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

Initial Traditional Evaluation

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

Basal Body Temperature Chart And Initial Female Evaluation

- Baseline US
- E2, FSH
- Progesterone
- HSG, SIS, SA, SA

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

What Can’t Ultrasound Do?

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

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

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

Ovarian Volume and AFC

Mean size varies by Age:
- Premenopausal
  - 4.8 cm³
- PCO
  - >10 cm³
- Post Men.
  - 2.2 cm³

Ovarian Volume by Vocal

Smaller due to:
- Poor ovarian reserve
- Aging (>37) or POF
- Birth Control Pills (by 50%)

Larger due to:
- PCO (>10 cm³)
- Increased risk for OHSS
- Ovarian cysts or masses

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

Table 1
Criteria for the Diagnosis of Polycystic Ovary Syndrome
(Other Hormonal or Androgen Excess Conditions Being Previously Excluded)6

<table>
<thead>
<tr>
<th>NB/ECIDH</th>
<th>ESHRE/ASRM</th>
<th>Androgen Excess Society 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>(must meet both criteria)</td>
<td>(Rotterdam criteria: 2004)</td>
<td>2006</td>
</tr>
<tr>
<td>Includes all of the following</td>
<td>Includes two of the following</td>
<td>Includes all of the following</td>
</tr>
<tr>
<td>• Clinical and/or biochemical hyperandrogenism</td>
<td>• Clinical and/or biochemical hyperandrogenism</td>
<td>• Clinical and/or biochemical hyperandrogenism</td>
</tr>
<tr>
<td>• Minimal dysfuntion</td>
<td>• Minimal dysfuntion</td>
<td>• Minimal dysfuntion</td>
</tr>
<tr>
<td>• Polycystic ovaries</td>
<td>• Polycystic ovaries</td>
<td>• Polycystic ovaries</td>
</tr>
</tbody>
</table>

Criteria Change: Antral Follicle Count of 2-9 mm
AFC > 25 Or (Same for Volume ≥ 10 cm³)

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

Comparison of Ovarian Reserve Tests:

Jayaprakasan K et al Fert Steril 2010;93:855--64
AFC and Ovarian Volume

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

Ovarian Reserve

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

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).

Simple Cyst:

Use Doppler to evaluate a mass

Endometrioma

90% accurate diagnosis, if typical
Hemorrhagic Corpus Luteum Cysts

Jiggle the probe, “Jello sign”

Dermoid

Hemorrhagic Corpus Luteum Cyst

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

Levine D et al. Radiology 2010;256(3):943-54
35 yo G3P0030 presenting with infertility. Baseline:

Baseline Ultrasound on cycle day 3

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

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

- Move the reference Dot to the middle of the endometrium

Uterus: Baseline Ultrasound and Sonohysterography

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

Abuhmad 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.


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Keyboard has 3 Knobs: X, Y, and Z

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

Activate Plane B

Rotate Z knob, so TRV is horizontal

---

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
Müllerian Duct Anomalies

No Uterus or Hypoplasia

- Single horn develops, alone or with partial horn
- Both horns develop, no fusion

CXA: Accuracy of Imaging

<table>
<thead>
<tr>
<th>Type</th>
<th>Percent Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D Ultrasound</td>
<td>92-100%</td>
</tr>
<tr>
<td>MRI</td>
<td>96-100%</td>
</tr>
<tr>
<td>TV ultrasound</td>
<td>85-92%</td>
</tr>
<tr>
<td>HSG</td>
<td>6-55%</td>
</tr>
</tbody>
</table>

3D Ultrasound in GYN

Critical for detecting both:
- Congenital Uterine Anomalies and
- IUD Placement localization

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)

Hysterosalpingogram (HSG)

Advantages:
- Uterine Cavity assessment
- Tubal Patency
- Film

Disadvantages:
- Ionizing radiation
- Iodinated contrast
- Radiology suite
- Inner contour only
- Pain
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?

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

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

SIS Distension Media and Prep

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

<table>
<thead>
<tr>
<th>Catheter Type</th>
<th>Nulliparous</th>
<th>Multiparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acorn</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Balloon</td>
<td>Good</td>
<td>Often falls out of cervix if used, place in uterine cavity. Deflate at end</td>
</tr>
</tbody>
</table>
**Catheters in Place**

Acorn is placed at external os and ADJUST catheter

**Pain & Catheter Placement**

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

**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

**2D SIS**

**SIS: 2D Transverse**

**SIS with 3D capture**
**SIS with 3D**

- Rendered coronal view
- Remember to “slice through” the uterus so you don’t miss anything

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**SIS With Doppler to Diagnose Polyp**

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**Prevalence of Acquired Uterine Abnormalities**

*Tur-Kaspa et al 2006*

<table>
<thead>
<tr>
<th></th>
<th>Infertile</th>
<th>AUB</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>600</td>
<td>409</td>
</tr>
<tr>
<td>Polyps</td>
<td>13%</td>
<td>30%</td>
</tr>
<tr>
<td>Intramural fibroids</td>
<td>20%</td>
<td>37%</td>
</tr>
<tr>
<td>Submucous fibroids</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Arcuate uterus</td>
<td>15%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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**Accuracy of Polyp Diagnosis**

*Soares et al 2000*

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

<table>
<thead>
<tr>
<th></th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSG</td>
<td>50</td>
<td>82</td>
<td>29</td>
<td>92</td>
</tr>
<tr>
<td>TVS</td>
<td>75</td>
<td>96</td>
<td>75</td>
<td>96</td>
</tr>
<tr>
<td>SIS</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
**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**

Solid, well-circumscribed, round

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**Subserosal Fibroid**

Hypoechoic subserosal

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**Baseline US: Uterus**

Fibroid impacting the endometrium
Some Fibroids May Be Difficult To See

Fibroid Location and Fertility


Power Doppler Helped
**Fibroid Location & Fertility**

**REMEmB**

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

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**3D Coronal Views of Luteal Phase Uterus**


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**Submucous 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>No cavity</th>
<th>Distorts</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check</td>
<td>20%</td>
<td></td>
<td>38%</td>
</tr>
<tr>
<td>Eldar-Geva</td>
<td>34%</td>
<td>10-16%</td>
<td>30%</td>
</tr>
<tr>
<td>Farhi</td>
<td>25%</td>
<td>9%</td>
<td>29%</td>
</tr>
<tr>
<td>Hart</td>
<td>15%</td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td>Stovall</td>
<td>33%</td>
<td></td>
<td>48%</td>
</tr>
<tr>
<td>Surrey</td>
<td>49%</td>
<td></td>
<td>57%</td>
</tr>
</tbody>
</table>
**Submucosal Fibroids**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Fibroid diameter</th>
<th>Implanted rate</th>
<th>Clinical pregnancy rate</th>
<th>Spontaneous abortion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate et al.</td>
<td>10</td>
<td>79%</td>
<td>2.7%</td>
<td>30.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Kato et al.</td>
<td>37</td>
<td>57%</td>
<td>1.7%</td>
<td>26.3%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Math-Cass et al.</td>
<td>45</td>
<td>11%</td>
<td>4.4%</td>
<td>12.5%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Kato et al.</td>
<td>100</td>
<td>24%</td>
<td>5.9%</td>
<td>15.7%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

19 Studies

- 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)

**Large Fibroids and Pregnancy Outcome**

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

**Intrauterine Adhesions (IUA)**

- 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

**Intramuscular 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)
**Uterine Synechiae**


**Intrauterine Adhesion**

Puscheck

**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

**Tubes?**

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

**Hydrosalpinx:**

- Tubular shape
- Incomplete septa
- Cogwheel sign
- Laparoscopy

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

Treatments for Hydrosalpinx

- 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)

Ultrasound and 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)

SIS: Determine Tubal Patency?

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

**3D Power Doppler and Tubal Patency**

**Air contrast for Tubal Patency**
SIS 79% agreement with 85.7% sens and 77.2% specific

**Femvue or Abbi Devices for Agitated Saline SIS**

**SIS vs HSG**

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIS</td>
<td>52%</td>
<td>95%</td>
<td>79%</td>
<td>84%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HSG</td>
<td>38%</td>
<td>96%</td>
<td>79%</td>
<td>84%</td>
<td></td>
</tr>
</tbody>
</table>

**Echovist of Fallopian Tubes**
(Not FDA approved)
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!

Thank You!

Any Questions?

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