Forty-second Annual
Postgraduate Program

October 18, 2009
Atlanta, GA

Ultrasound In Reproductive Medicine Part II

Course 17

Sponsored by the
American Institute of
Ultrasound in Medicine
and the
American Society for
Reproductive Medicine

New Procedure to Obtain CME Credits

Dear Postgraduate Course Participant:

The Accreditation Council for Continuing Medical Education now requires that ASRM document learning for participants in CME programs. Thus, the procedure for claiming CME credits has changed. We ask your cooperation in following the steps below to ensure that your credits are provided correctly to you.

1. Within 3 days after the Annual Meeting you will be sent an email asking you to complete an online evaluation of this postgraduate course. A personalized Web link to the evaluation will be provided in your email. Please do not share this unique link.
2. In late November you will be sent a second email with a personalized Web link asking you to complete the post-test on the content of the course. This test is identical to the pre-test and will enable ASRM to assess the effectiveness of this postgraduate course as a learning activity. For your convenience, the test questions are printed in the course syllabus.

After both steps have been completed, you will be able to claim your CME credits and/or ACOG Cognates and receive a printable CME certificate. Please note that you must provide your 10-digit ACOG Membership Number to have your ACOG Cognates reported to ACOG. Results of both the course evaluation and the post-test are anonymous.

Both steps must be followed completely by **December 31, 2009** in order to receive CME credits. A maximum of 6.5 CME credits can be claimed for the postgraduate course. Please be aware that some email systems flag emails with Web links as junk mail, and you may need to check your junk-email folder for your notifications.

Please DO NOT forward the links. In case of difficulty please email *pfenton@asrm.org*

********Deadline for receiving CME credits = December 31, 2009********

Continuing Medical Education

Continuing medical education is a lifelong learning modality to enable physicians to remain current with medical advances. The goal of ASRM is to sponsor educational activities that provide learners with the tools needed to practice the best medicine and provide the best, most current care to patients.

As an accredited CME provider, ASRM adheres to the Essentials and policies of the Accreditation Council for Continuing Medical Education (ACCME). CME activities now must first, address specific, documented, clinically important gaps in physician competence or performance; second, be documented to be effective at increasing physician skill or performance; and third, conform to the ACCME Standards for Commercial Support.

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Developed in Cooperation with the

AMERICAN INSTITUTE OF ULTRASOUND IN MEDICINE

ANNUAL MEETING POSTGRADUATE COURSE

ATLANTA, GA

OCTOBER 18, 2009

"ULTRASOUND IN REPRODUCTIVE MEDICINE PART II"

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All speakers at the 2009 ASRM Annual Meeting and Postgraduate Courses were required to complete a disclosure form. These disclosures were reviewed and potential conflicts of interest resolved by the Subcommittee on Standards of Commercial Support of the Continuing Medical Education Committee. The faculty has revealed the following information as potential conflicts of interest:

Elizabeth E. Puscheck, M.D.: Wyeth, Ethicon: Research

Steven R. Goldstein, M.D.: Boehringer Ingelheim, Eli Lilly, Pfizer, Glaxo SmithKline, Merck, Novo Nordisk, Novartis, Proctor & Gamble, Upsher Smith, Wyeth: Advisory Board, Cook ObGyn, Ackrad Labs (A Cooper Co.), Philips Ultrasound: Speakers Bureau, Sonosite: Stockholder, Philips Ultrasound: Consultant

Alexander Hartman, M.D.: Nothing to disclose

This activity may include discussion of off-label or otherwise non-FDA approved uses of drugs or devices.

Accreditation statement:
The American Society for Reproductive Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Designation statement:
The American Society for Reproductive Medicine designates this educational activity for a maximum of 6.5 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

American College of Obstetricians and Gynecologists (ACOG)
The American College of Obstetricians and Gynecologists has assigned 6.5 cognate credits to this activity.

***

Please turn off/mute cell phones and pagers during the postgraduate course and all Annual Meeting sessions.

Thank you.

ULTRASOUND IN REPRODUCTIVE MEDICINE PART II

NEEDS ASSESSMENT AND COURSE DESCRIPTION

Can one imagine ART being performed today without imaging? Ultrasound has become an integral component not just of ART, but also of the daily practice of reproductive medicine, infertility, and gynecology. New practice guidelines for ultrasound in reproductive medicine have been published by AIUM in collaboration with ASRM in 2009 (J Ultrasound Med 28(1):125-138, 2009). Surveys of members of the Society for Reproductive Endocrinology and Infertility, the Imaging Special Interest Group, and ASRM have revealed a strong desire for continuing medical educaton in ultrasonography that would prepare reproductive medicine professionals and gynecologists for accreditation by the American Institute of Ultrasound in Medicine (AIUM). To accommodate physicians' educational needs, this course has been designed to be taken either as a two- or a one-day course. The curriculum for each day has been designed as a free standing course, so Part I is not a prerequisite for Part II.

The objectives of this course are to provide a comprehensive survey of the use of ultrasonography in the female pelvis for physicians, nurses and ultrasonographers actively involved in reproductive medicine, infertility and gynecology. There will be a live scanning demonstration during Part I to review the ultrasound techniques in performing a pelvic ultrasound examination. The faculty will review critically the application of ultrasonography to the evaluation, diagnosis, treatment and complications of infertility. Although ultrasonography has advanced early pregnancy evaluation and monitoring, the pitfalls and limits of diagnostic ultrasonography for assessment of pregnancy and its complications also will be addressed. Many other gynecologic findings on ultrasound such as congenital uterine anomalies, ovarian masses, tubal disease and other uterine pathologies will be discussed along with their impact on fertility. The course will cover a variety of reproductive problems throughout the reproductive lifespan from puberty through menopause from an ultrasound perspective. Newer technologies will also be discussed with current or potential application, such as 3D ultrasound and Doppler. Cases and controversies will offer the audience an opportunity to actively participate. Finally, the faculty will introduce the audience to the potential importance, requirements and benefits of AIUM accreditation.

ACGME COMPETENCY

Patient Care
Medical Knowledge

LEARNING OBJECTIVES

At the conclusion of this course, participants should be able to:

1. Summarize the appropriate use of ultrasonography in the evaluation of infertility, uterine abnormalities and the pathology of the reproductive tract.
2. Describe the proper assessment of early pregnancy and list findings on early pregnancy assessments that are associated with poor outcomes.
3. Discuss new developments in ultrasonography, the importance of 3-D ultrasonography in reproductive medicine, and the importance of Doppler blood flow assessment in reproductive medicine and gynecology.
4. List the requirements and benefits of a clinical practice attaining accreditation in ultrasonography.

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ANNUAL MEETING POSTGRADUATE COURSE

ATLANTA, GA

OCTOBER 18, 2009

"ULTRASOUND IN REPRODUCTIVE MEDICINE PART II"

Elizabeth E. Puscheck, M.D., Chair

Sunday, October 18, 2009

08:15 – 08:30	Course Introduction and Orientation **Elizabeth E. Puscheck, M.D.**
08:30 – 09:05	Polyps, Fibroids and Fertility: With a Focus on Ultrasound **Elizabeth E. Puscheck, M.D.**
09:05 – 09:15	Questions and Answers
09:15 – 09:50	Menopausal Dilemmas: The Role of Ultrasound **Steven R. Goldstein, M.D.**
09:50 – 10:00	Questions and Answers
10:00 – 10:30	Break
10:30 – 11:05	Sonohysterograms to Evaluate the Uterus and Tubes **Alexander Hartman, M.D.**
11:05 – 11:15	Questions and Answers
11:15 – 11:50	Ovarian Masses: Benign, Malignant and Fertility **Elizabeth E. Puscheck, M.D.**
11:50 – 12:00	Questions and Answers
12:00 – 13:00	Lunch
13:00 – 13:45	Adenomyosis **Alexander Hartman, M.D.**
13:45 – 14:00	Questions and Answers
14:00 – 14:45	IVF, ET and Early Pregnancy **Elizabeth E. Puscheck, M.D.**
14:45 – 15:00	Questions and Answers

Sunday, October 18, 2009 (continued)

15:00 – 15:30	Break
15:30 – 16:05	Ectopic Pregnancy vs. Pregnancies of Unknown Location: How Ultrasound Helps to Determine What to Do? **Steven R. Goldstein, M.D.**
16:05 – 16:15	Questions and Answers
16:15 – 16:50	Cases of the Day, AIUM Accreditation **All Faculty**
16:50 – 17:00	Questions and Answers

POLYPS, FIBROIDS AND FERTILITY: WITH A FOCUS ON ULTRASOUND

Elizabeth Puscheck, M.D., M.S.
Wayne State University
School of Medicine
Detroit, Michigan

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Assess common polyp and fibroid sonographic appearances, location and impact on symptoms and fertility.
2. Designate additional sonographic techniques that may assist in further evaluating the clinical impact of fibroids.
3. Describe some of the future roles for ultrasound in assisting in the treatment of fibroids.

Polyps, Fibroids and Fertility:

With a Focus on Ultrasound

Elizabeth Puscheck, M.D., M.S.
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- Describe some of the future roles for ultrasound in assisting in the treatment of fibroids.

Disclosure

Wyeth, Ethicon: Research

Baseline Ultrasound: Timing Is Everything!

- Early follicular phase of the cycle is when the endometrium is thin.
  - Distortion from a polyp is easier to detect
  - Polyps are hyperechoic, like the endometrium
- Luteal phase – the endometrium is homogenously hyperechoic
  - The endometrium acts as its own contrast material
  - Ideal time to detect fibroids
  - Fibroids are usually less echoic than endometrium
  - Indentations are easy to detect.

Uterine Polyps

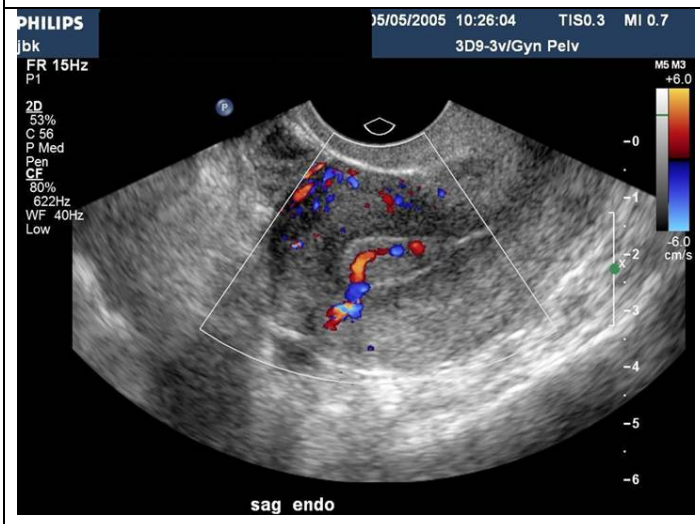
- Benign 99%
- Distorts uterine cavity
- Single vessel feeds polyp
- Concern about pregnancy loss
- Few data
- Easy to remove by hysteroscopy

Frequency of Polyps

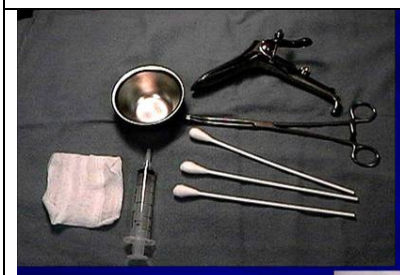
- 45% of infertile women (Mooney SB, Milki AA. Fertil Steril 2003;79:637-8.)
- 32% found during office hysteroscopy prior to IVF (Hinckley and Milki JSLS 2004;8:103-7)
- 8.3% vs. 37.5% clinical pregnancy rates with and without intrauterine abnormality in IVF (Shamma FN, Lee JN, Gutmann JN, and Lavy G. Fertil Steril 1992;58:1237-9)

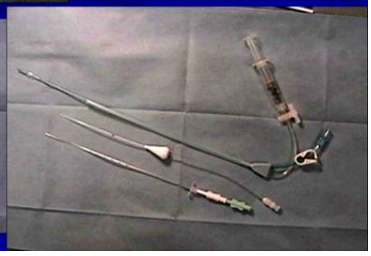
Polyps and Pregnancy Rate (PR)

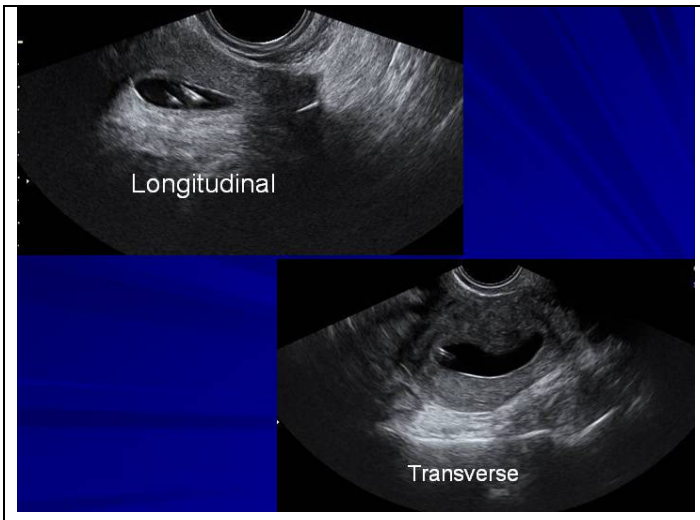
- Lass JARG 1999;16:410-5
  - Group 1: Fresh IVF no removal 22% PR, 27% sAB
  - Group 2: Frozen embryo transfer (FET), polypectomy. 30% PR, 14% spontaneous abortion (sAB)
  - Poor design
- Doldi Gynecol Endocrinol 2005;21:235-7
  - 300 prospective vs. 300 historical controls
  - 38% PR vs. 18%
- Mooney and Milki Fertil Steril 2003;79:637-8
  - Recent hysteroscopy (HSC) with polypectomy vs. remote/no polypectomy.
  - Viable PR 71% with recent HSC and 39% remote, p=0.01
- Perez-Medina HR 2005;20:1632-5. Prospective randomized trial
  - Risk ratio (RR) 2.1; HSC polypectomy prior to intrauterine insemination (IUI); no difference in size (80% <2 cm)



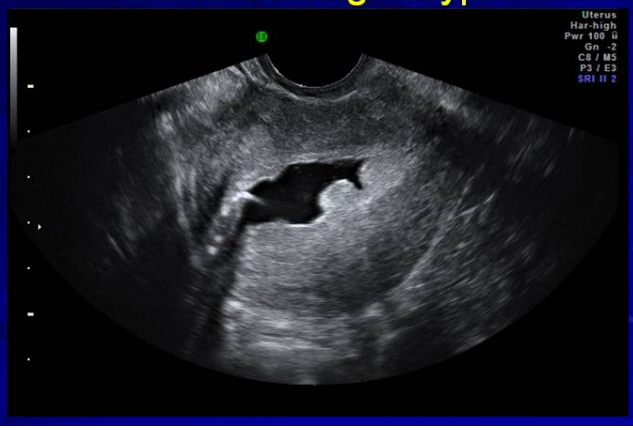
Saline Infusion Sonohystogram (SIS) Supplies







SIS Showing Polyps



Do We Remove the Polyp or Observe?

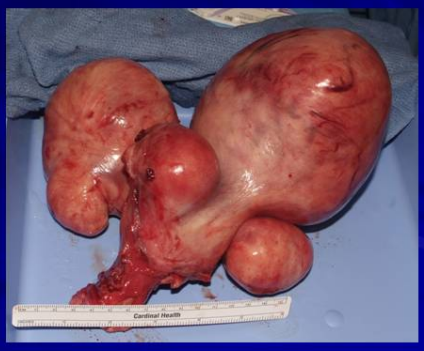
- There are very few data on observation. One study by DeWaar et al. showed that peri-/postmenopausal women may have spontaneous resolution in 2 years.
- No data on observation in couples desiring fertility.

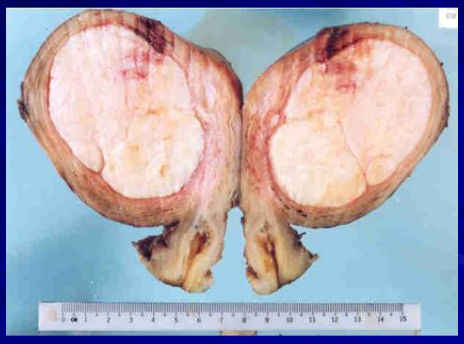
Removing Polyps During Stimulation

- Polyps <1.5 cm
- Hysteroscopic polypectomy
- During stimulation or FET preparation
- Procedure was done 2-16 days before embryo transfer (ET)
- No decrease in PR
- Limitations: small numbers, not randomized

Madani T et al. Reprod Biomed Online 2009;18:412-5

Fibroids





Incidence:

- Uterine leiomyomata are the most common solid pelvic tumor of the female genital tract.
- Clinically apparent in 25-50% of women.
- The prevalence may be as high as 80% in some populations.
- African-American women tend to have fibroids present more frequently, at a younger age and with more severe symptoms and more likely anemic.

Day Baird et al AJOG 2003;188:100-7

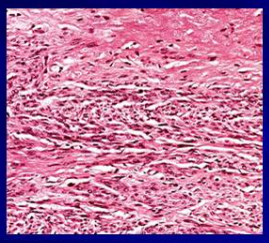
Fibroids

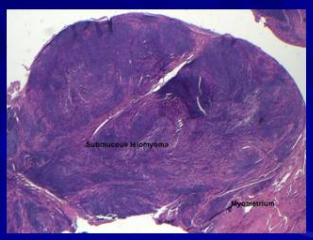
- Most common reason for hysterectomy
- In the United States, 30%-40% of all hysterectomies are due to fibroids—more than any gynecologic cancer.
- Increases healthcare costs:
  - Fibroids 2.6 times higher than controls
  - Estimated to be a $2 billion dollar cost/year

What Are Fibroids?

- These are benign tumors that arise from a *single myometrial cell.*
- There is thought to be a genetic alteration that causes an essentially clonal growth of this cell into a spherical/ellipsoidal mass over time.
- Growth of fibroids increases with estrogens; also regulated with progesterone and a number of local growth factors and receptors.

Normal to Fibroid





Risk Factors Regarding Fibroids

Increases fibroid risk:

- Race: African, African-American
- Genetic: close relatives with fibroids
- Nulliparity
- Increased body mass index (BMI)
- Diet high in alcohol (especially beer)
- Increase in age

Decreases fibroid risk:

- Race: Caucasian, Hispanic, Asian
- Delivered baby previously
- Oral contraceptive pills (OCP)/Depo Provera
- Smoking
- Diet high in fruits/vegetables
- Rare in young; decreases after menopause

Fibroids: Presenting Symptoms

- Incidental finding on annual exam or during infertility evaluation
- Abnormal bleeding/dysfunctional uterine bleeding (DUB)/menometrorrhagia
  - Heavy, prolonged, sometimes gushing
- Pressure sensation or pain
- Frequent urination
- Difficulty urinating or defecating

Symptoms Related to Location

- Intramural/subserosal more likely to cause pressure, pain, and distortion of adjacent organs
- Submucosal/intracavitary more likely to have menorrhagia, intermenstrual bleeding and increased risk of miscarriages

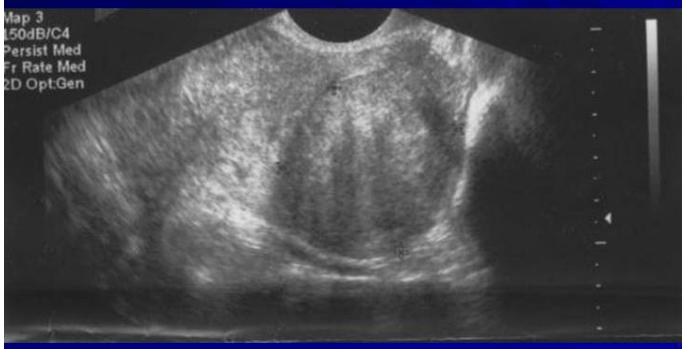
Ultrasound of Fibroids

- Easy
- Safe
- Quick
- Cheap
- Readily available
- First line of evaluation
- Fibroids are often suspected on exam

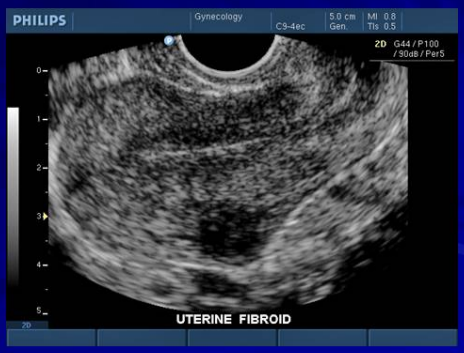
Ultrasound Typical Appearance:

- Solid, hypoechoic, round
- Arising from the myometrium
- Shadowing is not uncommon
- Poor transmission
- Transvaginal and transabdominal approaches may be necessary

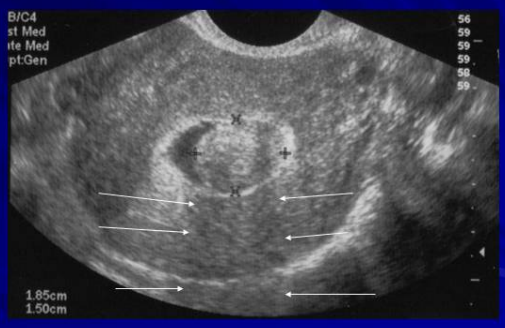
Typical Fibroid



Subserosal Fibroid



Shadowing



Characteristics on Ultrasound Over Time:

- Early findings: Enlarged uterus, irregular uterine serosal surface
- Middle: Well-circumscribed solid mass with smooth borders and shadowing
- Late: Calcifications, within or out at the periphery

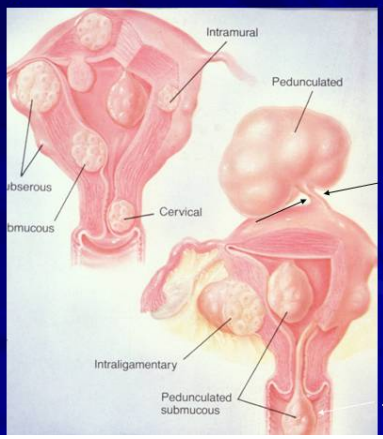
Sonographic Reliability

- Sensitivity, specificity and positive predictive values are all 90%-98%
- More than 95% are typical-appearing fibroids
- No further imaging tests are needed

Role of Ultrasound

- Size
- Number
- Location
- Doppler (optional)
- SIS may help delineate fibroids within the uterine cavity and to assist in determining the type of surgical approach
- Evaluate the adnexa, which may not be palpable

Multiple Locations: Look All Over!

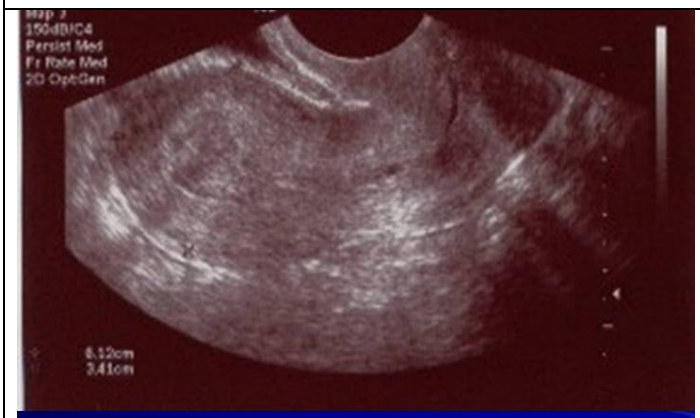


May need to do an ***abdominal scan*** to see the pedunculated fibroids and their stalks

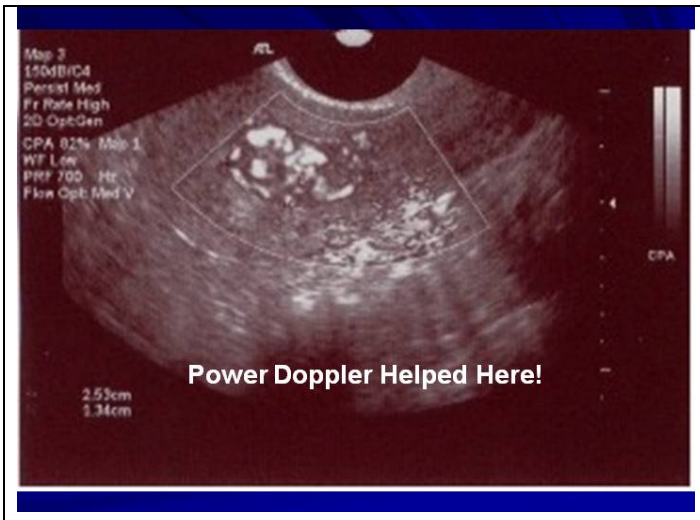
May extrude through the cervix

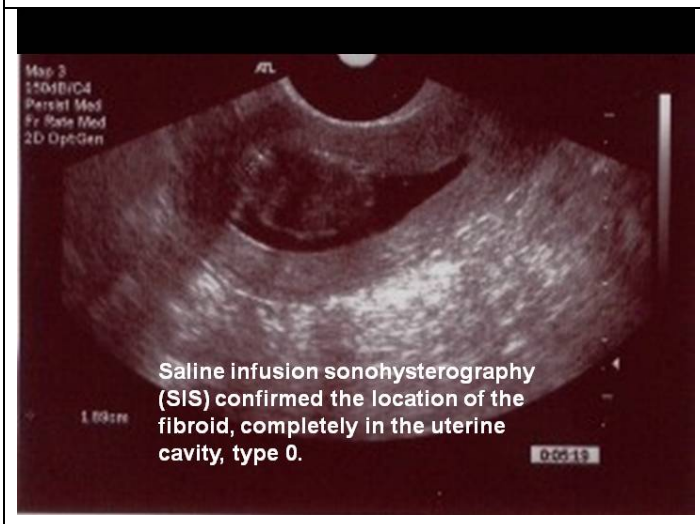
Watch Out for the Pedunculated Fibroid!

- Make sure to scan the serosal surface completely.
- If you see a solid mass that you are not sure is of uterine or ovarian origin, try the following:
  - Sliding-organ sign
  - Look for bridging vessels or "claw sign"
  - Use Doppler to help
- Remember: Adnexal masses (ovarian or bowel) will not have bridging vessels.

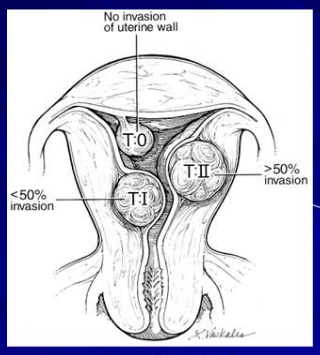


Some Fibroids May Be Difficult To See





Fibroid Location and Fertility

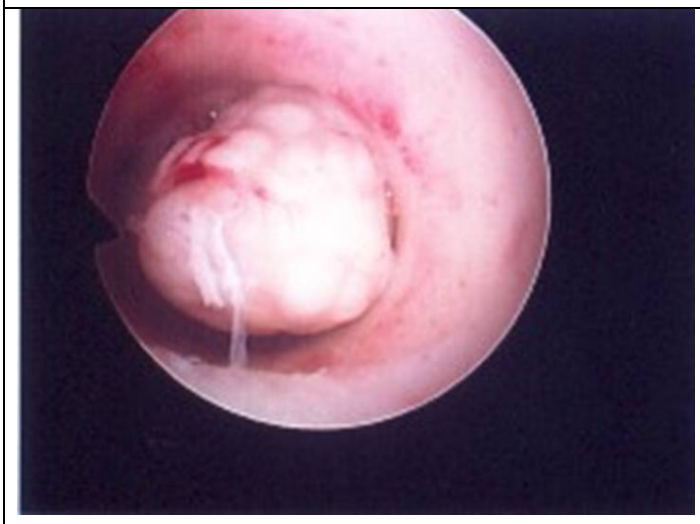


REMEMBER: Measure the outer fibroid surface to the serosal borders for type I and II submucosal fibroids.

Cohen L, Valle R. Fertil Steril 2000;73; 197-204

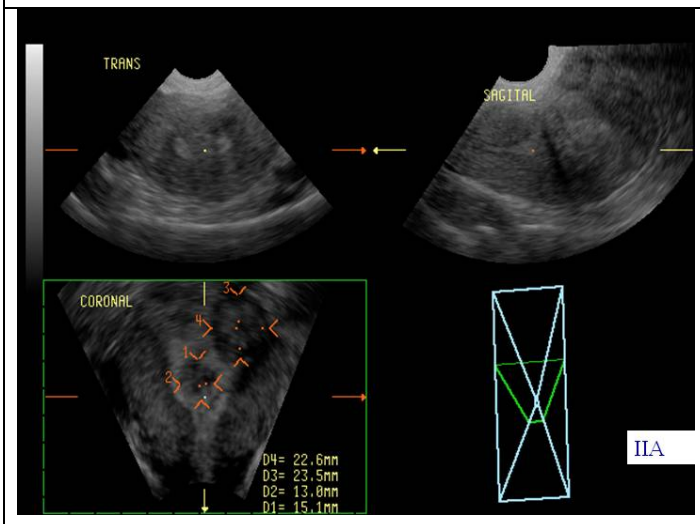
Fibroids

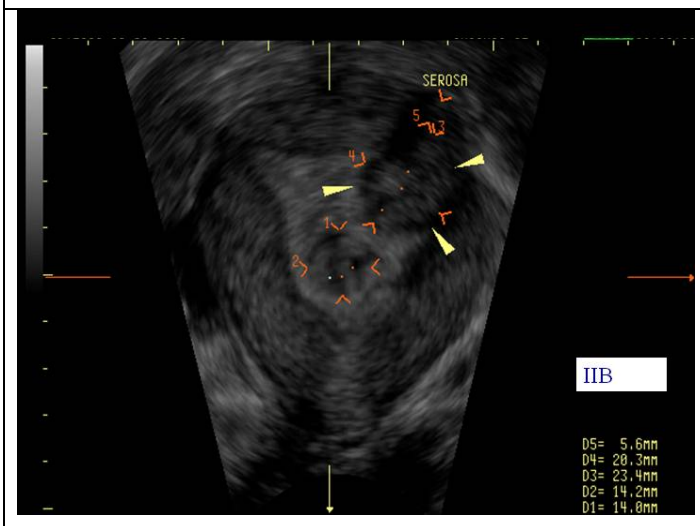
- Types:
  - Type 0: Hysteroscopic removal
  - Type 1: Hysteroscopic candidate, consider laparoscopy-assisted
  - Type 2: Abdominal myomectomy (occasionally serial HSC myomectomy with laparoscopy)
- Intrauterine masses decrease pregnancy rates and increase miscarriage rates.



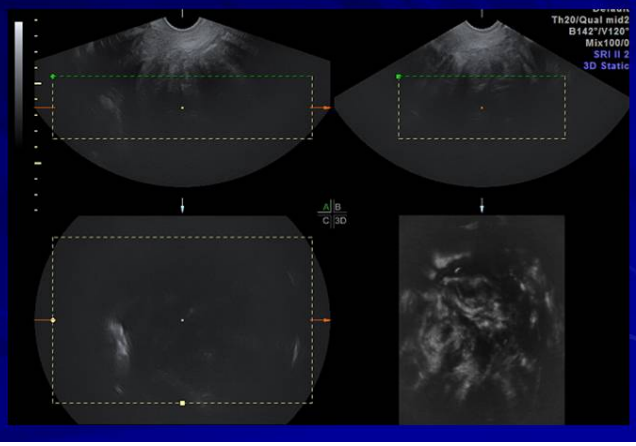
Alternative to the Sonohysterogram: Consider Doing the Ultrasound in the Luteal Phase….

In the luteal phase, the endometrium will be hyperechoic and will act like contrast material and 3-dimentional (3-D) ultrasound can help.





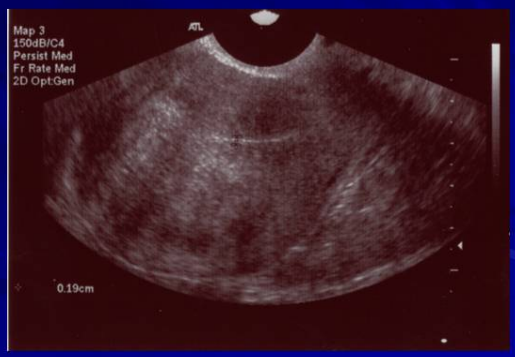
The Difficult-To-Scan Fibroid



Ultrasound Techniques To Try:

- Change probe to lower frequency so greater depth
- Change focal length
- Add more foci
- Add harmonics
- "Optimize" button
- Change probes
- Some may still be difficult to see.

Some Are Less Obvious



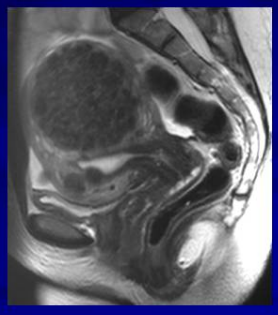
Need To Differentiate Fibroid from Focal Adenomyosis

- We have another talk focusing on ultrasound characteristics of adenomyosis today.
- Consider magnetic resonance imaging (MRI) if still not certain.

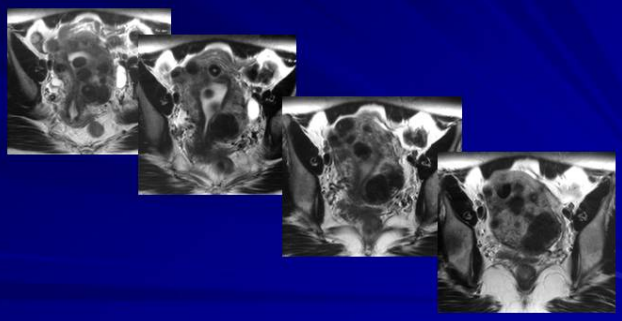
Limitations of Ultrasound

- Too big does not fit on the screen; cannot accurately measure or map
- Too much shadowing
  - Fibroids that are anterior in location
  - Califications
- Cannot find the ovaries, thought due to shadowing
- Not sure if it is a fibroid or adenomyosis
- Feel a mass but do not see one on ultrasound (pedunculated fibroid and missed the stalk on ultrasound).

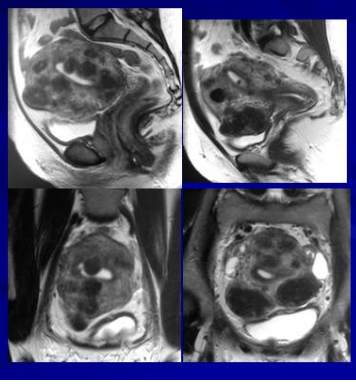
Consider MRI



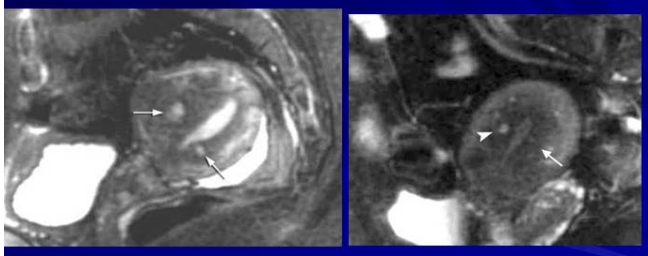
41-Year-Old Female: Long-Axis Views



In some situations, the uterus is too large for an adequate ultrasound or there are multiple fibroids, as in this 41-year-old female with menorrhagia



Adenomyosis on MRI



Increased intensity of adenomyosis and increased junctional zone

Additional Advantages of MRI

- Large fibroids can be mapped, when they cannot be mapped using ultrasound.
- The endometrium is bright, so it is possible to identify which fibroids are distorting the endometrium.
- Ovaries behind fibroids that often cannot be found by ultrasound can be seen on MRI
- The ureters can often be evaluated on the pelvic MRI or extend to abdominal MRI to include assessment of the kidneys, if needed.

Additional Ultrasound Techniques

- Ultrasound can be used to evaluate the kidneys for hydronephrosis, important when fibroids are large.
- Ultrasound with Doppler of the bladder can evaluate functioning ureters independently, without invasive measures, which MRI cannot.

What about Infertility and Fibroids?

- Infertility: About 10% of women with fibroids have infertility. But fibroids are estimated to be the cause in only 2%-3%.
  (Buttram VC. Fertil Steril 1981;36:433-5)
- In unexplained infertility, prospective cohort study noted:
  - 11% of women with fibroids conceived without intervention.
  - 25% of women without fibroids conceived.
  - 42% conceived after LSC myomectomy

  Donnez J and Jadoul P. Hum Reprod 2002;17:1424-30

IVF and Fibroids

- Fibroids impacting the uterine cavity or distorting the cavity impact outcome (72%)
  - Farhi J et al. Hum Reprod 1995; 10:2576-8.
  - Surrey ES et al. Fertil Steril 2001;75:405-10
- Lower IVF rates in women with intramural myomas, especially larger ones (>5 cm)
  - Somigliana E et al. Hum Reprod Update 2007;13:465-76
  - Kolankay A et al. Obstet Gynecolo Clin North Am 2006;33:145-52.

The Role of Intramural Myomas in IVF

Study	Year	Criteria	Outcome	Study group	Control group	Odds ratio (OR)
Stovall	1998	≤ 6cm	Delivery	34/91 37.4%	44/91 48.3%	0.64 (0.34,1.2)
Eldar-Geva	1998	2.4 cm (mean)	Clinical pregnancy	9/55 16.4%	98/318 30.8%	***0.44*** ***(0.19,0.98)***
Hart	2001	≤ 5 cm	Delivery	16/106 15.1%	91/322 28.3%	***0.45*** ***(0.24, 0.84)***
Check	2002	≤ 5 cm	Delivery	14/61 22.9%	23/61 37.7%	0.49 (0.21, 1.16)
Totals				73/313	256/792	0.64 (0.47,0.87)

Proposed Mechanisms for Infertility:

- Displaced cervix, reduces exposure to sperm
- Enlarged, distorted cavity may interfere with sperm transport
- Obstruction of tubes
- Increased/disordered contractions affect sperm, embryo transport
- Distorted or disrupted endometrium (atrophy, venous ectasia over myoma)
- Impaired endometrial blood flow
- Endometrial inflammation or secretion of vasoactive substances.

Other Complications of Pregnancy:

- Miscarriage rate up, especially with multiple fibroids (OR 1.6, CI 1.3-2.0)
  Growth occurs in the first trimester
- Increased cesarean section rate
  (OR 3.7, CI:3.5-3.9)
- Preterm delivery (OR1.5, CI 1.3-1.7)
- Other symptoms: Bleeding, abruptions, premature rupture of the membranes (PROM) – especially if fibroid is near the implantation site, malpresentation

CI = confidence interval

Fibroids Treatments:

- Expectant
- Medical
- Surgical
- Alternatives

Expectant Treatment:

- For asymptomatic patients
  - No fecundity data
  - Myomas may grow—need regular follow-up
  - No reason to operate if asymptomatic (less than 20 weeks' size)
  - Watch for rapid growth for leiomyosarcoma
    (0.1% incidence, 1.7% if over age 60)
    Cannot diagnose with imaging; needs histology to determine the number of mitoses per high power field.

Medical Treatment

- Mainly temporizing
- Reduce size and symptoms of myomas
- Delays fertility
- Gonadotropin-releasing hormone (GnRH) agonist
  - Shrinks myoma by induced hypoestrogenemia
  - May help for hysteroscopic approach
  - Standard therapy for over 2 decades
  - Consider with add-back if patient is perimenopausal and it controls symptoms
- OCP, Depo Provera
  - Suppress ovulation
  - Lower hormone levels than normal—thinner endometrium, less bleeding
  - Bleed-through: look for a submucosal myoma or polyp

Other Medical Therapies

- Other options:
  - Androgens: Gestrinone or Danazol--effective in small studies but adverse side effects
  - Mifepristone (progesterone antagonist)—decrease size
- Future: aromatase inhibitors, selective progesterone receptor modulators (SPRMs), selective estrogen receptor modulators (SERMs)
  - Not U.S. Food and Drug Administration (FDA)-approved or recommended

After Medical Therapy

- Myomas return back to pre-treatment size after stopping therapy
  - Temporizing effect unless close to menopause and "add back" therapy used
- May just ***delay fertility*** treatments and not help
- Medical pre-treatment can help:
  - Improve blood count, if anemic
  - Change the type of incision (vertical to horizontal)
  - Shrink size of intracavity lesions
  - Sometimes difficult planes for dissection, particularly with abdominal myomectomies (softer, too)

Surgical Treatments:

- Myomectomy-
  - Only therapy available for women desiring pregnancy
  - Thorough counseling regarding high likelihood of recurrence risk and more surgery
  - Pre-surgery evaluation:
    - Hysterosalpingogram (HSG) or SIS,
    - Complete blood count (CBC)
    - Possibly endometrial biopsy

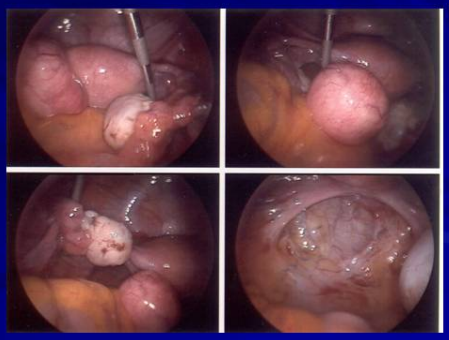
Hysteroscopic Myomectomy

- Limited to submucosal myomas, type 0 and type I
- Technique: Wire loop, bipolar, laser
- Complications:
  - Perforation
  - Bleeding
  - Fluid overload, and HYPONATRIEMIA (monitor intake and output closely)
- Post-surgical controversy:
  - No post-therapy
  - Balloon catheter to prevent adhesions plus estrogen therapy
  - Either approach with early second-look hysteroscopy to lyse adhesions
- Small cohort study: 72% conceived in 4 years after surgery, miscarriage rate 26% (compared to 62% miscarriage rate pre-surgery)

Abdominal Myomectomy:

- Vertical or transverse incision
- Tourniquet, clamps, dilute vasopressin
- Decrease intra-operative bleeding
- Complications:
  - 94% adhesions on posterior surface,
  - 55% on the anterior surface
- Consider barriers:
  - Oxidized regenerated cellulose=Interceed,
  - Sodium haluronate/carboxymethly cellulose (Seprafilm),
  - Expanded polytetrafluoroethlyene (Gortex).
  - All are effective for reducing postoperative adhesions

Laparoscopic Myoma



LSC Myomectomy

- Minimally invasive
- 2 studies show similar results to abdominal myomectomy:
  - Most excise myoma and do minilaparotomy for secure repair (multi-layer closure)
  - Minilaparotomy: easier, faster, less blood loss than laparoscopy; similar pregnancy rates
  - Limited to pedunculated or subserosal
  - Robotic instead – can do all types
  - Complication: Uterine rupture after LSC myomectomy

Adhesions Following Laparoscopic Myomectomy

Study	N	Myoma Size (cm)	Adhesions (%)
Nezhat, 1991	32	NR	56
Hasson, 1992	24	3-16	66
Mais, 1995	50	3-6	64
Bulletti, 1996	14	4-11	29
Stringer, 1996	49	5-7	64
Seinera, 1997	5	3-8	0
Darai, 1997	4	NR	100
Dubuisson, 1998	45	1-10	41
Total	223		52%

NR = not reported

Effect of Location and Surgery on PR

- Submucosal fibroids: 72% reduction in pregnancy rate ***without*** treatment compared to infertile controls and after hysteroscopic myomectomy achieved pregnancy rates similar to controls; no randomized controlled trial (RCT); routine HSC resections
- Intramural myomas more inconsistent
  - Hart (<5 cm intramural half PR vs. controls)
  - Most studies were retrospective, low numbers, and <3 cm fibroids
  - Higher miscarriage rates 15%-54%
- No difference in PR with subserosal myomas

Follow-up after Myomectomy

- Up to 80% of women report relief of symptoms
- 27% have recurrence after more than 10 years
- Recurrence: more common with more fibroids
  - One fibroid removed , 11% recurrence rate
  - Multiple fibroids removed, 26% recurrence rate
- Term pregnancy rates in 40%-50% range
- Similar results with LSC and HSC myomectomy as with abdominal myomectomy
- Improved miscarriage rate
- Most studies are retrospective and have small numbers

Risks of Uterine Rupture:

- Abdominal myomectomy, 0.002%
- Cesarean section, 0.1%
- Laparoscopic myomectomy ?

Newer Technologies:

- Laparoscopic myolysis
  - Thermal destruction via cryoprobes or electrocautery needles, or fiberoptic lasers, or MRI-guided needles
  - Radiofrequency ablation (Halt Lap RFA)
  - Lacking short- and long-term outcomes—not for those desiring fertility

Uterine Artery Embolization (UAE)

- Fluoroscopic guidance, inject triacryl gelatin microspheres or polyvinyl alcohol particles
- Occludes uterine vessels = 94% blood supply to fibroids, transient ischemia
- Fibroids infarct
- Global uterine treatment
- FIBROID (Fibroid Registry for Outcomes Data)
- EMMY trial (RCT for EMbolization vs. hysterectoMY)

UAE: Premature Ovarian Failure (POF) and Fertility

- Observational study
  - N=66 premenopausal women, followed 12-77 weeks
  - Ovarian failure: no menses and lab values elevated
  - 43% of patients >45 years old (n=21) ; age-related (similar to hysterectomy)
- Second study, 108 patients trying to conceive after UAE, 33 did conceive
  - 56 completed pregnancies, 33 successful (58.9%)
  - Cesarean section: 72.7%
  - Pre-term delivery: 18.2%
  - Postpartum hemorrhage 18.2%
  - Miscarriage 30.4%
  - Termination n=3; stillbirth n=2; ectopic n=1
  - ACOG Does not recommend UAE if fertility desired

ACOG = American College of Obstetricians and Gynecologists

MRI-Guided High-Intensity Focused Ultrasound (HIFU)

- No incisions
- Ultrasound therapy to heat and destroy fibroid tissue; multiple sonications over 2-4 hours
- MRI provides thermal map to watch for under-/over-treatment
- Disadvantages:
  - One fibroid at a time
  - Not for pedunculated fibroids or those near other organs
  - **Not recommended for future fertility**
- Follow-up: 109 at 6 months and 82 at 12 months:
  - 72% success in improved quality of life (QOL)
  - Fibroid size decreased 13% at 6 months and 9.4% at 12 months
- Risks: transfusion, 3%; rehospitalization, 7%; skin burn, 5%

Future of Ultrasound in Fibroid Treatment

- HIFU (High Intensity Focused Ultrasound) with MRI is under trial: NCT00837161 (Phase I and II) and in the U.K. NCT00159328 (Phase IV-completed)
- GYNECARE GYNOCCLUDE: Doppler-guided uterine artery occlusion device using vaginal stablizer clamp with Doppler within the clamp is under study NCT00496080
- Halt Trial is an intra-operative laparoscopic ultrasound-guided procedure to treat fibroids with radiofrequency ablation under study. NCT00874029

www.clinicaltrials.gov

Summary of Polyps

- Polyps have not been thoroughly studied in any RCT.
- Polyps are easy to detect by ultrasound in the early follicular phase if the rest of the endometrium is thin.
- Saline infusion sonohysterogram can easily identify polyps
- Doppler ultrasound can identify the single central vessel.
- Polyps are easy to remove with minimal complications.
- Removal of polyps relieves symptoms of DUB.

Summary of Fibroids

- Ultrasound characteristics are reliable with well-circumscribed masses with shadowing, some have calcifications.
- Doppler and sonohysterograms may help identify and locate the myomas.
- Ultrasound can further assess the impact on the urologic system.
- MRI may be needed in certain circumstances.
- The only therapeutic approach for maintaining fertility is myomectomy—abdominal or hysteroscopic; UAE has small numbers of pregnancies post-procedure, including some in women with POF.

Future Technologies May Involve More Ultrasound Technology

- MR HIFU – multiple studies reported
- Specialized Doppler-guided vaginally placed uterine clamp (GYNECARE GYNOCCLUDE study)
- Laparoscopic intra-operative ultrasound-guided radiofrequency ablation of fibroids (Halt Lap RFA study)

REFERENCES

1. Cohen L, Valle R. Fertil Steril 2000;73; 197-204
2. Day Baird et al AJOG 2003;188:100-7. Parsons A., Hill A, and Spicer D. Frontiers in Biosci 1996;1;1-5.
3. Donnez J and Jadoul P. Hum Reprod 2002;17:1424-30.
4. Farhi J et al Hum Reprod 1995; 10:2576-8.
5. Maizlin ZV, Vos PM, Cooperberg PL. Is it a fibroid? Are you sure? Ultrasound Quarterly 2007;23:55-62.
6. Mooney SB, Milki AA. Effect of hysteroscopy performed in the cycle preceding controlled ovarian hyperstimulation on the outcome of in vitro fertilization. Fertil Steril
7. 2003;79:637-8
8. Madani T et al. Hysterocscopic polypectomy without cycle cancellation in IVF cycles. Reprod Biomed Online 2009;18:412-5
9. Surrey ES et al. F&S 2001;75:405-10.
10. Somigliana E et al. Hum Reprod Update 2007;13:465-76.
11. Kolankay A et al. Obstet Gynecolo Clin North Am 2006;33:145-52.
12. Stovall 1998.
13. Eldar-Geva 1998.
14. Hart 2001
15. Check 2002
16. Here Nezhat, 1991
17. Hasson, 1992
18. Mais, 1995
19. Bulletti, 1996
20. Stringer, 1996
21. Seinera, 1997
22. Darai, 1997
23. Dubuisson, 1998

NOTES

MENOPAUSAL DILEMMAS: THE ROLE OF ULTRASOUND

Steven R. Goldstein, M.D.
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Director of Gynecologic Ultrasound
Co-Director, Bone Densitometry
New York University School of Medicine
New York, New York

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Discuss the value of ultrasound in menopausal patients.
2. Describe normal transvaginal ultrasound appearances of the endometrium in post-menopausal women.
3. Explain the evolution of postmenopausal cystic adnexal masses.
4. List tamoxifen-induced uterine changes.
5. Assess postmenopausal endometrial fluid collections.

Menopausal Dilemmas: The Role of Ultrasound

Steven R. Goldstein, M.D.
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Disclosure

Boehringer Ingelheim, Eli Lilly, Pfizer, Glaxo SmithKline, Merck, Novo Nordisk, Novartis, Proctor & Gamble, Upsher Smith, Wyeth: Advisory Board, Cook ObGyn, Ackrad Labs (A Cooper Co.), Philips Ultrasound: Speakers Bureau

Sonosite: Stockholder, Philips Ultrasound: Consultant

- An explosion in the use of imaging in a variety of clinical scenarios, coupled with the amazing SENSITIVITY of imaging ("sonomicroscopy") has resulted in a multitude of incidental findings in all sorts of patients.
- This lecture will concentrate on these findings in postmenopausal patients.

Transvaginal Ultrasound: "Sonomicroscopy"

- Information obtained with advancingly refined technology cannot simply be handled according to old, established principles. New studies must be performed before clinical recommendations may be made.

Transvaginal Ultrasound: "Sonomicroscopy"

- Must be careful not to over-interpret such findings that may be much more common and less ominous than previously believed. Further study warranted!

Incidental Findings (Postmenopausal Women)

- Simple adnexal cysts
- "Endometrial" thickening
- Endometrial fluid collections

But First…

…the perfunctory introduction to menopause and "normal" (or rather) "expected" findings

Menopause

Defined as the FINAL menstrual period (obviously a retrospective diagnosis)

A patient is considered menopausal after cessation of menstruation for at least 12 months due to a depletion of ovarian follicles.

Climacteric Phase

The phase in the aging process that marks the transition from the reproductive stage of life to the non-reproductive stage (not always linear or smooth)

Endometrium in Menopause

- Becomes thin and atrophic
- No epithelial stimulation by estrogen
- Atrophic mucosa prone to superficial punctate ulceration
- Such "senile endometritis" is the most common cause of post-menopausal bleeding (PMB); must be distinguished from hyperplasia or adenocarcinoma

Ultrasound Appearance:

- Thin "pencil line" echogenicity
- Intact hypoechoic " halo" surrounds

Postmenopausal Ovaries

Anatomy of a Postmenopausal Ovary

- Folliculogenesis ceases
- Tunica albuginea becomes very dense, causing the surface of the ovary to become scarred and shrunken
- Eventually ovary is inert, consisting mainly of connective tissue; clings to posterior leaf of the broad ligament
- Can no longer be palpated on bimanual exam (basis for Barber's thesis)

Ovarian Anatomy and Ultrasound: Premenopause

- Sonolucencies of follicles make visualization relatively simple.
- When a women assumes lithotomy position, freely mobile premenopausal ovary is lateral to uterus and easily seen on vaginal probe ultrasound immediately adjacent to the pelvic side wall (iliac artery and iliac vein).

Ovarian Anatomy and Ultrasound Postmenopause

- Lack of normal folliculogenesis (no sonolucencies)
- Does not reach pelvic sidewall, therefore iliac vessels not so helpful in identification
- Loops of bowel everywhere

Lingering Question:

Will the absence of a normal ovary on ultrasound be as reassuring as definitively locating it and seeing that it is atrophic?

Postmenopausal Ovaries: Detection and Diagnosis

- **82% of ovaries seen; all abnormal ones were seen.**
- **Mean surgical diameter of non-visualized ovaries: 7.3 mm (range, 5-12 mm)**
- **No ovaries with normal ultrasound were abnormal at surgery.**
- **One microscopic Brenner tumor; ovary appeared grossly normal at transvaginal ultrasound (TVU) and to the eye.**

Rodriguez MH et al. Am J Obstet Gynecol. 159:1988

So What about Simple Cystic Masses Either Palpated or Discovered Incidentally?

Where Are We Today and How Did We Get Here?

Palpable Post Menopausal Ovary (PPMO) Syndrome
Barber and Graber *Obstet Gynecol* 1971;38:921

"An ovary that would be considered normal sized in a premenopausal woman should be considered abnormal in a postmenopausal woman…"

Palpable Post Menopausal Ovary (PPMO) Syndrome
Barber and Graber *Obstet Gynecol* 1971;38:921

"… and probably harbors a tumor, not necessarily malignant, but not functional or dysfunctional."

PPMO Revisited

"Patients with palpable postmenopausal ovary syndrome should not be followed or re-evaluated, but must be investigated promptly for the presence or absence of an ovarian tumor…"

PPMO Revisited

"… the only method of diminishing the mortality from ovarian cancer is the acceptance of more liberal indications of surgery."

Barber, 1984

The Postmenopausal Cystic Adnexal Mass: The Potential Role of Ultrasound in Conservative Management

STEVEN R. GOLDSTEIN, M.D., BALA SUBRAMANYAM, M.D., JON R. SNYDER, M.D., UZIEL BELLER, M.D., B. NAGESH RAGHAVENDRA, M.D. AND E. MARK BECKMAN, M.D.

Conclusions

"We concluded that small (≤5 cm) unilocular, unilateral postmenopausal adnexal cystic masses, with no septations or ascites, will have a very low incidence of malignant disease…"

Conclusions

"…therefore, serial ultrasound follow-up without surgical intervention may play a role in clinical management of such patients."

Ultrasound and Adnexal Cysts

- 85% of ovarian tumors are epithelial. Most will have some cystic component.
- Cystic structures are easily visualized on ultrasound.

Definition of a Simple Cyst

- Wall <3 mm thick and regular
- Anechoic fluid
- Round smooth wall
- Unilocular
- i.e., looks like a follicle

Adnexal Cysts in Postmenopausal Women

Levine, Gosink, Wolf et al. (Radiology, 1992;184:653)

- 184 women with 358 ovaries, 137 uteri
- 17.3% simple adnexal cysts at initial exam (range, 0.4 – 4.7 cm)
- Of these, 58% were 1.0 cm or less, 90% were 3.0 cm or less.
- No statistical difference whether or not on hormone replacement therapy (HRT).
- No mention of what % of patients with "cysts" had previous surgery.

Cysts < 10 cm in Asymptomatic Postmenopausal Women > 50 years

- Unilocular cysts in 3.3% (256 of 7705)
  - 49% resolved in 60 days; 51% persisted.
  - 45 women were operated, none of the cysts were malignant.
    - (32 cystadenomas)

Bailey CL et al. Gyncol Oncol 1998; 69:1-2

Simple Postmenopausal Cysts Are Not Malignant

(Van Nagell JR et al. Cancer, 2007)

- > 25,000 women screened annually over an 18-year period
- 3746 postmenopausal women with 6513 unilocular cystic ovarian masses
- Followed at 3- to 6-month intervals with transvaginal ultrasound (TVUS) without surgery
- Mean duration of follow-up: 4.6 years (range, 4 months – 16.5 years)
- No patient in this group has developed ovarian cancer.

Conclusions: Adnexal Cysts in Postmenopausal Women

1) Not all cystic adnexal structures are ovarian in origin.
2) None of what we see (at least those with surgical confirmation) are functional or physiologic cysts.
3) Vaginal ultrasound will identify many small sonolucencies (6-18 %).

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 postmenopausal (PM) bleeding actually bleed secondary to atrophic changes of vagina or endometrium
- Incidence of endometrial cancer in women with postmenopausal bleeding (PMB) ranges from 1%-14%

Transvaginal Ultrasound in PMB: Historical Perspective

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."

Goldstein SR. Endovaginal Ultrasound, 2nd ed. New York, NY: Wiley Liss; 1991

Transvaginal Ultrasound

- In the early 1990s, it was utilized in women with postmenopausal bleeding to see if it could predict which patients lacked significant tissue and could avoid dilation and curettage (D&C) or endometrial biopsy and their 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.

Transvaginal Ultrasound

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

Author	Year	Thinnest (mm) endometrium in a case of cancer	Thickest (mm) endometrium associated with inactive histology
Nasri	1989	8	8
Goldstein	1990	7	6
Varner	1991	5	5
Granberg	1991	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	≤ 5mm	97	0	100%
Gull 2003	≤ 4 mm	394	0	100%

Transvaginal Ultrasound Validation of Early Studies

- For endometrium ≤ 4 mm, incidence of malignancy is 1 in 917

Is Endometrial Biopsy Still Necessary?

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

Is Endometrial Biopsy Still Necessary? (Continued)

- The American College of Obstetricians and Gynecologists (ACOG) Committee Opinion (2/09): "When transvaginal ultrasound is performed for patients with postmenopausal bleeding and an endometrial thickness ≤ 4 mm is found, endometrial sampling is not required."

Transvaginal Ultrasound

General Principles

- Use the highest frequency transducer that still yields adequate penetration.
- Once endometrial 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.

Importance of "Endometrium 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 endometrial echo is not TOTALLY distinct, do NOT be afraid to indicate "endormetrial echo not well visualized."

Examples of "Good" Endometrial Echos Seen Originating from the Cervical Os

Endometrial 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 endometrial echo.

Endometrial Texture

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

Transvaginal Ultrasound in Non-bleeding Postmenopausal Patients

- The increasing use of imaging in a variety of clinical situations has led to the identification of thick endometrial findings in asymptomatic (i.e., non-bleeding) 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 the emergency department with lower abdominal pain

Clinical Case

- Afebrile
- Normal labs (blood and urine)
- Emergency department physician orders a computed tomography (CT) scan with diagnosis: "Rule out diverticular disease."

Clinical Case

- CT of 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 performed: "Thickened endometrial echo measuring 11.2 mm with some heterogeneous echoes. Suggest clinical correlation."
- Patient back to usual routine of 1-2 hours of tennis per day (singles, no less).

Clinical Case

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

Clinical Case

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

Clinical Case

- Patient is parous but had 2 cesarean sections, the last one 31 years ago.
- Because of inability to get tissue, patient is referred to another clinician in a teaching institution in a metropolitan area for a dilation and curettage 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 sample 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 endometrial 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 bled? (ACOG Committee Opinion 232, April 2000)

He responded, "Yes, that's correct." I pointed out that the woman we were discussing 1) was not on a drug that has cancer producing potential (tamoxifen); 2) has had no bleeding in 14 years; 3) has never had breast cancer; and 4) plays tennis two hours a day.

I asked why he felt so obliged to sample HER endometrium, 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: 1) How common is a <u>thick</u> endometrial echo in non-bleeding patients?

2) When present, what is its significance?

In POSTMENOPAUSAL Women

- Inactive, atrophic endometrium should be < 4-5 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. Euro J of Cancer 2000;36:S35-S36

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

Goruti G. Gyn Onc 2005;98:63-7

What Is the Risk of Malignancy in Such Polyps?

Fernandez-Parra et al. Int J Gynaecol Obstet, 2006,95:144-148

- Removed 117 polyps in postmenopausal women without bleeding
- NONE were mailgnant.
- Discussed importance of distinguishing endometrial carcinoma with polypoid growth from carcinoma arising in a polyp (base and surrounding endometrium must be benign)

Shushon 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%)
- Limitation of 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 A et al. BJOG 2005;112:379-382

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

So …In Postmenopausal Bleeding…

- "Cancer until prove otherwise"
- Role of high negative predictive value of a thin, distinct endometrial echo
- Perform transvaginal ultrasound first; sonohysterography, if necessary, to triage patients to: 1) no pathology; 2) global process (blind biopsy); 3) focal process (direct vision).

But…For an Incidental Finding of Endometrial Thickening…

- There is NO validation that these patients need AUTOMATIC endometrial sampling
- The incidence of thick endometrial echo is probably 10%-17% and is much like "simple" cyst of the post menopausal ovary was 20 years ago.
- Still appropriate (and always was) to use clinical JUDGMENT if high risk (obese, diabetic, hypertensive, nulliparous)

Transvaginal Ultrasound "Sonomicroscopy"

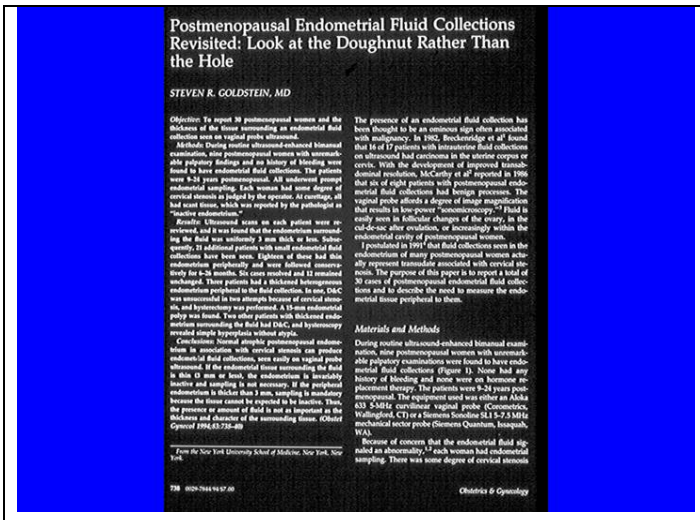
- Information obtained with advancing refined technology cannot simply be handled according to old established principles. New studies must be performed before clinical recommendations may be made.

Transvaginal Ultrasound "Sonomicroscopy"

- Must be careful not to over-interpret such findings that may be much more common and less ominous than previously believed. Further study warranted!

Endometrial Fluid Collections

- In the 1980s, endometrial fluid collection (on transabdominal ultrasound) was felt to be an ominous sign, very highly associated with malignancy (75% !!).



Postmenopausal Endometrial Fluid Collections Revisited: Look at the Doughnut Rather Than the Hole

STEVEN R. GOLDSTEIN, MD

Objective: To report 30 postmenopausal women and the thickness of the tissue surrounding an endometrial fluid collection seen on vaginal probe ultrasound.

Methods: During routine ultrasound-enhanced bimanual examination, nine postmenopausal women with unremarkable palpatory findings and no history of bleeding were found to have endometrial fluid collections. The patients were 9–24 years postmenopausal. All underwent prompt endometrial sampling. Each woman had some degree of cervical stenosis as judged by the operator. At curettage, all had scant tissue, which was reported by the pathologist as "inactive endometrium."

Results: Ultrasound scans on each patient were rereviewed, and it was found that the endometrium surrounding the fluid was uniformly 3 mm thick or less. Subsequently, 21 additional patients with small endometrial fluid collections have been seen. Eighteen of these had thin endometrium peripherally and were followed conservatively for 6–26 months. Six cases resolved and 12 remained unchanged. Three patients had a thickened heterogeneous endometrium peripheral to the fluid collection. In one, D&C was unsuccessful in two attempts because of cervical stenosis, and hysterectomy was performed. A 15-mm endometrial polyp was found. Two other patients with thickened endometrium surrounding the fluid had D&C, and hysteroscopy revealed simple hyperplasia without atypia.

Conclusions: Normal atrophic postmenopausal endometrium in association with cervical stenosis can produce endometrial fluid collections, seen easily on vaginal probe ultrasound. If the endometrial tissue surrounding the fluid is thin (3 mm or less), the endometrium is invariably inactive and sampling is not necessary. If the peripheral endometrium is thicker than 3 mm, sampling is mandatory because the tissue cannot be expected to be inactive. Thus, the presence or amount of fluid is not as important as the thickness and character of the surrounding tissue. (*Obstet Gynecol* 1994;83:750–4)

From the New York University School of Medicine, New York, New York.

738 0029-7844/94/$7.00

The presence of an endometrial fluid collection has been thought to be an ominous sign often associated with malignancy. In 1982, Breckenridge et al[1] found that 16 of 17 patients with intrauterine fluid collections on ultrasound had carcinoma in the uterine corpus or cervix. With the development of improved transabdominal resolution, McCarthy et al[2] reported in 1986 that six of eight patients with postmenopausal endometrial fluid collections had benign processes. The vaginal probe affords a degree of image magnification that results in low-power "sonomicroscopy."[3] Fluid is easily seen in follicular changes of the ovary, in the cul-de-sac after ovulation, or increasingly within the endometrial cavity of postmenopausal women.

I postulated in 1991[4] that fluid collections seen in the endometrium of many postmenopausal women actually represent transudate associated with cervical stenosis. The purpose of this paper is to report a total of 30 cases of postmenopausal endometrial fluid collections and to describe the need to measure the endometrial tissue peripheral to them.

Materials and Methods

During routine ultrasound-enhanced bimanual examination, nine postmenopausal women with unremarkable palpatory examinations were found to have endometrial fluid collections (Figure 1). None had any history of bleeding and none were on hormone replacement therapy. The patients were 9–24 years postmenopausal. The equipment used was either an Aloka 633 5-MHz curvilinear vaginal probe (Corometrics, Wallingford, CT) or a Siemens Sonoline SLI 5–7.5 MHz mechanical sector probe (Siemens Quantum, Issaquah, WA).

Because of concern that the endometrial fluid signaled an abnormality,[1,2] each woman had endometrial sampling. There was some degree of cervical stenosis

Obstetrics & Gynecology

In Summary

- Our approach to simple postmenopausal cysts has changed 180 degrees in the last 20 years.
- Incidental thickened endometrial echo in non-bleeding postmenopausal patients is common (10%-17%) and does not require automatic sampling.
- Postmenopausal endometrial fluid collections are a "naturally occurring" sonohysterogram, and are most often a sign of atrophy with cervical stenosis.

REFERENCES

1. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol. 2006;107:1475-8.
2. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 426: The role of transvaginal ultrasonography in the evaluation of postmenopausal bleeding. Obstet Gynecol. 2009;113:462-4.
3. Berlière M, Radikov G, Galant C, Piette P, Marbaix E, Donnez J. Identification of women at high risk of developing endometrial cancer on tamoxifen. Eur J Cancer. 2000;36:S35-6.
4. Barber HR, Graber EA The PMPO syndrome (postmenopausal palpable ovary syndrome). Obstet Gynecol. 1971;38:921-3.
5. Epstein E, Valentin L. Rebleeding and endometrial growth in women with postmenopausal bleeding and endometrial thickness < 5 mm managed by dilatation and curettage or ultrasound follow-up: a randomized controlled study. Ultrasound Obstet Gynecol. 2001;18:499-504.
6. Fernández-Parra J, Rodríguez Oliver A, López Criado S, Parrilla Fernández F, Montoya Ventoso F. Hysteroscopic evaluation of endometrial polyps. Int J Gynaecol Obstet. 2006;95:144-8.
7. Ferrazzi E, Torri V, Trio D, Zannoni E, Filiberto S, Dordoni D. Sonographic endometrial thickness: a useful test to predict atrophy in patients with postmenopausal bleeding. An Italian multicenter study. Ultrasound Obstet Gynecol. 1996;7:315-21.
8. Garuti G, Cellani F, Centinaio G, Sita G, Nalli G, Luerti M. Baseline endometrial assessment before tamoxifen for breast cancer in asymptomatic menopausal women. Gynecol Oncol. 2005;98:63-7.
9. Goldstein SR. Postmenopausal endometrial fluid collections revisited: look at the doughnut rather than the hole. Obstet Gynecol. 1994;83:738-40.
10. Goldstein SR. Postmenopausal adnexal cysts: how clinical management has evolved. Am J Obstet Gynecol. 1996;175:1498-501.
11. Goldstein SR, Nachtigall M, Snyder JR, Nachtigall L. Endometrial assessment by vaginal ultrasonography before endometrial sampling in patients with postmenopausal bleeding. Am J Obstet Gynecol. 1990;163:119-23.
12. Granberg S, Wikland M, Karlsson B, Norström A, Friberg LG. Endometrial thickness as measured by endovaginal ultrasonography for identifying endometrial abnormality. Am J Obstet Gynecol. 1991;164:47-52.
13. Hall DA, McCarthy KA The significance of the postmenopausal simple adnexal cyst. J Ultrasound Med. 1986;5:503-5.
14. Karlsson B, Granberg S, Wikland M, Ylöstalo P, Torvid K, Marsal K, Valentin L. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding--a Nordic multicenter study. Am J Obstet Gynecol. 1995;172:1488-94.
15. Lev-Sagie A, Hamani Y, Imbar T, Hurwitz A, Lavy Y. The significance of intrauterine lesions detected by ultrasound in asymptomatic postmenopausal patients. BJOG. 2005 ;112:379-81.
16. Levine D, Gosink BB, Wolf SI, Feldesman MR, Pretorius DH. Simple adnexal cysts: the natural history in postmenopausal women. Radiology. 1992;184:653-9.
17. Lieng M, Qvigstad E, Sandvik L, Jørgensen H, Langebrekke A, Istre O. Hysteroscopic resection of symptomatic and asymptomatic endometrial polyps. J Minim Invasive Gynecol. 2007;14:189-94.
18. Modesitt SC, Pavlik EJ, Ueland FR, DePriest PD, Kryscio RJ, van Nagell JR Jr. Risk of malignancy in unilocular ovarian cystic tumors less than 10 centimeters in diameter Obstet Gynecol. 2003;102:594-9.

19. Roman LD. Small cystic pelvic masses in older women: is surgical removal necessary? Gynecol Oncol. 1998;69:1-2.
20. Rodriguez MH, Platt LD, Medearis AL, Lacarra M, Lobo RA. The use of transvaginal sonography for evaluation of postmenopausal ovarian size and morphology. Am J Obstet Gynecol. 1988;159:810-4.
21. Rulin MC, Preston AL. Adnexal masses in postmenopausal women. Obstet Gynecol. 1987;70:578-81.
22. Shushan A, Revel A, Rojansky N. How often are endometrial polyps malignant? Gynecol Obstet Invest. 2004;58:212-5.
23. van Nagell JR Jr, DePriest PD, Ueland FR, DeSimone CP, Cooper AL, McDonald JM, Pavlik EJ, Kryscio RJ. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened . Cancer. 2007 1;109:1887-96.

NOTES

SONOHYSTEROGRAMS TO EVALUATE THE UTERUS AND TUBES

Alex Hartman, M.D.
True North Imaging
Thornhill, Ontario, Canada

LEARNING OBJECTIVES
At the conclusion of this presentation, participants should be able to:

1. Describe the uses of sonohysterography in infertility.
2. Decide when to use 3-dimensional (3D) sonohysterography.
3. Characterize sonohysterographic abnormalities.
4. Assess when ultrasound for tubal patency should be recommended.

Sonohysterograms to Evaluate the Uterus and Tubes

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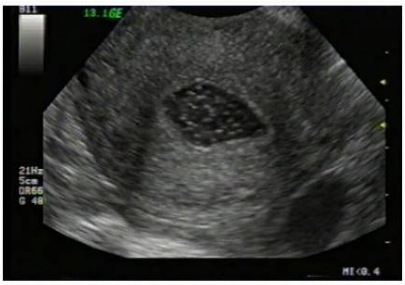
Disclosure

Nothing to disclose

Sonohysterography

An ultrasound technique in which the endometrial cavity is distended with saline, allowing evaluation of the single layer of the endometrium and the uterine cavity contents

Normal Uterus



Indications for Sonohysterography

- Abnormal uterine bleeding
- Infertility – primary and secondary, recurrent pregnancy loss (RPL)
- Abnormal transvaginal ultrasound
- Fibroids, pre- and post-operative
- Uterine malformations
- Postpartum (retained products, Asherman's)
- Tamoxifen
- Pre-endometrial ablation, intrauterine contraceptive device (IUCD)
- Pelvic pain (?)

Becker, Lev-Toaff, AJR, 2002

Contraindications

Absolute
- Pregnancy
- Active pelvic infection

Relative
- Cycle day
- Bleeding

Materials

1. Sterile saline
2. Cleansing solution
3. Speculum (preferably bivalved or disposable)
4. Disposable catheter (preferably 5 French)
5. Ultrasound unit with color Doppler
6. Tenaculum – used in 2%-3% of patients
7. Hysterosalpingo-contrast sonography (HyCoSy)– for tubal patency studies, if available

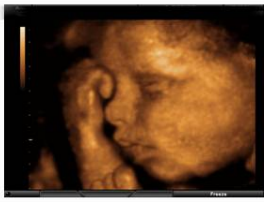
Premedication

Non-steroidal anti-inflammatory drugs (NSAIDs):
1. For discomfort/spasm
2. Tubal visualization

Antibiotics:
1. Not routine
2. Only for high risk

3D Ultrasound

3D ultrasound is playing an increasingly important role in ultrasound development. It involves a real-time capability to build and store a volume of ultrasound data, and display it in various ways.



Sonohysterography for Infertility Investigations...

Why bother ?

Sonohysterography

The prevalence of intracavitary and intramural uterine abnormalities: a prospective study of 1009 consecutive women.

Tur-Kaspa, Gal, Hartman, Hartman and Hartman,
Fertility and Sterility, 2006

600 consecutive infertility patients

Intramural abnormalities - **40.2%** (241 pts)
Intramural fibroids - **20.5%** (123 pts)
Adenomyosis - **24.0%** (144 pts)

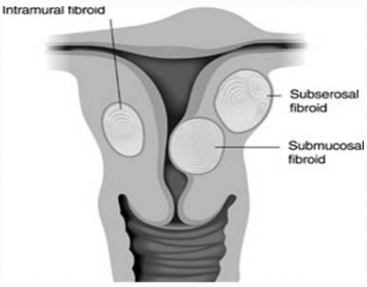
Leiomyomas

Sonohysterography is the test of choice for evaluating leiomyomas

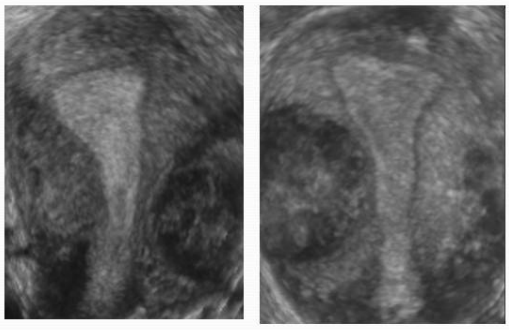
Lev-Toaff, Becker, JUM, 2002

Clinical - Account for 10% of postmenopausal bleeding (PMB)
- Dysfunctional uterine bleeding (DUB)
- Recurrent pregnancy loss (RPL)
- Premature labor
- Fetal malpresentation
- Complications of labor

Types of Fibroids



Intramural Fibroid



Adenomyosis

- **The single most common undiagnosed gynecological condition and the commonest cause of gynecological pain**

E. Lyons, ISUOG, November 2002

Adenomyosis

Pathology

- **Heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia**

Imaging

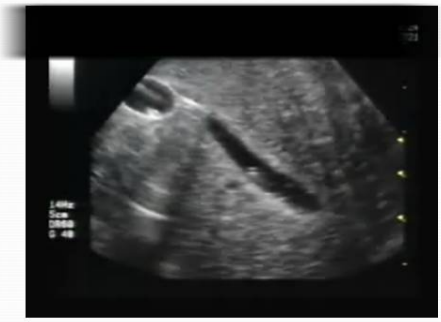
1. **Diagnosis**
2. **Extent**
3. **Evaluate conservative treatment**

Clinical Features

Typical scenario:

35 – 50 years old
Menorrhagia with clots
Cramps +++
"Bulky" uterus
Misdiagnosed as "poorly-defined" fibroids

Adenomyosis



Ultrasound Features

- **Abnormal myometrial echogenicity**
- **Heterogeneous myometrial echotexture**
- **Echogenic nodules or linear striations**
- **Myometrial cysts** (50% of cases)
- **Pseudowidening of endometrium**
- **Poor definition of endomyometrial junction**
- **Relative absence of mass effect**
- **Poor definition of lesion borders**

Myometrial Cysts

- Multiple
- 2-3 mm
- Tender
- Avascular
- Best seen in secretory phase
- Seen in 50%

Adenomyosis vs. Fibroids

(continued)

- Focal tenderness
- No edge shadowing
- No calcification
- Infiltrating
- Minimal mass effect
- Elliptical or globular-shaped uterus
- Increased echogenicity
- Echogenic nodules
- Linear striations

- Non-tender
- Edge shadowing
- Calcification common
- Non-infiltrating
- Mass effect
- Focal abnormality
- Decreased echogenicity

Adenomyosis vs. Fibroids

- Older patient
- Multiparous
- Poorly defined borders
- No capsule
- Asymmetric thickness
- Mixed echogenicity
- Myometrial cysts
- Central vessels (penetrating vascularity)
- Menorrhagia

- Younger patient
- Nulliparous
- Well-defined borders
- Pseudocapsule
- Focal masses
- Hypoechoic periphery
- No myometrial cysts
- Marginal vessels (draping vascularity)
- Usually no bleeding

Uterine Imaging

Intracavitary abnormalities:		**15.5%**	(93 patients)
Endometrial polyps	-	13.0%	(78 patients)
Submucosal fibroids	-	2.8%	(17 patients)
Adhesions	-	0.3%	(3 patients)

Total abnormalities - **48.2%** (289 patients)
(both intramural and intracavitary)

Sonohysterography (continued)

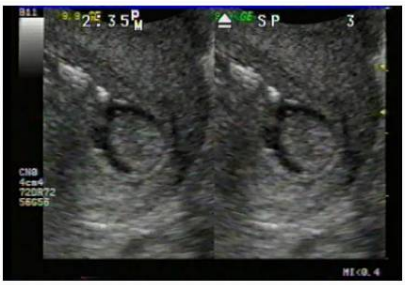
Polyps

Pathology – Localized overgrowth of glands and stroma

Clinical – cause of 30% of all postmenopausal bleeding:

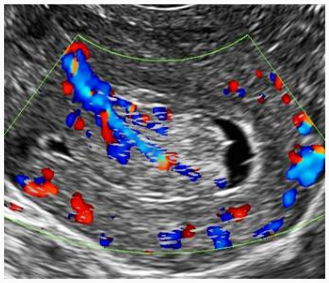
- **Intermenstrual bleeding**
- **Menometrorrhagia**
- **Infertility**

Polyp

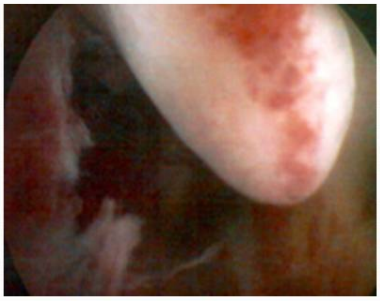


Polyp

28-year-old woman with dysfunctional uterine bleeding (DUB), infertility



Polyp on Hysteroscopy



Sonohysterography (continued)

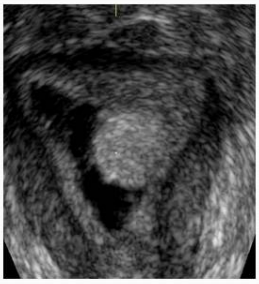
Polyps typical appearance

- Well-defined
- Homogeneous
- Isoechoic to endometrium
- Preserved endometrial-myometrial interface
- Vascular pedicle within stalk

Polyps atypical appearance

- Cystic
- Multiple
- Broad-based
- Irregular echogenicity

3D Sonohysterography - Polyp



Polyps

Is it a polyp, clot, or debris?

Mash it
Flood it
Doppler it

Submucosal Leiomyomas

European Hysteroscopy Society (EHS) Classification – 1993

Type 0 – Intracavitary – pedunculated submucosal myoma with no intramural extension

Type 1 - Sessile myoma with an intracavitary component of greater than 50%

Type 2 - Sessile myoma with an intracavitary component of less than 50%

Leiomyomas

The sonohysterography report must include:

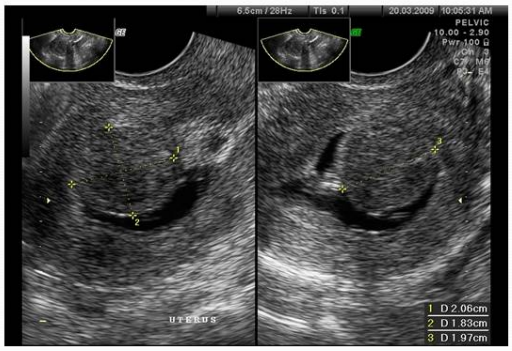
- **Confirmation of the fibroid**
- **Number**
- **Location**
- **EHS classification**
- **Distance from serosa**
- **Vascularity**
- **Other abnormalities**

Submucosal Leiomyomas

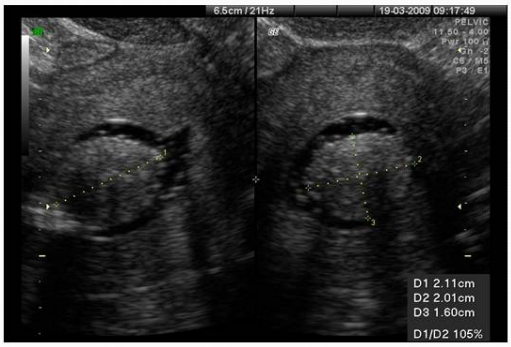
Usual appearance:
- Broad-based
- Hypoechoic
- Well-defined
- Shadowing
- Covered by endometrium

Atypical appearance:
- Pedunculated
- Lobulated
- Prolapsed

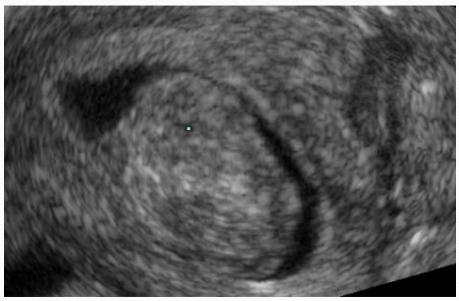
Type 0 Submucosal Fibroid



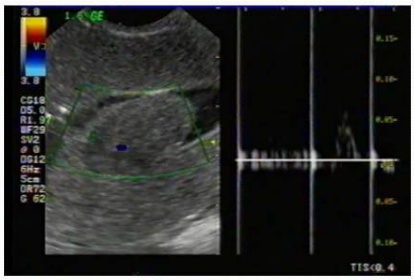
Type 0 Submucosal Fibroid



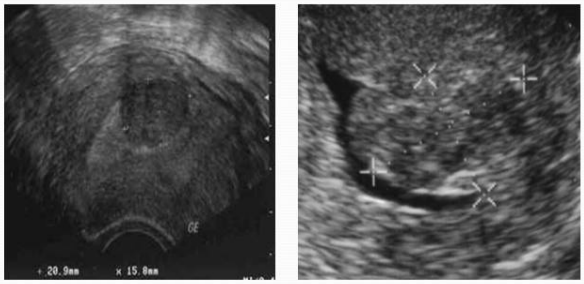
3D Sonohysterography – Type 0 Submucosal Fibroid



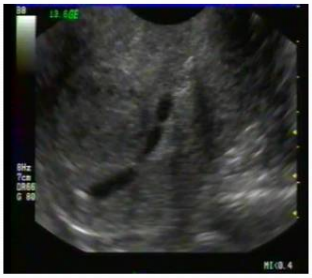
Type I Submucosal Fibroid > 50% in Cavity



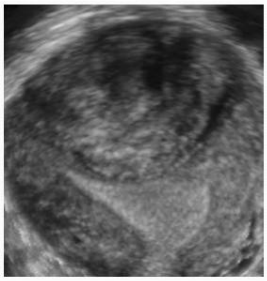
Type 1 Submucosal Fibroid > 50% in Cavity



Type 2 Submucosal Fibroid
< 50% in Cavity



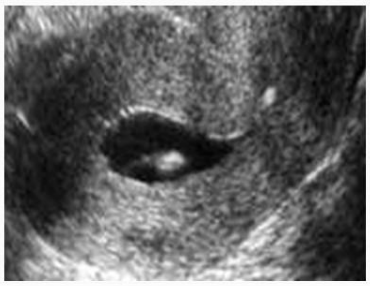
Type 2 Submucosal Fibroid
< 50 % in Cavity



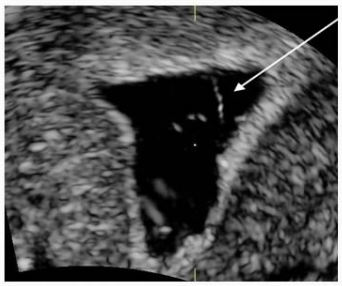
Adhesions

- Uterine scars
- Causes – trauma, infection, pregnancy, IUCD, instrumentation
- Signs – decreased or absent menses
- Can lead to – infertility
  - recurrent miscarriages
  - pelvic pain

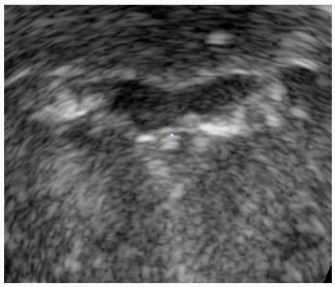
Adhesions



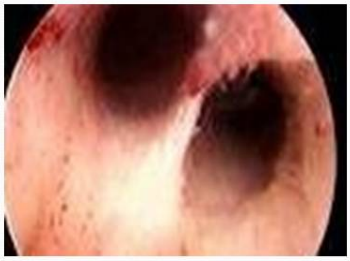
Adhesion



3D Sonohysterography - Adhesions



Adhesions



Endometrial Hyperplasia

Pathological and clinical

Proliferation of endometrial glands of irregular size and shape, with an increase in the gland/stroma ratio

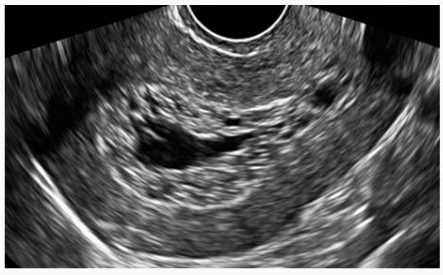
-accounts for 4% of postmenopausal bleeding

DUB

Ultrasound appearance:

- Diffuse thickening of the echogenic endometrial stripe
- Focal thickening

Endometrial Hyperplasia



Sonohysterography

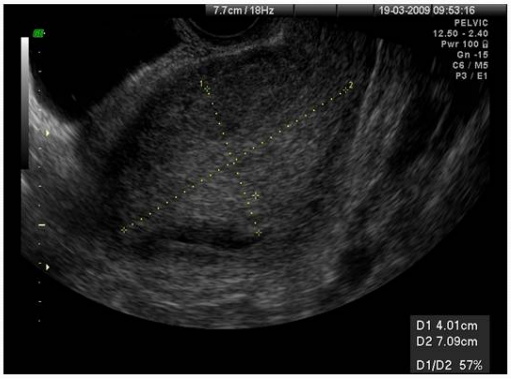
Risk factors for hyperplasia and cancer

- ✓ ↑ unopposed estrogen
- ✓ Tamoxifen
- ✓ Nulliparity
- ✓ Obesity
- ✓ Hypertension
- ✓ Diabetes

Endometrial Carcinoma

- ✓ Most common gynecologic malignancy
- ✓ Average age of patient, 59 years
- ✓ Accounts for 4%-5% of postmenopausal bleeding

PMB - Endometrial Carcinoma



Endometrial Carcinoma

Ultrasound appearance

- ✓Non-specific thickening
- ✓Single layer > 8 mm
- ✓Irregular
- ✓Broad-based
- ✓Poorly marginated
- ✓Polypoid
- ✓Decreased uterine distensibility
- ✓Use as little saline as possible

Uterine Anomalies

3D ultrasound vs. Sonohysterography for the Diagnosis of Uterine Anomalies: A Prospective Blinded Study of 1000 Consecutive Women

Hartman and Tur-Kaspa, ASRM, 2004

Infertile Patients (n = 591 Patients)

Type of malformation	3D	SHG
Normal	415 (70%)	473 (80%)
Arcuate	137 (23%)	86 (15%)
Septate*	36 (6%)	16 (3%)
Others	3 (<1%)	2 (<1%)

*includes subseptate

3D Ultrasound vs. 3D Sonohysterography in the Diagnosis of Uterine Anomalies

Michael Hartman, MD, Jason Hartman, BA, Brian Hartman, Carmen Oprea and Alex Hartman MD

Fertility and Sterility, 2008; 90 (S1)

Results

	3D ultrasound (n=600)	3D SHG (n=600)
Arcuate	18.7% (112)	28.3% (170)
Borderline arcuate/partial septum	1.8% (11)	1.8% (11)
Partial septum	1.5% (9)	2.2% (13)
Complete septum	1.2% (7)	1.7% (10)
Bicornuate	0	0.2% (1)
Total	23.2% (139)	34.2% (205)

HyCoSy: For Tubal Patency

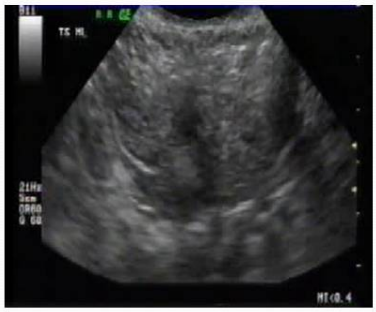
(Hysterosalpingo–contrast sonography)

The estimated percentage of tubal factor as a contributing cause of infertility is 25% - 40%

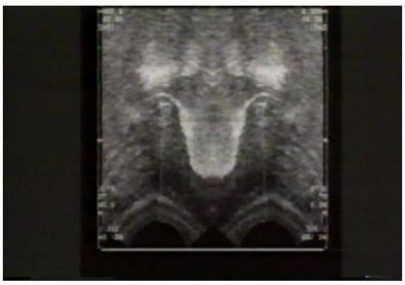
Ultrasound salpingography

- Air insufflation
- Doppler +/- 3D
- HyCoSy – Saline + air
  - Carbohydrate molecule

HyCoSy: 28-Year-Old Gravida 0



HyCoSy



HYCOSY: For Tubal Patency (continued)

HyCoSy vs. "Lap and Dye" + HSG

- Accurate
- Real-time
- Safe
- No radiation
- No anesthetic
- Well tolerated
- Cost-effective

HYCOSY: For Tubal Patency (continued)

Accuracy

The concordance rates/tube of HyCoSy with

HSG and L and D

83% 83% (VS. 76% HSG and LTD)

Molz, 1997, Meta-analysis

HyCoSy: For Tubal Patency (continued)

False negative

1. Tubal spasm
2. Differential resistance between the tubes
3. Incorrect technique
4. Patient size
5. Overlying bowel

False positive

1. Misinterpretation of partial patency, e.g., hydrosalpinx
2. Peritubal adhesions

Conclusions

- Sonohysterography (SHG) provides important information for the evaluation of the infertility patient.
- 3D and Doppler assessment can be beneficial adjuncts to SHG.
- HyCoSy studies provide an easy, well-tolerated and accurate appraisal of tubal patency.

REFERENCES

1. Becker E Jr, Lev-Toaff A.S, Kaufman EP, Halpern EJ, Edelweiss MI, Kurtz AB. The added value of transvaginal sonohysterography over transvaginal sonography alone in women with known or suspected leiomyoma. J Ultrasound Med. 2002 Mar; 21(3):237-47.
2. Davis PC, O'Neill MJ, Yoder IC, Lee SI, Mueller PR. Sonohysterographic findings of endometrial and subendometrial conditions. Radiographics. 2002 Jul-Aug; 22(4):803-16.
3. Lev-Toaff AS, Pinheiro LW, Bega G, Kurtz AB, Goldberg BB. Three-dimensional multiplanar sonohysterography: comparison with conventional two-dimensional sonohysterography and X-ray hysterosalpingography. J Ultrasound Med. 2001 Apr;20(4):295-306.
4. Perez-Medina T, Bajo J, Huertas MA, Rubio A. Predicting atypia inside endometrial polyps. J Ultrasound Med. 2002 Feb;21(2):125-8.
5. Alcazar JL, GalanMJ, Minguez JA, Garcia-Manero M. Transvaginal color Doppler sonography versus sonshsysterography in the diagnosis of endometrial polyps. J Ultrasound Med. 2004 Jun;23(6):743-8.
6. Hann LE, Kim CM. Sonohysterography compared with endometrial biopsy for evaluation of the endometrium in Tamoxifen-treated women. J Ultrasound Med. 2003; 22:1173-9.
7. Williams PL, Laifer-Narin SL, Ragavendra N. US of abnormal uterine bleeding. Radiographics. 2003; 23:703-18.
8. Berridge DL, Winter TC. Saline infusion sonohysterography. J Ultrasound Med. 2004; 23:97-112.
9. Jorizzo JR, Riccio GJ, Chen MYM, Carr JJ. Sonohysterography: the next step in the evaluation of the abnormal endometrium. Radiographics. 1999;19:S117-S130.
10. Tur-Kaspa I, Hartman A, Hartman M, Hartman J. The prevalence of intracavitary and intramural uterine abnormalities: a prospective study of 1009 consecutive women. Fertil Steril. 2004 Oct; 82:Suppl.2#P-98.
11. de Kroon CD, de Bock GH, Dieben SWM, Jansen FW. Saline contrast hysterosonography: a systemic review and meta-analysis. Amer. Instit of Ultrasound in Med. Annual meeting 2002.
12. Goldstein, S. Abnormal Uterine Bleeding. International Society of Ultrasound in Ob Gyn. 2002 Nov. Lecture.
13. Benacerraf B. 2D versus 3D sonohysterography. Advances in 3D/4D Ultrasound. 2004 May. Lecture.
14. Frates MC, Doubilet PM. Role of Doppler Ultrasonography in the prediction of pregnancy outcome in women with recurrent spontaneous abortion. J Ultrasound Med. 1996; 15(8):557-62.
15. Steer CV, Campbell S. The use of transvaginal color flow imaging after in vitro fertilization to identify optimum uterine conditions before embryo transfer. Fertil Steril. 1992; 57: 372-6

NOTES

OVARIAN MASSES: BENIGN, MALIGNANT AND FERTILITY

Elizabeth Puscheck, M.D., M.S.
Wayne State University
School of Medicine
Detroit, Michigan

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Distinguish the characteristics of benign versus malignant ovarian masses.
2. Identify masses outside of the ovary that may mimic ovarian masses.
3. Discuss the impact of ovarian masses on fertility.

Ovarian Masses: Benign, Malignant and Fertility

Elizabeth Puscheck, M.D.
Wayne State University
School of Medicine
2009

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- Identify masses outside of the ovary that may mimic ovarian masses.
- Discuss the impact of ovarian masses on fertility.

Disclosure

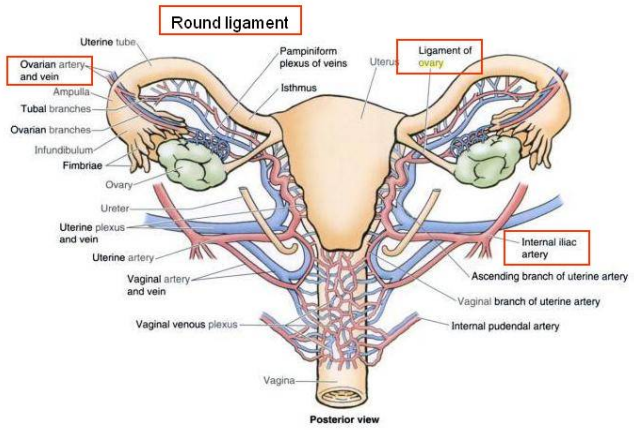
Wyeth, Ethicon: Research

Outline

- How to find and assess ovaries
- List common extra-ovarian masses that mimic ovarian masses
- Characteristics of benign masses
- Common benign tumors
- Characteristics of malignant masses
- Examples of malignant masses
- Cases: benign or malignant?
- Summary

Normal Ovary

- Location
- Landmarks to finding the ovary
- Technique to help locate the hard-to-find ovary



http://anatomytopics.files.wordpress.com/2008/12/blood-supply-uterus-vagina-ovary-uterine-tube.jpg

Ultrasound Image

- Ovary
- Internal iliacs
- Round ligament
- Maybe ovarian vessels

Difficult Cases

- Postmenopausal ovary
  - Smaller ovaries with few or no follicles
  - May be high, consider transabdominal approach if not seen
  - Extended pelvic exam
- Large mass
  - May be in the abdomen
- Uncertain whether mass is in the ovary or next to the ovary
  - Extended pelvic exam

Extended Pelvic Exam

- Use a hand on the patient's abdomen while using the transvaginal probe to scan for the ovary
- Use a gentle sweeping motion from the lateral and bring hand down and medial to the transducer like a pelvic exam.
- Follow the internal iliacs by ultrasound; up and down.
- Look for the round ligament and the ovarian vessels.

Mass: Ovarian or Extra-ovarian

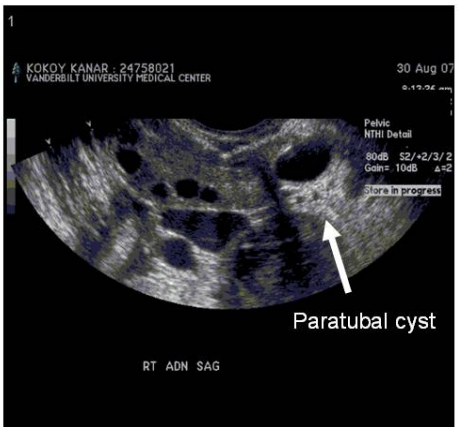
- Ultrasound extended pelvic exam
- Sliding-organ sign
- Follow the mass
- 3D ultrasound may be helpful

Extra-Ovarian Mases

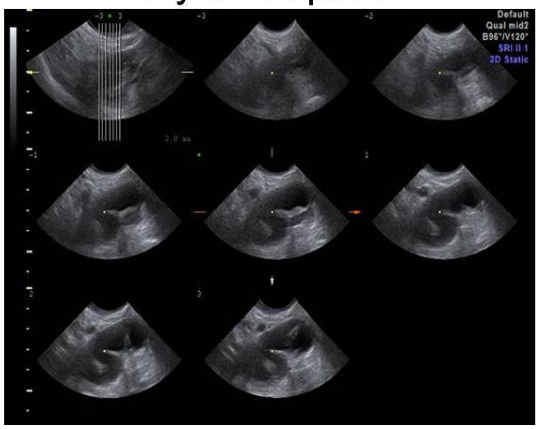
- Cystic
  - Paraovarian/paratubal cyst
  - Hydrosalpinx
  - Peritoneal inclusion cysts
  - Unusual: bladder diverticulum, lymphocele, abscess, perineural/root sleeve cyst, paraovarian cystadenoma
- Solid
  - Pedunculated fibroid
  - Rudimentary uterine horn
  - Rare: lymphadenopathy, neural neoplasm
- Variable
  - Ectopic pregnancy
  - Rare: fallopian tube neoplasm, gastrointestinal (GI) tract lesions (neoplasms, appendicitis or mucocele, Meckel's diverticulum)

Para-ovarian or Para-tubal Cyst

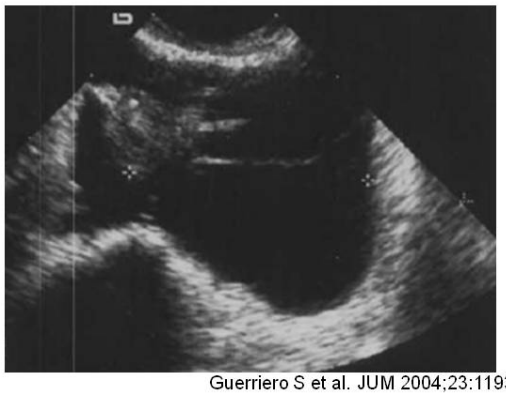
Fleischer et al. JUM 2008



Hydrosalpinx

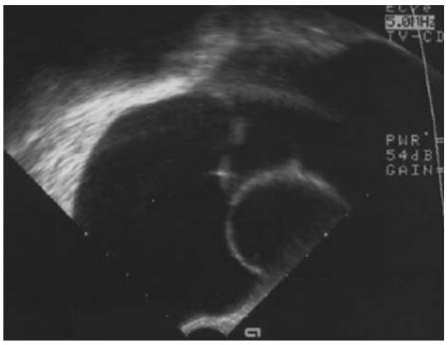


Peritoneal Inclusion Cyst



Guerriero S et al. JUM 2004;23:1193-1200

Peritoneal Cyst



Guerriero S et al. JUM 2004;23:1193-1200

Characteristics of Benign Ovarian Masses

- Unilocular cyst
- Smooth walls
- Thin septations
- No Doppler flow within the mass
- No projections
- No solid components

International Ovarian Tumor Analysis (IOTA) Study

- Multicenter: 9 centers
- Transvaginal (TV) first, then transabdominal (TA) ultrasound if the entire mass was not seen
- Grey scale and color Doppler
- 42 grey-scale variables
- 6 Doppler variables
- Surgery if mass persisted > 6-12 weeks
- Earlier if symptoms, malignancy suspected, patient request

Simple Rules for Benign Tumors

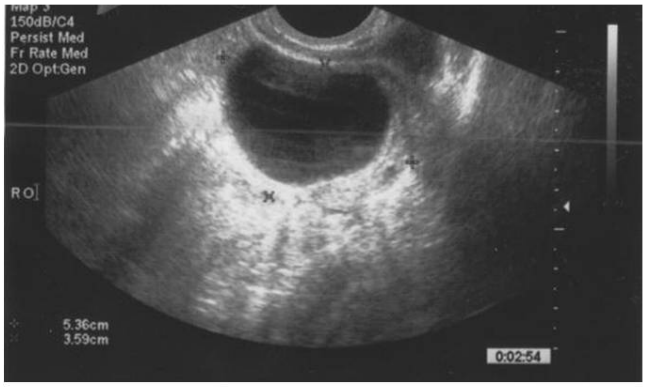
Timmerman Ultrasound Obstet Gynecol 2008;31:681-690

1. Unilocular cyst
2. Presence of solid components, where the largest solid component is <7 mm in largest diameter
3. Acoustic shadows
4. Smooth multilocular tumor less than 100 mm in largest diameter
5. No detectable blood flow on Doppler examination

Benign Ovarian Masses

- Physiologic:
  - Periovulatory follicle or simple cyst?
    Normal range for ovulatory follicle (17-30 mm)
  - Corpus luteum
- Common benign ovarian masses:
  - Simple ovarian cyst
  - Hemorrhagic corpus luteum
  - Endometrioma
  - Mature cystic teratoma

Simple Cyst



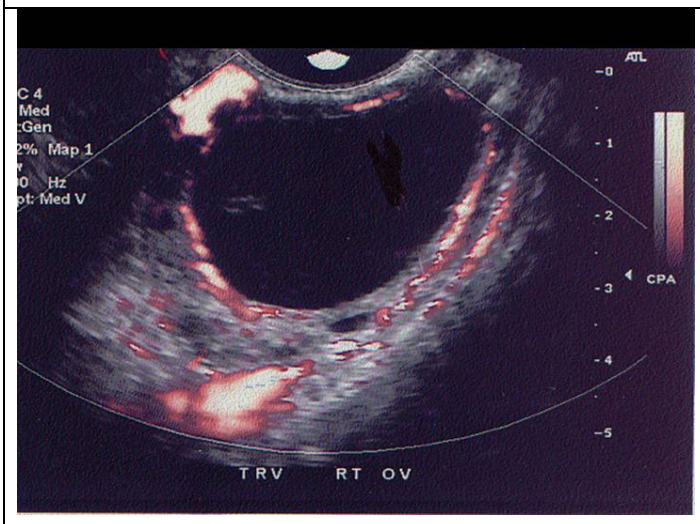
Simple Ovarian Cysts

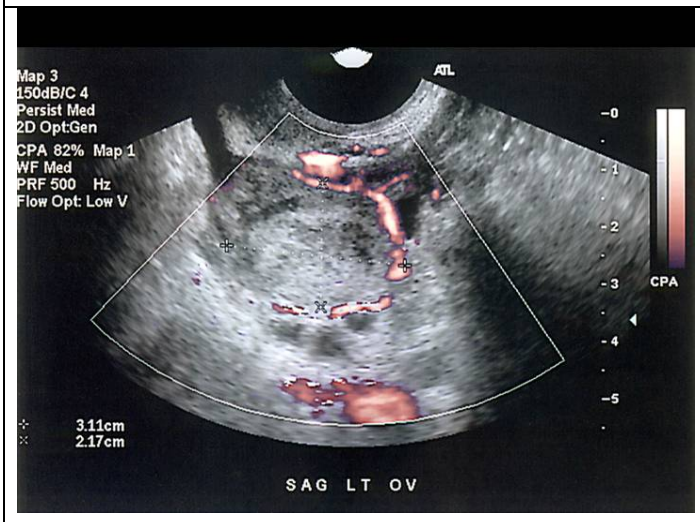
- Simple cysts:
  - Premenopausal woman,
    - Common, follow- up if > 3 cm
  - Postmenopausal woman, frequency 3.5%-17%,
  - Less than 10% increase in size
  - Most are less than 5 cm
  - Observe,
  - If enlarges or changes appearance, consider surgery

Frequency of Malignancy in Simple Cysts:

- Premenopausal woman, 0.7%
- Postmenopausal woman, 1.6%
- All malignancies reported were >7.5 cm in size
- Pathology revealed small mural nodules

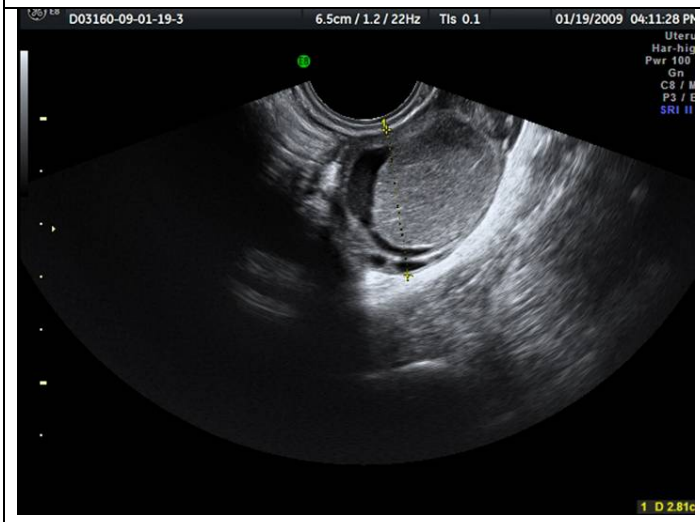
Brown DL. Ultrasound Quarterly 2007;23:87-104





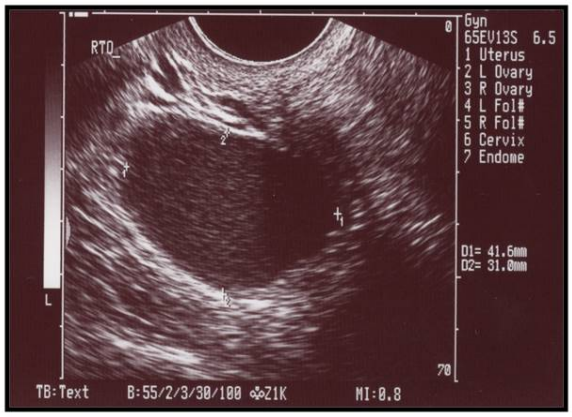
Hemorrhagic Cysts: Appearance Varies

- Hyperechoic
- Internal echoes with fine "reticular" lines from fibrin strands (heterogeneous)
  - Described as thin lines, like fishnet or lace; not septa
  - Sensitivity 90%, specificity 98%, likelihood ratio (LR) = 40.
- Retracting clot
  - Solid echoes with a concave margin
  - Sensitivity 30%, specificity 100%, LR > 67
- Absence of Doppler flow into clot
- Smooth walls, no septa, fibrin strands:
  - Sensitivity 90%, specificity 100%, LR = 200
- Uncertain? Follow-up in 6-8 weeks; it should resolve in most cases

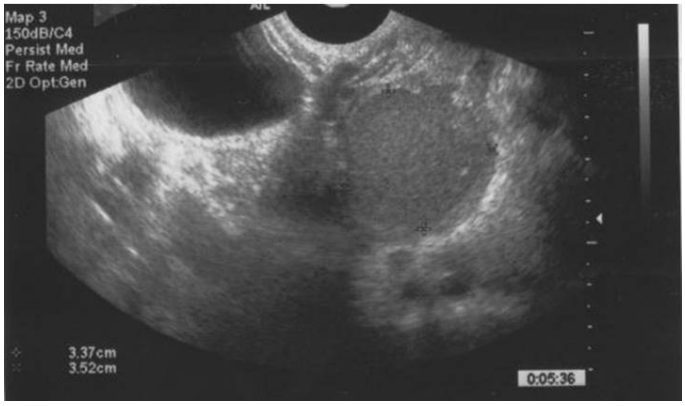


Endometrioma

- Homogeneous low-medium level echoes
- "Ground glass" appearance
- Smooth walls
- Overlapping appearance with hemorrhagic corpus luteum
- No acoustic streaming present



Atypical Endometrioma

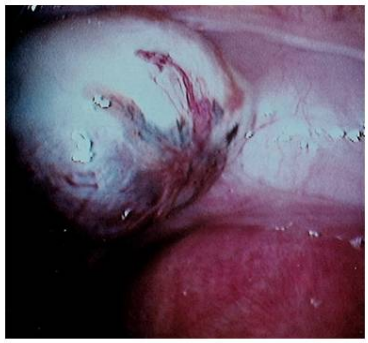


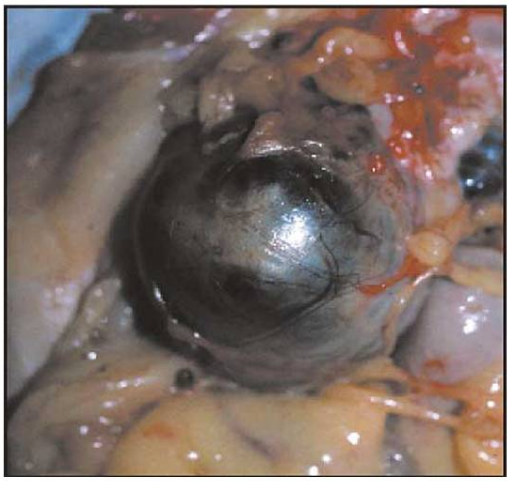
Alternative Findings in Endometriomas

Also commonly found:

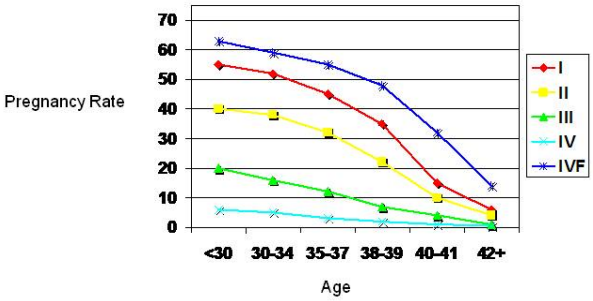
- Septations and multilocularity is common – 45% of endometriomas
- Hyperechoic foci within the cyst – 35% of endometriomas
- Wall nodularity – 20% of endometriomas
  - Check Doppler – typically no flow due to clot
  - However, if it is focal endometrium, there may be Doppler flow.
- Solid appearance, infrequent for endometriomas (older, fibrosis?)
- Extra-ovarian implants may get large enough to be seen by ultrasound and tend to be solid.

Endometrioma





Treatment Success of Endoscopic Surgery in Women with Endometriosis



Ovarian Reserve After Laparoscopic Cystectomy

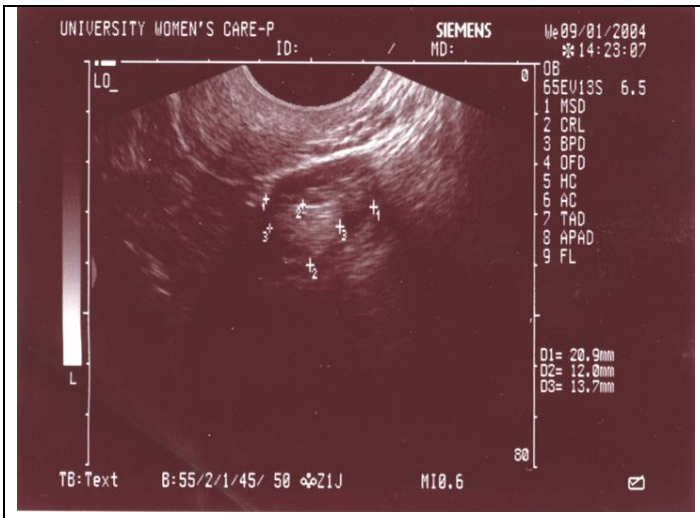
- Chang et al. Impact of laparoscopic cystectomy on ovarian reserve... Fertil Steril 2009
  - Ovarian volumes and serial anti-müllerian hormone (AMH) values
  - Endometriomas had the largest decrease compared to non-endometriotic cystectomy first week post-operatively (33.9% vs. 69.2% of preoperative level)
  - 3 months later AMH recovered to 65% of pre-operative level
- Dilak et al. Excision of endometriotic cyst wall may cause loss of functional ovarian tissue. Fertil Steril 2006
  - Compared drainage, fenestration, stripping and coagulation, cystectomy review
  - Removes primordial and primary follicles with cyst wall
  - Cystectomy better for symptom relief
  - Affected ovary performs more poorly after surgery than unaffected ovary
  - Older age worsens ovarian reserve after cystectomy
  - Controversy about impact on ovarian reserve

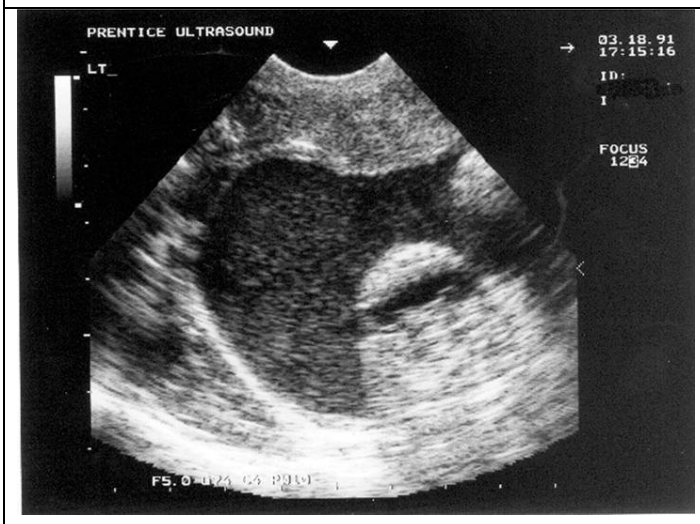
Recurrence of Endometriosis

- 5%-15% within 1 year
- 10%-40% within 2 years
- 25%-60% within 5 years.

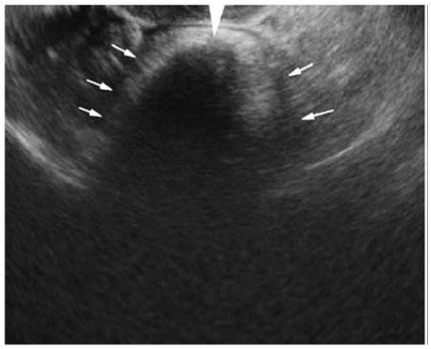
Mature Cystic Teratoma or Dermoid

- Most can be diagnosed by ultrasound
- Increased risk for torsion
- Ultrasound findings:
  - Hyperechoic area that attenuates sound
    - Dermoid plug, Rokitansky protuberance, echogenic nodule or mass
  - "Tip of the iceberg" sign – marked shadowing so that the deeper part of the mass is not seen
  - Fluid levels may be present
  - No Doppler flow within



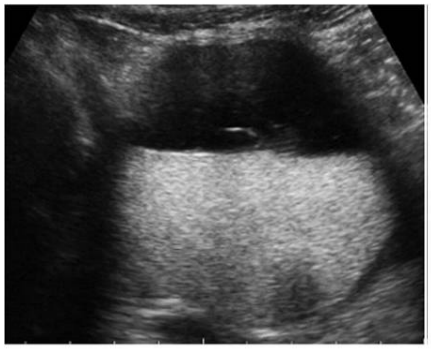


"Tip of the Iceberg"

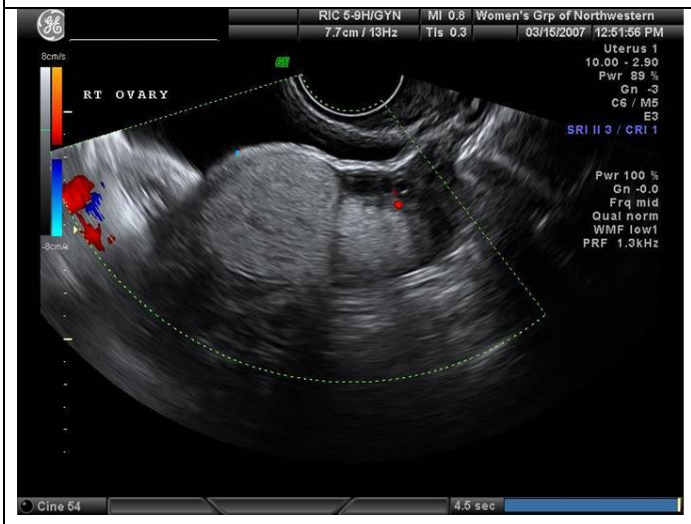


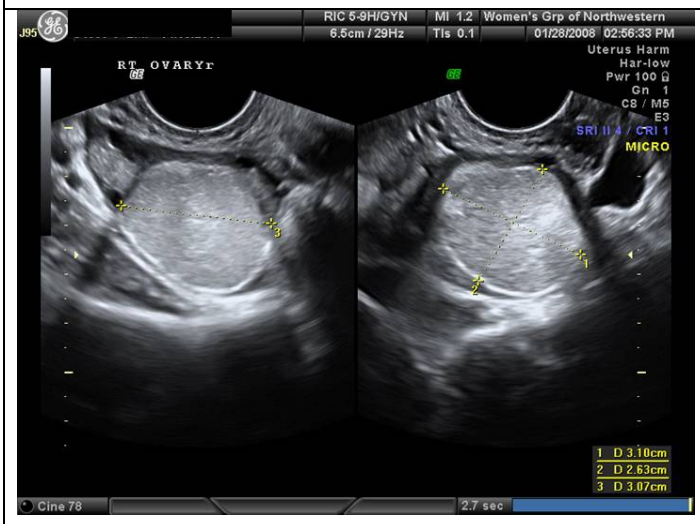
Tongsong T, Luewan S, Phadung P, et al. Int J Gynecol Obstet 2008;103:99-104.

Dermoid with Fluid Levels



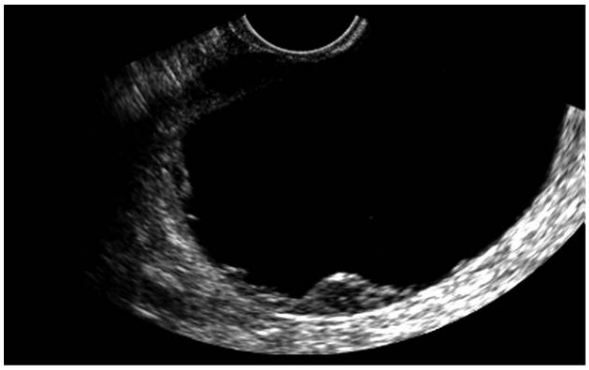
Tongsong T, Luewan S, Phadung P, et al. Int J Gynecol Obstet 2008;103:99-104.





Mucinous Cystadenoma (Benign)

Fleischer JUM 2008;27:1011-1018



Characteristics of Malignant Ovarian Masses

- Solid mass
- Irregular mass
- Complex mass: cystic and solid components
- Solid projections into the mass
- Doppler flow going into the mass

- Valentin L. Eur J Obstet Gynecol Reprod Biol 1997:72:63-72. Subjective evaluation of color flow distinguished benign from malignant
- Kurjak A et al. Ultrasound Obstet Gynecol 1993;3:137-54 reported **central vessel** within the mass or papillary projection along with a **diffuse vascular pattern with resistance index (RI) < 0.4** were tumors that were likely to be malignant
- Brown DL et al. Radiology 1998;208:103-110 described 4 features to differentiate benign from malignant by the presence or absence of:
    1. Any solid component
    2. Color Doppler flow
    3. Free intraperitoneal fluid
    4. Thickness of septations

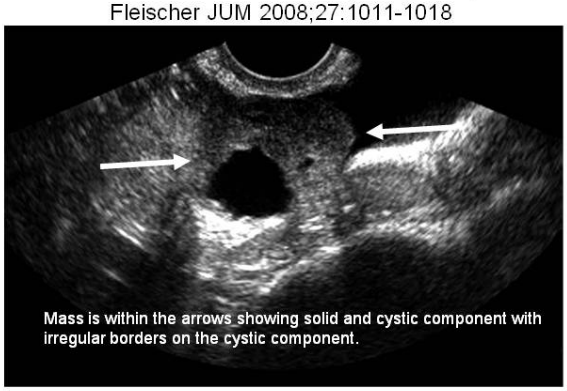
Simple Ultrasound Rules for Diagnosing Ovarian Cancer

International Ovarian Tumor Analysis (IOTA)

- Malignancy rules:
  1. Irregular solid
  2. Ascites
  3. At least 4 papillary structures
  4. Irregular multilocular solid tumor with largest diameter 100 mm
  5. Very high color content on color Doppler examination

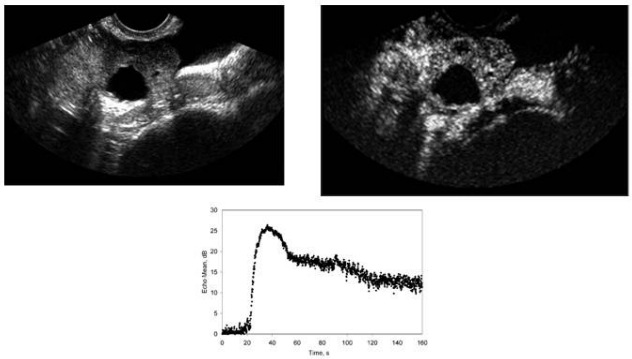
Solid Mass with Serous Adenocarcinoma (Malignant)

Fleischer JUM 2008;27:1011-1018



Mass is within the arrows showing solid and cystic component with irregular borders on the cystic component.

Serous Adenocarcinoma with Contrast

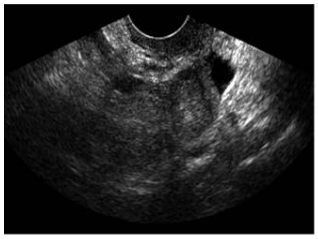


Fleischer A et al. JUM 2008;27:1011-1018

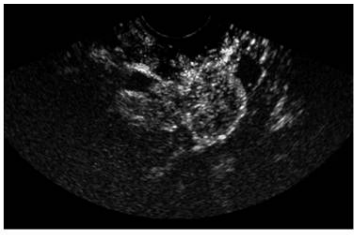
Contrast of Serous Adenocarcinoma (Left Ovary)

Fleischer JUM 2008 2008;27:1011-1018

Definity Contrast (Off FDA Label Use—Research)



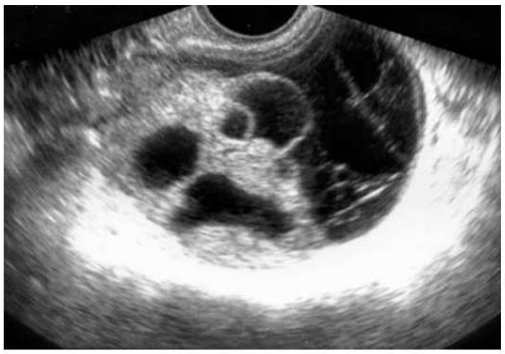
Pre-contrast



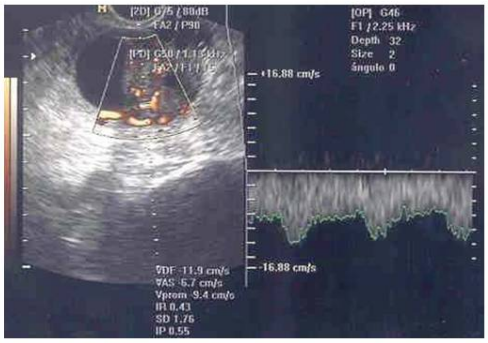
Post-contrast

Primary Ovarian Cancer

Alcazar JUM 2003; 22:243-47

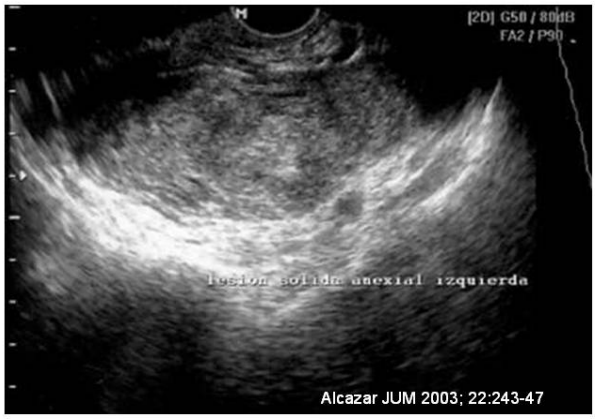


Metastases to the Ovary: Doppler Flow into the Mass

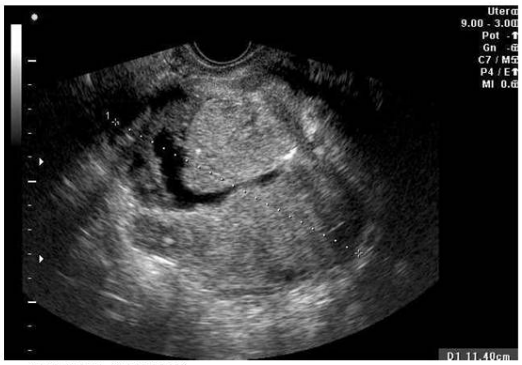


Alcazar JUM 2003; 22:243-47

Metastases to Ovary

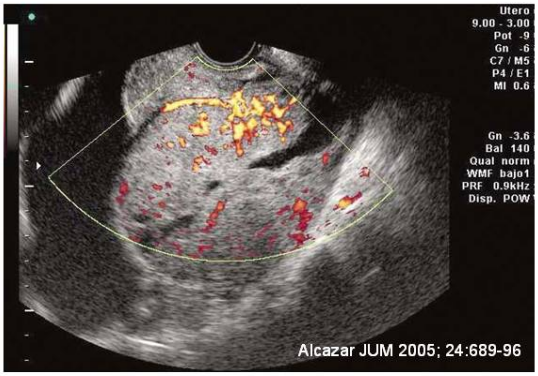


Solid Mass Within the Ovary

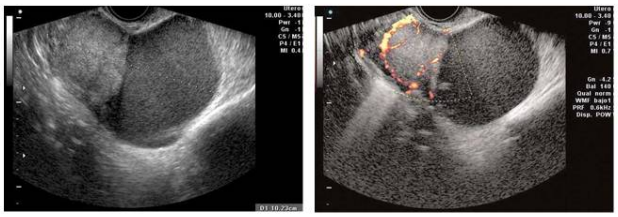


Alcazar JUM 2005; 24:689-96

Color Flow into the Mass



Endometrial Carcinoma of the Ovary



Alcazar JUM 2005; 24:689-96

Malignant Changes

- Neovascularization is thought to be an early change.
- Color Doppler may help find areas of angiogenesis.
- Expect low impedance of the intra-tumor blood flow for ovarian cancer and the **resistance index is < 0.4.**
- Pulsatility index (PI) measures blood flow impedance distal to the point of sampling and values **PI <1.0** is suggestive of borderline or malignant ovarian tumors (Medeiros Int J Gynecol Cancer 2009;19:230-236).
- Hemorrhagic corpus luteum could give a false positive, so plan the ultrasound early in the cycle.
- Kurjak transvaginal color Doppler to detect stage I ovarian cancer

Accuracy of Color Doppler in Ovarian Tumors

Medeiros et al. Int J Gynecol Cancer 2009;19:230-6

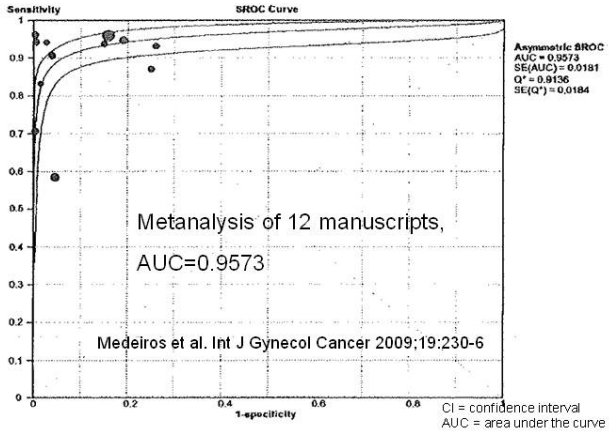
- 1990-2007
- 5 MHz transvaginal probe with color Doppler
- Cancer with RI $\leq$ 0.5
- Histologic confirmation
- 12 studies of 2398 women; meta-analysis
- Inclusion required that masses be categorized as benign, borderline or malignant

Malignant or borderline versus benign ovarian tumors

Study	N	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
Chou et al[19]	108	0.96 (0.8–1)	1 (0.95–1)	2727 (107–69.102)
Emoto et al[20]	143	0.90 (0.7–0.9)	0.96 (0.9–0.98)	234 (55.7–982)
Guerreiro et al[21]	347	0.58 (0.4–0.7)	0.95 (0.9–0.97)	28.9 (13.6–61)
Guerreiro et al[22]	826	0.95 (0.9–0.98)	0.84 (0.8–0.86)	124.2 (53.5–288)
Itakura et al[23]	95	0.87 (0.7–0.96)	0.75 (0.62–0.85)	20.2 (6.1–66.7)
Kurjak et al[24]	56	0.87 (0.4–1)	1 (0.89–1)	335 (12.3–9056.4)
Kurkak et al[25]	174	0.93 (0.7–1)	0.74 (0.62–0.83)	38.3 (8.3–176)
Kurjak and Predanic[26]	83	0.97 (0.8–1)	1 (0.97–1)	6825 (272.4–170,979)
Predanic et al[27]	83	1 (0.59–1)	0.85 (0.76–0.92)	85.4 (4.5–1600)
Tepper et al[28]	217	0.7 (0.56–0.82)	1 (0.9–1)	800.8 (46.8–13,684)
Weiner et al[29]	53	0.94 (0.7–1)	0.97 (0.85–1)	560 (32.9–9529.6)
Wu et al[30]	222	0.94 (0.87–0.98)	0.8 (0.73–0.86)	76.3 (25.7–225.9)
Total	2,400	0.87 (0.84–0.9)	0.9 (0.87–0.9)	125.43 (55.4–283.9)

Medeiros et al. Int J Gynecol Cancer 2009;19:230-6

Ultrasound with Doppler for Detecting Ovarian Cancer with 95% CI



CI = confidence interval
AUC = area under the curve

Summary

Medeiros et al. Int J Gynecol Cancer 2009;19:230-6

- Systematic review of 12 studies to distinguish between benign, borderline and malignant ovarian tumors
- Sensitivity for detecting malignant ovarian cancer using ultrasonography with Doppler was 87%.
- Specificity was 90%.
- Limitations:
  1. All studies were retrospective
  2. Not blinded
  3. Small numbers
- Ultrasound with Doppler is a useful preoperative test of the prediction of benign or malignant nature of pelvic mass.

ACOG: Ultrasound and Demographics

- CA125
  - > 35 units/mL postmenopausal
  - > 200 units/mL premenopausal
- Ascites on ultrasound or computed tomography (CT)
- Nodular or fixed pelvic mass
- Abdominal/distant metastases on CT
- Family history of at least 1 first-degree relative with ovarian or breast cancer
- Tested on 837 patients
- Sensitivity 79%, specificity 93% premenopausal; 70% and 60%, respectively, postmenopausal

ACOG = American College of Obstetricians and Gynecologists

Prospective Validation Study To Assess IOTA

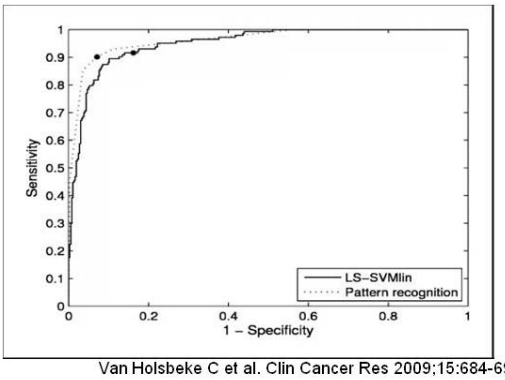
- 3 IOTA centers
- Prospective, 507 patients
- Mathematical models and pattern recognition by expert sonologist
- 28-33% malignancy rate
- AUC range 0.945-0.950
- Sensitivity 91.6%-95.1%
- Specificity 73.9%-83.8%

Van Holsbeke C et al. Clin Cancer Res 2009;15:684-691.

Expert Sonologists

- Pattern recognition
- Increased recognition with experience
- Most take into account the clinical scenario
- Perform similarly to the IOTA mathematical models and the simple rules

IOTA and Pattern Recognition



Van Holsbeke C et al. Clin Cancer Res 2009;15:684-691.

IOTA: 10 Rules (Combined) Were Applicable Prospectively!

- 76% of all tumors (386/507)
- But 24% of tumors, rules were not applicable
- 93%-95% sensitivity (106/112)
- 90%-91% specificity (249/274)
- If simple rules cannot be applied, then expert examination may be useful

Van Holsbeke C et al. Clin Cancer Res 2009;15:684-691.

Suspicious Masses

- Obvious, if mass looks like it may be cancer, refer and get the diagnosis.
- Don't delay!
- Confirm where the mass arises from and how extensive:
  - Ovarian
  - Uterine
  - Tube
  - Cervix, etc

Cases: Benign or Malignant, Ovarian or Other Origin?

Summary

- The ovary can often be found if the landmarks are found and followed
- Occasionally transabdominal ultrasound is needed in addition to transvaginal.
- Obviously benign masses are likely to be benign.
- Benign masses may be monitored. Classic endometriomas or mature teratomas may undergo stimulation, retrieval and pregnancy without removal if they look classic.
- 76% of masses meet the IOTA rules, so suspicious masses should be referred for further evaluation.

Top Ten Rules

Benign

1. Unilocular cyst
2. Presence of solid components, where the largest solid component is < 7 mm in largest diameter
3. Acoustic shadows
4. Smooth multilocular tumor less than 100 mm in largest diameter
5. No detectable blood flow on Doppler examination

Which Criteria Are Met?

Benign
1. Unilocular
2. Solid parts < 7 mm
3. Acoustic shadow
4. Smooth multilocular < 10 cm
5. No Doppler flow in mass

Malignant
6. Irregular solid
7. Ascites
8. 4 or more papillary projections
9. Irregular multilocular with solid components
10. High Doppler flow within mass

Top Ten Continued

- Malignancy
  6. Irregular solid
  7. Ascites
  8. At least 4 papillary structures
  9. Irregular multilocular solid tumor with largest diameter 100 mm
  10. Very high color content on color Doppler examination

REFERENCES

1. Alcazar JL, et al. Transvaginal gray scale and color Doppler sonography in primary ovarian cancer and metastatic tumors to the ovary. JUM 2003; 22:243-47
2. Alcazar JL, Merce LT, Manero MG. Three-dimensional power Doppler vascular sampling: a new method for predicting ovarian cancer in vascularized complex adnexal masses. JUM 2005; 24:689-96 2005
3. Brown DL. A practical approach to the ultrasound characterization of adnexal masses. Ultrasound Quarterly 2007;23:87-105.
4. Fleischer A et al. Contrast-enhanced transvaginal sonography of benign versus malignant ovarian masses: preliminary findings. J Ultrasound Med 2008;27:1011-1018.
5. Medeiros LR et al. Accuracy of ultrasonography with color Doppler in ovarian tumor: a systematic quantitative review. Int J Gynecol Cancer 2009;19:230-236.
6. Testa AC and Bourne TH. Characterising pelvic masses using ultrasound. Best Practice & Research Clin Obstet Gynaecol 2009;1-14 (in press doi:10,1016/j.bpobgyn.2009.02.002.
7. Timmerman D, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol 2008;31:681-690.
8. Tongsong T, Luewan S, Phadung P, et al. Pattern recognition using transabdominal ultrasound to diagnose ovarian mature cystic teratoma. Internat J Gynecol Obstet 2008;103:99-104.
9. Van Calster B, et al. Discriminating between benign and malignant adnexal masses by specialist ultrasound examination versus serum CA-125. J Natl Cancer Inst 2007;99:1706-14.
10. Van Holsbeke C et al. Prospective internal validation of mathematical models to predict malignancy in adnexal masses: results from the international ovarian tumor analysis study. Clin Cancer Res 20090;15(20:684-691.
11. Yazbek nJ et al. Effect of quality of gynaecological ultrasonography on management of patients with suspected ovarian cancer: a randomised controlled trial. Lancet Oncol 2008;9:124-31.

NOTES

NOTES

ADENOMYOSIS

Alex Hartman, M.D.
True North Imaging
Thornhill, Ontario, Canada

LEARNING OBJECTIVES
At the conclusion of this presentation, participants should be able to:

1. List the causes of uncertainty in diagnosing adenomyosis.
2. Describe the relationship between adenomyosis and menorrhagia.
3. Characterize the imaging findings in adenomyosis.
4. Explain the importance of adenomyosis in infertility.

Adenomyosis

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Disclosure

Nothing to disclose

Adenomyosis

- **The single most common undiagnosed gynecological condition and the most common cause of gynecological pain**

E. Lyons, *ISUOG*, November 2002

Adenomyosis

Why is it "undiagnosed"?

1. Pathological diagnosis: inconsistent
2. Clinical: is it not just "normal"?
3. Imaging: too often ignored

Definition

Bird, *AJOG*, 1972

"The benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium."

Ferenczy, *Human Reproduction Update*, 1999

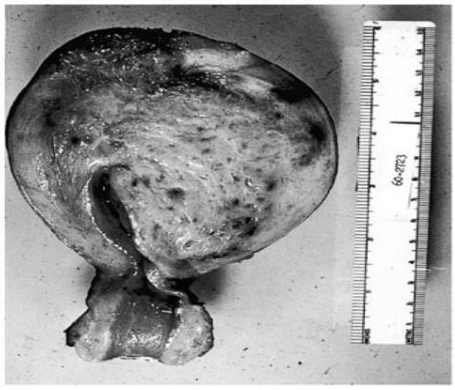
Further qualified as "presence of endometrial glands and stroma located haphazardly and deep within the myometrium."

Adenomyosis

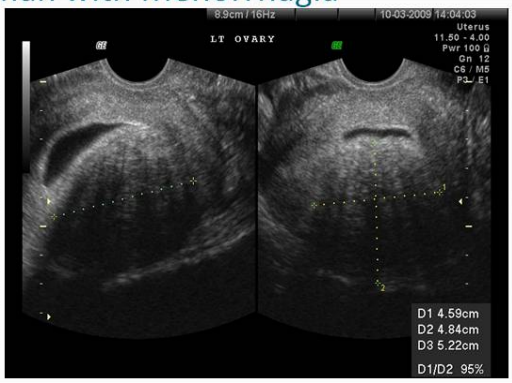
An estrogen-dependent disease of "ectopic endometrium" infiltrating the myometrium. Also called *endometriosis interna.* The condition is usually symptomatic, causing menorrhagia, uterine enlargement and often pelvic pain.

Diffuse adenomyosis

Ferenczy, *Human Reproduction Update,* 1998



Sonohystogram (SHG) – 46-Year-Old Woman with Menorrhagia

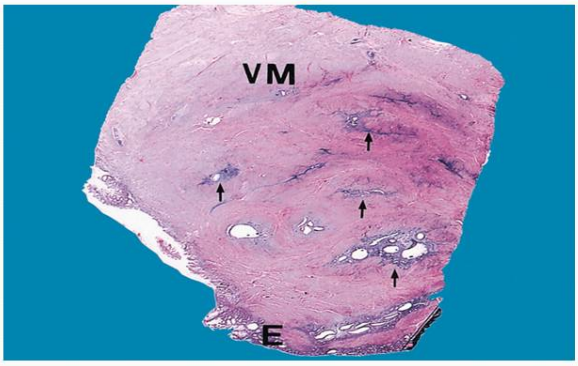


Pathology

Adenomyosis is an estrogen-dependent uterine condition manifesting as a poorly demarcated infiltrative process. Heterotopic endometrial glands and stroma from the basal layer invade the myometrium with surrounding densely packed smooth muscle reaction.

Variable echogenicity

Reinhold, *Radiographics*, 1999



Variable echogenicity

Ferenczy, *Human Reproduction Update*, 1998

Pathology

First described by Rokitansky (1860)

Found in 19%-62% of pathology specimens

Causes uterine enlargement in 26% of hysterectomy specimens

Process can be diffuse or focal

Posterior wall more commonly affected

Glandular extension below the endometrial-myometrial interface (EMI) should be >2.5 mm.

Usually a soft and diffusely enlarged uterus.

Variable amounts of smooth muscle are seen, as a reaction to invasion or muscle bundles that have been displaced. *Outwater, AJR, 1998*

Pathology

- 35%-55% of cases associated with fibroids
- 90% of cases seen in multiparous women
- 8/14 postmenopausal women on tamoxifen had reactivation of pre-existing adenomyosis (Cohen, *Gyn Onc*, 1995).

Ferenczy, *Human Reproduction Update*, 1998

Pathogenesis

Down-growth and invagination of the basalis endometrium into the myometrium

EMI consists of the basal endometrium and subendometrial myometrium and is the functional unit for sperm transport.

Triggered by a weakness in smooth muscle tissue and/or an increased intrauterine pressure (i.e., increased progesterone).

In predisposed women - invasion of myometrium "weakened" by birth, or trauma. Increased in patients with chronic endometritis or hyperestrogenemia.

Answer Me These Questions Three!

Answer Me These Questions Three!

1. Why do these patients bleed?
2. Why are "chocolate cysts" not seen?
3. Why do they get dysmenorrhea?

Multiple theories for bleeding –

1. Prostaglandins F2α
2. Poor contractility of adenomyotic uterus and compression by submucous adenomyosis or fibroids

Are there "chocolate cysts" in the uterus?

Rarely get cystic hemorrhages, since in adenomyosis tissue originates from stratum basalis vs. functionalis, which is much less responsive to hormonal stimuli

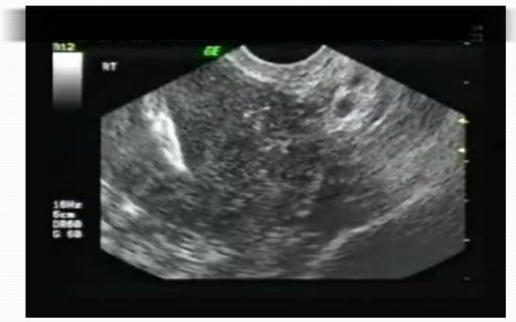
Why dysmenorrhea?

Because of uterine irritability due to blood loss, possibly cavity distention.

Ferenczy, *Human Reproduction Update*, 1998

Adenomyosis

38-year-old woman with dysfunctional uterine bleeding (DUB)



Clinical Features

Typical scenario:

35 – 50 years old
Menorrhagia with clots
Cramps +++
"Bulky" uterus
Misdiagnosed as "poorly-defined" fibroids

Clinical Features

70% of affected women are symptomatic.
70%-80% of patients are parous women aged 40-50 years.

Symptoms - Menorrhagia (40% – 50+ %)
Dysmenorrhea (30% – 50 %)
Metrorrhagia (10% – 12 %)
Pelvic tenderness (often focal)
Dyspareunia
Infertility

Devlieger, *Human Reproduction Update*, 2003

You Know It Is Adenomyosis When You Hear……

- "I am passing clots."
- "Pieces of liver are coming out of me."

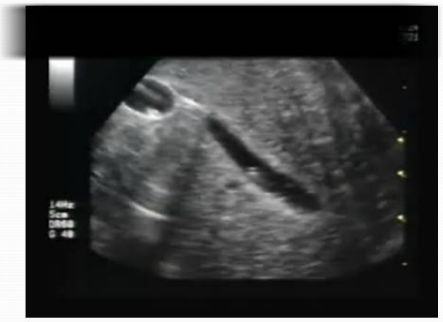
or you see

- Myometrial cysts on ultrasound

Imaging

1. **Diagnosis**
2. **Evaluate extent of disease**
3. **Evaluate conservative treatment**

Adenomyosis



Ultrasound Features

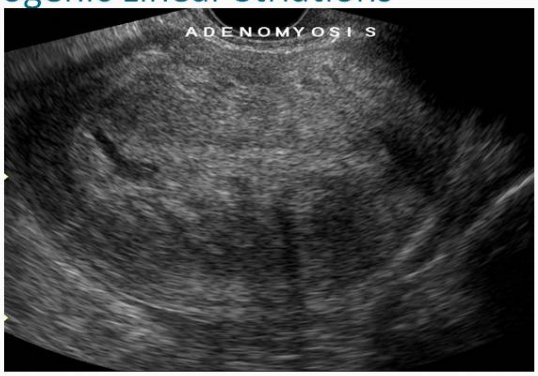
- Enlarged uterus
- Abnormal myometrial echogenicity
  - Hypoechoic (75% of cases)
  - Isoechoic
  - Hyperechoic
- Heterogeneous myometrial echotexture
  - Focal
  - Diffuse
- Myometrial cysts (50% of cases)
- Echogenic nodules or linear striations
- Pseudowidening of endometrium
- Poor definition of endomyometrial junction
- Relative absence of mass effect
- Poor definition of lesion borders
- Elliptical (globular) myometrial abnormality

Echogenic linear striations –
represent the ectopic endometrial tissue that is in direct continuity with the endometrium.

Hyperechoic nodules –
represent large islands of heterotopic endometrium.

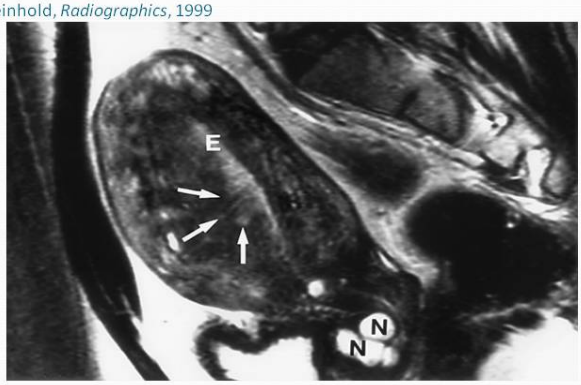
Pseudowidening of the endometrium-
represents small or indistinct infiltration with heterogeneous echogenicity.

Echogenic Linear Striations

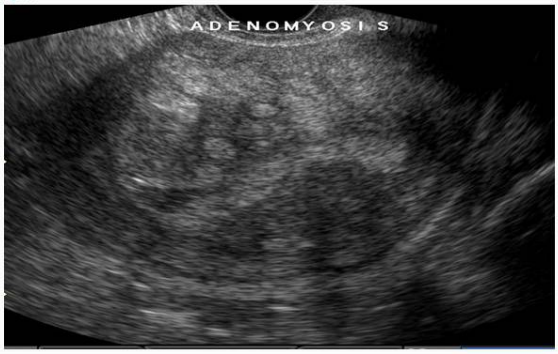


Echogenic Linear Striations

Reinhold, *Radiographics*, 1999



Hyperechoic Nodules



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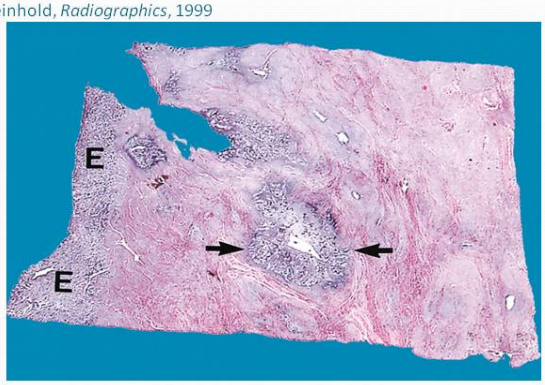


Myometrial Cysts

- Dilated cystic glands or hemorrhagic foci
- Multiple
- 2-3 mm
- Tender
- Avascular
- Best seen in secretory phase
- Seen in 50%

Which Ultrasound Findings Are Most Accurate?

Kepkep, *UOG*, 2007

70 consecutive ultrasounds pre-hysterectomy:

Highest accuracy –

1. Echogenic linear striations
2. Globular configuration
3. Myometrial cysts

Most specific finding – echogenic linear striations (95.5%)

Accuracy of Diagnosis

Reinhold, *Radiology*, 1996

- Prospective double-blind study
- 119 women
- Ultrasound and magnetic resonance imaging (MRI) pre-hysterectomy

No statistically significant difference

Accuracy of Diagnosis

Ultrasound		MRI	
Sensitivity	89%	Sensitivity	89%
Specificity	89%	Specificity	89%
PPV	71%	PPV	65%
NPV	96%	NPV	95%

PPV = positive predictive value
NPV = negative predictive value

Adenomyosis vs. Fibroids

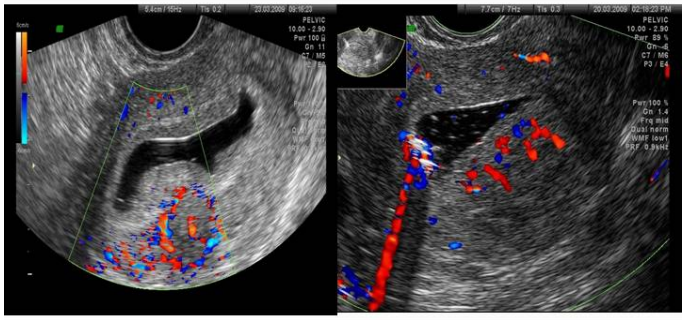
Older patient	Younger patient
Multiparous	Nulliparous
Poorly defined borders	Well-defined borders
No capsule	Pseudocapsule
Asymmetric thickness	Focal masses
Mixed echogenicity	Hypoechoic periphery
Myometrial cysts	No myometrial cysts
Central vessels (penetrating vascularity)	Marginal vessels (draping vascularity)
Menorrhagia	Usually no bleeding

Adenomyosis vs. Fibroids

(continued)

Focal tenderness	Non-tender
No edge shadowing	Edge shadowing
No calcification	Calcification common
Infiltrating	Non-infiltrating
Minimal mass effect	Mass effect
Elliptical or globular-shaped uterus	Focal abnormality
Increased echogenicity	Decreased echogenicity
Echogenic nodules	
Linear striations	

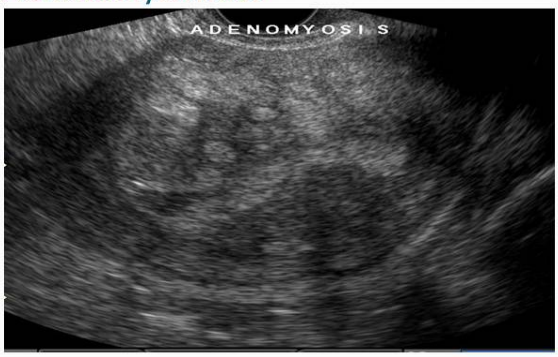
Draping vs. Penetrating Vascularity



Focal Adenomyosis (Adenomyoma)

- Circumscribed masses (usually echogenic) of adenomyosis within the myometrium
- May contain cysts
- Ill-defined borders
- Doppler ultrasound shows vascularity within the mass (penetrating pattern) vs. only in the periphery of the mass (draping pattern).

Adenomyomata



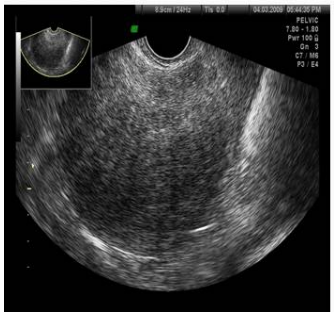
Sonohysterography and Adenomyosis

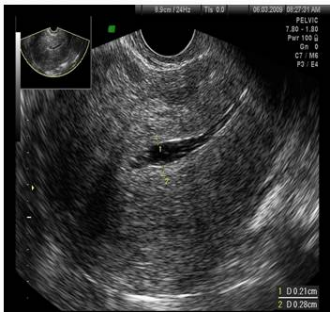
Why Bother?

Sonohysterography and Adenomyosis

- Assists in diagnosis
- Identifies endometrium
- Part of abnormal uterine bleeding (AUB) work-up
- Rule out intracavitary structural abnormalities
- Dysmenorrhea work-up
- Pelvic pain investigation

If Adenomyosis Is an Intrauterine Condition, Why Do a Saline Infusion Sonography (SIS)?





Adenomyosis in AUB

The prevalence of intracavitary and intramural uterine abnormalities: a prospective study of 1009 consecutive women.

Tur-Kaspa, Gal, Hartman, Hartman & Hartman, *Fertility & Sterility*, Dec 2006.

409 consecutive AUB patients

Intramural abnormalities - 71.4% (292 pts)

Intramural fibroids - 37.2% (152 pts)

Adenomyosis - 52.3% (214 pts)

Adenomyosis Differential Diagnosis

- **Fibroids (nodular form)**
- **Endometrial cancer**
- **Myometrial contractions**
- **Muscular hypertrophy**

Adenomyosis and Infertility

- Why does adenomyosis impede fertility?

  Previously, it was felt that the abnormal structure of the EMI and myometrium, especially in the fundus, could interfere with implantation (affecting uterine receptivity). Could EMI disruption affect sperm transport?

  However, Camargo, *Fertil.Steril*, 2001, suggested adenomyosis by classical ultrasound criteria had no impact on the rate of implantation.

  Devlieger, *Human Reproduction Update*, 2003

Adenomyosis and Infertility

Adenomyosis may reduce the expansile capacity of the uterus in pregnancy:

1. Replacing normal myometrium and connective tissue with adenomyotic tissue, distorting the spiral arrangement of the muscle fibers and the 3-dimensional network of collagen.
2. EMI consists of the basal endometrium and subendometrial myometrium, and is the functional unit for sperm transport.
3. Adding scar tissue subsequent to excision of the adenomyosis.

Wood, *Human Reproduction Update*, 1998.

Adenomyosis in Infertility

The prevalence of intracavitary and intramural uterine abnormalities: a prospective study of 1009 consecutive women.

Tur-Kaspa, Gal, Hartman, Hartman & Hartman, *Fertility and Sterility*, 2006

600 consecutive infertilty patients

Intramural Abnormalities - **40.2%** (241 pts)

Intramural Fibroids - **20.5%** (123 pts)

Adenomyosis - **24.0%** (144 pts)

Ultrasound to Predict Extent

Ultrasound done within 2 months of hysterectomy:

46 patients - MILD adenomyosis

18 patients - SEVERE

9 patients - Focal

Conclusions:

In the absence of fibroids, ultrasound diagnosis of diffuse disease relates to pathological evidence of severity.

Visualization of the endometrium does not relate to severity.

Hulka, *AJR*, 2002

Ultrasound vs. MRI

Ultrasound advantages:

1. Inexpensive
2. Readily available
3. Well tolerated

Ultrasound disadvantages:

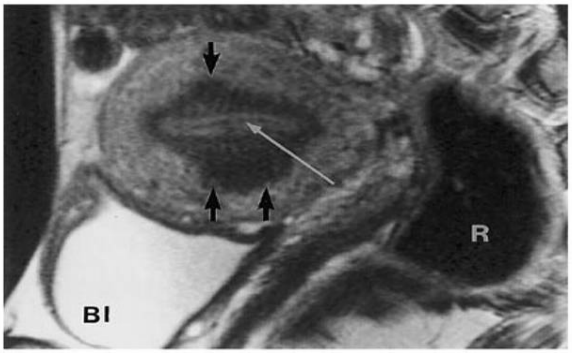
1. Operator-dependent
2. Relative lack of standardization

MRI

- Appears as widening of the junctional zone, from a normal of < 8 mm, to > 12 mm (diagnostic).
- Areas of decreased signal on T2 similar to junctional zone (represents the hyperplastic smooth muscle reaction)
- Focal areas of increased signal on T2 – representing endometrial glands and stroma
- Focal areas of thickening or spiculated masses
- Advantages over ultrasound:
  - Less operator-dependent
  - Standardized, reproducible images

Thickened Junctional Zone

Reinhold, *Human Reproduction Update*, 1998



Associated Pathology

- Fibroids 35%-55 %
- Endometriosis 6%-20%
- Endometrial polyps 2.3%
- Adenocarcinoma 1.4%
- Endometrial hyperplasia 7%

Ferenczy, *Human Reproduction Update*, 1998

Marcus, *AJOG*, 1961 from Wood, *Human Reproduction Update*, 1998

60% with endometrial carcinoma had adenomyosis vs. 39% of controls; however, no negative influence on prognosis.

When adenocarcinoma is found in adenomyosis, it is often with preceding estrogen use, is low grade and has good prognosis.

Sonohysterography: An Adjunct Investigation To Evaluate Chronic Pelvic Pain

Hartman J and Hartman M

SOGC, 2009

Adenomyosis and Pelvic Pain

- 200 consecutive women, ages 24-53 years, referred for SIS
- Pelvic pain as primary or secondary indication
- Postmenopausal and endometriosis patients excluded

Assessed – Adenomyosis
- Dysmenorrhea
- Reproduction of pain

Adenomyosis and Pelvic Pain

Of 200 women with pelvic pain, SIS demonstrated:

- 145 had adenomyosis on SIS
- 132 had dysmenorrhea by history
- 113 had reproduction of their pain

1. 89 had both adenomyosis and reproduced pain. **
2. 80 had dysmenorrhea and reproduced pain.

** P< .02

Adenomyosis and Pelvic Pain

Conclusions

Sonohysterography can be a helpful adjunct in localizing the pain to the uterus in the work-up of chronic pelvic pain. It is especially helpful when adenomyosis is suspected, and possibly if the patient has dysmenorrhea. Further investigation is warranted.

Treatment – Hormonal

"Target tissue" (ectopic endometrium) is the same as endometriosis. Medical treatment is based on the hormonal dependency.

- Systemic hormonal treatment
- Gonadotropin-releasing hormone (GnRH) agonists
  - Create a pseudomenopausal, hypoestrogenic state
  - Same rationale as other diseases based on ovarian steroidogenesis, endometriosis and fibroids.
  - Cause menopausal side-effects: hot flushes, mood swings and bone demineralization.

Treatment – Hormonal

- Intrauterine levonorgestrel- or danazol- releasing devices

  Fedele, *Fertil. Steril.* 1997.

25 patients with adenomyosis-associated menorrhagia

10% decrease in uterine size after 1 year with levonorgestrel-releasing intrauterine system (LNG-IUS)

All patients experienced a decrease in symptoms.

Is this a potential treatment option in adenomyosis and infertility?

Treatment - Surgical

- Problems – Diagnosis
  - Extent
  - Technical difficulties – ill-defined, tough tissue, wound-apposition difficulties
  - Excision decreases myometrial mass (fertility)
    1 – Decreased uterine capacity – increased abortions and premature labor
    2 – Produce scars – may contain foci of adenomyosis with reduced tensile strength

Treatment - Surgical

Ablation/resection

mild adenomyosis <3 mm of myometrium (limited to endomyometrial junction)

Laparoscopic myometrial electrocoagulation

shrinks adenomyosis by necrosis. It causes scarring. For patient >40 years old who want to avoid more extensive surgery.

Myometrial excision – partial hystercetomy

If fairly localized and not too large. Often combined with preop GnRH analogues or danazol.

Wood, *Human Reproduction Update*, 1998.

Vessel Embolization

- Reported series are small
  Siskin, *AJR*, 2001
- MRI-diagnosed adenomyosis
- Improvement in 12/13 patients
  (many had concurrent fibroids)

Treatment - Surgical

Laparoscopic partial hysterectomy

>1/3 of uterus affected

Fertility not required

Advantages (vs. total hysterectomy)

Decreased operating time, blood loss, risk of genitourinary (GU) trauma, risk of bladder or sexual function.

Disadvantages

Risk of recurrence, difficult removal of rectovaginal adenomyosis or adenomyomata, future cervical problems.

Wood, *Human Reproduction Update*, 1998.

Treatment – Surgical

Total hysterectomy

Definitive, nearly always ensures cure

1%-2% ureteric, bowel, or bladder trauma.

Vaginal vs. laparoscopic

1. Shorter operating time
2. ? decreased cost

But 1 – More bleeding

2 – More infection

Laparoscopic Check at the Completion of a Vaginal Hysterectomy?

1. Enables detection and removal of associated endometriosis.
2. Easier to deal with very large uteri (> 500 grams)
3. Evaluation of adnexal pathology.

Wood, *Human Reproduction Update*, 1998.

Conclusions

1. Adenomyosis is a common cause of menorrhagia and dysmenorrhea.
2. The imaging features of adenomyosis are becoming more clearly recognized.
3. The effect on fertility is not yet clearly understood.

REFERENCES

1. Atri M, Caroline Reinhold, Amira R. Mehio, William B. Chapman, Patrice M. Bret. Adenomyosis: US Features with Histologic Correlation in an in Vitro Study. Radiology 2000; 215:783-790
2. Devlieger R, Thomas D'Hooghe, Dirk Timmerman. Uterine adenomyosis in the infertility clinic. Human Reproduction Update, Vol.9, No.2 pp. 139-147, 2003
3. Dueholm M. Transvaginal ultrasound for diagnosis of adenomyosis: a review. Best Pract Res Clin Obstet Gynaecol. 2006 Aug; 20(4):569-82. Epub 2006 Mar 20
4. Dueholm M, Ludforf E. Transvaginal ultrasound or MRI for diagnosis of adenomyosis. Curr Opin Obstet Gynecol. 2007 Dec;19(6): 505-12
5. Fedele L, Bianchi S, Frontino G. Hormonal treatments for adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2008 Apr; 22(2):333-9. Epub 2007 Aug 30
6. Alex Ferenczy. Pathophysiology of adenomyosis. Human Reproduction Update 1998, Vol. 4 pp. 312-322
7. Hulka CA, Hall DA, McCarthy K, Simeone J. Sonographic findings in patients with adenomyosis: can sonography assist in predicting extent of disease? ARJ Am J Roentgenol. 2002 Aug;179(2):379-83
8. Kepkep E, Y. A. Tuncay, G. Goynumer, E. Tutal. Transvaginal sonography in the diagnosis of adenomyosis which findings are most accurate? Ultrasounds Obstet Gynecol 2007; 30: 341-345
9. Kuligowska E, Linda Deeds, Kang Lu. Pelvic Pain: Overlooked and Underdiagnosed Gynecologic Conditions. Radiographics 2005; 25:3-20
10. Matalliotakis IM, Katsikis IK, Panidis DK. Adenomyosis: what is the impact on fertility? Curr Opin Obstet Gynecol. 2005 Jun;17(3):261-4
11. Vance McCausland, Arthur McCausland. The response of adenomyosis to endometrial ablation/resection. Human Reproduction Update 1998. Vol. 4, No. 4 pp. 350-359
12. Outwater EK, Evan S. Siegelman, Vivianne Van Deerlin. Adenomyosis: Current Concepts and Imaging Considerations. AJR 1998; 170:437-441 0361-803X/98/1702-347
13. Rabinovici J, Stewart EA. New interventional techniques for adenomyosis. Beast Pract Rest Clin Obstet Gynaecol. 2006 Aug; 20(4):617-36. Epub 2006 Aug 24.
14. Reinhold C, Shirley McCarthy, Patrice M. Bret, Amira Mehio, Mostafa Atri, Rita Zakarian, Yvon Glaude, Lijin Liang, Robert J. Seymour. Diffuse Adenomyosis: Comparison of Endovaginal US and MR imaging with Histopathologic Correlation. Radiology 1996; 199:151-158.
15. Reinhold C, Faranak Tafazoli, Amira Mehio, Lin Wang, Mostafa Atri, Ecan S. Siegelman, Lori Rohoman. Uterine Adenomyosis: Endovaginal US and MR Imaging Features with Histopathologic Correlation. Radiographics. 1999;19:S147-S160
16. Reinhold C, Faranak Tafazoli, Lin Wang. Imaging features of adenomyosis. Human Reproduction Update 1998, Vol. 4, No. 4 pp.337-349.
17. Thomas Jr. JS, John F.J. Clark. Adenomyosis: A retrospective view. Journal of the Nations Medical Association , Vol. 81, No. 9
18. Williams PL, Sherell L. Laifer-Narin, Nagesh Ragavendra. US of Abnormal Uterine Bleeding. Radiographics: 2003; 23:703-718.
19. Wood C. Surgical and medical treatment of adenomyosis. Human Reproduction Update 1998, Vol. 4, No. 4 pp.323-336.

NOTES

NOTES

IN VITRO FERTILIZATION, EMBRYO TRANSFER AND EARLY PREGNANCY

Elizabeth Puscheck, M.D., M.S.
Wayne State University
School of Medicine
Detroit, Michigan

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe current and new uses of ultrasound in in vitro fertilization (IVF), embryo transfer (ET), and early pregnancy.
2. Discuss the literature regarding ultrasound-guided embryo transfers.
3. Explain the use of 3-dimensional (3D) ultrasound on ET and early pregnancy.
4. List and assess techniques that assist with stimulation surprises and difficult oocyte aspirations and embryo transfers.

In Vitro Fertilization (IVF), Embryo Transfer (ET) and Early Pregnancy

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Disclosure

Wyeth, Ethicon: Research

Ultrasound for IVF

- Yesterday:
  - Ovarian reserve
  - Ovarian hyperstimulation
    - Protocol selection
    - Monitoring
  - Doppler of the ovaries and endometrium
- Stimulation surprises
- Oocyte retrieval
- Embryo transfer
- Difficult retrievals and transfers
- Early pregnancy

Surprises Found During Monitoring

- Polyp
- Hydrosalpinx
- Ovarian cyst (mentioned in earlier talk)

- WHAT DO YOU DO?

Incidental Finding of Polyp During Stimulation

- Mandi T, Ghaffari F, Kiani K, Hosseini F. Hysteroscopic polypectomy without cycle cancellation in IVF cycles. Reprod Biomed Online 2009;18:412-5
- This study is retrospective
- Polyps <1.5 cm can be removed hysteroscopically during stimulation.
- 2-12 days before human chorionic gonadotropin (hCG)
- Concern about disrupting the endometrium
- Pregnancy rates were the same.

Hydrosalpinx Appears on Ultrasound During Stimulation

- Hydrosalpinges decrease pregnancy rates by 50% (Cochrane review Johnson 2002).
- Preferred approach is salpingectomy or ligation prior to stimulation to improve pregnancy rates.
- Sometimes it is not safe or feasible (e.g., severe pelvic adhesions) or a hydrosalpinx appears during stimulation.
- Now what do you do?

Hammadieh et al. Hum Reprod 2008;23:1113-7

- Study of ultrasound-guided aspiration of hydrosalpinges at oocyte collection option
- Randomized, blinded;1220 assessed
- 66 subjects: 32 aspiration vs. 34 no aspirations.
- Antibiotic prophylaxis (intravenous augmentin 1.2 grams and oral azithromycin 500 mg daily x 3)
- Addendum to the study included re-scans after oocyte aspiration on days 2-3 and 14 days after oocyte aspiration to look for re-accumulation of fluid.
  - 26 of 32 were evaluated.

Hammadieh et al Hum Reprod 2008;23:1113-7

	Aspiration	No aspiration
Age	33.4	33.9
Bilateral hydrosalpinges	8 (25%)	6 (17.7%)
Days of stim	11.6±1.3	11.6±1.4
Oocytes	14.1 + 7.1	12.4 + 7.1
# Fertilized	9.2 + 5.2	7.0 + 4.6
# Embryos transferred	2.3 + 0.58	2.1 + 064
Biochemical*/clinical pregnancy rate (PR)	**43.8*%/**31.3%	**20.6*%/**17.6%
Spontaneou abortion (Sab) rate	28.6%	42.9%
Infection/ectopic	0/0	0/0

Hammadieh et al. Hum Reprod 2008;23:1113-7

- Rescanned patients to evaluate re-accumulation of fluid in hydrosalpinges.
- Large number did re-accumulate.
- 30% of the aspiration group re-accumulated by 14 days after the aspiration.
- Implies that the window of opportunity may be present at oocyte aspiration, but not significantly earlier.
  - Aboulgar 1990 reported that aspiration 1 month prior to retrieval did not improve pregnancy rates.

Hammadieh et al.: Study Limitations and Advantages

- Antibiotics were given to aspiration group only and may improve pregnancy outcome
  - Brooke 2006 randomized study showed no improvement in pregnancy outcome with antibiotics in general IVF population.
  - Hurst 2001- retrospective study showed doxycycline reported high live-birth rate (LBR) (8/17; 47%). Weak methods.
- Study terminated prior to reaching required sample size. Underpowered to confirm that non-significance is true
- Advantage: Sensitivity analysis of age, # ET, infertility cause, basal follicle-stimulating hormone (FSH) level, and unilateral vs. bilateral hydrosalpinges: no difference

Oocyte Retrieval

- Standard IVF retrieval
- Transvaginal probe with 5-9 mHz
- 16-17-gauge needle
- Empty bladder prior to starting

"Empty Follicle Syndrome"

- No oocytes retrieved after aspirating follicles and no mature granulosa cells
- Try stopping the retrieval, check hCG level and repeat hCG, do second retrieval 34-36 hours later
- Mature oocytes can be retrieved.
  - (some even from previously aspirated follicles)
- Pregnancies from frozen embryo transfer (FET), not fresh

Meldrum DR. 2008.
Sahebkashaf H et al ASRM 2008; P-265
Penarrubia J HR 1999;14:1703-6

The Difficult Ovary: Transuterine

- Wisanto A. HR 1989;7:790-3
  - Table
- ***AVOID Endometrium***
- Davis LB et al. Fertil Steril 2004;81:320-2
  - 85 cycles
  - Crossed myometrium vs. matched controls
  - PR 27% vs. 39% (NS)
  - No complications

	Study	Control
Cycles	32	496
Oocyte	8.5	8.4
Fertilization rate	58%	55%
PR/retrieval	41%	26%

NS = not statistically significant

High Ovary: Tenaculum

- If the ovary is high and hard to reach with transvaginal probe, have an assistant provide abdominal pressure.
- If still not in a good position, apply a tenaculum on the cervix and pull the uterus down while advancing the transvaginal probe toward the ovary.
- A lot of pressure may be needed.

Licciardi FL et al. Fertil Steril 1995;63:677-9

The Difficult Ovary

- Either transuterine or tenaculum-assistance approach does better than a transabdominal approach for oocyte retrieval.

Goal of the ET:

- Atraumatic, smooth, comfortable transfer technique associated with the best pregnancy outcome and lowest complication rate

Embryo Transfer (ET) Technique

- Place speculum
- Wash off cervix (with or without cervical mucus removal)
- Embryologist loads catheter (usually soft)
- Catheter placed by clinician
- Embryos placed in the uterine cavity
- Catheter removed, flushed, reviewed for retained embryos

Ultrasound-guided ET: Similiar

- ***Full bladder for transabdominal ultrasound (US)***
- ***Technician to do the ultrasound***
- Place the speculum
- Wash off cervix (with or without cervical mucus removal)
- Embryologist loads catheter (usually soft)
- Catheter placed by clinician
- ***Ultrasound confirmation of position***
- Embryos placed in the uterine cavity
- ***Ultrasound imaging of fluid bubble in uterine cavity***
- Catheter removed, flushed, reviewed for retained embryos

Factors That May Affect ET

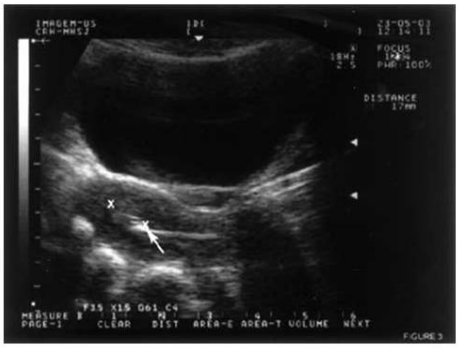
- Patient selection
- Experience of the physician
- Type of equipment
- Catheter type
- Appropriate placement within the uterus
- Difficulty of transfer and trauma
- Retained embryos
- Cramps or uterine contractions
- [Ultrasound machine and user experience]

First US-guided ET

- 1985- Strickler RC et al.
- 16 US ET vs. 12 ET by feel
- Key advantages for ultrasound-guided:
  - Easier with less catheter distortion
  - ET with patient in supine, lithotomy position
  - Accurate positioning of catheter tip in the fundus
  - Ejection and persistence of the "transfer bubble" into the uterus
  - Comforting to the patient

Strickler et al. Fertil Steril 1985;43:54-61

Transabdominal Ultrasound



Why Do Ultrasound-guided Embryo Transfer?

Potential advantages:

- Known orientation of the uterus and cervix
- Molding the ET catheter
- Less trauma at ET
- Less likely to need a tenaculum
- Known length of the endometrial cavity, which may change during stimulation
- Confirm appropriate location
- Decrease anxiety for patient and physician
- Improve training (or retrain) physicians

Disadvantages of US ET?

- Need ultrasound equipment
- Need technician
- Need full bladder
- Increases duration of ET

Outcomes of ET

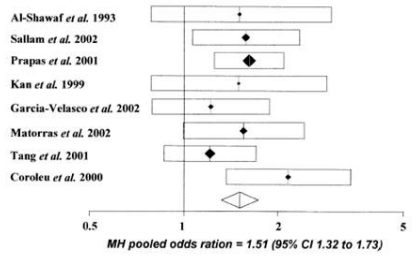
- ET factors:
  - Ease of transfer, comfort, blood on catheter
- Pregnancy outcome:
  - Implantation rate
  - Clinical pregnancy rate
  - Live-birth rate
- Complications:
  - Ectopic pregnancy rate
  - Miscarriage rate
  - Multiple rate

Buckett et al. 2003 Meta-analysis

- 8 prospective studies
- 4 truly randomized; 4 quasi-randomized (alternate, available ultrasound machine)
- Power analysis:
  - 5% difference with 80% power in 2-tailed analysis with 25% clinical pregnancy rate
  - Need 2500 patients per arm
  - No individual study meets this requirement
  - One study had 800, which is sufficient to detect 8% difference
- Findings of meta-analysis: sample size: 4,196 ET
  - Large enough to detect a 4% difference in pregnancy rates
- Bias? Extensive search to avoid publication bias; funnel plots confirm selection bias unlikely

Meta-analysis of Ultrasound-guided ET

Overall odds ratio for clinical pregnancy per embryo transfer in all prospective controlled trials of ultrasound-guided embryo transfer.



Buckett. Meta-analysis of ultrasound-guided ET. Fertil Steril 2003.

Meta-analysis by Sallam 2003

- 14 studies; 4 met randomized controlled trial (RCT) requirements (same as Buckett et al.)
- Transabdominal (TA) US vs. blind touch
- 336/1034 US ET (32.8%) vs. 259/1027 (25.2%) ($p<0.0001$)
- **OR= 1.49 (1.22-1.82) in favor of US-guided**
- No statistical difference in ectopic PR, multiples, or miscarriage rates

Sallem et al. Fertil Steril 2003;80:1042-6

OR = odds ratio

Incidence of Retained Embryos

- 3.2%-10% retained embryos prior to US guided ET
  - 35% touched the top of the uterus
- 0.8% retained embryos the year after initiating US guidance with mid-uterine ET
  - Still 25% inadvertent touch
- Improved PR
- 2009 embryo transfers
- Retained embryos lead to increased risk of blood on the catheter. Blood on the catheter decreased PR.

Silberstein T et al. Fertil Steril 2005;84:1510-2

Other Non-randomized Studies

- US ET is associated with:
  - Ease of transfer
  - Assistance in how to mold the catheter
  - Decreased use of tenaculum
  - Decreased incidence of blood in the catheter
  - Confirmation of position within the uterus

- Matorras R et al. Hum Reprod 2002;17:1762-6.
- Mirkin S et al. JARG 2003;20:318-22.
- Flisser E and Grifo J Fertil Steril 2007;87:1-5.

More Recent Studies: No Significant Improvement with US

- Flisser E et al. Fertil Steril 2006;85:353-7
  - Retrospective
  - 249 patients: under-powered (their estimate, 57,000)
  - No significant difference in US ET vs. ET
  - Clinical PR 49.0% US ET and 51.0% blind ET
- Karmas IP et al. Hum Reprod 2007;1-8 (epub).
  - RCT, double-blind
  - 300 patients (stopped early)
  - Under-powered. (estimate 772 patients. α=0.05, 80% power for 7% difference)
  - PR 53.3% US ET and 51.3% blind ET

Other Suggestions

- Avoid fundal touch—touch associated with blood on catheter, tissue in catheter, retained embryos, and uterine contractions
- Prior mock trial may be helpful
  - Flisser et al.: yes
  - Henne MB and MIlki AA: no. Uterus may change position 55% of 223 ETconverted from retroverted (RV) to anteverted (AV) (p<0.001)
- Full bladder to straighten the utero-cervical angle: mixed
- Curve the ET catheter
- ET at middle part of the uterine cavity

Sallam HN Curr Opin Obstet Gynecol 2005;289-98
Flisser E and Grifo JA. Fertil Steril 2007;87:1-5

Location of the Uterus and Cervix

- Anteverted uterus would benefit from full bladder to straighten cervical-uterine junction
- Retroverted uterus may be worsened with a full bladder.
- Occasionally, the speculum acoustic shadowing obscures the view. An experienced sonographer can usually angle the TA probe to get the appropriate view.
- However, sometimes the view is still difficult
- Occasionally, the catheter may "feel" like it is in the "right" place but it may turn out that the soft catheter has curled in the cervical canal. Ultrasound can confirm that the catheter is in the uterine cavity.

The Difficult ET

- Why? Cervical canals can be tortuous and internal cervical canals can have stenosis.
- Transabdominal ultrasound is excellent for seeing the cervical canal to lower uterine segment, except in certain circumstances (obesity, bowel gas, etc.)
- Alternatives:
  - Changing the position of the speculum can affect the orientation of the cervix and uterus.
  - Use the transvaginal probe (gel on the inside of the sterile sheath, not the outside) to get a better orientation of the cervical canal.

Difficult ET

- Anticipation is KEY!
- If known cervical stenosis, dilate cervix the cycle before.
- Trial transfer during prior cycle or at oocyte retrieval
- If problematic, dilate the cervix again.
- Consider placing a cervical stitch to get the right orientation.

Cochrane 2007: Ultrasound vs. Clinical Touch

- 13 RCT
- US ET 682/1843 vs. clinical touch 513/1779
- **Improved clinical pregnancy rate with US-guided ET**
- **OR=1.49 (CI 1.29-1.72), p<0.00001**
- No statistical difference for ectopic pregnancy, miscarriage, or multiple gestation

CI = confidence interval

Cochrane 2007: Blood on Catheter

- 3 of 13 papers and 1 personal communication report blood on catheter tip as adverse event.
- US ET 41/635 vs. CT 81/638
- OR= 0.48 (95% CI 0.33-0.70) p<0.0001
- Some evidence of heterogeneity: caution
- **Ultrasound guidance lowered the incidence of blood on the catheter tip.**

Cochrane 2007: Difficulty of ET

- 7 studies reported on this factor
- US ET111/1291 vs. CT 130/1250
- OR=0.80 (95%CI=0.61-1.04) p=0.10
- Heterogeneity accounted for in 1 study
- Removal of that study resulted in

No statistically significant effect observed

- Caveat: subjective finding

Clinical-Touch ET

- Ultrasound after "good feel for clinical touch" technique revealed
- 7.4% catheter tip is near fallopian tube opening
- 17.4% catheter is abutting the fundus
- 24.8% catheter is below the endometrial surface

Woolcott R et al. Hum Reprod 1997;12:963-6

Should We Do Ultrasound-guided Embryo Transfers?

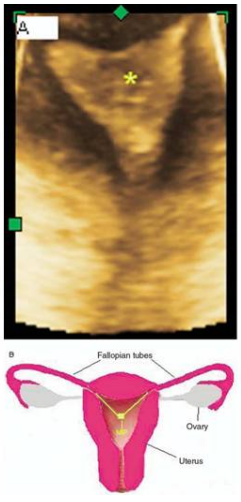
- The meta-analyses support it. Yes
  - Improved clinical pregnancy rates
  - Cochran review also showed improved live-birth rates.
  - No difference in complication rates.
- Additional papers support with suggestions:
  - Ease of transfer
  - Decreased trauma (less blood in the catheter)
  - Reduced incidence of retained embryos
  - Improved comfort
- Underpowered or non-randomized papers say no improvement with US-guided ET and concur with no difference in complication rates.

Alternative Ultrasound Approaches:

- Transvaginal-assisted ET
- 3-dimensional (3D)/4-dimensional (4D) ultrasound-assisted ET
- None have RCT!!!

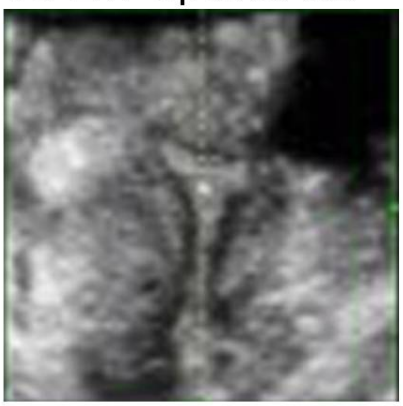
3D/4D ET

- MIP = maximal implantation potential
- 1222 patients
- PR 36%
- Patient and physician satisfaction
- No comparison group
- Still controversy in the literature over best spot



Gergely RZ et al. Fertil Steril 2005;84:500-3

3D ET: Optimal MIP



Implantation?

- Few reports on ultrasound between ET and first pregnancy test
- Zohav et al.
- Evaluation of endometrium from hCG shot to pregnancy test
- Significant increase in volume and thickness of the endometrium during this 2-week period was associated with increased pregnancy rates ($p<0.02$).
- 28 patients; 7 conceived

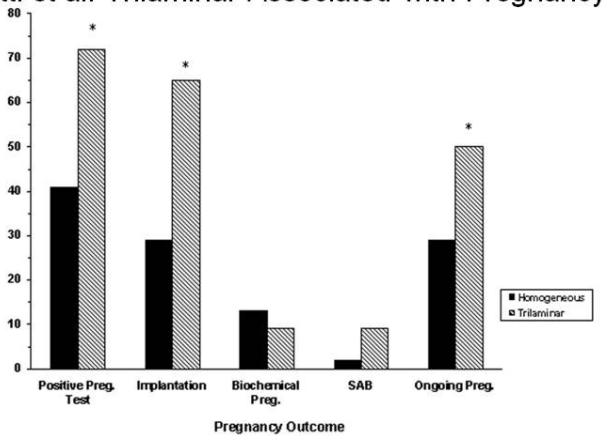
Zohav et al.: Endometrial Thickness and Volume Compared on ET Date and 2 Weeks Later

	Patients who conceived n=7			Patients who did not conceive n=21		
	Day of ET	2 weeks later	Mean difference	Day of ET	2 weeks later	Mean difference
Endometrial thickness	11.7 ± 1.2	15.7 ± 3.7	4.5 ± 3.08	10.2 ± 3.01	8.7 ± 3.5	-1.31 ± 3.9
(range)	(10-13)	(9.5-20)	(-0.5-7)	(5.1-13.5)	(3-13.3)	(-7.5-3.6)
Endometrial volume	4.5 ± 2.9	8.9 ± 2.9	5.7 ± 3.09	3.0 ± 2.0	2.7 ± 2.0	-0.09 +2.4
(range)	(2.5-10.1)	(4.25-12.2)	(1.66-8.5)	(0.83-5.5)	(0.27-8.4)	(-2.5-3.5)

Detti et al. 2008 Endometrial Thickness Dynamics

- Retrospective, cohort study, 115 cycles
- Gonadotropin-releasing hormone (GnRH) antagonist protocol
- Measured endometrial thickness daily
- 37% thinner endometrium on hCG trigger day than at beginning had a net decrease in endometrial thickness. All other studies showed increase, but used GnRH agonist protocol.
- No change in pregnancy rate

Detti et al. Trilaminar Associated with Pregnancy



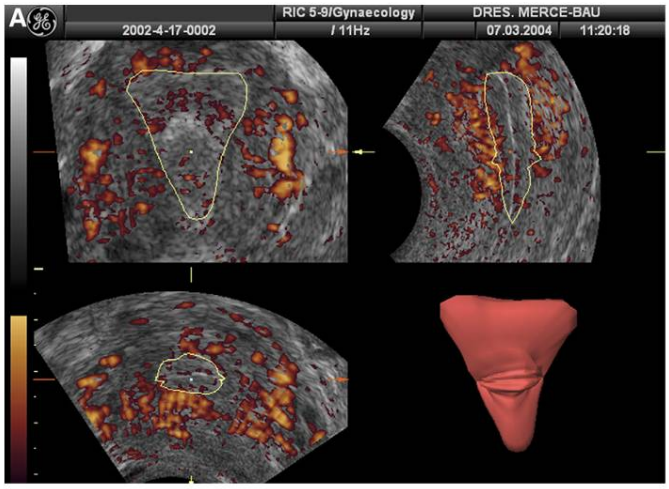
Doppler and Implantation

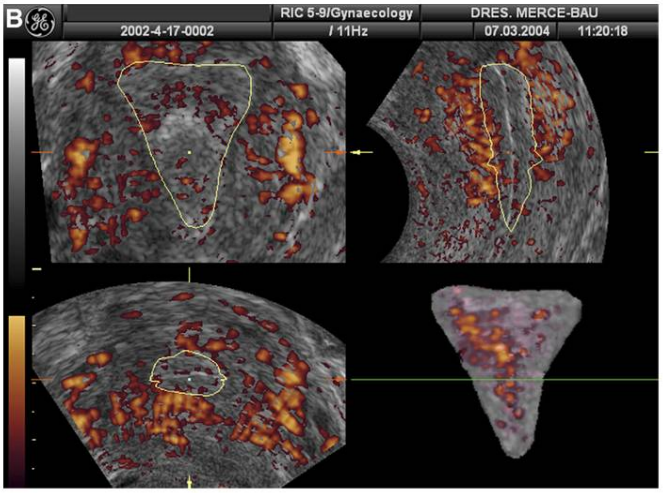
- Hoozemans DA. US OB/GYN 2008;31:432-8
- Prospective; 102 patients
- Doppler of uterine arteries through IVF
- 1=not preg, 2=preg, 3=biochemical pregnancy or miscarriage
- No difference noted

	1	2	3	P Value
Base-line	2.18	2.32	2.18	0.51
hCG	2.11	2.19	2.15	0.78
Aspiration	2.08	2.13	2.15	0.82
ET	1.84	2.04	1.98	0.2
+7-9	1.72	1.75	1.73	0.94
Pregnancy test	1.89	1.85	1.87	0.94

Merce et el. Fertil Steril 2008;89:111-7

- Evaluation of the endometrium
- Thickness
- Pattern
- 3D volume
- 3D power Doppler
- Hypothesis: the receptive endometrium will have increased vascularity.





Merce et al. Fertil Steril 2008;89:111-7

	Pregnant n=38	Nonpregnant n=39	P value
EM thickness (mm)	12.29 ± 2.71	12.15 ± 2.31	0.810
EM volume (mL)	5.63 (2.67-16.64)	4.82 (2.05-9.24)	0.022
EM pattern			0.259
Triple line	33(52.4)	30 (47,6)	
Not triple	5 (35.7)	9 (64.3)	
VI (%)	21.19 ± 8.91	16.05 ± 9.84	0.019
FI (0-100)	28.12 ± 3.90	24.27 ± 3.71	<0.001
VFI (0-100)	6.30 ± 4.46	3.64 ± 2.75	0.014

EM = endometrium; VI = vascularization index; FI = flow index; VFI = vascularization flow index

Merce et al. Fertil Steril 2008;89:111-7

0-1 grade 1 embryo transferred **>1 grade 1 embryos transferred**

	AUC	95% CI	P value	AUC	95% CI	P
EM volume	0.746	0.595-0.898	0.010	0.596	0.378-0.814	0.385
VI (%)	0.724	0.560-0.888	0.018	0.421	0.208-0.633	0.473
FI (0-100)	0.828	0.681-0.974	0.001	0.646	0.435-0.857	0.186
VFI (0-100)	0.800	0.647-0.954	0.002	0.342	0.158-0.525	0.151

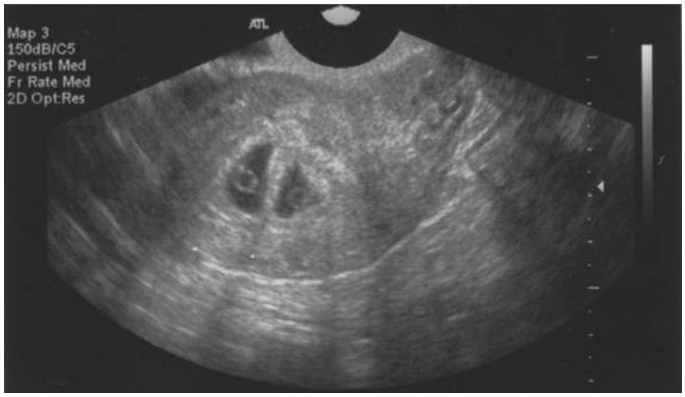
Rate of change (ROC) calculation

AUC = area under the curve

Results:

- No difference in outcome from endometrial thickness or pattern
- Endometrial volume and 3D power Doppler vascular indices predicted outcome if 0-1 grade 1 embryo was transferred BUT it did not hold up if 2 or more were transferred.

Early Twin Pregnancy

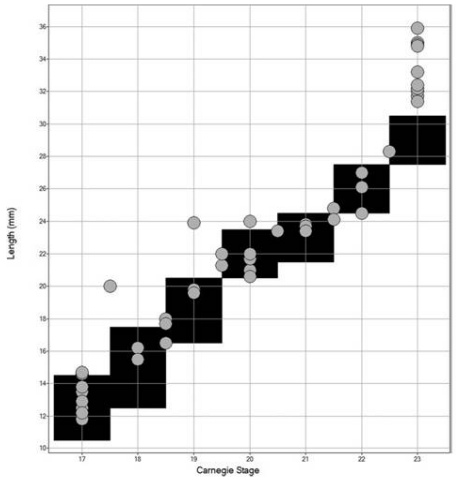


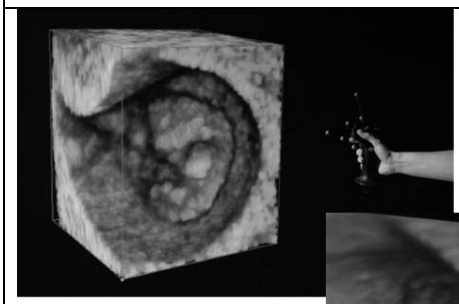
Embryo Staging with 3D Virtual Reality System

- Hypothesis: Can Carnegie staging system be applied to early pregnancies using 3 D virtual reality system?
- Evaluated 48 scans of 19 pregnancies, 7-10 weeks' gestation
- 3D ultrasound volume transferred to 4D-view, saved as Cartesian rectanglar volumes, then transferred to Barco I-Space.
- Images are then generated in SGI prism visualization system with 8 graphic cards and then the images can be visualized in a viewing room with special polarizing glasses to see the depth.
- CAVORE rendering program converts the images into 3D holograms that can be manipulated with wireless control
- Staged morphologically (mainly limb development), then crown-rump length (CRL) measured and compared to gestational age based on oocyte retrieval date and Carnegie staging model.

- Carnegie staging describes embryos through the first 9 weeks of pregnancy and classifies them into 23 different stages based on internal and external physical characteristics of the embryo.

- Carnegie stage on the X-axis
- CRL (mm) on the Y-axis
- Linear

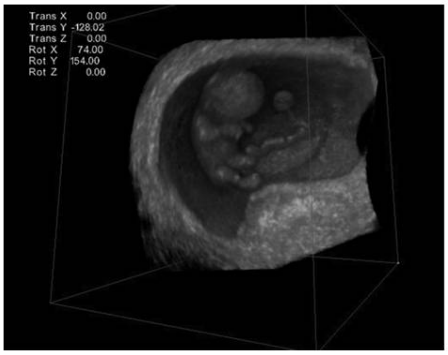




39 days after oocyte retrieval

53 days after oocyte retrieval

56 Days after Retrieval: Carnegie Stage 23



Verwoerd-Dikkeboom CM et al. Hum Reprod 2008;23:1479-84

- All 48 scans could be classified into Carnegie stages easily.
- In 28 of 48 scans, pregnancies were reaching Carnegie stages earlier in time than the original Carnegie collection by 1-5 days.
- ANOVA calculation: 1.08 mm average daily increase in length (0.04 SEM)
- Limitations of Carnegie staging: based on embryologist data from miscarriages and based on menstrual age
- This study used IVF pregnancies with known dates and live ongoing pregnancies.
- Combining growth and early embryo development is promising new technology.

ANOVA = analysis of variance; SEM = standard error of the mean

Summary

- Ultrasound is critical in IVF procedures
- Improved number of oocytes retrieved
- Improved pregnancy rate with US guidance
- Predict pregnancy outcome with 3D vascular indices: controversial
- Newer technologies to evaluate early embryo growth and development are emerging.

REFERENCES

1. Anderson RE et al. Transvaginal ultrasound-guided embryo transfer improves outcome in patients with previous failed in vitro fertilization. Fertil Steril 2002;77:769-75
2. Buckett WM. A meta-analysis of ultrasound-guided versus clinical touch embryo transfer. Fertil Steril 2003;80:1037-41.
3. Brown JA, Buckingham K, Abou-Setta A, Buckett W. Ultrasound versus 'clinical touch' for cateheter guidance during embryo transfer in women. Cochrane Database Syst Rev 2007;Jan 24;(1):CD006107.
4. Davis LB, Ginsburg ES. Transmyometrial oocyte retrieval and pregnancy rates. Fertil Steril 2004;81:320-2.
5. Detti L et al. Endometrial thickness dynamics and morphologic characteristics during pituitary downregulation with antagonists in assisted reproductive technologies. J Ultrasound Med 2008;27:1591-96.
6. Gergely RZ, DeUgarte CM, Danzer H, et al. Three dimensional/four dimensional ultrasound-guided embryo transfer using the maximal implantation potential point. Fertil Steril 2005;84:500-3.
7. Henne MB and Milki AA. Uterine position at real embryo transfer compared with mock embryo transfer. Hum Reprod 2004;19:570-2.
8. Hoozemans DA et al. Serial uterine Doppler velocity parameters and human uterine receptivity in IVF/ICSI cycles. Ultrasound Obstet Gynecol 2008;31:432-8.
9. Letterie GS Three-dimensional ultrasound-guided embryo transfer: a preliminary study. Am J Obstet Gynecol 2005;192:1983-8
10. Mandi T, Ghaffari F, Kiani K, Hosseini F. Hysteroscopic polypectomy without cycle cancellation in IVF cycles. Reprod Biomed Online 2009;18:412-5
11. Matorras R et al. Ultrasound guided embryo transfer improves pregnancy rates and increases the frequency of easy transfers. Hum Reprod 2002;17:1762-6.
12. Merce L et al. Are endometrial parameters by 3D ultrasound and power Doppler angiography related to in vitro/embryo transfer outcome? Fertil Steril 2008;89:111-7.
13. Mirkin S et al. Impact of transabdominal ultrasound guidance on performance and outcome of transcervical uterine embryo transfer. JARG 2003;20:318-22.
14. Sallam HN. Embryo transfer: factors involved in optimizing the success. Curr Opin Obstet Gynecol 2005;17:289-98.
15. Sallam HN et al. Ultrasound-guided embryo transfer: a meta-analysis of randomized controlled trials. Fertil Steril 2003;80:1042-6.
16. Shah AA et al. Heterotopic cervical pregnancy treated with transvaginal ultrasound-guided aspiration resulting cervical site varices within the myometrium. Fertil Steril 2009; 91:934 (epub)
17. Silberstein T et al. Ultrasound-guided miduterine cavity embryo transfer is associated with a decreased incidence of retained embryos in the tranfer catheter. Fertil Steril 2005;84:1510-2.
18. Strickler RC et al Ultrasound guidance for human embryo transfer. Fertil Steril 1985;43:54-61.
19. Verwoerd-Dikkeboom CM et al. Embryonic staging using a 3D virtual reality system. Hum Reprod 2008;23:1479-84
20. Woolcott R et al. Potentially important variables identified by transvaginal ultrasound. Hum Reprod 1997;12:963-6.
21. Wisanto A, Bollen N, Camus M, et al. Effect of transuterine puncture during transvaginal oocyte retrieval on the results of human in-vitro fertilization. Hum Reprod 1989;4:790-3
22. Zohave E et al. Early endometrial changes following successful implantation: 2 and 3-dimensional ultrasound study. Clin Exp Obstet Gynecol 2008;35:255-6.

NOTES

ECTOPIC PREGNANCY VS. PREGNANCY OF UNKNOWN LOCATION: HOW CAN ULTRASOUND HELP DETERMINE WHAT TO DO?

Steven R. Goldstein, M.D.
Professor of Obstetrics and Gynecology
Director of Gynecologic Ultrasound
Co-Director, Bone Densitometry
New York University School of Medicine
New York, New York

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Differentiate abnormally developing early pregnancies from normal pregnancies based on sonographic correlation of anatomic findings.
2. "Stay out of trouble" in dealing with early pregnancies of questionable viability.
3. Determine the role karyotyping of failed pregnancies plays in distinguishing patients in need of further evaluation from those with very low recurrence risk.

Ectopic Pregnancy vs. Pregnancy of Unknown Location: How Can Ultrasound Help Determine What To Do?

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Disclosure

Boehringer Ingelheim, Eli Lilly, Pfizer, Glaxo SmithKline, Merck, Novo Nordisk, Novartis, Proctor & Gamble, Upsher Smith, Wyeth: Advisory Board, Cook ObGyn, Ackrad Labs (A Cooper Co.), Philips Ultrasound: Speakers Bureau

Sonosite: Stockholder, Philips Ultrasound: Consultant

What Is a Pregnancy of Unknown Location (PUL)?

Let's Start with…

What Is a Pregnancy?

In the simplest of terms…when an egg meets a sperm!

Process of conception, implantation, development and birth is a long arduous journey (odyssey).

Infertility

- Multitude of reasons why the process never initiates

Pregnancy failure

- Reasons why losses occur after conception prior to the birth process

When and Why Do Pregnancies Fail?

What Is the Prognostic Significance of Pregnancy Failure?

Incidence of Early Loss of Pregnancy

Wilcox et al. *NEJM* 318:189,1988

- 221 women attempting to conceive
- Daily urine chorionic gonadotropin (UCG) by radioimmunoassay
- 22% of pregnancies detected by assay were lost prior to clinical recognition ("chemical pregnancy")
- Of these, 35% became *clinically* pregnant the next cycle, 65% *clinically* pregnant by the third cycle, 83% by the sixth cycle, and 95% within 2 years.

Chemical Pregnancy

Previously: Loss occurs prior to clinical recognition

Current: Loss prior to the onset of the embryonic period

Chemical Pregnancies

Reasons for loss (speculative)

- Hormonal (inadequate luteal phase)
- Chromosomal (? type and incidence compared to embryonic losses)
- Defective implantation

Embryonic Losses: Chromosomal Abnormalities

Ohno, N. et al. *Obstet Gynecol* 1991;77:394

- 144 spontaneous abortions
- Direct preparation of villi
- 69.4% had abnormal chromosomes:
  - Autosomal trisomy (64%)
  - Polyploidy (9%)
  - Monosomy x (7%)
  - Structural rearrangements (6%)

Chromosomal Pregnancy Failure: (70% of Embryonic Losses)

- Errors of gonadogenesis during meiosis (autosomal trisomies)
- Errors of fertilization (triploidy form dispermy)
- Errors of the first division of zygote (tetraploidy, mosaicism)
- Would not be expected to be repetitive (except in very rare instances of balanced translocations or inversions in one parent)

Non-Chromosomal Pregnancy Failure (30% of Losses)

- Uterine abnormalities (septa , myomas, incompetent cervix)
- Luteal-phase defects (?)
- Autoimmune factors (antiphospholipid syndrome,thrombophilias?)
- Infectious agents : T-strain mycoplasmas
- Alcohol
- Smoking
- Molecular genetic abnormalities with NORMAL karyotypes

PREGNANCY FAILURE: Can Ultrasound Findings Predict Those Cases with Abnormal Karyotypes?

Goldstein SR, Kerenyi T, Scher J, Papp C. Ultrasound in Obstet Gynecol 8:314-317;1996

THESIS

Karyotyping of a failed pregnancy with abnormal chromosomes
- Allows for no further work-up at that time
- Gives the parents a definitive diagnosis

Karyotyping of a failed pregnancy that produces normal chromosomes
- Can result in work-up of the various other causes without first having to have a subsequent loss.

Materials and Methods

- 102 patients
- Sonographic evidence of early pregnancy failure
- Elective dilation and curettage
- Products of conception sent for karyotyping

Results

58 had NORMAL KARYOTYPES (57%) :
52 were 46XX
6 were 46XY

Average maternal age 36.8 years
Average gestational age 9.1 weeks by dates

RESULTS

44 had ABNORMAL KARYOTYPES (43%):

- 33 trisomies (75%) including 24 autosomal trisomies, 4 double trisomies, 1 triple trisomy, 3 mosaics and 1 translocation
- 11 (25%) included 4 triploidy, 1 tetraploidy, 2 monsomy X, 4 others (isochromosome, unbalanced complement, etc.)

An abnormal yolk sac (> 6 mm and/or abnormal morphology) was a non-specific sign present in 17.2% of normal karyotypes and 18.2% of abnormal karyotypes.

Embryonic Trends in Abnormal Karyotypes

Trisomy 22: 3/4 developed embryos with cardiac activity (11 mm, 11 mm, 18 mm)

Mosaic trisomies: 3/3 developed embryos with cardiac activity (9 mm, 19 mm, 16 mm)

Monsomy X: 2/2 developed embryos with cardiac activity (14 mm, 24 mm)

Embryonic Trends in Abnormal Karyotypes

Trisomy 16: 6/8 developed no embryonic structure; largest embryo 4 mm, no cardiac activity

Multiple trisomies: 4/5 developed no embryonic structure.

Isolated variants: 4/4 developed no embryonic structure.

Conclusions

Expertise in separation of villi with attached chorion from decidua will reduce the incidence of maternal contamination (46XX) that results from merely submitting "products of conception" for karyotyping.

Early Pregnancy: A Changing Playing Field

New Insights: Where Did They Come From?

- Assisted reproductive technologies
- High-resolution endovaginal ultrasound
- Ability to detect minute levels of human chorionic gonadotropin (hCG)
- PULs: gap between biochemical detection and sonographic confirmation

Prior to the vaginal probe, sonography was a tool of the obstetrician. Early equipment had barely enough resolution to localize placenta, find fetal lie and measure biparietal diameter (BPD).

Sonomicroscopy

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

hCG

- Produced by trophoblastic tissue
- Detectable 8 days post-conception
- Erroneously still referred to as "beta subunit" or simply "beta" to distinguish it from alpha subunit shared with thyroid stimulating hormone (TSH) and other molecules.
- Current tests, however, measure INTACT hCG molecule.

hCG Levels

- Over-the-counter home pregnancy tests turn "positive" at 30 mIU/mL (time of missed menses).
- hCG normally rises a MINIMUM of 66% every 48 hours (often doubles every 48 hours).
- 15%-20 % of ectopic pregnancies follow NORMAL doubling times of hCG (ones that usually end up with an embryo +/- heartbeat
- Pregnancy seen on transvaginal ultrasound (TVUS) by hCG >1000mIU (modern "discriminatory" zone)

Discriminatory vs. Threshold Level

- Threshold level is the EARLIEST you sometimes see something (e.g., gestational sac, yolk sac, cardiac activity.
- Discriminatory level is the point at which a structure MUST be visualized if it is normal.

Discriminatory Level of hCG

- Original description (Kadar and Romero,1981) was 6500 mIU/mL (IRP) and by transabdominal ultrasound (TAUS)
- Updated by Nyberg et al.1985 at 1800 mIU/mL (2nd IS) = 3600 mIU/mL I.R.P.
- Vaginal probe…??? (approximately 1000 mIU…depends on equipment, frequency, magnification, coexisting myomas and, when applicable, multiple gestations

IRP = International Reference Preparation
2nd IS = Second International Standard

Serial Determinations of hCG

- If hCG is less than a discriminatory level, it should be repeated when it is expected to have surpassed that level (approximately 1000 mIU/mL).
- The endometrium, while lacking a gestational sac, should at least have an appearance COMPATIBLE with an early normal pregnancy (lush, homogeneous, decidualized/secretory in appearance).

Gestational Sac

- Sonographic, not anatomic, term
- First definitive sign of pregnancy
- Echogenic rind around a sonolucent center
- Recognized by its appearance, not its location

Yolk Sac

- Not appreciated originally by transabdominal ultrasound
- First structure visualized within the gestational sac
- Round, bright rim
- < 6 mm
- Enlarged ("hydropic"), solid or duplicated yolk sac is a very poor prognostic sign.

First Trimester as a Concept…

- Traces its origins as the point when uterus goes from a pelvic to an abdominal organ.
- Pregnancy through first 12 weeks after last menstrual period (LMP)
- Arbitrary time divider; does not reflect naturally occurring events (anatomically, developmentally, loss rates)

Embryonic Period

- Five-week window from 35 days after LMP to 70 days after LMP
- Period of organogenesis, thus concerns about teratogens
- "Embryo" from the Greek for "metamorphosis"

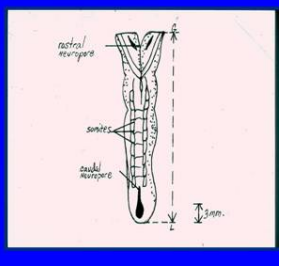
Fetal Period

- Begins after 70 days after LMP
- Period of growth and differentiation, not development
- "Fetus" from the Latin for "offspring," "having a human appearance"

Embryonic Period

Somite stage (45 days after LMP)

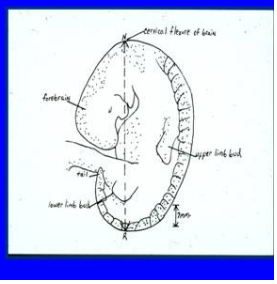
- Neural tube forms opposite the somites.
- Rostral and caudal neuropores form distally.
- Measurement of size is its greatest length.



Embryonic Period

C-shaped, tadpole-like (49 days after LMP)

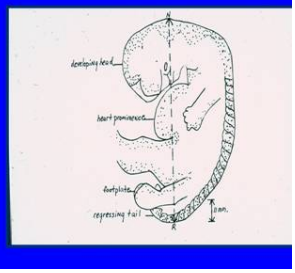
- Forebrain develops from rostral neuropore.
- Caudal neuropore develops into tail.
- Limb buds develop.
- Greatest length is no longer straight; measurement is along the long axis.



Embryonic Period

Further unfolding (53 days after LMP)

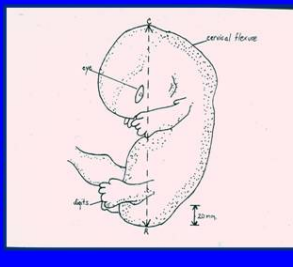
- Forebrain develops into head.
- Tail is regressing.
- Measurement along longest axis is from rump to cervical flexure.



Embryonic Period

Crown-rump length(60 days after LMP)

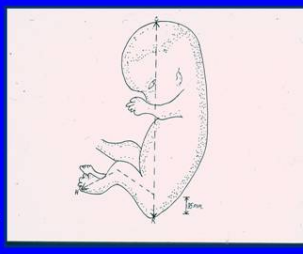
- Further extension and development of head
- Further regression of tail
- Longest measurement is from crown to rump.



Fetal Period

(Begins at 70 days after LMP)

- Crown-rump length represents sitting height.
- Totally recognizable as a human offspring
- Landmarks for measurement easily found, even in days of static arm scanners.



Current Issues

- But first a little story…

Little Story

- Recently, a resident presented a case of a dilation and curettage for a "missed abortion."
- When asked how the diagnosis was made, she responded, "By ultrasound."
- I pressed on, "I know by ultrasound, but by what criteria?"
- "There was no fetal heart (FH)", she responded.

Little Story…(continued)

- How big was the embryo?" I asked.
- "8 weeks," she responded.
- "That's how OLD the pregnancy was," I said, "How BIG was the embryo?"
- She had no idea…
- I asked "How big should an embryo be when you absolutely will see cardiac activity?"
- "7 weeks," she volunteered sheepishly.

Keys to Successful Use of Early Pregnancy Ultrasound

- What early pregnancy looks like and why (we already covered that)
- Difference between acceptable growth and continued well-being from an intrauterine gestation (IUG) that is absolutely destined to fail
- PULs (pregnancies of unknown location)

When Should You See a Gestational Sac?

- Usually by 5 weeks after LMP (3 weeks post-conception)
- Should not usually go by dates…often notoriously unreliable
- hCG levels…concept of a discriminatory level vs. threshold level

When Should You See a Yolk Sac?

- Threshold level

When Should You Absolutely See a Yolk Sac?

- Rowlins et al. 1999
  MSD =13 mm (5 MHz transducer)
  MSD = 5 mm (9-5MHz transducer)

The sac size at which a yolk sac is DEFINITIVELY seen will depend on frequency, as well as other potential factors.

MSD = mean sac diameter

What About Cardiac Activity?

Cardiac Activity: Threshold Level

- **Realize that any pregnancy in which the outcome is ultimately normal had cardiac activity present in the early embryo prior to our ability to image it.**

The question is not, "how early can I see cardiac activity (threshold level)?"…

The question is, "At what point, if cardiac activity is not seen, is a pregnancy definitively nonviable (discriminatory level)?"

Cardiac Activity

- Levi et al. Radiology 176:71, 1990
  - All normal outcomes had cardiac activity by embryo of 4 mm or more.
- Brown et al. J Ultrasound Med 1990;9:631
  - One case of 4-mm embryo lacking cardiac activity that ultimately proved normal.

Cardiac Activity

Goldstein SR. Obstet Gynecol 1992;80:670-2

- 41% of embryos 3 mm or less without discernable cardiac activity ultimately proved normal.
- ALL cardiac activity, when ultimately present, was seen by 4-mm embryonic size.

Cardiac Activity Updated

Abaid LN. J Reprod Med 2007;52:375

- Retrospective analysis;179 gestations
- 8-MHz vaginal transducer
- Embryo > 3.1 mm (with or without bleeding) and no discernable cardiac activity was 100% predictive of embryonic demise.

Cardiac Activity: Conclusions

Ability to see cardiac activity sonographically will depend on…

- Type of equipment
- Frequency of equipment
- Degree of magnification
- Visual acuity of observer
- Anatomic variations (maternal obesity, uterine version, co-existing fibroids)

Heart Rate (HR)

- (Benson and Doubilet,1994)…40 patients <8 weeks' gestation
- Embryonic heart rate < 90 bpm resulted in 80% death in first trimester; when HR between 70 and 79 bpm, 91% died (n=11); HR < 70 bpm = 100% death (n=7)
- BE CAUTIOUS! Shenker et al.,1986, showed PRIOR to 7 weeks before maturing of the sinoatrial node, HR often less than 70 bpm!

bpm = beats per minute

When Are Serial hCG Determinations Appropriate?

- To rule out ectopic pregnancy, utilizing hCG and discriminatory zone
- Once ectopic pregnancy is excluded, embryonic well-being depends on serial ultrasound examinations, NOT serial hCG determinations!

Once Ectopic Pregnancy Is Ruled Out, Utilize This Information:

- Embryo grows 1 mm per day
- Gestational sac grows 1 mm per day

Endovaginal Ultrasound Measurement of Early Embyronic Size (EES) as a Means of Assessing Gestational Age

GOLDSTEIN SR,WOLFSON R
JUltrasound Med 1994;13;27-31

Materials and Methods

- 143 patients
- No history of bleeding
- All delivered a singleton within 2 weeks of estimated date of confinement (EDC) set by date of LMP.
- All had a single EES measurement between 1 and 25 mm (cross-sectional study).

Gestational Age (Days) = Embryonic Size (mm) + 42

R (correlation coefficient) = 0.87

± 2 SD = ± 3 days

-Realize this means embryonic growth (up to 25 mm) is linear and grows 1mm/day. This is EXTREMELY useful is assessing embryonic well-being!

SD = standard deviation

Pitfalls of Using Serial hCG After Ectopic Pregnancy Ruled Out (Bree,1989)

Yolk sac	Embryo with heartbeat	(n)	Average hCG (mIU/mL)	95% CI
-	-	14	933	627-1,390
+	-	16	2630	713-9,705
+	+	41	11,749	6,636-24,491

CI = confidence interval

So What Is a Pregnancy of Unknown Location (PUL)?

- The patient who presents to us with biochemical evidence of a pregnancy event will fall into one of three categories:

Patients Who Are Pregnant:

- ***Definitive*** **IUG**
- ***Definitive*** **ectopic pregnancy**
- **Everything else (PULs)**
  - **Quantitative hCG (often serial)**
  - **Discriminatory zone**
  - **Villi vs. decidua**

Normal IUG

Definitive IUG That May Not Be Normal

Patients Who Are Pregnant:

- ***Definitive*** IUG
- ***Definitive*** ectopic pregnancy
- Everything else (PULs)
  - Quantitative hCG (often serial)
  - Discriminatory zone
  - Villi vs. decidua

Patients Who Are Pregnant:

- ***Definitive*** IUG
- ***Definitive*** ectopic pregnancy
- Everything else in the middle (PULs):
  - Quantitative hCG (often serial)
  - Discriminatory zone

Early Pregnancy of Unknown Location (PUL)

- It is this "everything else in the middle" category that is on the rise because of the widening gap between biochemical detection (hCG = 30-50 mIU/mL) and the ability to see a sac on transvaginal ultrasound (discriminatory level around 1000 mIU/mL)

+hCG and No IUG on Ultrasound….

- What does this potentially represent?
  - -Early IUG too early to visualize
  - -Failed IUG without definitive sonographic confirmation
  - -Ectopic pregnancy (which may or may not be "thriving")

What If the hCG > Discriminatory Level and There Is No IUG on Ultrasound?

- Original approach: dilation and curettage to look for villi vs. decidua (villi prove an IUG)
- This approach was also advocated in the original description of methotrexate for medical management of ectopic pregnancy.

Methotrexate

- Folic acid antagonist inhibits DNA synthesis and cell reproduction, primarily in actively proliferating tissue like malignant cells,t rophoblast ,and fetal cells.
- Widely used in cancer, psoriasis, rheumatoid arthritis and, most recently, ectopic pregnancy
- Increase in non-surgical treatment makes tracking hospital admissions for incidence obsolete.

Methotrexate

(ACOG Practice Bulletin Number 3 ,1998)

- Unruptured mass < 3.5 cm in greatest dimension
- No cardiac activity present
- Patients whose hCG level does not exceed a predetermined value (6,000-15,000 mIU/mL)
- Patient able to return for follow-up care
- No contraindications to methotrexate

Methotrexate

- Remember…works on trophoblast
- Quality and health of the trophoblastic tissue will be a more important determinant of success, not just absolute size or hCG level.
- For instance…

  -Ultrasound mass > 3.5 cm that is mostly blood, clot and fibrin (e.g., hematosalpinx) will do better than a normal-looking sac of 2.0 cm with a yolk sac!

  -hCG of 2000 that was 1800 48 hours ago will do better than an hCG of 1500 that was 750 48 hours ago.

Methotrexate

(ACOG Practice Bulletin Number 94 ,2008)

- No longer gives a LEVEL of hCG nor a SIZE of the mass as a criterion.
- Check serum creatinine, liver function tests (LFTs), and rule out any blood dyscrasias PRIOR to administration.
- Expect a 15% drop in hCG levels from day 4 to day 7; if not, additional methotrexate or surgical intervention
- "Not unusual …to experience abdominal pain 2-3 days after administration, presumably from the cytotoxic effect causing tubal abortion."

IS Dilation and Curettage Always Necessary?

Example #1

- 38 days after LMP, staining, positve home pregnancy test
- Ultrasound shows homogeneous decidualized endometrium, no IUG
- hCG 740 mIU/mL
- 48 hours later, hCG 210 mIU/mL
- Diagnosis: Failed pregnancy, uncertain location
- Plan: Expectant management

EXAMPLE #2

- 38 days after LMP, staining, positive home pregnancy test
- Ultrasound shows homogeneous endometrium, no IUG
- hCG 740 mIU/mL
- 48 hours later, hCG 815 mIU/mL (10%increase)
- Diagnosis: Non-normal pregnancy, undetermined location, hCG rising (i.e., some viable trophoblast)
- Plan: Dilation and curettage OR single shot of methotrexate???

Does Every Patient With a Spontaneous Abortion Need hCG Followed Until It Is Negative?

- Condos et al. (BJOG,2005,112:827-9) studied 152 women diagnosed with completed abortion using transvaginal ultrasound.
- Regardless of how much bleeding occurred by history, 6% with apparent complete miscarriage ultimately proved to have ectopic pregnancies
- They concluded "A diagnosis of complete miscarriage based on history and scan findings alone is unreliable. These women should be managed with serum hCG follow-up."

Final Pearl…

What we recognize with ultrasound will depend on how *NORMALLY* a pregnancy is developing, not *WHERE* it is located.

In Summary

- What constitutes a pregnancy
- What early pregnancy looks like and why it looks that way
- Pregnancy failure, its recognition, and reasons for it

In Summary

- Biochemical detection of hCG at 30-50 mIU/mL
- Transvaginal ultrasound detection at approx 1000 nIU/mL
- PULs increasing issue with gap between biochemical and transvaginal ultrasound detection
- Management issues regarding dilation and curettage vs. empiric methotrexate still unresolved

REFERENCES

1. Abaid LN, As-Sanie S, Wolfe HM. Relationship between crown-rump length and early detection of cardiac activity. J Reprod Med. 2007;52:375-8
2. ACOG Practice Bulletin No. 94: Medical management of ectopic pregnancy. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2008 ;111:1479-85
3. Benson CB, Doubilet PM. Slow embryonic heart rate in early first trimester: indicator of poor pregnancy outcome. Radiology. 1994192:343-4
4. Bree RL, Edwards M, Böhm-Vélez M, Beyler S, Roberts J, Mendelson EB. Transvaginal sonography in the evaluation of normal early pregnancy: correlation with HCG level. AJR Am J Roentgenol. 1989;153:75-9
5. Brown DL, Emerson DS, Felker RE, Cartier MS, Smith WC. Diagnosis of early embryonic demise by endovaginal sonography. J Ultrasound Med. 1990 ;9:631-6.
6. Condous G, Okaro E, Khalid A, Bourne T. Do we need to follow up complete miscarriages with serum human chorionic gonadotrophin levels? BJOG. 2005; 112:827-9.
7. Goldstein SR. Significance of cardiac activity on endovaginal ultrasound in very early embryos. Obstet Gynecol. 1992;80:670-2
8. Goldstein SR, Wolfson R. Endovaginal ultrasonographic measurement of early embryonic size as a means of assessing gestational age. J Ultrasound Med. 1994;13:27-31
9. Goldstein SR, Kerenyi T, Scher J, Papp C. Correlation between karyotype and ultrasound findings in patients with failed early pregnancy. Ultrasound Obstet Gynecol. 1996;8:314-7.
10. Ohno M, Maeda T, Matsunobu A. A cytogenetic study of spontaneous abortions with direct analysis of chorionic villi. Obstet Gynecol. 1991;77:394-8.
11. Rowling SE, Langer JE, Coleman BG, Nisenbaum HL, Horii SC, Arger PH. Sonography during early pregnancy: dependence of threshold and discriminatory values on transvaginal transducer frequency. AJR Am J Roentgenol. 1999;172:983-8.
12. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. N Engl J Med. 1988;319:189-94.

NOTES

Course #17 Test Questions

1. According to the literature, what percentage of simple postmenopausal cystic adnexal masses are cystedenomas?

    a. 0%
    b. 10%
    c. 33%
    d. 66%
    e. 100%

2. Once ectopic pregnancy is definitively ruled out, embryonic well-being is best monitored by which one of the following?

    a. Normal doubling times of human chorionic gonadotropin (hCG)
    b. Clinical growth of uterine size
    c. Amount of vaginal bleeding
    d. Follow-up ultrasound in 4-5 days
    e. Serial beta subunit determinations

3. The normal early embryo should:

    a. Double every 48 hours
    b. Demonstrate cardiac activity if real-time equipment is used
    c. Grow approximately 1 mm/day
    d. Demonstrate normal doubling times of hCG
    e. Be visible on ultrasound with an hCG>1500 IU

4. A 42-year-old woman with menorrhagia and dysmenorrhea has an ultrasound report stating she has myometrial cysts. The most likely diagnosis is which one of the following?

    a. Intramural fibroid
    b. Adhesion
    c. Submucosal fibroid
    d. Endometrial polyp
    e. Adenomyosis

5. A 31-year-old woman with primary infertility has been told that she has an intracavitary abnormality in her uterus. The most likely diagnosis is which one of the following?

    a. Intramural fibroid
    b. Adhesion
    c. Submucosal fibroid
    d. Endometrial polyp
    e. Intrauterine contraceptive device (IUCD)

(continued)

6. A 37-year-old woman with 2 years of infertility presents for evaluation. On baseline ultrasound, a 5 cm mass is seen within the right ovary. It has smooth borders, but there are hypoechoic areas on top and hyperechoic echoes on the bottom with shadowing. There is a 4 mm nodular hyperechoic area with shadowing protruding into the hypoechoic area. There is no flow into the mass by color or power Doppler. There is no ascites present. Explain the best next step in management of this case.

    a. This mass is complex and the ovary should be removed.
    b. This mass has features consistent with a dermoid cyst and a laparoscopic cystectomy can be performed prior to infertility treatment.
    c. This mass may be cancer. Given her age and the complex nature of this mass, she ought to proceed directly to IVF for fertility, and then remove the ovary.
    d. A computed tomography (CT) scan is warranted to further evaluate this mass.
    e. Refer this patient to an oncologist and counsel her that her health is more important than her fertility.

7. A 35-year-old woman with a 14-week size uterus is interested in conceiving. She complains of menorrhagia during her periods. She denies any intermittent bleeding. On ultrasound there appears to be a 2.5-cm well-circumscribed mass in the intramural or possibly submucosal area. She also has fibroids located subserosally, which range in size from 0.9 – 1.5 cm in diameter. The most appropriate next step would be which one of the following?

    a. MRI to better map these potential fibroids prior to an abdominal myomectomy
    b. CT scan to evaluate the pelvis prior to surgery, and consider a vaginal or abdominal hysterectomy.
    c. Saline infusion sonohysterogram followed by hysteroscopic removal if type 0 or 1 fibroid found.
    d. Uterine artery embolization to control her bleeding, then she can proceed with conception.
    e. Hysterectomy or ablation, since her symptoms indicate that she probably has adenomyosis.

8. A 32-year-old woman is undergoing IVF. She has known cervical stenosis due to prior cervical procedures, which were performed due to abnormal Pap smears. The best approach to her embryo transfer (ET) would be which one of the following?

    a. Have the most experienced physician do the ET with ultrasound guidance
    b. Do a trial transfer in the month preceding the IVF and dilate the cervix if needed, so that the cervix will be fine for traditional ET.
    c. Do a trial transfer in advance and dilate if needed, retest at aspiration and if smooth, proceed with the ultrasound-guided ET.
    d. Do a trial transfer the month preceding the IVF, dilate if needed, reevaluate at aspiration, place a stitch in the cervix to be sure you can control the angle for ET whether it is smooth at aspiration or not, and use ultrasound guidance for transfer.
    e. Pretreat the cervix with Cytotec the night before the embryo transfer.