

# The Use of Ultrasound in Perimenopausal and Postmenopausal Bleeding

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## Disclosures

Steven R. Goldstein, MD

### Relevant Financial Relationships:

Gyn Advisory Board: AbbVie, Azure Biotech, IBSA, JDS Therapeutics, Juniper Pharma, Pfizer, Radius, Sermonix, Therapeutics MD

Equipment Loan: Philips

Consultant: Cook OB/GYN, Cooper Surgical

Equity held: Azure Biotech, Sermonix

Speakers Bureau: JDS Therapeutics, Pfizer, Shionogi

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## Learning Objectives

After completing this presentation, the learner will be able to:

1. Understand ultrasound based triage for women with abnormal uterine bleeding
2. Understand the shortcomings of blind endometrial sampling
3. Appreciate the indications for saline infusion sonohysterography (SIS)
4. Optimize their technique of saline infusion sonohysterography (SIS)

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## Lecture Outline

1. Endometrial normal and abnormal anatomy and pathophysiology:
  - Functional and basalis
  - Proliferative endometrium
  - Secretory endometrium
  - Postmenopausal endometrium
  - Atrophic endometrium
2. Definitions and demographics of bleeding
  - Perimenopausal vs. postmenopausal
  - Anatomic causes (polyps, myomas, hyperplasia, carcinoma)
  - Non-anatomic causes (DUB atrophy)

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## Lecture Outline Cont'd

3. Role of transvaginal ultrasound
  - Negative predictive value of a thin distinct echo
  - Supporting data
  - Irregularities of endometrial surface
  - Ultrasound based triage of abnormal bleeding
4. Role of saline infusion sonohysterography (SIS)
  - Technique
  - Limitations of blind biopsy
5. Ultrasound limitations
  - Adenomyosis
  - Coexisting myoma
  - Axial uterus
  - Marked obesity
  - Previous surgery

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## Lecture Outline Cont'd

6. Tips for enhanced success of SIS
  - Timing of procedure
  - Inability to thread catheter
  - Avoid performing during active bleeding
  - Avoid placing air into endometrial cavity
7. Latest recommendations from ACOG
  - Role of biopsy and its limitations
  - Role of transvaginal ultrasound, sonohysterography, office hysteroscopy
  - Change in the standard of care

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**Successful use of ultrasound in patients with bleeding begins with a short lesson in pathophysiology.**

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**Ultrasound findings will simply reflect what is present (or not) anatomically.**

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**What are normal or expected findings?**

**This will depend on what hormones are present and when they are present (or absent).**

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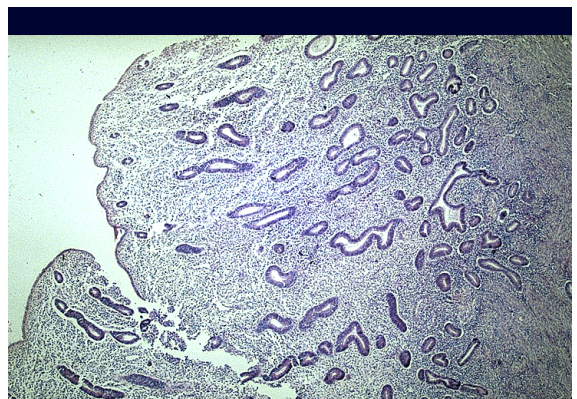
- **THE ENDOMETRIUM CONSISTS OF A BASALIS AND A FUNCTIONALIS**
- **ESTROGEN CAUSES THE FUNCTIONALIS TO PROLIFERATE**

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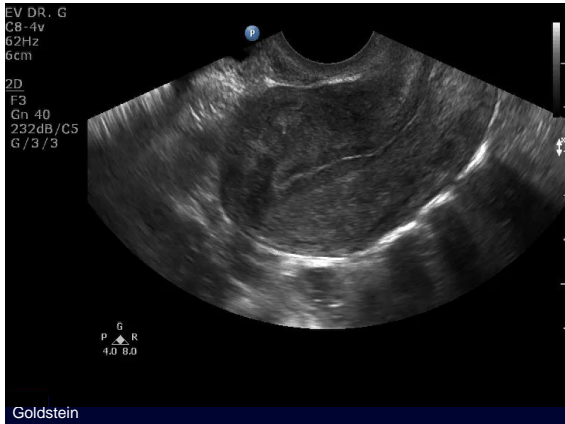
## **PROLIFERATIVE EM**

- **Mitoses**
- **Note AMOUNT (or HEIGHT) of tissue**

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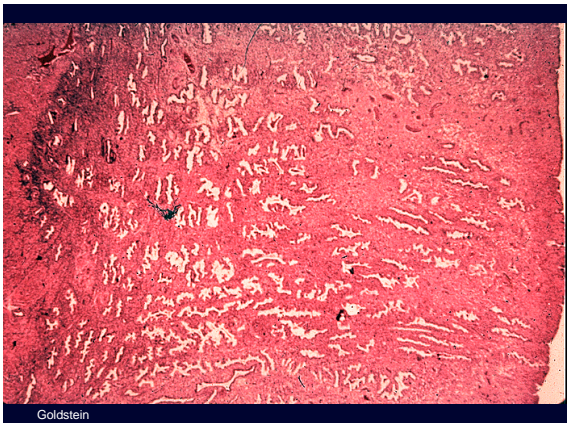
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- **PROGESTERONE (OR IN SEQUENTIAL HORMONE THERAPY THE USE OF A PROGESTIN) WILL CONVERT AN ESTROGEN PRIMED ENDOMETRIAL FUNCTIONALIS TO A SECRETORY PHASE**

**SECRETORY EM**

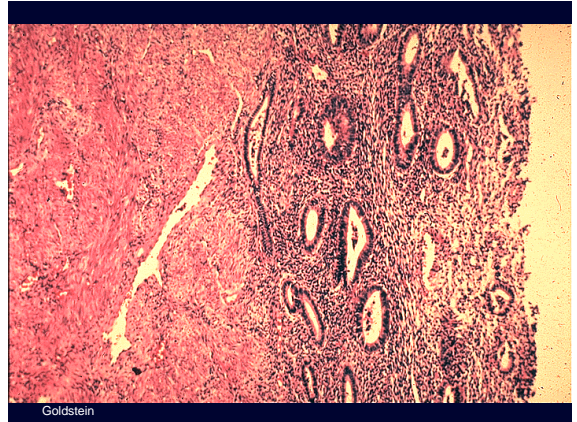
- Glands line up in a linear fashion
- This results in a fiercely echogenic appearance on U/S



- **AFTER SHEDDING OF THE FUNCTIONALIS THE BASAL ENDOMETRIUM THAT REMAINS IS INITIALLY QUITE THIN AND WILL APPEAR AS SUCH ON TV U/S**

## POST MENSTRUAL EM

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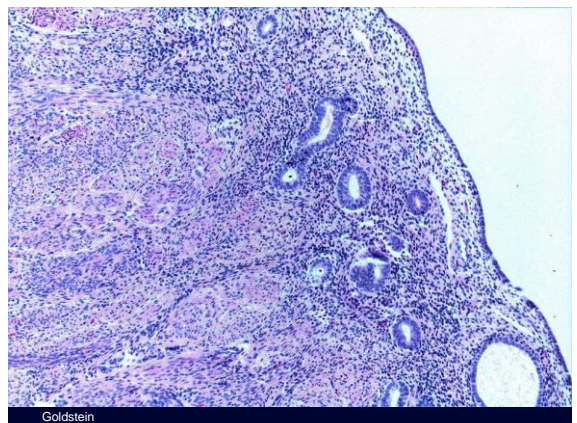
- IN MENOPAUSE THERE IS NO ESTROGENIC STIMULATION OF THE FUNCTIONALIS AND THE ENDOMETRIUM IS ATROPHIC

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## ATROPHIC EM

- Simple tubular glands
- Lacks mitotic activity
- Fibrotic stroma with increased collagen fibers

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**SINCE THERE IS NO "NORMAL" WIDTH OF ENDOMETRIAL THICKNESS...**

**WHAT IS THE PROPER USE OF THE ENDOMETRIAL ECHO CLINICALLY?**

## 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

## CLINICAL REALITY

- 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

## Demographics of bleeding

- 1/3 of all visits to the gynecologist are for AUB<sup>1</sup>
- 70% of Gyn consults in the peri and postmenopausal years are for bleeding

1. ACOG Practice Bulletin #128, July 2012

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## Demographics of bleeding (cont'd)

- Of perimenopausal women with AUB, roughly 80% will have no EM pathology (dysfunctional, anovulatory)<sup>1</sup>
- Of postmenopausal women with bleeding (PMB) 3-7% will have EM cancer (range 1-14%). The majority of PMB is secondary to atrophy<sup>2</sup>

1. Goldstein SR et al. Ultrasonography-based triage for perimenopausal patients with abnormal uterine bleeding. Am J Obstet Gynecol. 1997;177:102-8

2. Goldstein SR. Modern evaluation of the endometrium. Obstet Gynecol. 2010;116:168-76

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## Great Divide

- Anatomic pathology (polyps, myomas, hyperplasia, carcinoma)
- Absence of anatomic pathology (dysfunctional anovulatory in premenopause, atrophy in post menopause)

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## Ultrasound cannot make a histologic diagnosis

- Greatest contribution:
  - High negative predictive value in a thin distinct echo in excluding cancer
  - Ability of saline infusion enhancement to distinguish global vs. focal process

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## What is the data?

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## TRANSVAGINAL ULTRASOUND

In the early 1990's, TV U/S 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.

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.

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## TRANSVAGINAL ULTRASOUND

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

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## EARLY OBSERVATIONAL STUDIES

AUTHOR	YEAR	THINNEST EM IN A CASE OF CANCER	THICKEST EM ASSOCIATED WITH INACTIVE HISTOLOGY
Goldstein	90	7	6
Vарner	91	5	5
Granberg	91	9	15

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## TRANSVAGINAL U/S VALIDATION OF EARLY STUDIES

- A series of large prospective studies from Western Europe were collected on postmenopausal women with bleeding

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## Endometrial Thickness and Cancer Findings in Postmenopausal Women With Bleeding

Reference	Endometrial thickness*	Number of women	Number of cancers	Negative Predictive Value
Karlsson 1995	$\leq 4$ mm	1,168	0	100%
Ferrazzi 1996	$\leq 4$ mm	930	2	99.8%
	$\leq 5$ mm		4	99.6%
Gull 2000	$\leq 4$ mm	163	1	99.4%
Epstein 2001	$\leq 5$ mm	97	0	100%
Gull 2003	$\leq 4$ mm	394	0	100%

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## Composite Data on women with PMB

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

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## IS ENDOMETRIAL BIOPSY STILL NECESSARY?

- 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"

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## WHAT IS THIS BASED ON...?

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## IS ENDOMETRIAL BIOPSY STILL NECESSARY? (con't)

- False negative rate of TV U/S  $\leq 4$ 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

Elsadabese, D. J Obstet Gynecol, 2005

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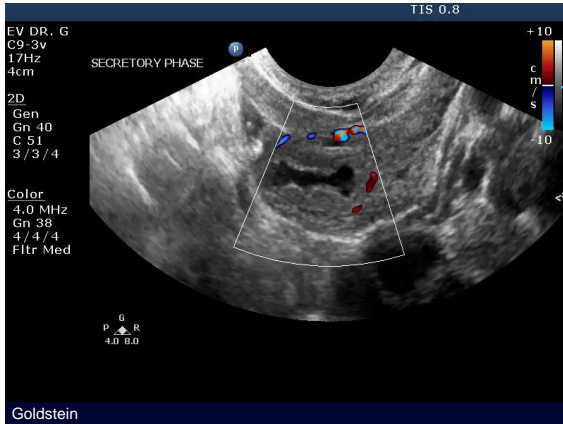
In premenopausal women in whom the EM undergoes cyclical change, timing is crucial.

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As the EM proliferates, it is not always topographically homogenous secondary to previous deliveries, D & C's, Cesareans, myomectomies, etc.

Author Last Names



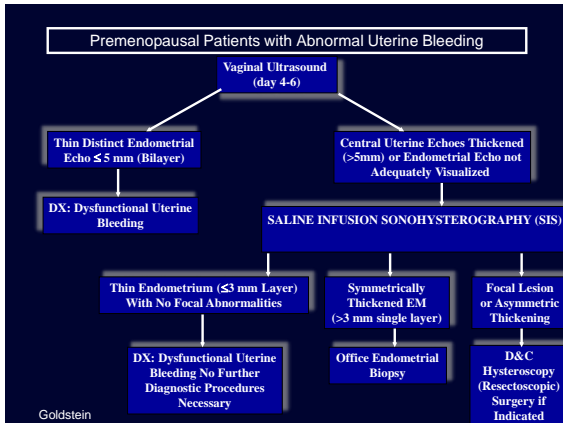


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**An algorithm of transvaginal ultrasound and saline infusion enhancement was proposed and tested prospectively.**

Ultrasonography-based triage for perimenopausal patients with abnormal uterine bleeding, Goldstein SR et al, *Am J Obstet Gynecol* 1997;177:102-8

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## MATERIALS AND METHODS

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

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## ABNORMAL PERIMENOPAUSAL BLEEDING:

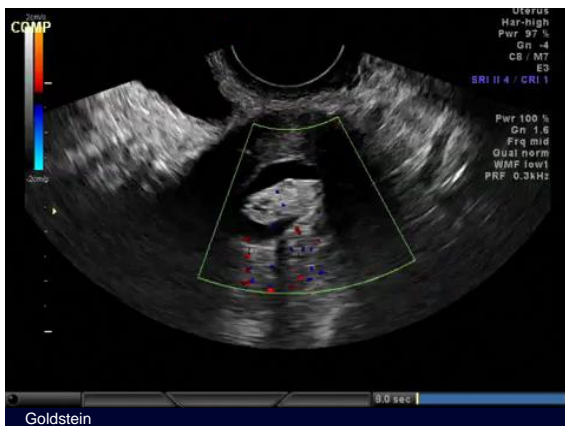
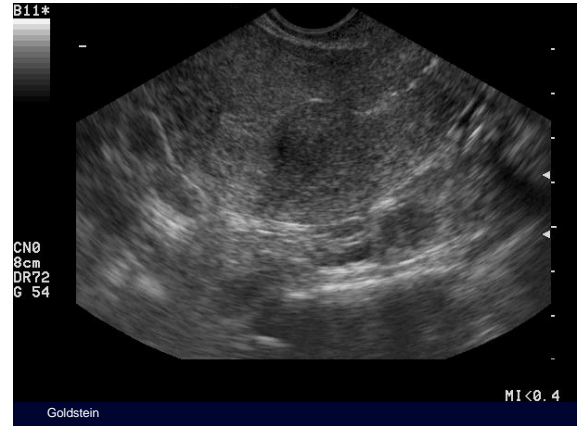
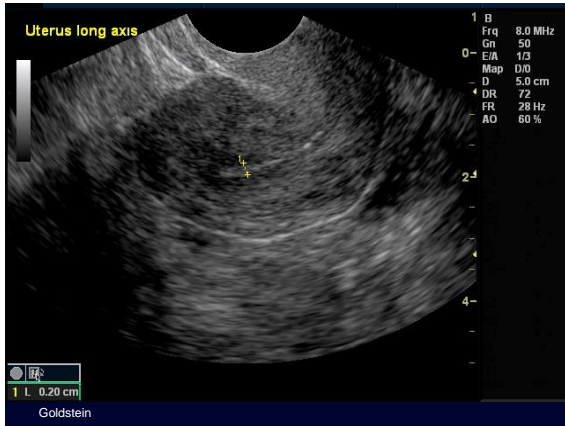
**433 PATIENTS**  
 Unenhanced Vaginal Ultrasound  
 280 patients  $\leq$  5mm (day 4-6)  
 153 patients > 5mm or nonvisualization of EM

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## SALINE INFUSION SONOHYSTEROGRAPHY

**153 patients**  
 44 (29%) for nonvisualization of EM  
 109 (71%) for EM > 5mm

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**RESULTS: 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)

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## RESULTS: 15 PATIENTS HAD HYPERPLASIAS, OF WHICH...

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

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Blind EM biopsy (Pipelle) could have missed up to 79% non-global lesions (18%) in patients with polyps, submucous myomas, focal hyperplasia

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## SO WHY IS THERE AN ISSUE WITH BLIND BIOPSY (e.g. PIPELLE)?

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## 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

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## PIPELLE

- Rodriguez (1993) did pre hysterectomy sampling with both Pipelle and Vabra . 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

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## PIPELLE ENDOMETRIAL SAMPLING

Guido R. et al (J Reprod Med, 1995)

- 65 pts with known carcinoma of EM  
Pipelle under anesthesia prior to TAH
- missed 11/65 (16%) of cancers, of which
    - 3 were < 5% EM area
    - 4 were 6-25% EM area
    - 4 were 26-50% EM area
  - 5/11 had tumor in polyps that were missed
  - none that were >50% of surface area were missed

Authors concluded "Pipelle is excellent for detecting global processes in the endometrium"

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### FALSE NEGATIVE RATE OF PIPELLE IN PATIENTS WITH KNOWN CARCINOMA (OTHER STUDIES)

- 7% (missed 2/26)
- 17% (missed 14/80)
- 33% (missed 12/37)
- Not nearly as reliable as the original work by Stovall

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### This study using U/S based trriage in perimenopausal women resulted in...

- 65% to have an ultrasound exam only
- 17% to have only ultrasound and SIS
- 2.3% to have U/S, SIS and then pipelle bx
- 15.9% to have U/S, SIS D&C hysteroscopy for proven anatomic pathology

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### Ultrasound cannot give 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 )

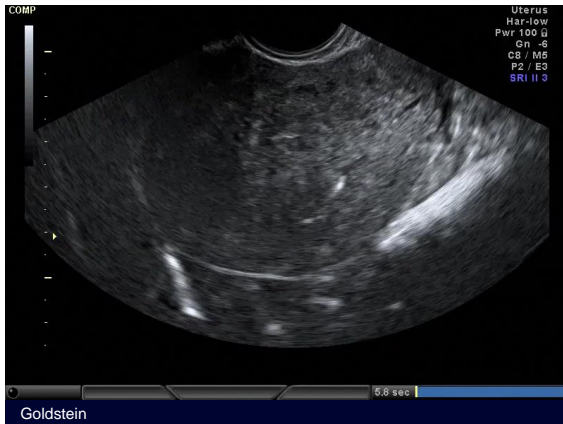
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### Crucial Caveat

- Not all uteri lend themselves to a meaningful ultrasound evaluation of endometrial thickness:
  - Adenomyosis
  - Coexisting myomas
  - Axial uterus
  - Marked obesity
  - Previous surgery

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## Recall the perimenopausal bleeding study... Use of SIS

- 153 patients had SIS out of 433 pts
- 44 (29%) for nonvisualization of EM
- 109 (71%) for EM > 5mm

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- **THUS 44/433 (10.2%) OF PERIMENOPAUSAL WOMEN WITH AUB HAD AN EM ECHO THAT WAS NOT ADEQUATE TO BE USED DIAGNOSTICALLY WITHOUT SALINE INFUSION**

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- In such cases, SIS will enhance the transvaginal ultrasound.

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**Sonohysterography should be thought of as a subset of TV U/S when:**

- 1) EM echo is not thin
- 1) EM echo is not well visualized

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## SONOHYSTEROGRAM

- FLUID INSTILLATION TO ENHANCE U/S DETAIL OF THE ENDOMETRIUM
- BECAUSE FLUID ENHANCES SOUND TRANSMISSION THESE WILL BE AMONG EASIEST U/S EXAMS TO INTERPRET

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## SONOHYSTEROGRAM: TECHNIQUE

- Pelvic scan, unenhanced (baseline appearance)
- Palpatory bimanual (anteverted, retroverted)
- Insert speculum
- Cleanse cervix
- Thread catheter (flush air first)

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## SONOHYSTEROGRAM: 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
- Consider 3D scan ,if available

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## Tips to fine tune success for sonohysterography

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## 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.

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## INABILITY TO THREAD THE CATHETER

- Change position of speculum
- Use a “cervical stabilizer” (a fine toothed tenaculum)
- Small dilator (#13 Pratt) as last resort.

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## INADEQUATE DISTENSION OF THE CAVITY

- Requires very little fluid to outline cavity
- Same problem in hysteroscopy (some cavities are more difficult to distend)
- Check position of catheter

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## 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 Endometrial heterogeneity)

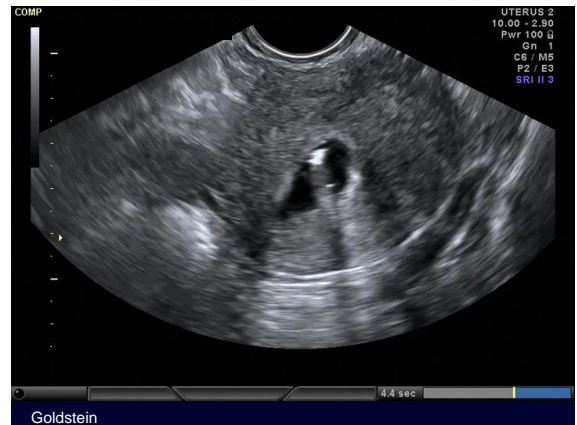
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**AVOID  
SONOHYSTEROGRAPHY  
WITH ACTIVE BLEEDING !!**

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**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 curettage” and then time the sonographic evaluation to the withdrawal bleed

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**AVOID GETTING AIR INTO THE  
CATHETER OR THE SYRINGE (AIR  
IS VERY ECHOGENIC !!)**

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

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

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**“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).”**

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

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“Endometrial biopsy has high overall accuracy in diagnosing endometrial cancer when an adequate specimen is obtained and when the endometrial process is global”

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“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.”

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### THIS IS BASED ON THE DATA FROM GUIDO (1995)

65 pts with known carcinoma of EM  
Pipelle under anesthesia prior to TAH

- missed 11/65 (16%) of cancers, of which
  - 3 were < 5% EM area
  - 4 were 6-25% EM area
  - 4 were 26-50% EM area
- 5/11 had tumor in polyps that were missed
- all cancers > 50% of surface area were found

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

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

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

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• 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!

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## Conclusions

1. Understanding causes of bleeding in peri- and postmenopausal women allows better understanding of how to use transvaginal ultrasound.

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## Conclusions

2. There is a great divide between anatomic vs. no anatomic pathology.

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## Conclusions

3. A thin distinct EM echo will exclude significant anatomic pathology.

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## Conclusions

4. Sonohysterography (SIS) is a subset of transvaginal ultrasound when the EM echo is either not thin or not well visualized.

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## Conclusions

5. Transvaginal ultrasound and sonohysterography will be time sensitive in patients whose EM is cycling (and should be performed just as the bleeding cycle ends).

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## Conclusions

6. Transvaginal ultrasound is the first step in triage of AUB and PMB and when done properly will reduce any further invasive procedures in the majority of patients.

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## Key References

Goldstein SR. Modern Evaluation of the endometrium. *Obstet Gynecol* 2010; 116: 168-76

The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. ACOG Committee Opinion 440, August 2009, Reaffirmed 2015

Diagnosis of abnormal uterine bleeding in reproductive aged women. ACOG Practice Bulletin 128, July 2012, Reaffirmed 2014

Sonohysterography. ACOG Technology Assessment 8, June 2012, Reaffirmed 2014

Goldstein SR, Zeltser I, Horan CK, Snyder JR, Schwartz LB. Ultrasonographically based triage for perimenopausal patients with abnormal uterine bleeding. *Am J Obstet Gynecol* 1997; 177: 102-8

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