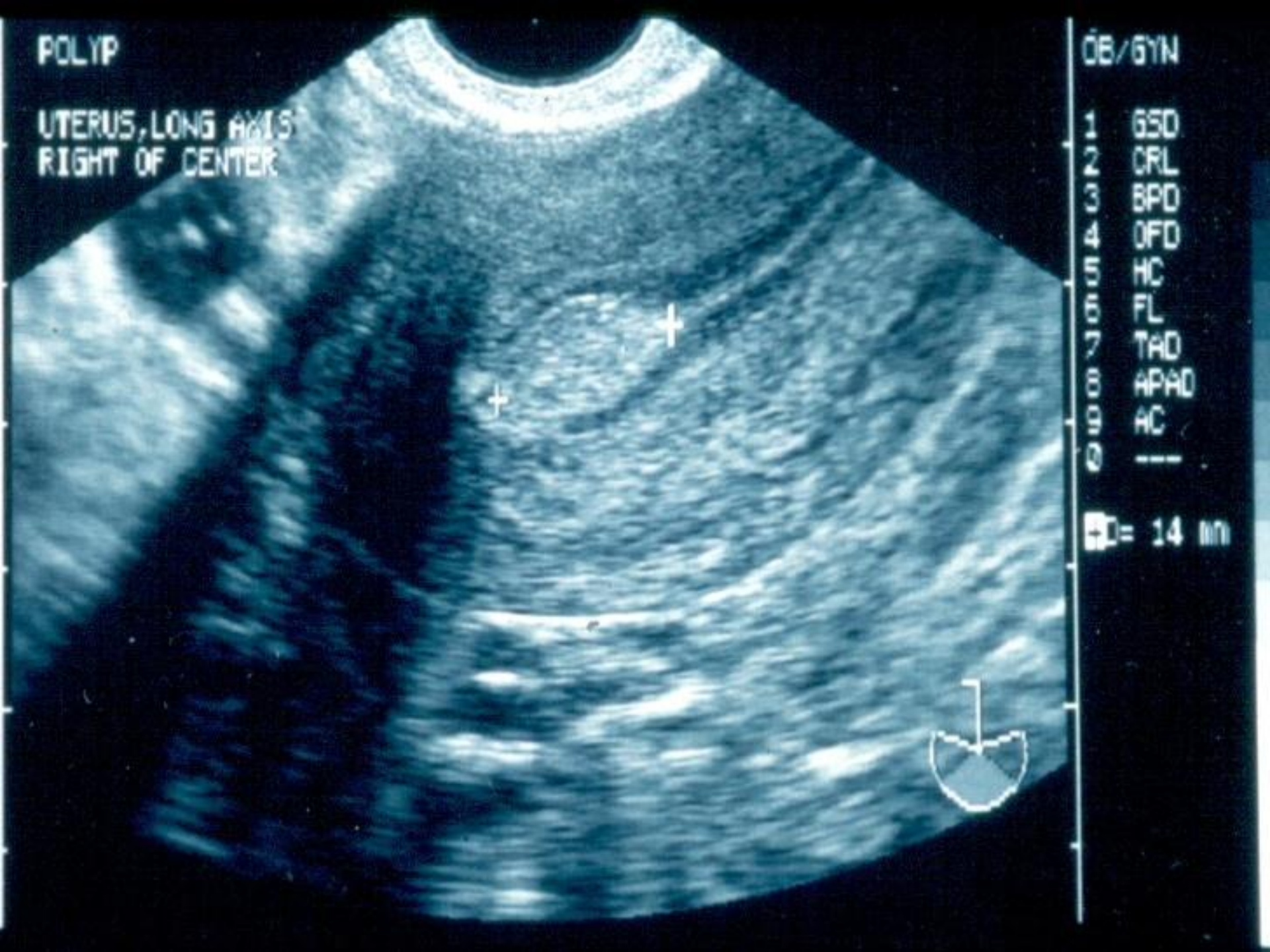
POLYP

UTERUS, LONG AXIS
RIGHT OF CENTER

OB/GYN

- 1 650
- 2 CRL
- 3 BPD
- 4 OFD
- 5 HC
- 6 FL
- 7 TAD
- 8 APAD
- 9 AC
- 0 ---

 = 14 mm



08/6YN

UTERUS, CORONAL

7.5MHz E-U
Depth 60
Offset 0
Focus
FPS d10
Edge 0
Dyn Rng 60
Fr Avg 3
Out -0dB
Gain 29dB



UTERUS, CORONAL

OB/GYN

| | |
|---|------|
| 1 | 650 |
| 2 | CRL |
| 3 | BPD |
| 4 | OFD |
| 5 | HC |
| 6 | FL |
| 7 | TAD |
| 8 | APAD |
| 9 | AC |
| 0 | --- |

D= 13 mm



TRANSVAGINAL ULTRASOUND IN NONBLEEDING POSTMENOPAUSAL PATIENTS

- The increasing use of imaging in a variety of clinical situations has led to the identification of thick EM findings in asymptomatic (ie, nonbleeding) postmenopausal women. What is the significance of such a finding, and how should it be handled clinically?

CLINICAL CASE

65-year-old woman:

- 14 years since menopause.
- Excellent overall health.
- On no medications.
- Presents to emergency room (ER) with lower abdominal pain.

CLINICAL CASE

- Afebrile.
- Normal labs (blood and urine).
- ER physician orders computed tomographic (CT) scan with diagnosis of “rule out diverticular disease.”

CLINICAL CASE

- CT of the pelvis and abdomen: “totally unremarkable except region of decreased attenuation centrally located within the uterus. Recommend transvaginal ultrasound.”
- Patient has a rather large bowel movement with total resolution of her symptoms.

CLINICAL CASE

- Transvaginal ultrasound is performed: “thickened endometrial echo measuring 11.2 mm with some heterogeneous echoes. Suggest clinical correlation.”
- Patient back to usual routine of 1 to 2 hours of tennis per day (singles, no less).

CLINICAL CASE

- Patient referred to her gynecologist, who attempts suction piston EM biopsy in the office. She is unable to get into the EM cavity secondary to a stenotic os

CLINICAL CASE

- Patient is in excellent health.
- Patient has no risk factors for EM cancer (no diabetes, hypertension, or obesity).

CLINICAL CASE

- Patient is parous but had 2 cesarean sections, the last one 31 years ago.
- Because of an inability to get tissue, patient is referred to another clinician in a teaching institution in a metropolitan area for a D&C and hysteroscopy under anesthesia

CLINICAL CASE

- Despite using fine lacrimal probes and ultrasound guidance, the cavity is not successfully entered.
- In fact, it was the impression of the operator that a false channel had been created.

CLINICAL CASE

- Patient sees gynecologic oncologist in consultation.
- Patient undergoes hysterectomy.
- Final pathology report:
“submucous myoma, inactive.”

**WHAT IS THE POINT OF
THIS CASE?**

In discussing this case with a friend who is a gynecologic oncologist, I remarked how interesting it was that these clinicians felt so obliged to get a tissue sampling on the basis of what they perceived to be an abnormal finding on an imaging study and an incidental finding, at that!

He said he probably also would have wanted EM tissue sampling! I found this quite perplexing. I said to him, “Doesn’t the gynecologic oncology community recommend that tamoxifen patients not undergo endometrial sampling unless they have bleeding? (ACOG committee opinion 232, April 2000)

He responded, “Yes that’s correct.” I pointed out that the woman we were discussing was

- (1) not on a drug that has cancer-producing potential (tamoxifen),
- (2) had no bleeding in 14 years,
- (3) never had breast cancer, and
- (4) plays tennis 2 hours a day.

I asked why he felt so obliged to sample her EM since he felt tamoxifen patients should be left alone UNLESS they bleed. A look of realization slowly came over his face, and he said “I guess I see your point.”

So:

- How common is a thick EM echo in nonbleeding patients?
- When present, what is its significance?

In POSTMENOPAUSAL women:

- An inactive atrophic EM should be <4 to 5 mm.
- But what is the incidence of inactive polyps or old myomas that do not need clinical intervention?

No good prospective
studies exist, but consider
this . . .

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.

Berliere et al. Eur J Cancer 2000; 36:S35-S36.

11% of 191 newly diagnosed postmenopausal breast cancer patients in Italy had unsuspected asymptomatic polyps prior to tamoxifen therapy.

Garuti G et al. Gynecol Oncol 2005; 98:63-67.

- 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
ASYMPTOMATIC
POLYPS?

FERNÁNDEZ-PARRA ET

AL (Int J Gynaecol Obstet 2006;
95:144-148)

- Removed 117 polyps in postmenopausal 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).

SHUSHAN ET AL

(Gynecol Obstet Invest 2004; 58:212-215)

- 300 consecutive women with polyps who underwent hysteroscopic removal.
- Combined peri- and postmenopausal patients.
- 73 (24.3%) were asymptomatic, and polyps were discovered incidentally.
- ALL asymptomatic polyps were benign.

LIENG ET AL (J Minim Invasive Gynecol 2007; 14:189-194)

- 74 asymptomatic postmenopausal women.
- Malignancy or complex atypical hyperplasia in 2/74 (2.6%).
- A limitation of the study was that it was a retrospective review of their surgical database, and it was unclear why these asymptomatic patients were selected for surgery.

LEV-SAGIE 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, and 1 polyp with simple hyperplasia.
- NO complex hyperplasia or carcinoma.
- 3.6% total complication rate (2 perforations and 1 difficult intubation).

Ferrazzi E. et al Am J Obstet (Gynecol 2009, 200:235)

- 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

Gerber et al.

(Eur J Cancer 2001, 57:64-71)

- U/S detection of Asx EM cancer in screened PM women offers no prognostic advantage over symptomatic disease that had uterine bleeding for less than 8 weeks
- Thus for the negligible risk that an Asx polyp MIGHT harbor a cancer (<1 in a 1000) there is no therapeutic advantage over waiting until it results in bleeding; and such an approach would spare the other 999 out of a 1000 any intervention and its risks ,discomfort and expense

SO . . . IN POSTMENOPAUSAL BLEEDING . . .

- “Cancer until proven otherwise.”
- Role of high negative predictive value of a thin, distinct EM echo
- Perform transvaginal ultrasound first, sonohysterography if necessary, to triage patients to (1) no pathology, (2) a global process (blind biopsy), or (3) a 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 a thick EM echo is probably 10% to 17% and is much like the “simple” cyst of the postmenopausal ovary was 20 years ago.
- Still appropriate (and always was) to use clinical JUDGMENT if high risk (obese, diabetic, hypertensive, or nulliparous).

ACOG COMMITTEE OPINION (2/09) RECOMENDATIONS

- Any vaginal bleeding in a postmenopausal woman requires assessment to exclude malignancy.
- Women with postmenopausal uterine bleeding may be assessed initially with either EM biopsy or transvaginal ultrasound; this initial evaluation does not require performance of both tests.

ACOG COMMITTEE OPINION (2/09) RECOMENDATIONS

- When EM biopsy is performed and tissue is reported as insufficient for diagnosis, some further investigation is necessary, and transvaginal ultrasound may be performed
- When transvaginal ultrasound is performed for patients with PMB and an EM thickness ≤ 4 mm is found, EM sampling is not required.

ACOG COMMITTEE OPINION (2/09) RECOMENDATIONS

- Endometrial thickness of greater than 4 mm in a patient with PMB should trigger alternative evaluation, as should an inability to adequately visualize thickness.
- Meaningful assessment of the EM by ultrasonography is not possible in all patients. In such cases, alternative assessment should be completed.

ACOG COMMITTEE OPINION (2/09) RECOMENDATIONS

- When bleeding persists despite negative initial evaluations, additional assessment is usually indicated.
- The significance of an EM thickness greater than 4 mm in an asymptomatic postmenopausal patient has not been established.

IN SUMMARY

- In postmenopausal women with bleeding, transvaginal ultrasound (and sonohysterography when necessary) is a simple inexpensive well-tolerated office procedure to triage patients to (1) no anatomic EM pathology (treated expectantly), (2) globally thickened EM tissue (candidates for blind sampling), or (3) abnormally thickened tissue but focal (including polyps and nonglobal pathology) in need of visually directed sampling.

IN SUMMARY

- In women without bleeding, incidental abnormal findings on various imaging studies have not been scientifically evaluated. Benign quiescent anatomic structures may be common, never before detected, and easily seen with the improved resolution of all imaging modalities.

IN SUMMARY

- Additional testing and evaluation have not been shown to be necessary or clinically relevant and in some cases may result in more harm to patients than good. Obviously, decisions about what to do with incidental unexpected findings should be made on a case-by-case basis depending on a multitude of factors.

IN SUMMARY

- A thin, distinct EM echo in a woman with bleeding has a very high negative predictive value, but a thick EM echo in a woman without bleeding is unvalidated and does not require automatic tissue sampling.

THANK YOU