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Ultrasound of the Endometrium, Parts 1 and 2

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Ultrasound of the Endometrium: More than a Measurement

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Objectives of Talk

• Review histology
  • Cyclical changes in reproductive years
  • Decidualization-not only seen in pregnancy

• Define accurate endometrial measurements, tips, thresholds

• Analyze endometrial abnormalities
  • Endometrial polyp analysis
  • Post-menopausal bleeding
  • Is there a normal for post menopausal, non-bleeding pts?
  • Asymptomatic polyps in pre-menopausal pts.
  • Miscellaneous “endometrial “ abnormalities- calcifications, “aborting” fibroid, cervical CA, pyometrium, intra-cavitary blood
Back to basics: the Endometrium

• Definition: mucosa or “lining” of the uterus
• Epithelium- Pseudo-stratified columnar cells which form deep glands
• Atrophic in pre-pubertal times
• Very dynamic/interesting in reproductive years
• Menorrhagia= heavy bleeding during a period
• Metrorrhagia= bleeding/spotting between periods
• Undergoes cycling ~450 times per woman’s life
• A normal menstrual cycle has a frequency of 21-35 days, menses lasts 4-8 days
• Lining of columnar cells
• Interstitium of stromal cells, lymphocytes, few neutrophils
• Nests of deep glands very responsive to estrogen, progesterone
Normal Menstrual Cycle
Proliferative phase  Secretory phase
Endometrium and Myometrium
22 yo thin endometrium - early proliferative phase
40 yo: Tri-laminar, mid-cycle appearance
25 yo-mid secretory phase
3D Pelvic US in 25 y.o. – surface rendering
Normal thickness-pre-menopausal

- during menses (day 1-5): 2-4 mm
- early proliferative phase (day 6-10): 5-7 mm
- late proliferative / preovulatory phase (day 10-15): ~12 mm
- secretory phase (day 15-30): 7-16 mm
- Lacking hard data, but after 35 years of experience, I have adapted ~18 mm. as upper limit of normal in pre-menopausal
Measuring the Endometrium

• Round to nearest mm.
• Measure the widest portion at orthogonal angles
• If asymmetric, and no mass, measure widest half in each direction on longitudinal scan

Ultra ObGyn, 2010, 35;1; 103-112
Indeterminate endometrium- 58 yo w/ AUB
Ill-defined endometrium in 45 yo AUB
How to measure endometrium-51 yo with pelvic pain, no vaginal bleeding
Endo. Measurements-Don’t include the “hole”, just the echogenic ring (donut)
Abnormal Uterine Bleeding (AUB)

• Abnormal uterine bleeding
  • Premeno-bleeding occurs erratically, or excessive amounts of regular menstrual bleeding.
  • Post-meno- any vaginal bleeding.

• A uterus normally sheds ~ 80 ml of blood during each menstrual period

• The most common Post-Meno causes of abnormal uterine bleeding include submucosal fibroids, endometrial polyps, atrophic vaginitis, endometrial hyperplasia, endometrial cancer.
  • Primary Premenopausal Causes- Pregnancy, Anovulation, Polyps
and characteristics of premenopausal and postmenopausal women with abnormal uterine bleeding

• Premenopausal (n = 307) vs. Postmenopausal (n = 43)
• Age (years) 43.0 ± 6.6 vs. 54.8 ± 7.5
• Body mass index (kg/m²) 29 ± 5.6 vs. 35 ± 3.4
• Gravidity 3.2 ± 2.0 vs 4.1 ± 1.3, Parity 2.4 ± 1.2 vs. 3.7 ± 1.9
• Endometrial thickness (mm) 6 ± 2.9 vs. 11 ± 3.5

• Sonographic appearance of endometrium
  • Normal: 214 (69.7%) vs. 30 (69.8%)
  • Endometrial polyp: 36 (11.7%) vs. 2 (4.7%)
  • Homogeneous thickening: 40 (13.0%) vs 7 (16.3%)
  • Cystic thickening: 17 (5.5%) vs. 4 (9.3%)

• 4 cases of Endo CA: 3 with thickened endometrium, 1 normal

AUB and US Endo Thickness/Bx

- Histopathological analysis of endometrial samplings
  - proliferative endometrium (36%)
  - secretory endometrium (25%)
  - decidualization (11%)
  - endometrial polyp (8%)
  - endometritis (7%)
  - endometrial hyperplasia (5%), irregular shedding (4%), atrophic endometrium (3%), endometrial cancer (1%) and placental retention (1%).
Decidualization of Endometrium Stromal Cells (ESC)

- Decidualization - differentiation of elongated, fibroblast-like mesenchymal cells (ESC) in the uterine stroma to rounded, epithelioid-like cells during the latter half of menstrual cycle and pregnancy.

- Humans – one of few mammalian species in which decidualization always starts during the latter half of each menstrual cycle and is independent of the conceptus.

- Implies that the health of a pregnancy is determined even before the blastocyst arrives - “primary driver of pregnancy health is the quality of the soil, not the seed”.

- 3 Pregnancy factors: Decidualization/Implantation/Placentation

Decidualization

• Prepare (decidualize) the endometrium hormonally, biochemically, and immunologically in anticipation of the approaching blastocyst

• Downregulation of genes involved in the pro-inflammatory response and resisting tissue invasion

• Increased expression of genes that promote
  • angiogenesis
  • immune tolerance
  • facilitate tissue invasion

• Leading to normal placentation $\rightarrow$ ultimately to positive pregnancy outcome.

Decidualization

- Decidualization is a process of stromal differentiation that is confined to species in which embryo implantation occurs interstitially, creating an interface between trophoblast and the maternal uterine stroma. In women, decidual cells start to appear at the mid-secretory-late secretory transition, about day 23 of the cycle.
Causes of PMB

• Proliferative endometrium (PEM) emerges most commonly within the first two years after menopause and disappears by the seventh year of the postmenopausal period

• Estrogen release from the ovaries and peripheral tissues continues at reduced concentrations for several years after permanent cessation of menstrual periods-enough to cause EM proliferation

• Atrophic endometrium-33% of cases

• Decidualization- also seen in Post-Meno. pts EndoM. Biopsies
AUB in Post-menopausal pts.--

U/S Thresholds

- vaginal bleeding (not on tamoxifen):
  - suggested upper limit of normal is ≤5 mm 5mm.
  - the risk of carcinoma is ~7% if the endometrium is >5 mm and 0.07% if the endometrium is <5 mm
  - on hormonal replacement therapy: upper limit is 5 mm

- no history of vaginal bleeding**:
  - the acceptable range of endometrial thickness is less well established, cut-off values of 8-11 mm have been suggested (Smith-Bindman, UCSF)
  - the risk of carcinoma is ~7% if the endometrium is >11 mm, and 0.002% if the endometrium is <11 mm 8-10 mm.

- if on tamoxifen & VB: < 5 mm (although ~50% of those receiving tamoxifen have been reported to have a thickness of >8 mm).
  - 8 mm. in non-bleeding pts.
Endometrial thickness threshold in non-bleeding (NB) PM women

- PM bleeding associated with 1-10% risk of endometrial cancer
- How thick is too thick in NBPM women?
- UCSF study-Theoretical study of women over 50 yrs
- Calculated risk of cancer in bleeding in PM, endo > 5 mm.
- Calculated endometrial thickness in NBPM with same risk
- 11 mm. chosen as risk of endometrial cancer for sampling
- In general, if EM > 11mm. risk for Endo Cancer is 7% in NBPM.
Do Asx endometrial lesions on US require removal? recent Chinese study

- 792 patients with symptom-free focal masses
  - 558 patients with pre- or post-menopausal endometrial polyps
  - 234 patients with postmenopausal endometrial thickening
- Highly sensitive (94%) for pre-menopausal polyps
- Specificity and PPV of 84 and 93%, respectively, for postmenopausal polyps
- ET cut-off value of 13 mm yielded a sensitivity of 73% and specificity of 86%.
- TVUS was valuable for ruling out polyps
- **Recommend: follow-up alone, no EMB or surgery for women with asymptomatic uterine polyps, particularly those who are pre-menopausal**

BMC (UK) Women’s Health 2019 May 6;19(1):61
Endometrial Polyp Guidelines

- Asx polyps in premenopause < 1 cm. have ~30% regression rate
  - Conservative Rx

- Polyps > 1 cm., symptomatic polyps, or infertility should undergo hysteroscopy/EBM
Endometrial Polyps

- Benign uterine lesions ~prevalence 10% of premenopausal and postmenopausal women
- Histologically composed of endometrial glands surrounding a fibrous stromal core.
- Majority of these polyps are asymptomatic, but abnormal uterine bleeding may occur
- Strong association with decreased uterine receptivity—decreased implantation & pregnancy rates
- Associated with obesity (BMI > 30)
  - Not HTN, DM
- Recurrent polyps 6%, not assoc. w/ CA
- Some series—Low sensitivity of US for detection--25-45%, significant false + too
Endometrial Polyps-US DX

• US Signs of a polyp
  • Thickened endometrium
  • Hyperechoic, oblong or rounded, rarely hypoechoic focus
• Secondary findings
  • Tiny endometrial cysts
  • Vascular pedicle or “stalk” on Color Doppler
  • Increased endometrial Color Doppler flow
38 yo pt w/ Endometrial polyp-classic US appearance
Endo Polyps on Hysteroscopy
Endo polyp(s)-tiny cysts in 35 yo w/ AUB

2018-EMB-neg for polyps,
SHG 2021- 7 mm. polyp, awaiting hysteroscopy/D & C
Multiple endometrial polyps - vascular stalk in 35 yo w/ PCOS
62 yo w/ AUB—thick endo w/ cysts:
10/20 EMB – atrophy
2/21 D & C - benign polyp
Endo. polyp in 40 yo w/ no vag. bleeding

30% PreMeno asx polyps regress spontaneously
24 yo w/ vag bleeding post-coit., exercise
24 yo runner with AUB post-coitus, runs, exercising
Hysteroscopy/EMBx – prolif. endo. with intramural hemorrhage (pseudo-polyps)
Endo Cysts - 30 yo Asian woman with pelvic pain
Significance of Endometrial Cysts??

- 42 yo with AUB
- US-
  - thick endometrium
  - Multiple tiny endometrial cysts
- EMB
  - Endo polyps
- Literature on endometrial cysts not very helpful!
- Performing study at LAC now
Endometrial Polyp w/ Cysts
31 yo woman with AUB, IUD removal-multiple hypoechoic “polyps”
31 yo AUB–EMB showed scant proliferative endometrium + blood
The risk of malignancy in endometrial polyps: A systematic review and meta-analysis

• 52 studies with 35,345 women
• Polyp malignancy rate 3%
  • Pre-meno 1%
  • Post-meno 5%
• Symptomatic 5%
• Asymptomatic 2%
• Prospective 6%
• Retrospective 3%
The risk of malignancy in uterine polyps: A systematic review and meta-analysis

• Conclusion: 1) Symptomatic vaginal bleeding and 2) postmenopausal status in women with endometrial polyps = increase risk of malignancy

• May be helpful in triaging who gets biopsy or D & C.
51 yo woman with AUB-polyp??
54 yo AUB-US polyp??

EMB-prolif. endometrium
40 mm. thick endo in 46 yo w/ AUB

EMB- Inactive endometrium with stromal breakdown
86 yo w/ AUB, 1/26/22
86 yo with AUB, DOS 1/26/22

GYN rec: repeat US in 3-4 mos.
Endo polyp in 40 yo – utility of 3D US
53 yo Hx of Endometrial Polyps in 2019
56 yo pt in 2022-recurrent AUB
AUB 2022-hx of polyps in 2019

3D US helpful
Sonographer went back and confirmed polyp
43 yo w/ AUB
3D imaging “better” than 2D imaging
Submucosal fibroids

- Fibroids: Prevalence of 20-40% in reproductive years
- US study:
  - 80% prevalence by age 50 in African-Americans
  - 70% prevalence by age 50 in White Americans
- Risk factors
  - Early menarche
  - Increased Alcohol, Caffeine intake
  - Decreased risk: parity
- Submucosal: comprise 5-20% of fibroids
Classic Submucosal Fibroid - 38 yo w/ AUB
Submucosal fibroid + thick endometrium in 54 yo w/ AUB-polyp?

EMB-atrophic endometrium
43 yo pt w/ AUB, dyspareunia, post-coital bleeding

Had EMB 11/21, ++ polyps, still Sx
43 yo AUB, dyspareunia, PC bleeding
Endometrial Hyperplasia (EH)

• Prevalence:
  • Simple (non-neoplastic)-142/100,000 woman-years
  • Complex-213/100,000 woman-years
  • Atypia (neoplastic)-56/100,000 woman-years

• Atypia- associated with pre-malignancy
  • 1/3 of cases co-exist with CA
  • 3 fold increased risk for developing cancer

• Risk of endometrial hyperplasia is high in perimenopausal women with abnormal uterine bleeding
WHO (2014) classes of Endo. Hyperplasia

- 2 kinds:
  - Hyperplasia without atypia (non-neoplastic, simple)
  - Atypical hyperplasia (endometrial intraepithelial neoplasm, complex)
- Atypia increases risk of cancer
- Def: proliferation of endometrial glands resulting in a greater gland-to-stroma ratio (>50 percent) than observed in normal proliferative endometrium
- Pathology-"surrogate" markers of invasion
  - cribriform glands-sheets of glands with perforations or lumina
  - invasive pattern of glands infiltrating reactive stroma (most definitive feature)
  - confluent growth (lack of stroma between glands)
Histology of Endometrial Hyperplasia

Proliferative endometrium

Note the straight non-convoluted glands, without glandular crowding.

Complex endometrial hyperplasia
Endometrial Carcinoma (ECa)

- Most common type of GYN cancer in the world
- PM vaginal bleeding: assoc. w/ 1-10% prevalence of Endo. Ca
- Estrogen exposure increases risk
  - Obesity, anovulation, PCOS, nulligravid or low gravid states
  - Unopposed estrogen HRT, Granulosa Cell tumor, Tamoxifen
- Hypertension, diabetes, hereditary nonpolyposis colorectal cancer, prior pelvic radiation also associated
- Ranked highest among obesity-associated cancers in women
Endometrial Carcinoma

- Median age of 61, highest decade is 60’s
- 66k cases estimated in 2021, 13k deaths (ACS data)
- 5% occur before 40 years
- 20-25% are pre-menopausal
- Lifetime risk: 1 in 50 women in U.S. will develop Endo. Ca
- Overall: Good Survival rate – 5 years about 80%
Endometrial Thickness on Transvaginal Ultrasound and Corresponding Histopathologic Diagnosis in Postmenopausal Bleeding

• age ≥ 55 years

• postmenopausal bleeding

• TVUS within 30 days of their endometrial biopsy

• 304 patients, divided into 4 groups:
  • group A (n=198) benign/atrophic endometrium
  • group B (n=44) polyps
  • group C (n=30) hyperplasia
  • group D (n=32) carcinoma

Int J Gynecol Pathol 2017 Jul;36(4):348-355
Endometrial Thickness on Transvaginal Ultrasound and Corresponding Histopathologic Diagnosis in Postmenopausal Bleeding

• mean endometrial thickness (mm):
  - Group A benign/atrophic endometrium- 8
  - Group B polyps- 12
  - Group C hyperplasia- 15
  - Group D carcinoma- 17 (4 pts. had endo \leq 4 \text{ mm.})

• Threshold of 4 mm. Sensitivity= 92%
• Threshold of 3 mm. Sensitivity= 97%
• But lower specificity, accuracy, PPV at lower thickness

Int J Gynecol Pathol 2017 Jul;36(4):348-355
Endo Thickness and endometrial cancer-Post-menopausal patients

• Prevalence of Endometrial CA in PMB pts- up to 10%
• Large, controlled prospective studies - a thin distinct endometrial echo ≤ 4 mm in a postmenopausal woman with bleeding will have an incidence of malignancy of about 1 in 1000 (0.1%)
  • 10-20% of non-bleeding post-menopausal pts have a polyp(s)
  • incidence of malignancy in such polyps reported to be between 0-2.4%
66 yo PMB and 40 mm thick endometrium ++ color Doppler flow

FIGO Grade 2, 9 cm endometrioid CA.
Endometrial cancer, stage 1a, 40 y.o. pre-menopausal presenting with AUB
70 yo with vaginal bleeding

Endo bx x 2 in 3 months - benign polyps
50 yo with AUB, perimenopausal
EMB--Poorly Differentiated Carcinoma
Endometrial calcifications

- Usually benign
- Glandular calcifications most common
- Prior surgery, trauma or infection
- Large recent study*
  - 4% nullips
  - 60% of primips
  - 60-87% of prior C/S pts (at site of scar)
- Indicates an injury to basalis layer of endometrium

*Obstetrics & Gynecology: May 2018 - Volume 131
Endometrial Calcifications in 31 yo w/ AUB

EMB-secretory endometrium, no calcs++
Endometrial punctate calcifications - benign
Endo. large dystrophic calcs.-SM Fib?
Miscellaneous Endometrial Pathology
Endometrial lipoleiomyoma (submucosal)
Histology slide of specimen X 10 H & E
Endometrial Lipoleiomyoma (LLM)

- Rare type of leiomyoma with large amount of adipocytes
- Mimicker of endometrial calcifications
- Turkey study - women with 76 LLM
  - Age 34 to 77 years (mean 55 years)
  - Size 0.5 to 55 cm in diameter (mean 5.5 cm)
  - All benign
  - 91% in body of uterus, 7% in cervix, 1 broad ligament, 1 retroperit.

Intramural lipoleiomyoma
50 yo with brisk vaginal bleeding
50 yo w/ AUB w/ ?

“Aborting” fibroid
Prolapsing or “Aborting” SM fibroid
Submucosal fibroid on a long pedunculated stalk, uterine contractions, gravity push fibroid to introitus
Aborting Fibroid
Prolapsing Submucosal Fibroid

• Uncommon but not rare in young women of reproductive age
• Asx or symptoms of vaginal bleeding, discharge, or pelvic pain
• Often removed with hysteroscopy, sometimes vaginal myomectomy
• Rarely, need hysterectomy
Cervical Cancer – 59 yo Vietnamese pt
Cervical Cancer - not an U/S diagnosis
Tamoxifen Effect in the Endometrium

• selective estrogen receptor modulator (SERM)
• treatment of breast cancer and for chemoprophylaxis in high risk women
• increased incidence of endometrial cancer and uterine sarcoma

• endometrial polyps: occurs in ~8-36% of women treated
• endometrial hyperplasia: occurs in ~1-20% of women treated
• cystic endometrial atrophy
• endometrial carcinoma
Tamoxifen Effect—Endometrial Hyperplasia
Tamoxifen effect-thick, cystic endo
Hematometros in 33 yo woman, AUB
Pyometra from endometrial-colon fistula
Endometrial Conclusions

• Normal Pre-menopausal endometrial thickness ~ 18 mm.

• Asx polyps in pre-menopausal women-f/u, no surg, 30% regression rate
  • But strong association with decreased uterine receptivity → inc. infertility rates

• Normal Post-meno thickness
  • With bleeding, ≤ 4 or 5 mm.
  • Without bleeding, probably 10-11 mm. (but little good data)
  • Tamoxifen/Hormones - 8 mm (without bleeding)

• Cysts in Endometrium
  • Think polyps, cystic hyperplasia (but not much data in literature)

• Use 3D US imaging for improved detection of polyps

• 2 predictors for Endo CA—Post-menopausal and bleeding (10% cases)
The End

• Thank you!!