Ultrasound Evaluation in the Infertile Female

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Disclosures

Elizabeth Puscheck, M.D., M.S., M.B.A.

Relevant Financial Relationships:
I am involved in a number of industry sponsored multi-centered clinical trials. Current companies include:

AbbVie
Allergan
Bayer
Ferring
ObsEva

These studies do not involve infertility and should not bias this lecture

Learning Objectives

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

1. Describe the role of ultrasound in the infertility evaluation

2. Discuss the consequences of abnormalities with in the ovaries, uterus, and tubes regarding infertility

3. Describe treatment options to optimize fertility outcomes

Lecture Outline

1. Infertility definition and frequency
2. Differential diagnoses for infertility
3. Ovarian reserve testing
4. Common ovarian abnormalities
5. Evaluation of the uterus and tubes
6. Common uterine abnormalities
7. Common tubal factors
8. Types of fertility treatments
9. Conclusions

Infertility Diagnosis and When to Evaluate:

- 85% of United States couples conceive within 1 yr
- Infertility Defined: One year of unprotected intercourse without a resulting pregnancy
- Start evaluation after 1 year of unprotected sex
- *Earlier evaluation* *when:*
  Female age over 35 *6 months*
  >40 yo *Immediate*
  History of known cause: *Immediate*

Evaluate both partners concurrently!

Traditional Evaluation of the Infertility Couples

- History on both
- Physical exam,
- Preconceptual counseling and
- Evaluations of infertility:
  - Laboratory tests
  - Ovarian reserve testing
  - Ovulation detection
  - Uterine cavity and tubes
  - Semen Analysis

Etiologies of Infertility

Etiologies:
- 40% Male etiology
- 40% Female etiology
- 15-20% Unexplained

20-25% Couples have more than one etiology

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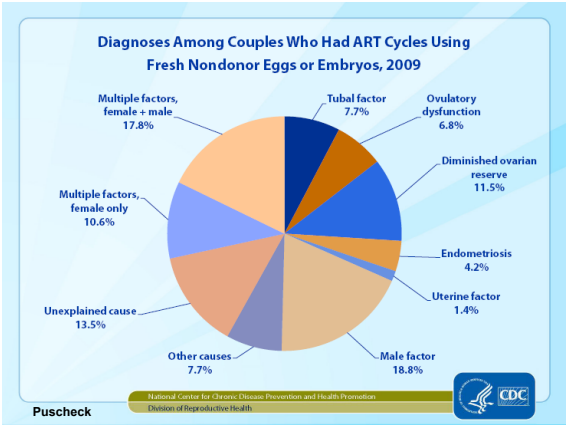

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Initial Traditional Evaluation

• Male	Semen analysis
• Female	
▪ Ovulation	OPK, BBT, P4>3
▪ Uterus/Tubes	HSG
▪ Cervix	Exam
▪ R/O other disorders	TSH, Prolactin

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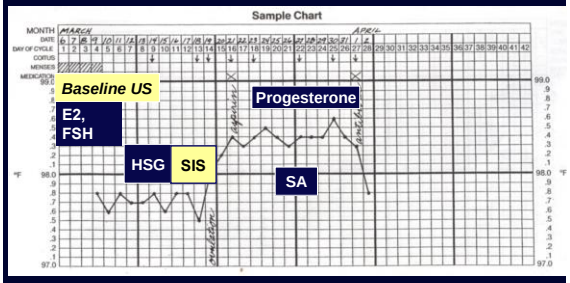
Basal Body Temperature Chart And Initial Female Evaluation



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Baseline Ultrasound in Infertility

- Best done in the early follicular time (i.e. cd 3) to be most informative
- Transvaginal probe
- Use a systematic approach
  - Empty bladder
  - Watch as you are placing the transducer
  - Look at the Bladder and Cervix (length and location)
  - Uterus: orientation, size, endometrial thickness,
  - Ovaries: location, size, and number of follicles
  - 3D is helpful, especially in luteal phase or with SIS

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What Can't Ultrasound Do?

- Minimal and Mild Endometriosis??
- Pelvic adhesions (especially filmy ones)
- Some tubal abnormalities

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Ovaries

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Ovaries

- Baseline ultrasound:
  - Ovarian reserve
  - Polycystic ovaries
  - Ovarian masses
- Series of Ultrasounds?
  - Ovulation detection?

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Ovarian Reserve Testing

- Goal: Identify women at risk for poor/good response or pregnancy
- Most predict response, not pregnancy rate
- Tests:
  - Cycle day 3 FSH and estradiol levels
  - Anti-Mullerian Hormone (AMH)
  - Ultrasound measures:
    - Ovarian volume and antral follicle counts

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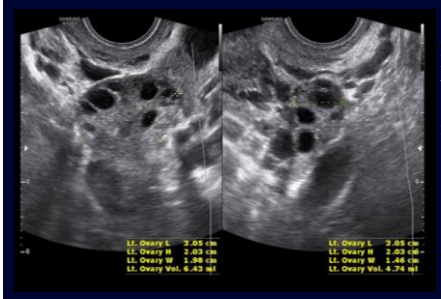
Ovarian Volume and AFC



Mean size varies by Age:
- Pre-menopausal
  - 4.8 cm^3
- PCO
  - >10 cm^3
- Post Men.
  - 2.2 cm^3

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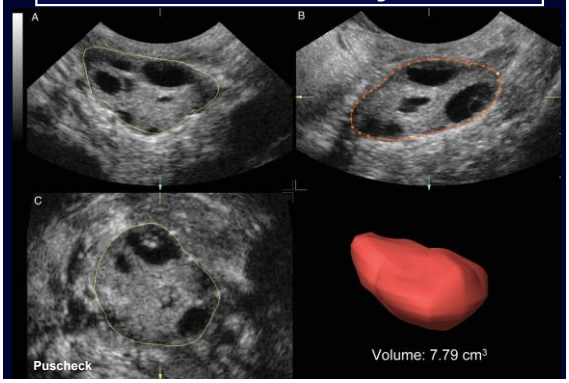
Ovarian Volume by Vocal



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Ovarian Volume:

- Smaller due to:
  - Poor ovarian reserve
  - Aging (>37) or POF
  - Birth Control Pills (by 50%)
- Larger due to:
  - PCO (>10 cm^3)
  - Increased risk for OHSS
  - Ovarian cysts or masses

Birch Petersen K et al. Hum Reprod 2015; 30:2364-75

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Poor Ovarian Reserve

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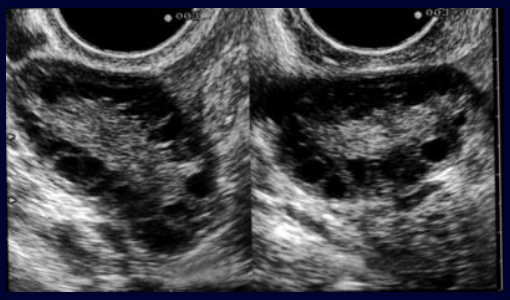
PCO Appearing Ovaries



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Polycystic Ovary Syndrome

Table 1
Criteria for the Diagnosis of Polycystic Ovary Syndrome
(Other Hormonal or Androgen Excess Conditions Being Previously Excluded)[a]

NIH/NICHD (must meet both criteria)	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	• Oligo-ovulation or anovulation	• Ovarian dysfunction and/or
	• Polycystic ovaries	polycystic ovaries

Abbreviations: ESHRE/ASRM = European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH/NICH = National Institutes of Health/National Institute of Child Health and Human Disease.
[a] Adapted from *Clin Epidemiol*. 2014;6:1-13.

Criteria Change: Antral Follicle Count of 2-9 mm AFC > 25 Or (Same for Volume ≥ 10 cm ^{3})

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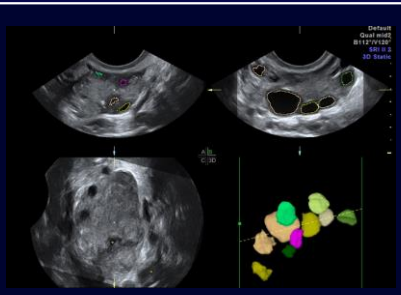
Automatic 3D AFC



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Is 3D Required?

Neither Ovarian Vocal Volume or 3D automated AFC did better than the 2D evaluation for volume and AFC

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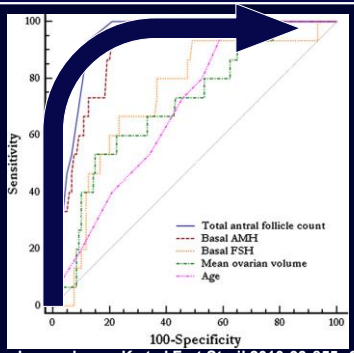
Comparison of Ovarian Reserve Tests:



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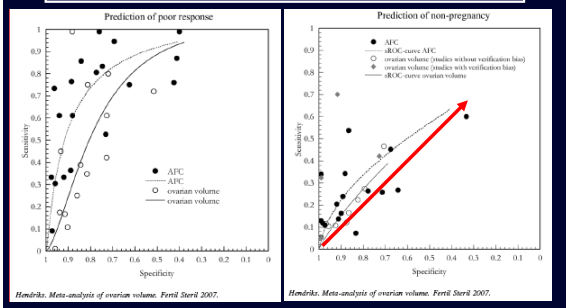
Jayaprakasan K et al Fert Steril 2010;93:855--64

AFC and Ovarian Volume



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Meaning of Ovarian Reserve

- Low Ovarian volume, Low AFC, Low AMH
  - Poor ovarian reserve: older age, POF, …
  - Birth Control pills
- High Ovarian volume, high AFC, High AMH
  - PCO, Risk for OHSS
- High ovarian volume, lower AFC
  - Ovarian cysts or masses

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Ovarian Reserve

- Clinically, we use these tests in context:
- Choose protocols and adjust dosing, especially based on AFC + AMH
- Counseling our patients

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Baseline US may Detect Ovarian Masses:

Physiologic
- Follicular
- Simple
- Corpus Luteum

Pathologic:
- Endometrioma
- Mature Cystic Teratoma
- Borderline
- Malignancy

Typically, we recommend further evaluating the mass prior to ovarian stimulation with fertility treatment (repeat US, laparoscopy).

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Simple Cyst:

Use Doppler to evaluate a mass

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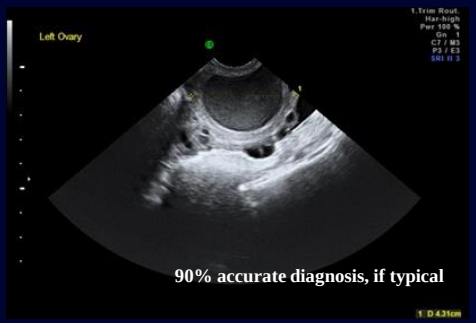
Endometrioma



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Hemorrhagic Corpus Luteum Cysts

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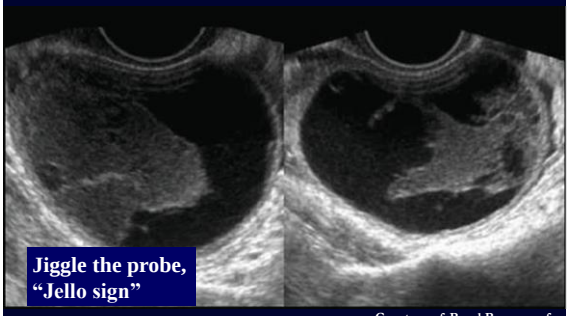
Hemorrhagic Corpus Luteum



Courtesy of Beryl Benacerraf

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Dermoid

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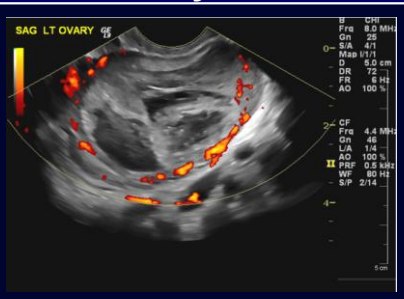
Hemorrhagic Corpus Luteum Cyst



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Radiology

Deborah Levine, MD
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Elizabeth Puscheck, MD
Rebecca Smith-Bindman, MD

Management of Asymptomatic Ovarian and Other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference Statement[1]

The Society of Radiologists in Ultrasound convened a panel of specialists from gynecology, radiology, and pathology to arrive at a consensus regarding the management of ovarian and other adnexal cysts imaged sonographically in asymptomatic women. The panel met in Chicago, Ill, on October 27–28, 2009, and drafted this consensus statement. The recommendations in this statement are based on analysis of current literature and common practice strategies, and are thought to represent a reasonable approach to asymptomatic ovarian and other adnexal cysts imaged at ultrasonography.

©RSNA, 2010

Levine D et al. Radiology 2010;256(3):943-54

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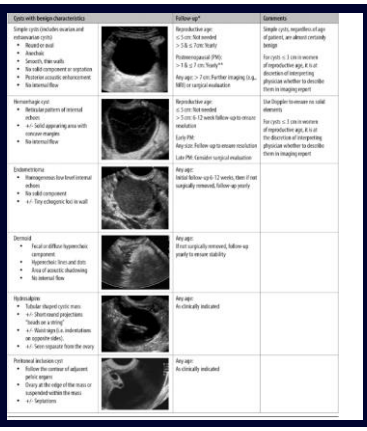

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Cysts with indeterminate, but probably benign, characteristics		Follow-up*	Comments
Findings suggestive of, but not classic for, hemorrhagic cyst, endometrioma or dermoid		Reproductive age: 6–12 week follow-up to ensure resolution. If the lesion is unchanged, then hemorrhagic cyst is unlikely, and continued follow-up with either ultrasound or MRI should then be considered. If these studies do not confirm an endometrioma or dermoid, then surgical evaluation should be considered. Postmenopausal: Consider surgical evaluation	
Thin-walled cyst with single thin septation or focal calcification in the wall of a cyst		Follow-up based on size and menopausal status, same as simple cyst described above	
Multiple thin septations (< 3 mm)		Consider surgical evaluation	Multiple septations suggest a neoplasm, but if thin, the neoplasm is likely benign
Nodule (non-hyperechoic) without flow		Consider surgical evaluation or MRI	Solid nodule suggests neoplasm, but if no flow (and not echogenic as would be seen in a dermoid) this is likely a benign lesion such as a cystadenofibroma
Cysts with characteristics worrisome for malignancy		**Follow-up***	**Comments**
Thick (> 3 mm) irregular septations		Any age: Consider surgical evaluation	
Nodule with blood flow		Any age: Consider surgical evaluation	

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Uterus: Baseline Ultrasound and Sonohysterography

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35 yo G3P0030 presenting with infertility. Baseline:

Baseline Ultrasound on cycle day 3

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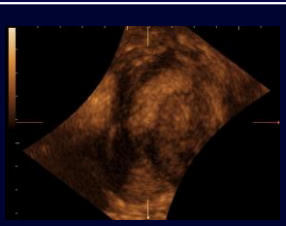
35 yo G3 P0030 had baseline ultrasound read as Normal on 2D. 3D coronal view showed this:



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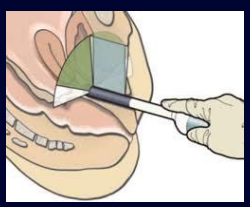
What is 3D Ultrasound?

- It is an imaging technique that captures a volume of information called voxels with a single automated sweep.
- Once the volume is acquired, the volume may be displayed in 3 orthogonal planes
  - longitudinal,
  - transverse, and
  - coronal
- 3D multi-planar and rendering have improved diagnostic accuracy



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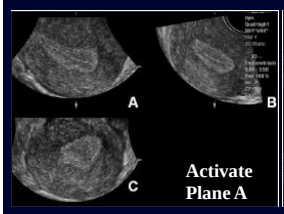
3D Multi-planar view of the uterus: Z Technique



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Abuhamad AZ, etc. J Ultrasound Med 2006;25:607-612

Z Technique: Mid-Coronal Plane

- **Step 1**: position the reference marker (dot) in the middle of the endometrium on a mid-saggital plane (A)
- ***Step 2**: Use the Z-knob to rotate the long axis to horizontal position*
- **Step 3**: Activate plane B which should have the uterus in the transverse plane.
- **Step 4**: Put the reference dot at the middle of the endometrium in plane B (mid-and rotate with the Z knob to the horizontal)
- **Step 5**: Activate the coronal plane (C) and use the Z knob to rotate the image vertically. You may need to make a few minor adjustments but this should be the mid-coronal plane. J Ultrasound Med 2006;25:607-612

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Keyboard has 3 Knobs: X, Y , and Z

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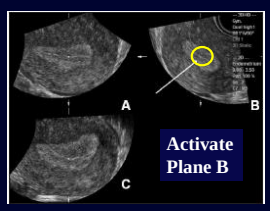
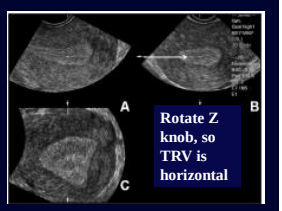
Turn the Z knob to horizontal, then Change to Plane B, Move Dot to middle and rotate with Z knob to the Horizontal





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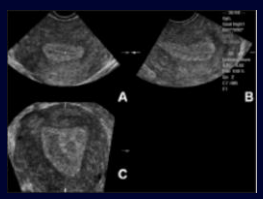
Now activate the Panel C and Rotate with Z



- The uterus is easy to see upright
- Uterus is normal

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Confusion-- 2D Ultrasound? Bicornuate vs. Septum vs. Arcuate?

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Transverse Uterus 2D

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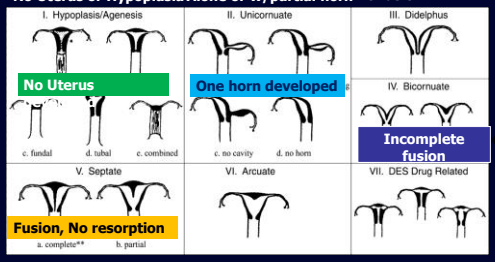
Müllerian Duct Anomalies

No Uterus or Hypoplasia | Single horn develops, Alone or w/partial horn | Both horns develop, No fusion



www.asrm.org Fertil Steril 1988;49:944-55

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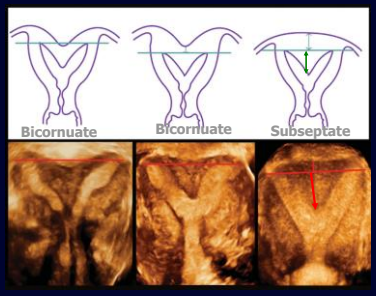

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CUA: Accuracy of Imaging

Type	Percent Accuracy
3D Ultrasound	92-100%
MRI	96-100%
TV ultrasound	85-92%
HSG	6-55%

Braun P, et al. Eur J Radiol2005;53:274-9; Doyle J Reprod Med 1992;37:33-8; Wu MH J Clin Ultrasound 1997;25:487-92;Jurkovic US Obstet Gyn 1995;5:233-7

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3D Ultrasound in GYN

Critical for detecting both:

- **Congenital Uterine Anomalies and**
- **IUD Placement localization**

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Uterine Cavity Evaluation

- **HSG or Saline Sonohysterogram**
- **Cycle days 6-12**
- **Evaluate as soon as the period is over**
- **Pretreat? Offer NSAIDS**
- **Antibiotic prophylaxis not needed, except in certain situations (tubal disease)**

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Hysterosalpingogram (HSG)

Advantages:

- Uterine Cavity assessment
- Tubal Patency
- Film

Disadvantages:

- Ionizing radiation
- Iodinated contrast
- Radiology suite
- Inner contour only
- Pain

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Saline Infusion Sonohysterogram (SIS) vs. HSG

Advantages:
- In Office
- Few Minutes
- View uterus & ovaries (not just cavity)
- No Radiation
- No iodinated contrast
- Less painful
- OK if light bleed
- No Tenaculum needed

Disadvantages:
- Patency?
- Tubal anatomy?

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Prior to the SIS:

- Baseline Ultrasound:
  - Screen for congenital anomalies
  - Screen for fibroids and adenomyosis
  - Screen for adnexal masses
  - Evaluate the endometrium
  - Evaluate for cornual tenderness
  - Screen for uterine positioning

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SIS Set-Up Equipment:
(Notice: No Tenaculum!)

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SIS Distension Media and Prep

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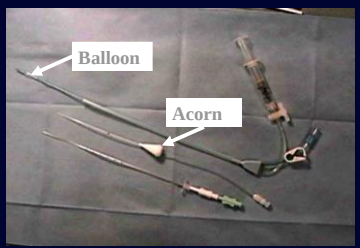
SIS Catheters



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Choosing the Catheter:

- Preference of the provider: Both work well
- Balloon: Best placed in the cervix to avoid compromising the view of the uterine cavity and less painful
- Acorn: more rigid catheter needs guiding

Catheter Type	Nulliparous	Multiparous
Acorn	Good	Good
Balloon	Good	Often falls out of cervix If used, place in uterine cavity. Deflate at end

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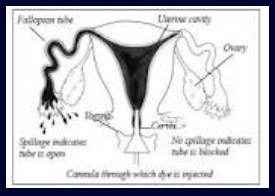
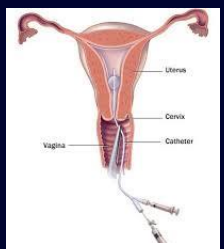
Catheters in Place



Acorn is placed at external os and ADJUST catheter



Balloon can be placed in the cervical canal or in the uterine cavity

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Pain & Catheter Placement

Pain less with intra-cervical than intrauterine w/initial placement. p=0.02
Time was same duration. Volume of distending media less in IC approach

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RCT: Pain with SIS Catheter

- 69-SIS w/ Balloon: 35 – Intracervical + 34- IU
- Pain: VAS: higher for G0 than multiparous
  - Initial Cervical (1±1) lower than IU (2 ± 3) *P=0.02*
  - End Cervical (1+3) same as IU (1±2) P=0.66
- Time: Cx 5.0 ± 2.7, Ut 4.3 ± 2.8 P=0.3
- Vol: Cx 19 +/- 16, Ut 40 +/- 32 *P=0.001*
- Touching fundus increases pain and vasovagal

Spieldoch et Obstet Gynecol 2008;111:15-21

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2D SIS

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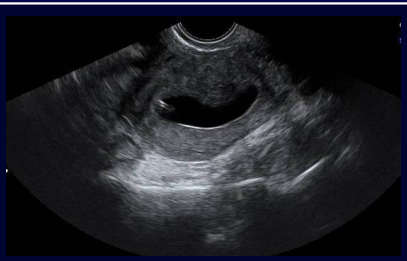
SIS: 2D Transverse



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SIS with 3D capture

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SIS with 3D

- Rendered coronal view
- Remember to "slice through" the uterus so you don't miss anything

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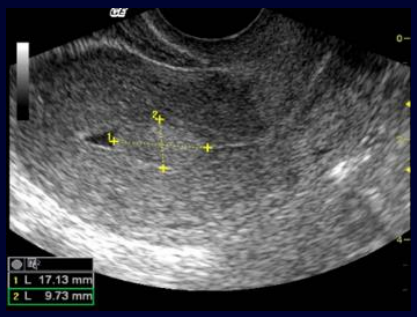

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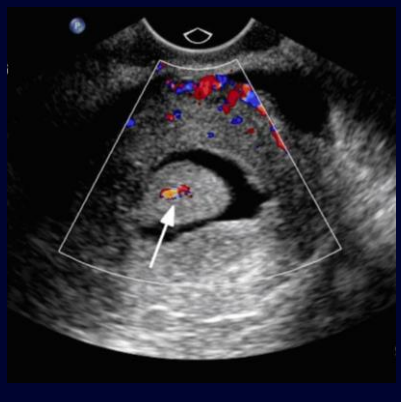

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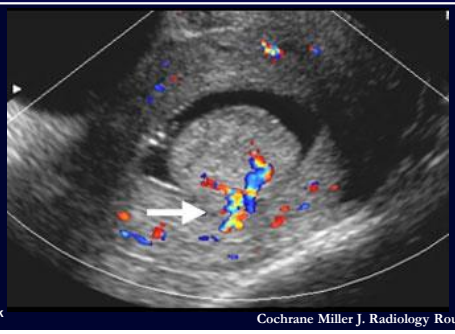
SIS With Doppler to Diagnose Polyp



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Cochrane Miller J. Radiology Rounds 20

Prevalence of Acquired Uterine Abnormalities

Tur-Kaspa et al 2006

	Infertile	AUB
N	600	409
Polyps	13%	30%
Intramural fibroids	20%	37%
Submucous fibroids	3%	9%
Arcuate uterus	15%	6%

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Accuracy of Polyp Diagnosis

Soares et al 2000

- N=65 Infertile women, Age range 19-43 yo
- Gold standard = Hysteroscopy

	Sens (%)	Spec (%)	PPV (%)	NPV(%)
HSG	50	82	29	92
TVS	75	96	75	96
SIS	100	100	100	100

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Polyps on Fertility

- Limited Data
- Polyps <2cm no effect on IVF PR, but increases miscarriage rate

Pregnancy rate in polypectomy vs. biopsy:
(after 4 hMG + IUI cycles)
N=101 Removal PR=63%
N=103 Biopsy only PR=28%

Lass et al 1999 and Perez Medina 2005

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Typical Fibroid

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Shadowing

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Subserosal Fibroid

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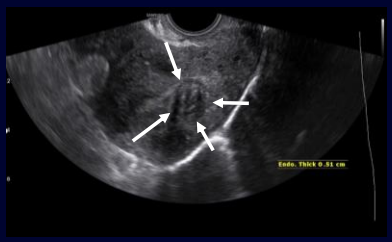
Baseline US: Uterus

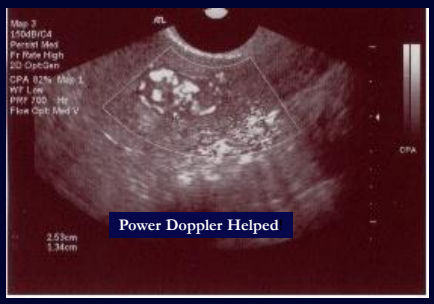


Fibroid impacting the endometrium

Puscheck

Some Fibroids May Be Difficult To See

Puscheck



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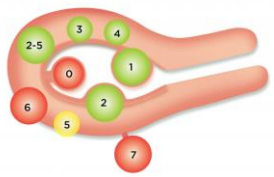
Submucosal	0	Pedunculated intracavity
	1	<50% Intramural
Intramural	2	≥50% Intramural
	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% Intramural
Subserosal	6	Subserosal <50% Intramural
	7	Subserosal Pedunculated
	8	Other (specify eg. cervical, parasitic
2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities respectively.	



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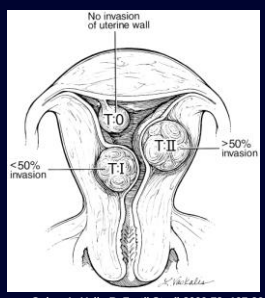
Fibroid Location and Fertility



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

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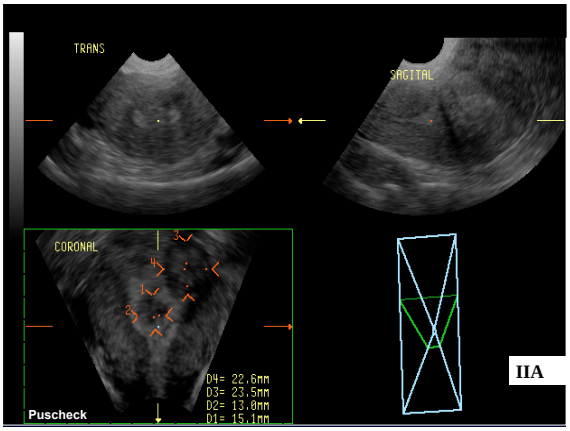
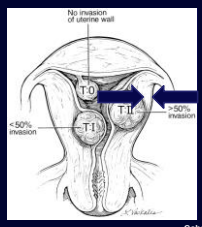


Puscheck

Fibroid Location & 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

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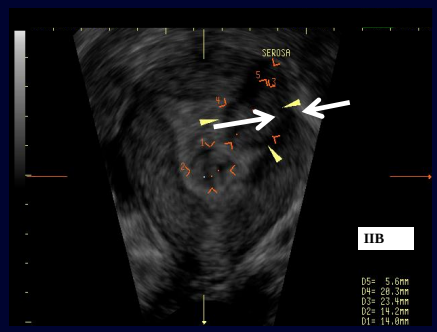

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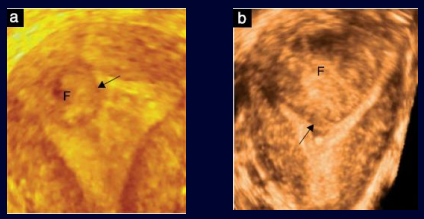
3D Coronal Views of Luteal Phase Uterus



Naftalin J, Jurkovic D. Ultrasound Ob Gyn 2009;34:1-11

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Submucus Fibroids

- **Types:**
  - Type 0: Hysteroscopic removal
  - Type 1: Hysteroscopic candidate, consider laparoscopy-assisted
  - Type 2: Abdominal myomectomy (Alternative: multiple HSC)
- **Role for intraoperative ultrasound guidance**
- **Intrauterine masses decrease pregnancy rates and increase miscarriage rates.**

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Fibroids and Infertility?

- No large-scale studies
- Many patients with infertility have fibroids
- Many patients with fibroids conceive easily
- "Clinical opinion" Fibroids play a role in infertility in 2-3% of patients

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Uterine Fibroids: IVF Pregnancy Rates

Study	No cavity	Distorts	Control
Check	20%		38%
Eldar-Geva	34%	10-16%	30%
Farhi	25%	9%	29%
Hart	15%		28%
Stovall	33%		48%
Surrey	49%		57%

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Submucosal Fibroids

TABLE 1
Submucosal fibroids

	Study design; number of patients	Fibroid diameter: mean (range)	Implantation rate[a]		Clinical pregnancy rate[b]		Spontaneous abortion rate[c]	
			Fibroids	No fibroids	Fibroids	No fibroids	Fibroids	No fibroids
Farhi et al[53]	Retrospective cohort. 18 IM fibroid patients, 50 controls	(<70 mm)	2.7% 5/179	9.8% 35/357	9.7% 5/55	25.2% 32/127	40% 2/5	25% 8/32
Eldar-Geva et al[56]	Retrospective cohort. 6 study patients, 249 controls.	45 mm ± 26	4.3% 1/23	12.3% 94/763	10% 1/10	30.8% 98/318	0% 0/1	16.3% 16/98
Cassini et al[14] (SM)	Prospective, observational. Spontaneous conceptions, following timed intercourse.	(<40 mm)			21.4% 9/42	40.4% 21/52	55.6% 5/9	42.9% 9/21
Cumulative rates			3.0% 6/202 OR 0.39 (0.24-0.65)	1.5% 29/1126	14% 15/107 OR 0.44 (0.28-0.70)	30.4% 151/497	46.7% 7/15 OR 3.85 (1.12-13.27)	21.9% 33/151

19 Studies

Klatsky et al. AJOG 2008: 357

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Intramural Fibroid and ART Outcomes: Meta-analysis

- 10 studies Intramural Fibroids and ART
- Combined data showed NO IMPACT on:
  - Pregnancy rate (OR=0.74, 95% CI 0.5-1.09)
  - Live birth rate (OR=1.17., 95% CI 0.62-2.22)
  - Miscarriage rate (OR 1.61, 95% CI 0.61-4.20)
  - Pregnancy rate AFTER myomectomy (OR 1.88, 95% CI 0.57-6.14)
  - Miscarriage rate AFTER myomectomy (OR 0.89, 95% CI 0.14-5.48)

Metwally M et al. Reprod Biomed Online 2011;23:2-14

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Large Fibroids and Pregnancy Outcome

Outcome	Large fibroids (n = 42)	Small fibroids (n = 53)	No fibroids (n = 95)	*P* value
GA at delivery, mean ± SD (wk)	36.5 ± 5.0	38.4 ± 2.9	38.6 ± 2.2	.002
EBL, mean ± SD (mL)	645.1 ± 437.7	535.6 ± 316.7	486.8 ± 275.6	.038
Short cervix at ≤32 wk GA (%)	14.3	1.9	3.2	.012
PPROM (%)	14.3	1.9	2.1	.004
Preterm delivery (%)	16.7	3.8	6.3	.050
Postpartum blood transfusion (%)	12.2	0.0	1.1	.001

Shavell et al. Fertil Steril 2012;107-110

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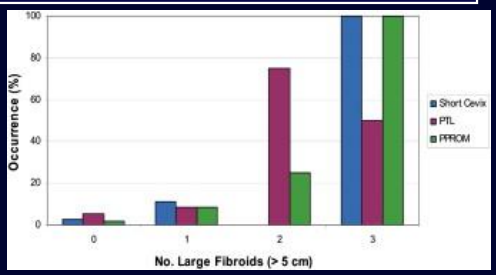
Large Fibroids and Pregnancy Outcome



Shavell et al. Fertil Steril 2012:107-110

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Intrauterine Adhesions (IUA)

Salle B J Clin Ultrasound 1999;27:131-134

- Ultrasound screening criteria for 2D:
  - Asymmetry of the endometrial echo
  - Areas of the endometrium <2mm
  - Echogenic area in the uterus
- Ultrasound accuracy (TV)
  - Sensitivity TV US is 52%
  - TV SIS is 93.5-99.4% accurate
  - Consider sonohysterogram

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Intrauterine Adhesion

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Uterine Synechiae

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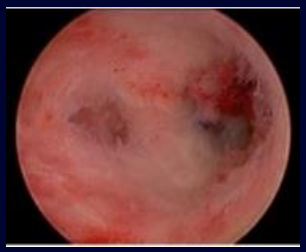
Steinkeler JA et al. RadioGraphics 2009;29:1353-1370.

Intrauterine Adhesion



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Synechiae Treatment

- Primarily, hysteroscopic surgical removal
- Balloon (intrauterine) after the procedure to keep the edges apart while the endometrium is healing
- Estrogen therapy to build the endometrium quickly

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Tubes?

- Ultrasound: Normally not seen
- Hydrosalpinx appearance
  - Tubular structure
  - Incomplete septa
  - Cogwheel sign
  - Small round projection
  - "Waist" sign

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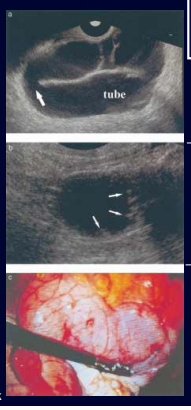
Puscheck



Hydrosalpinx:

- Tubular shape
- Incomplete septa
- Cogwheel sign
- Laparoscopy

Patel MD et al. AJR 2006;186:1033-8

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Hydrosalpinx:
Waist Sign(*) and Round Projection (arrow)

Puscheck

Patel MD et al. AJR 2006;186:1033-8

Patel et al. AJR 2006	Hydrosalpinx n=26	Cyst n=26	Para-ovarian mass n=5	**Likelihood Ratio for Hydrosalpinx**
Tubular shape	20	2	1	**10.5**
Incomplete Septum	17	10	3	**2.1**
Small Round Projection	17	8	2	**2.7**
Waist sign	13	1	0	**20.5**

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Hydrosalpinges & Fertility?

- Retrospective analyses of IVF cases have demonstrated that the presence of hydrosalpinx impairs IVF outcome:
- PR reduced by 50%
- Miscarriage rates increased 2 fold
- Possible increased ectopic rate

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Treatments for Hydrosalpinx

- Antibiotics- Not prospectively evaluated. Similar pregnancy rates in all groups. Cheap and simple. Needs RCT trial for efficacy.
- Aspiration at oocyte retrieval- No improved pregnancy rate or implantation rate (Sowter 1997, Van Voorhis 1998)
- Surgical: TL and Salpingectomy- RCT of 300 in Scandinavia (stopped at 185). Hydrosalpinges large enough for US have improved delivery rates after salpingectomy P=0.04 (40% vs 17%) (Strandell 2000 Hum Reprod Update)

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Ultrasound and Tubal Patency?

SIS: Determine Tubal Patency?

- Post-procedure Fluid in Pouch of Douglas
- Color Doppler or Power Doppler (2D vs 3D)
- Contrast material
  - Agitated Saline
  - Optison (off label use)
  - Echovist (off label use)

Spalding et al Hum Reprod 1997;12:306-9;
Fleischer et al J Ultrasound Med 1997;16:381-4

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Cul de Sac Fluid

- No fluid prior to SIS
- Post-SIS fluid
- At least 1 patent tube
- No further testing
- Pregnancy rate, if only one tube open, is reduced about 5%

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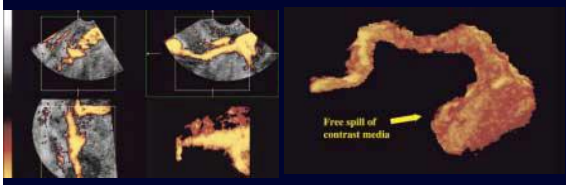
3D Power Doppler and Tubal Patency



Sladkevici et al. Obstet Gyncol 2001:98:325-331

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Air contrast for Tubal Patency

SIS 79% agreement with 85.7% sens and 77.2% specific

Jeanty et al JUM 2000;19:519-27

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Femvue or Abbi Devices for Agitated Saline SIS

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SIS vs HSG

Rezk et al 2015	Sens	Spec	PPV	NPV	P=
SIS	52%	95%	79%	84%	>0.05
HSG	38%	96%	79%	84%	

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Echovist of Fallopian Tubes
(Not FDA approved)

Ekerhovd Best Practices 2004

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Ultrasound in the Infertility Evaluation

- Ultrasound has revolutionized infertility evaluation
- The entire evaluation can be done in the office!
- Ovaries: Volumes and AFC predict response;
  - Rule out ovarian pathology
- Uterine pathology (CUA, polyps, fibroids, etc)
  - Needs SIS for more accurate polyp and adhesion diagnosis
- Tubes: Patency and Hydrosalpinges
- SIS has replaced HSG in 18% of offices
- Ultrasound is a mainstay in the infertility evaluation!

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Thank You!

Any Questions?

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