ULTRASOUND
LECTURE SERIES

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Council on Resident Education in Obstetrics and Gynecology

THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS
1951
WOMEN'S HEALTH CARE PHYSICIANS

Individualized Assistance Through Proper Understanding
ACOOG
1934
Women's Healthcare Physicians

Ultrasound Evaluation of the Infertile Female

Elizabeth Puscheck, MD

Professor of Obstetrics and Gynecology

Wayne State University School of Medicine

Detroit, Michigan

Ultrasound Evaluation of the Infertile Female: Outline

1. The ovary: normal follicular development
2. Corpus luteum assessment
3. Assessment of the endometrium
4. Doppler (color flow and pulsed) evaluations of:
   - The ovary
   - Endometrium
   - Uterus
5. Ultrasound assessment of infertility
   - Assessing ovarian function
   - Ovarian failure
   - Monitoring ovarian stimulation
   - Ovarian hyperstimulation

Outline Cont

6. Sonohysterography
7. Common infertility-related pathology
   - Polycystic ovary syndrome
   - Endometriosis
   - Fibroids
   - Adenomyosis
8. Ultrasound guidance for
   - Egg retrieval
   - Embryo transfer
9. Common congenital anomalies of the uterus
   - Septate
   - Arcuate
   - Unicornuate
   - Bicornuate

Infertility

- Defined as 1 year of unprotected intercourse without conception
- Etiologies include:
  - Ovarian factors
  - Uterine:
    - Uterine anomalies (congenital anomalies or acquired, like polyps, fibroids, adhesions)
    - Tubal factor
    - Cervical factors
  - Male factor
  - Unexplained

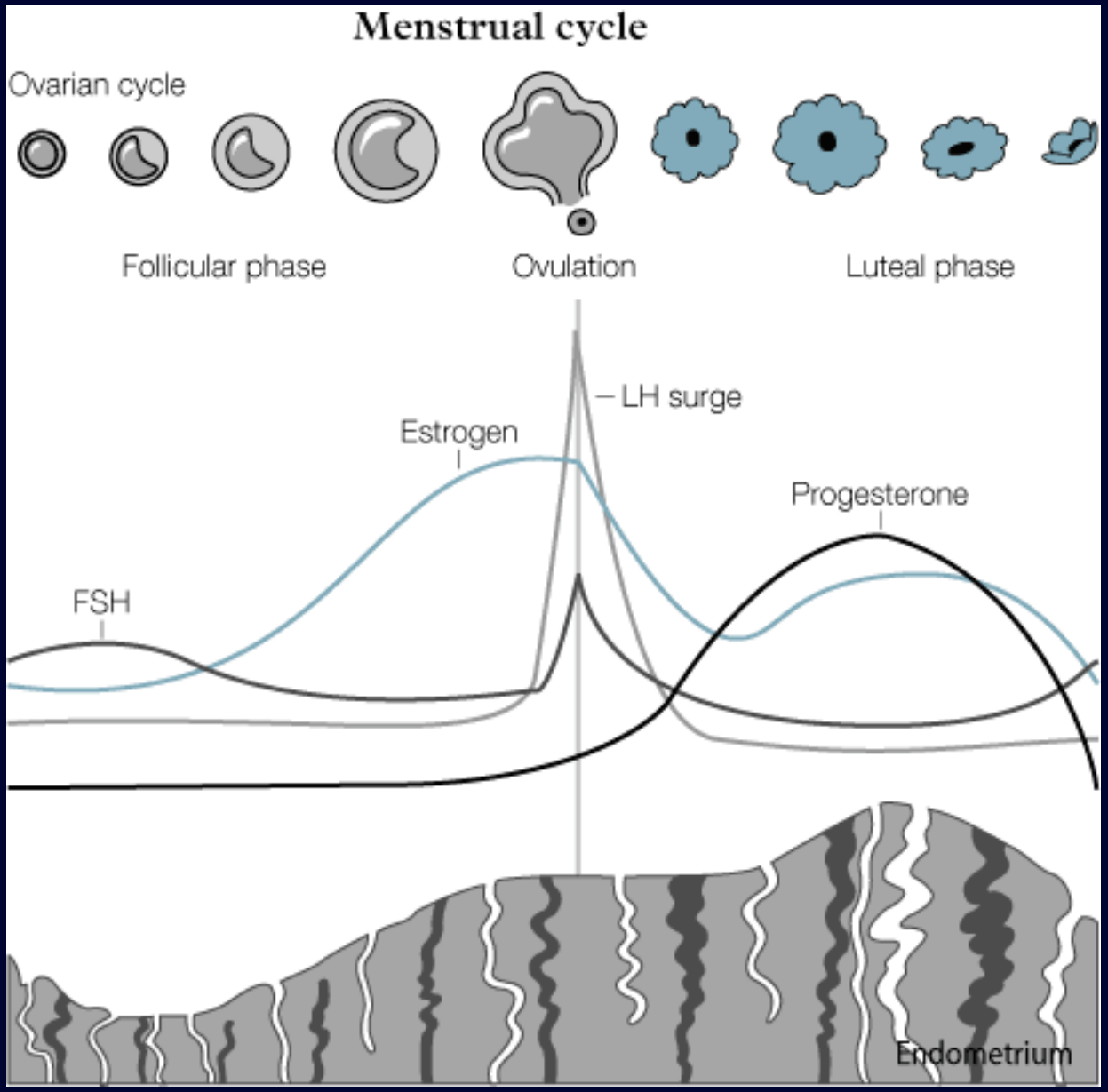
Ovary

Age has a Significant Impact on Follicle Number

- Women have a fixed number of oocytes.
- The peak number of primordial follicles occurs prior to birth at about 20 weeks' gestation (4-5 million).
- The number of follicles logarithmically decreases throughout life by recruitment and atresia.
  - At puberty, there are only about 0.5 million oocytes left.
  - Abrupt change in exponential loss occurs about 37-38 years old.
  - Anovulation is more prevalent 3-5 years before menopause.
  - Menopause occurs where there is <1000 oocytes remaining.

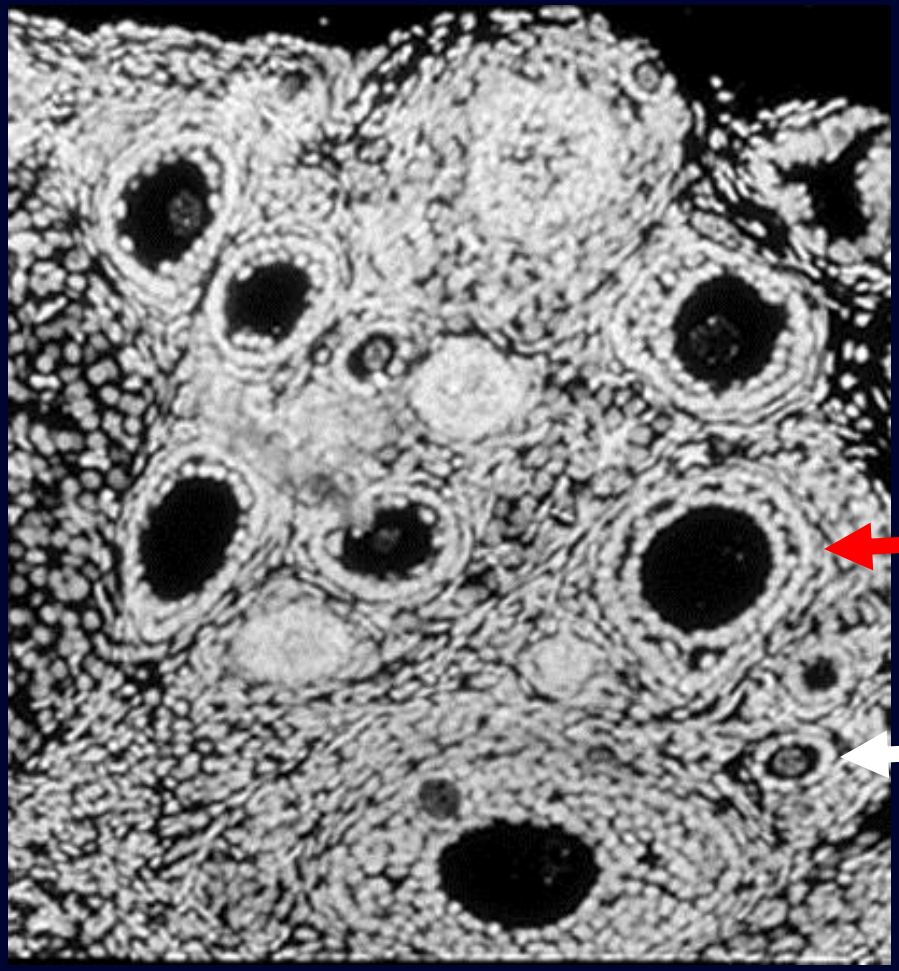
Follicular Development

- Follicles grow in 2 stages:
- Gonadotropin independent:
  - Follicles are recruited and initiate development as a cohort about 3 months prior to ovulation
  - Possibly genetically determined
- Gonadotropin dependent:
  - The last 2 weeks of follicular development is dependent on follicle-stimulating hormone (FSH) and a little luteinizing hormone (LH)
  - LH surge triggers ovulation



www.thaissuperiorart.com/images/menstrual.gif

Normal-Appearing Ovary on Histology

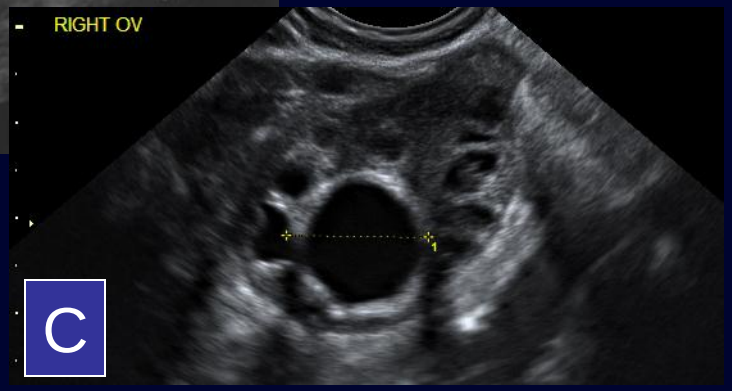


Late antral follicles

Small early antral follicles

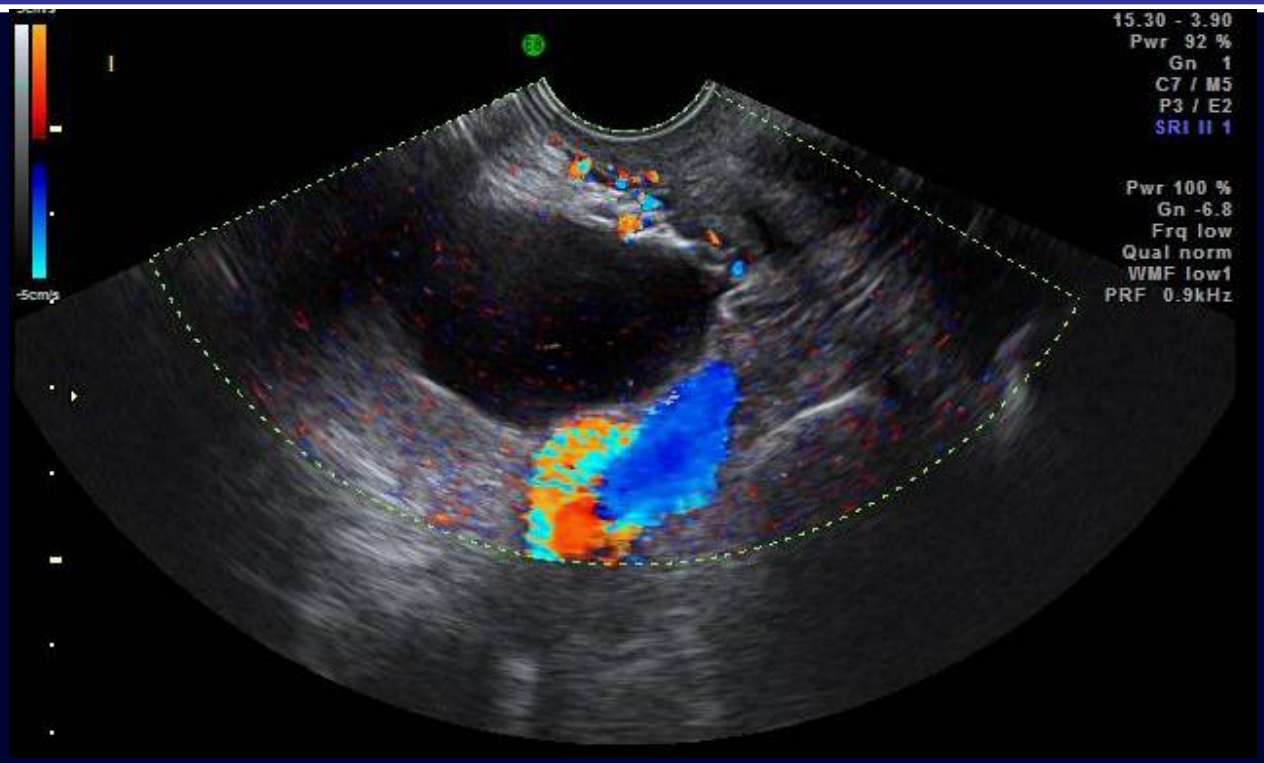
Ovarian Follicle Development: Early to Mid Follicular phase

-1. Early in the follicular phase of the menstrual cycle, there are multiple small follicles that can be seen (A). These follicles are less than 10 mm in size.



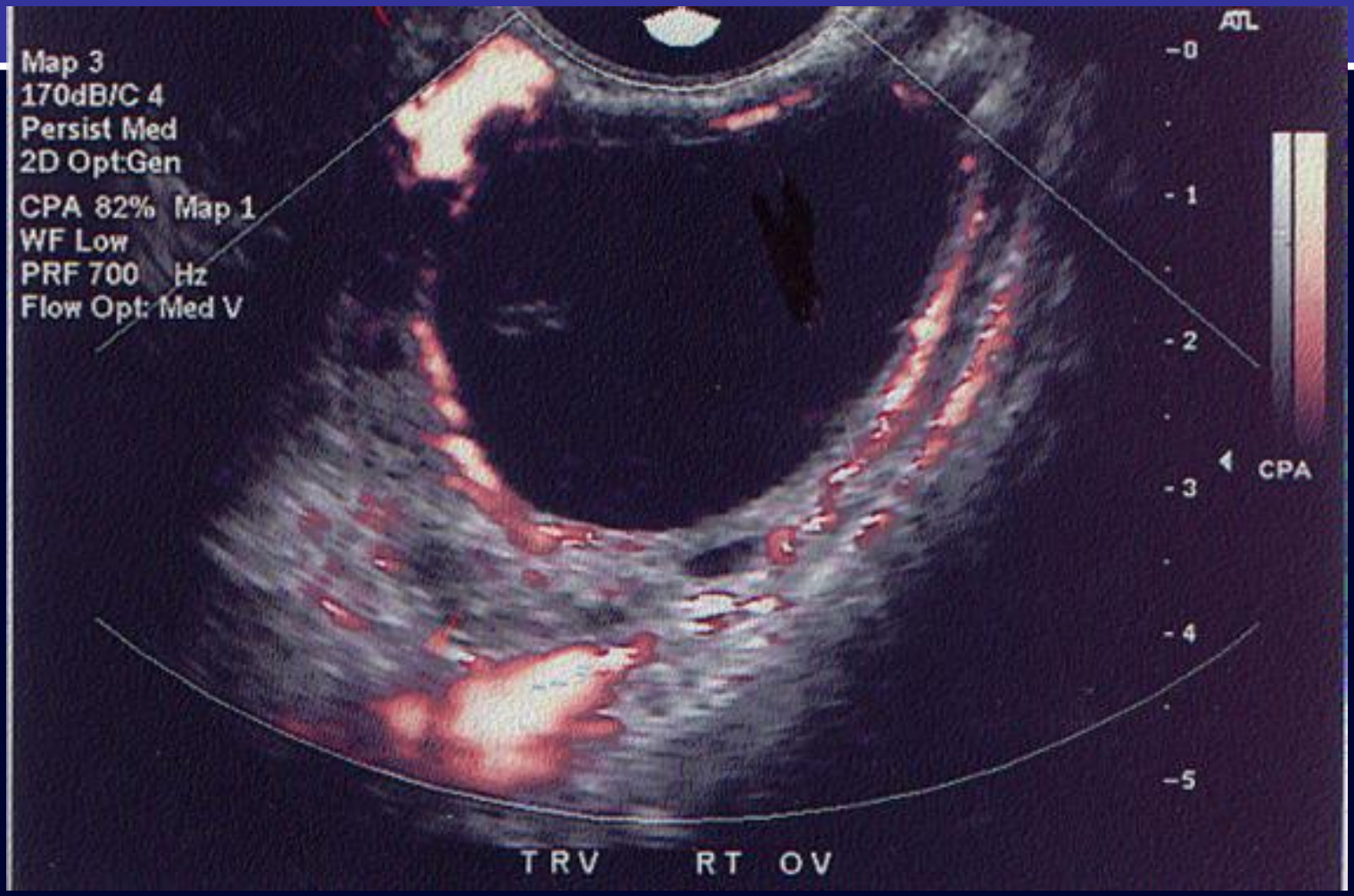
-2. As one follicle typically grows larger than the other follicles in a natural cycle, it becomes the dominant follicle (B and C). The peak size occurs just prior to ovulation in the natural cycle, 20-30 mm.

Periovulatory Follicle



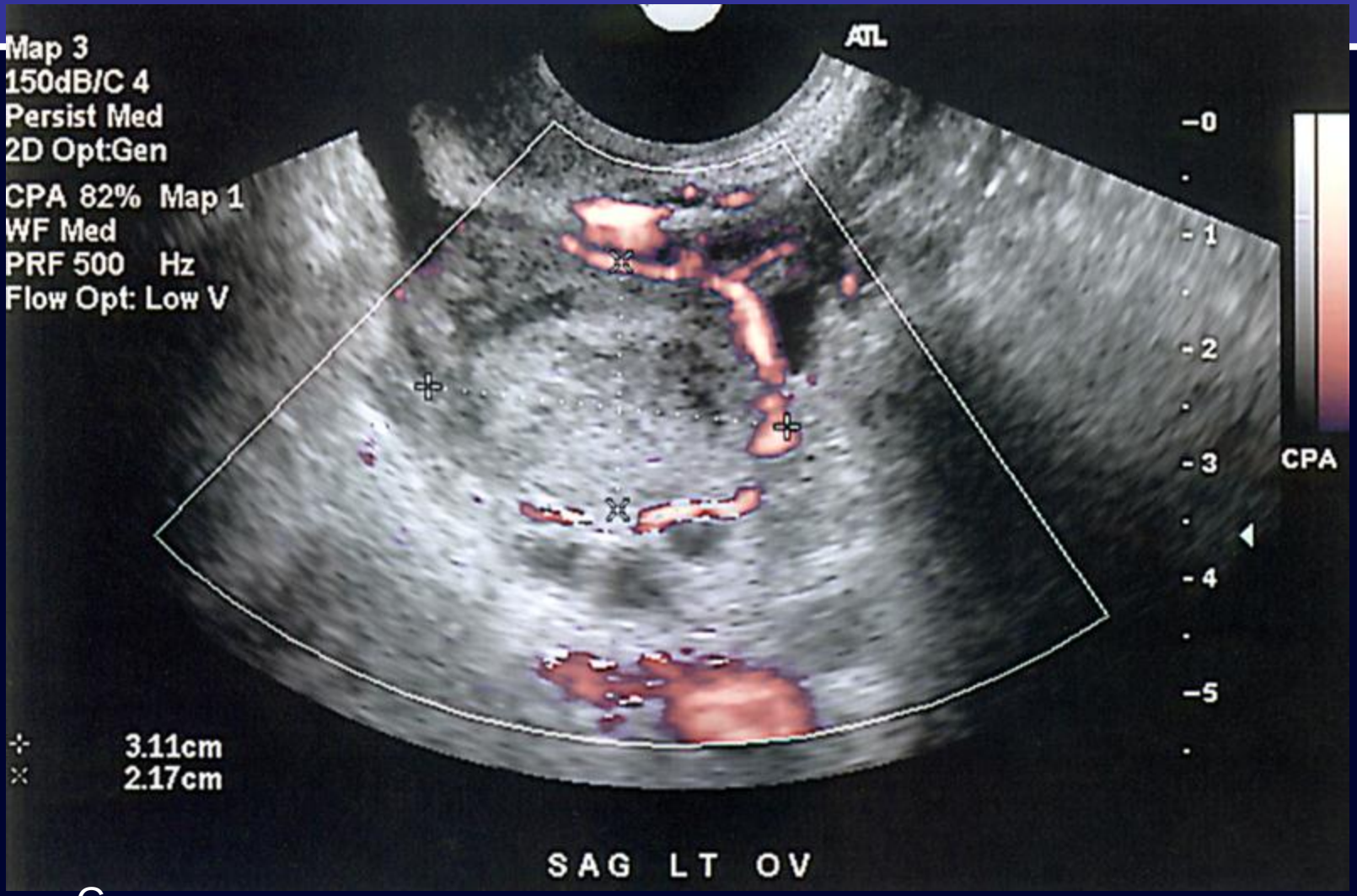
In the natural cycle, there is one periovulatory follicle, and it typically reaches 2-3 cm in size prior to ovulation, Blood flow as noted by color Doppler demonstrates the neighboring iliac vessel. No blood flow is noted within the follicle. The follicle consists of only of follicular fluid.

Luteinized Follicle



Courtesy of Leeber Cohen, MD.

Corpus Luteum and the “Ring of Fire”



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Courtesy of Leeber Cohen, MD.

Uterus

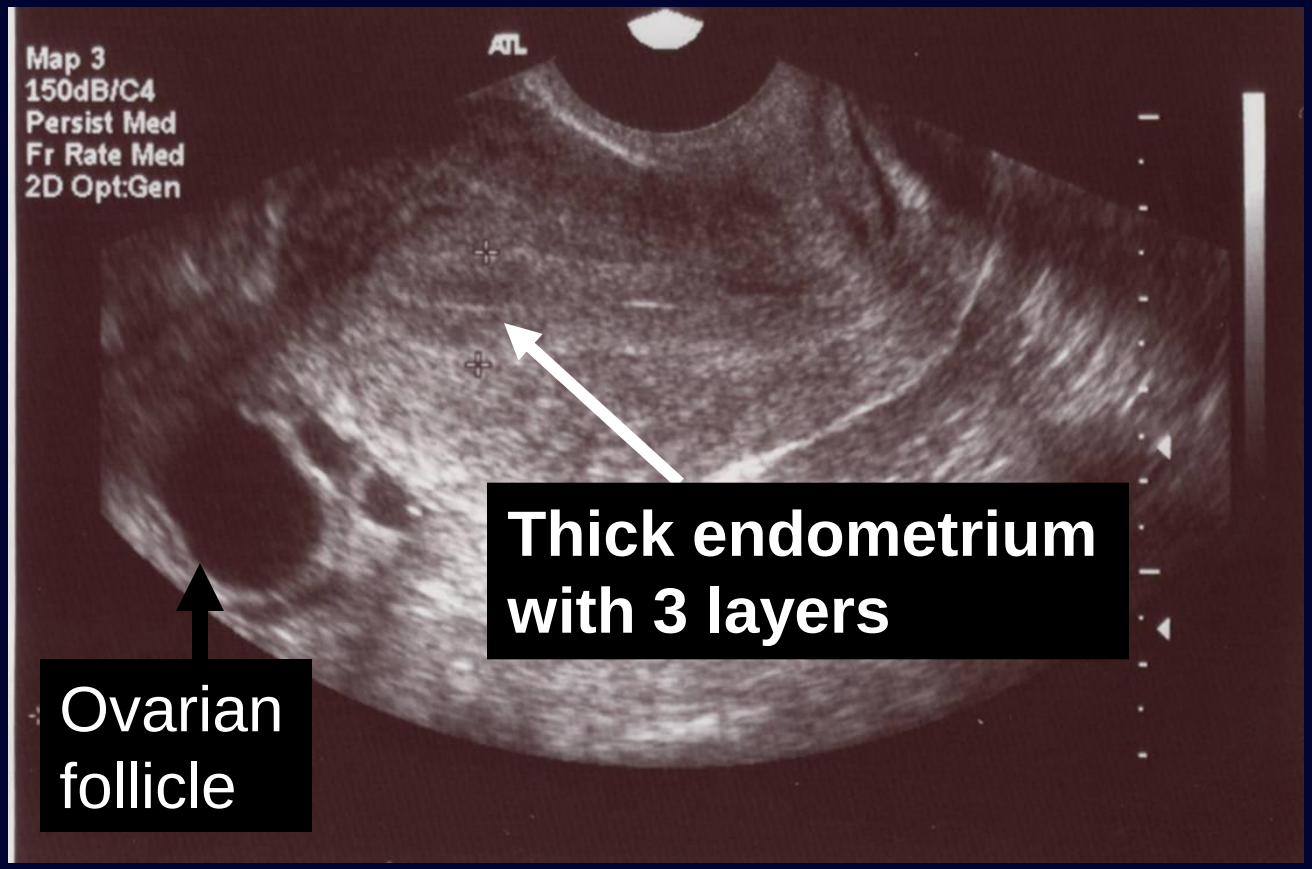
Uterus: Endometrium Assessment

- The endometrium is responsive hormonally.
- The menstrual cycle begins with the onset of menses, and the estradiol/progesterone levels are low. The endometrium is thin.
- Midcycle, at peak estradiol levels, the endometrium is thick and may have the appearance of 3 layers (trilaminar).
- After ovulation, the endometrium is decidualized and is still thick but appears more uniformly hyperechoic. It is preparing for implantation.
- Just prior to menses, there is a drop in estradiol and progesterone which signals the onset of menses.

Early Endometrium

- Early in the menstrual cycle, the endometrium should be thin. If it is not, there may be a polyp or other pathology. Don’t forget to consider an early pregnancy and check a human chorionic gonadotropin test.

Midcycle Endometrium



- Note trilaminar appearance of the endometrium, typical of proliferative endometrium.
- Mature follicle is also seen on this image.

Luteal Endometrium

Doppler: Color and Pulsed of the Ovary, Endometrium, and Uterus

- Although there are several papers that have been studying Doppler,
- None have shown benefit for fertility at this time in studies with large numbers.
- Doppler of the ovary can help distinguish a corpus luteum from other ovarian follicles or masses. However, it cannot determine whether or not a follicle contains a mature oocyte. It does not help with ovulation monitoring.
- Doppler continues to be studied because it makes sense that there is increased vascularity of the endometrium around implantation, but both endometrial and subendometrial Doppler results have not been able to predict pregnancies.

Infertility Assessment

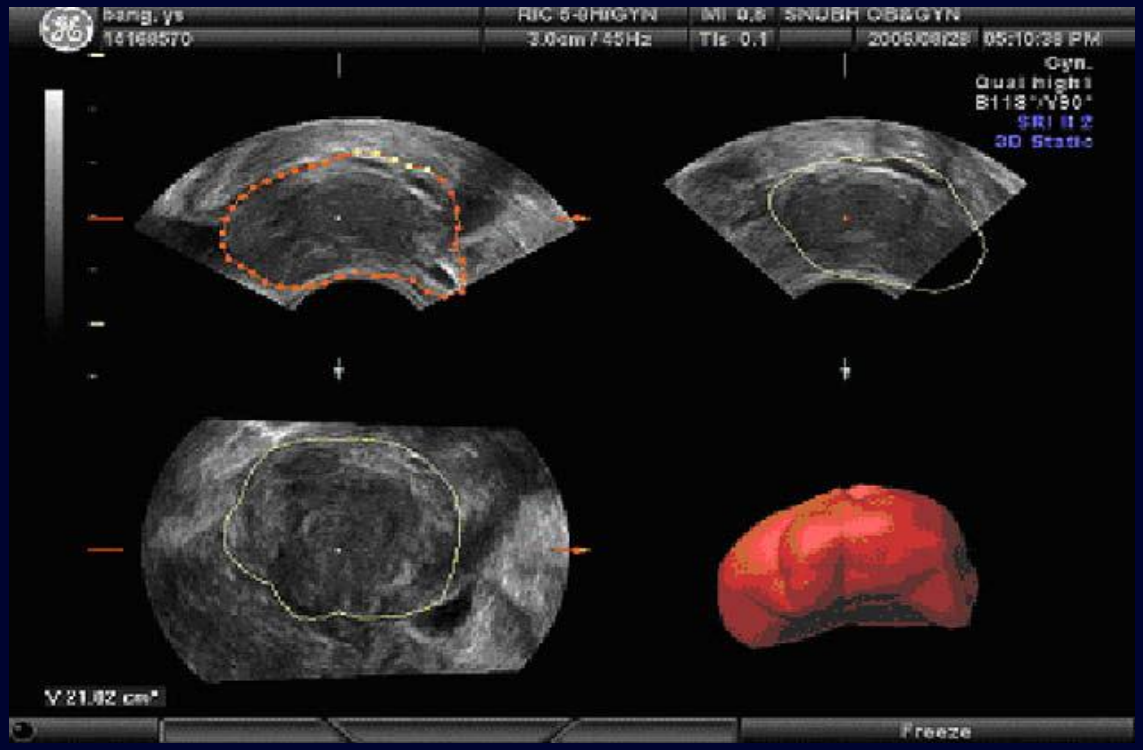
Ultrasound Assessment of Infertility

- Ultrasound is an integral part of the evaluation and treatment of infertility.
- Ultrasound of the ovary can indicate ovarian reserve and suggest treatment dosing.
- Ultrasound of the uterus can reveal anomalies within the uterus as well as assess the endometrial thickness.

Ultrasound in Assessing Ovarian Function

- As women age, the ovarian reserve decreases.
- Tests for assessing ovarian reserve include serum tests, such as:
  - Cycle day 3 FSH (the most popular test with the most literature)
  - Cycle day 3 estradiol
  - Anti-Müllerian hormone
  - Inhibin level
- With ultrasound, the ovarian reserve can be assessed by measuring the ovarian volumes and antral follicle counts. Both correlate with ovarian reserve but the antral follicle count (AFC) is more reliable when there are not large cysts present. AFC predicts response to treatment more so than pregnancy outcome.
- Age of the female is still the best predictor overall.

Ovarian Volumes



Chang et al. Fertil Steril 2009 (epub).

Ovarian Volumes

- Ovarian volumes can help predict responses. Sizes less than 3 cm^3 do poorly.
- However, there are situations which impact ovarian volumes. For instance, birth control pills (BCP) suppress ovarian function and thus result in decreasing the ovarian volume. Upon stopping the BCP, the ovarian volume increases in size in response to the increase in hormonal environment. Then the ovarian volume assessment will be more accurate.

Antral Follicle Count

- Another approach to assessing the ovarian reserve by ultrasound is the AFC.
- AFC is less impacted by external situations (ie, BCP or other situations).
- The presence of a large follicle may impact the number of follicles seen. Yet, if a good number is seen while a dominant follicle is present, then this patient should respond to therapy well. Low counts may need to be repeated at another time when the cyst resolves.
- AFC can be done anytime in the menstrual cycle, but the best time is in the early follicular phase when there is less likelihood to have a dominant follicle.

Ovarian Volume and AFC

- Ovarian volumes are calculated from 3 measures of the ovary (length, width, and height).
- The prolate ellipsoid formula is used:

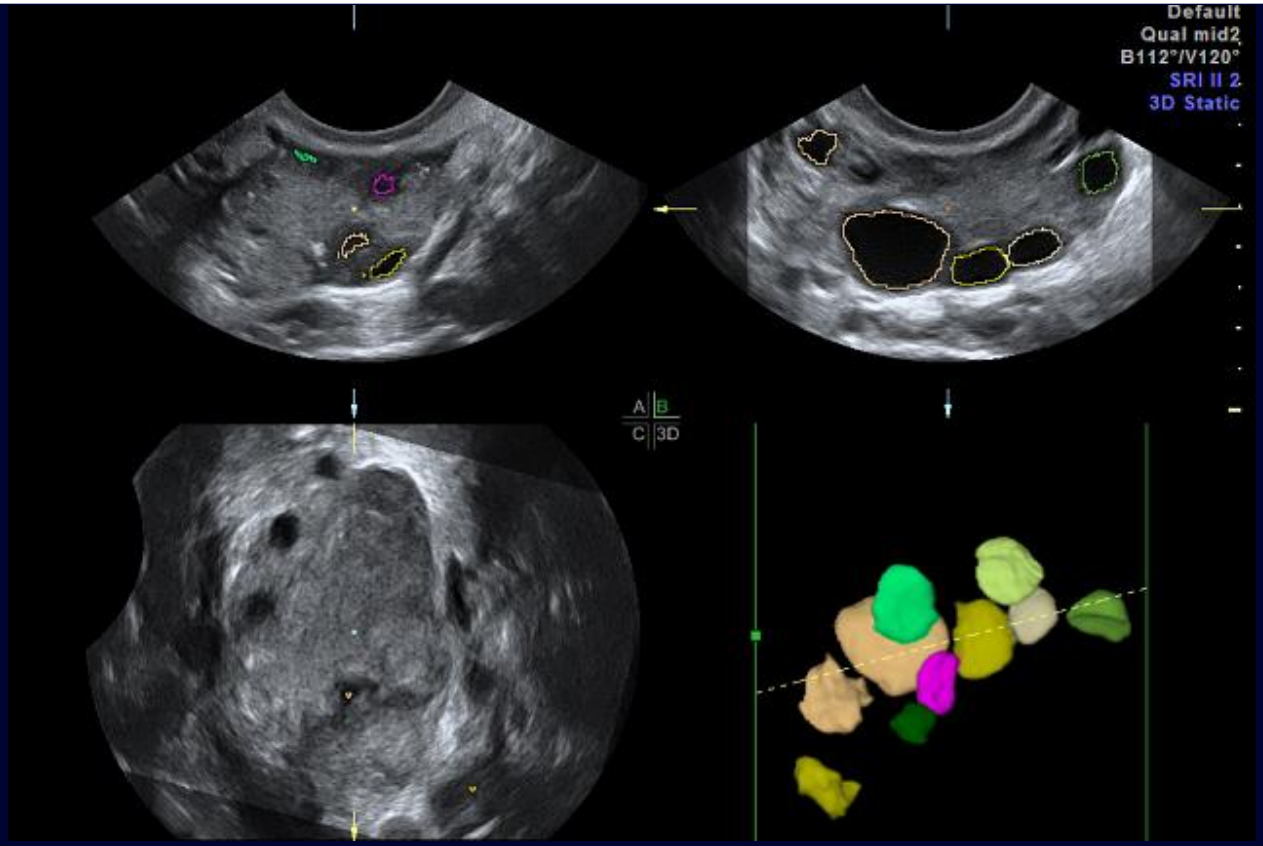
$$\text{Volume} = D1 \times D2 \times D3 \times 0.523$$

Wallace WH, Kelsey TW. Hum Reprod 2004; 19:1612-1617.

Antral Follicle Counts

- The small follicles which range in size of 2-8 mm within the ovary are the antral follicles.
- One counts the number of follicles that are in the appropriate size range in each ovary, and the numbers of ovarian follicles are added together, and that becomes the AFC.
- An AFC combined total of >10 is normal.
- An AFC total <3 is a poor reserve.
- An AFC between 3-10 is controversial.

AFC: Manual or Automatic

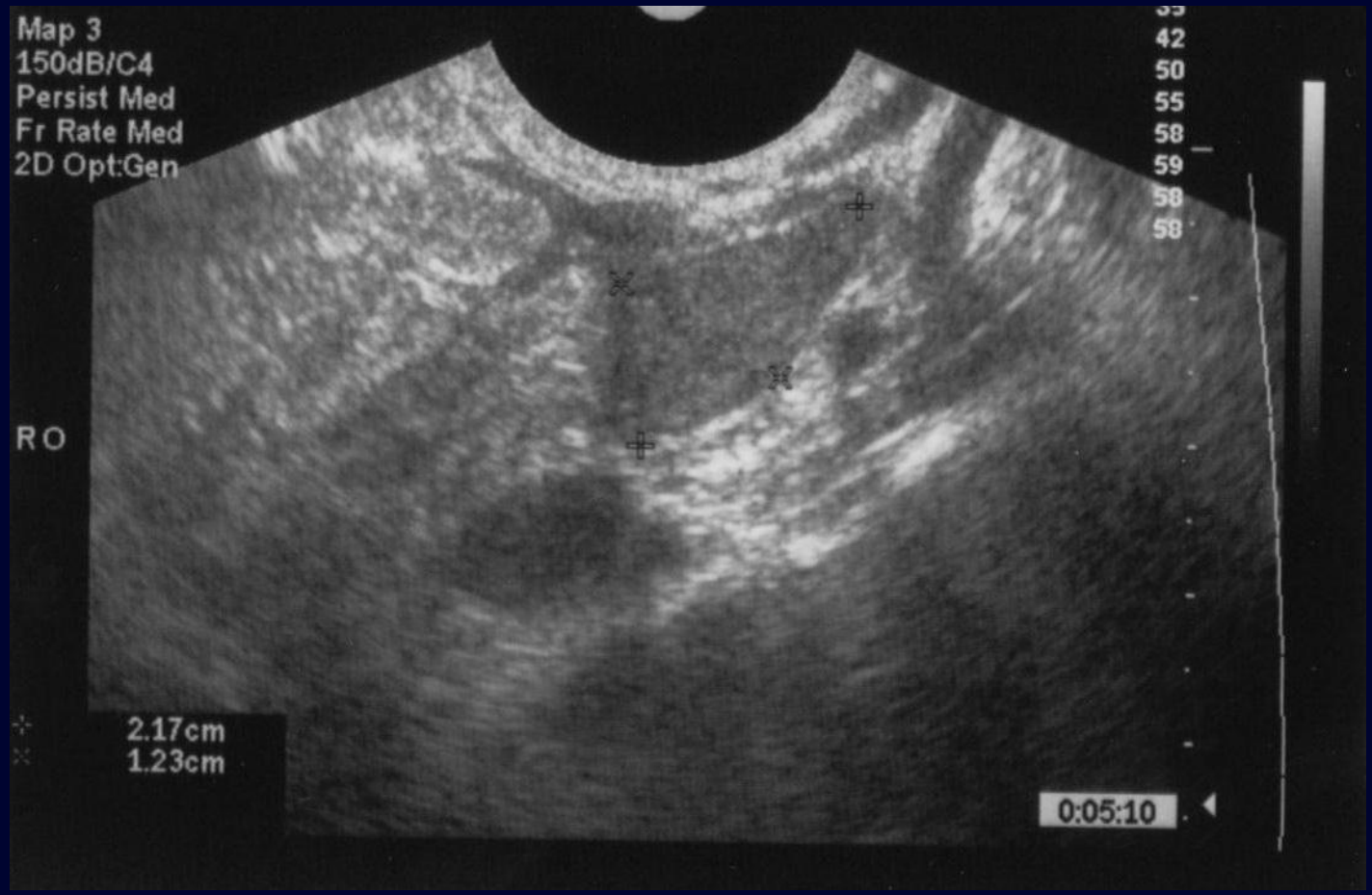


The black spots are follicles and can be easily counted manually. There is one ultrasound machine that carries a software program to count follicles, called SonoAVC. This program usually works better when follicles are growing during stimulation.

Ovarian Failure

- As menopause approaches, anovulation occurs more frequently. The perimenopause may occur 3-5 years before menopause.
- Ovarian failure may occur naturally and result in menopause. This typically occurs when there are fewer than 1000 oocytes remaining. The average age is 51 in the US with a range of 45-55.
- Ovarian failure occurring early (<40 years old) may result in premature ovarian failure, which affects less than 1% of patients.

Ovarian Failure



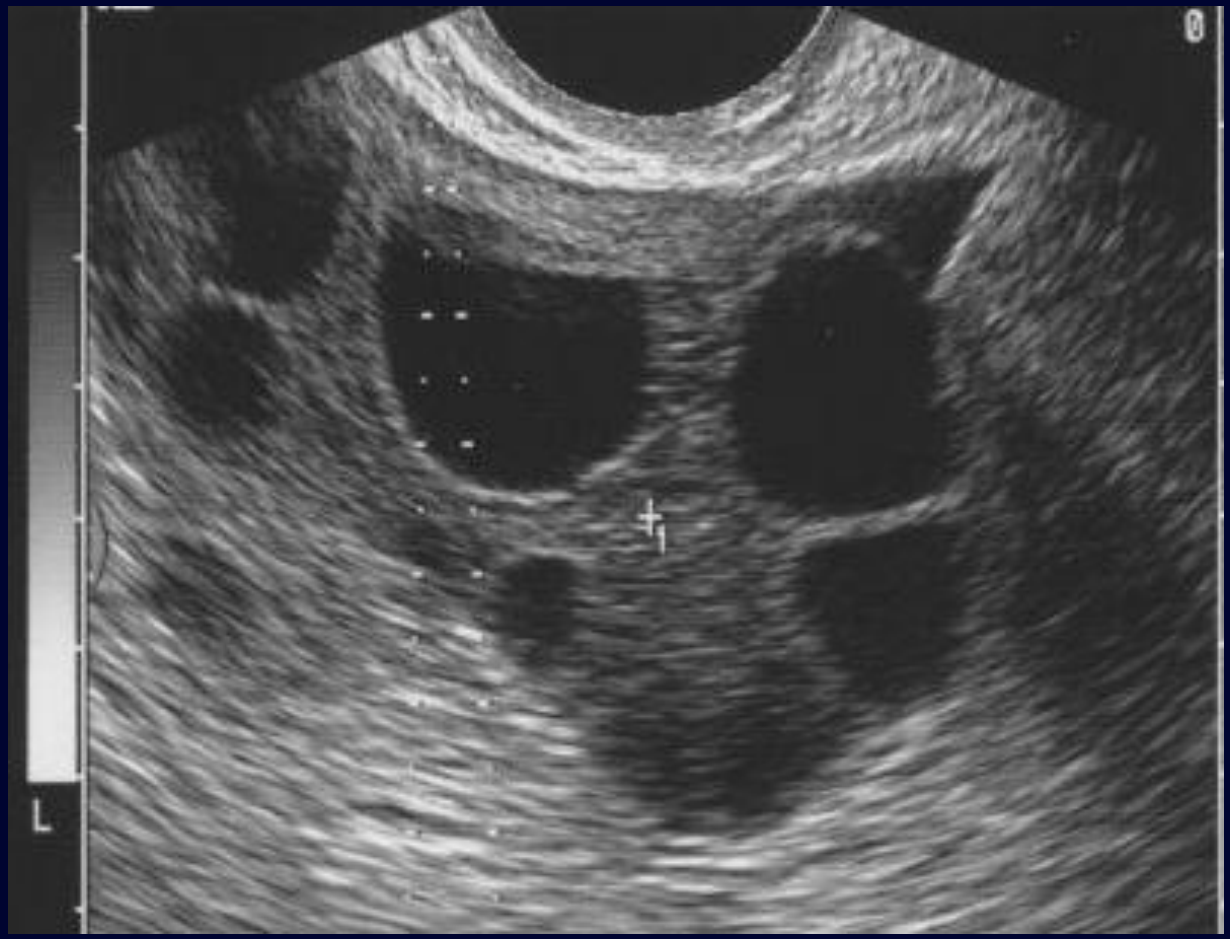
Monitoring Ovarian Stimulation: Oral Agents

- **Oral fertility drugs:**
  - Clomiphene citrate (CC)
  - Aromatase inhibitors
  - Both are usually given for 5 days during the early follicular phase.
- **It is not necessary to monitor the ovarian response.**
  - Patients tend to ovulate about 7 days after the last CC and slightly later after aromatase inhibitors.
  - Ovulation can be detected with ovulation predictor kits (OPK) prior to ovulation by measuring LH metabolites in the urine. Positive indicates ovulation in 10-48 hours later and allows for timing of intercourse or insemination.
  - Progesterone levels about a week later can confirm ovulation with a P4 >5.
- **However, if the patient has difficulty using OPK or is anxious, midcycle ultrasound can be done to determine if a mature follicle(s) has formed.**

Monitoring Ovarian Stimulation: Injectable Medications

- **Injectable medications:**
  - Recombinant FSH or human menopausal gonadotropins
- **It is important to monitor these patients closely.**
  - Typically, monitoring includes ultrasound and estradiol levels.
- **Ovulation induction:**
  - Adjust the medication dose as needed.
  - Limit to a few follicles grown to maturity to avoid multiple gestations as much as possible.
- **In vitro fertilization (IVF):**
  - We are typically stimulating these women harder (higher dose), because we will retrieve these oocytes and control the number of embryos we transfer to reduce the multiple gestation rate.
  - On average for IVF, we retrieve about 10 oocytes.
  - Many programs may cancel a cycle if there are not enough follicles

Ovarian Stimulation



Multiple follicles grow in response to gonadotropin stimulation.

Complications of Ovarian Stimulation With Gonadotropin Therapy

- Risks based on
  - Estradiol level
  - Number of mature and immature follicles
  - Patient's age and clinical history
- Multiple gestations: twins, triplets, or more
- Ovarian hyperstimulation syndrome (OHSS)

Ovarian Hyperstimulation Syndrome

- OHSS is an iatrogenic syndrome.
- The pathophysiology is not well delineated.
- Symptoms occur a few days to about 10 days after ovulation and may persist for 2-6 weeks.
- Patients will experience bloating and weight gain most commonly, but some may note shortness of breath and abdominal pain.
- The ovaries enlarge and are multicystic.
- There may be ascites, electrolyte imbalances, hemoconcentration, leukocytosis, pleural effusions, increased risk for deep venous thrombosis, and sometimes elevated liver enzymes.

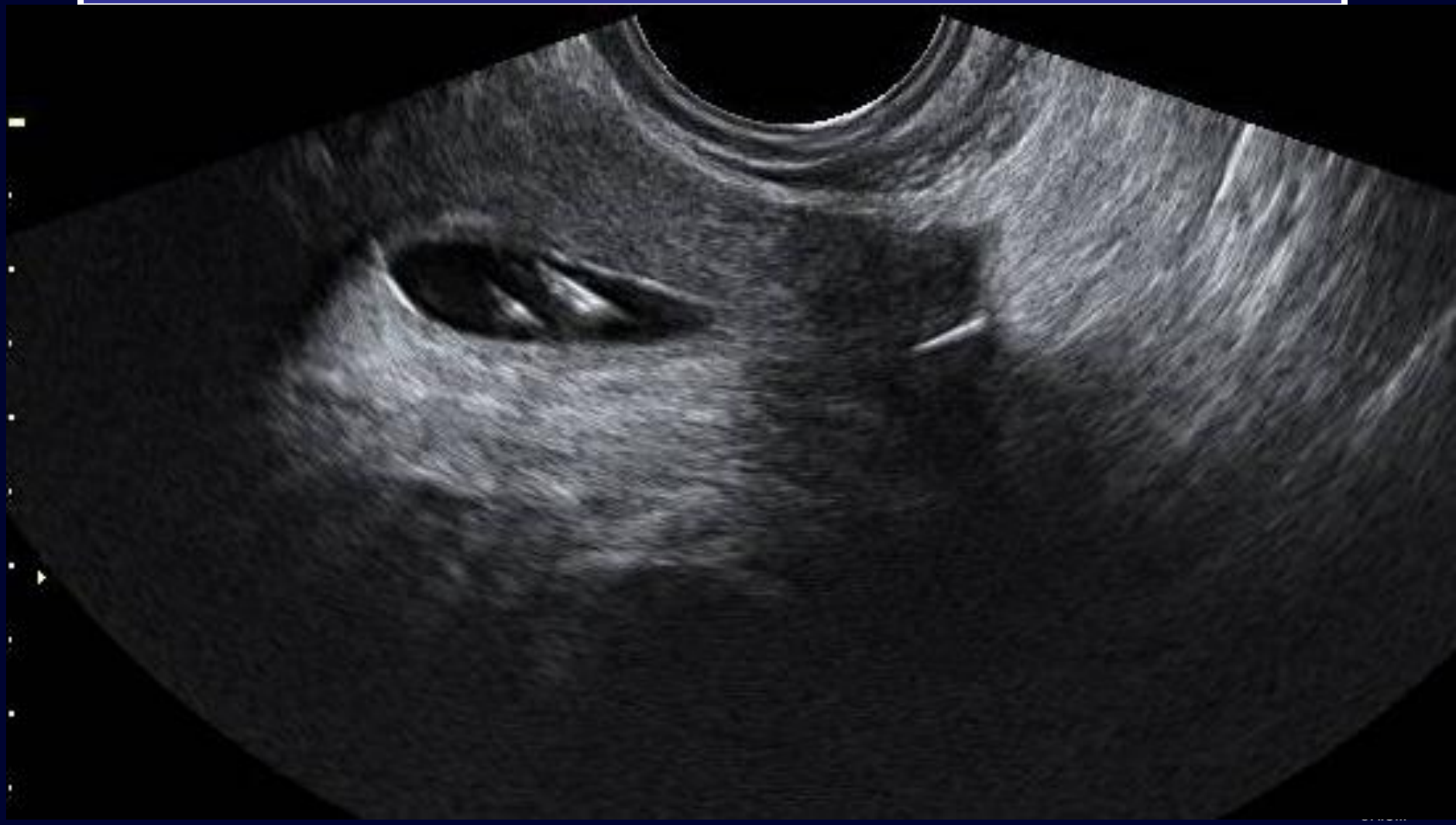
Ovarian Hyperstimulation Syndrome

- Ultrasound is essential in assessing the severity.
- Mild is associated with enlarged multicystic ovaries (<10 cm).
- Moderate to severe includes ascites (fluid is often seen by the liver and spleen), possible pleural effusions.

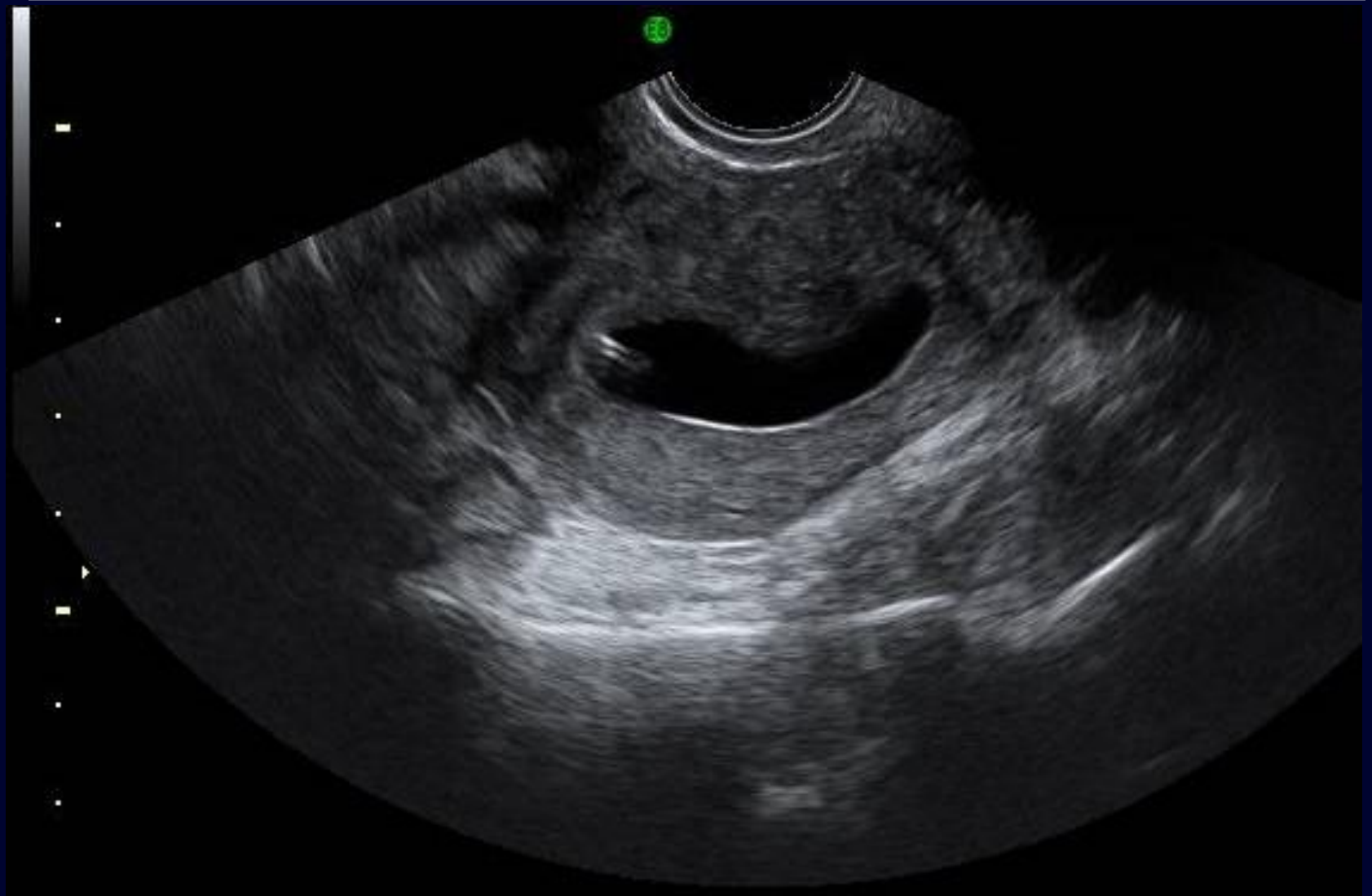
Sonohysterography

- This is an ultrasound approach for hysterosalpingograms (HSG).
- The procedure is essentially the same:
  - Place a speculum.
  - Wash the cervix with a disinfectant.
  - No tenaculum is needed.
  - Place the catheter of choice (balloon, acorn, etc).
  - Hold the catheter in place and remove the speculum.
  - Place a transvaginal probe with sterile sheath and gel.
  - Inject sterile saline or water through the catheter while ultrasound scanning. Scan longitudinally and transversely in a systematic manner to see the entire uterus.

Sonohysterogram: Longitudinal



Sonohysterogram: Transverse



Sonohysterography

- **Ultrasound is a better way to assess the uterine cavity than HSG because one can see the cavity, the endometrium, and the myometrium. So if there is a "filling defect," then the defect can often be identified during the same ultrasound exam (polyp, fibroid, etc).**
- **Polyps are usually hyperechoic, similar to the endometrium in appearance, and have a single central vessel if one applies Doppler.**
- **Fibroids tend to be more hypoechoic with shadowing since they are more dense, and the vessels are pushed to the side if Doppler is used.**
- **Intrauterine adhesions can be detected when one sees a connection between one side and another.**

Polyp

Sonohysterography and Tubal Patency

- HSG is still the gold standard for patency.
- Sonohysterography can be used to detect tubal patency indirectly by these methods:
  - Do a baseline ultrasound exam before the procedure. If no cul de sac fluid is present before the procedure and some is present after, then at least one tube is patent.
  - Agitated saline may be used. The bubbles are hyperechoic and can be watched going out of the cornua if the transvaginal (TV) probe is placed over the cornual regions
  - Contrast agents have been effectively used in other countries with ultrasound to confirm tubal patency. None have been approved by the Food and Drug Administration for use in sonohysterography in the US.

Common Infertility-Related Pathology

- Polycystic ovary syndrome
- Endometriosis
- Fibroids
- Adenomyosis

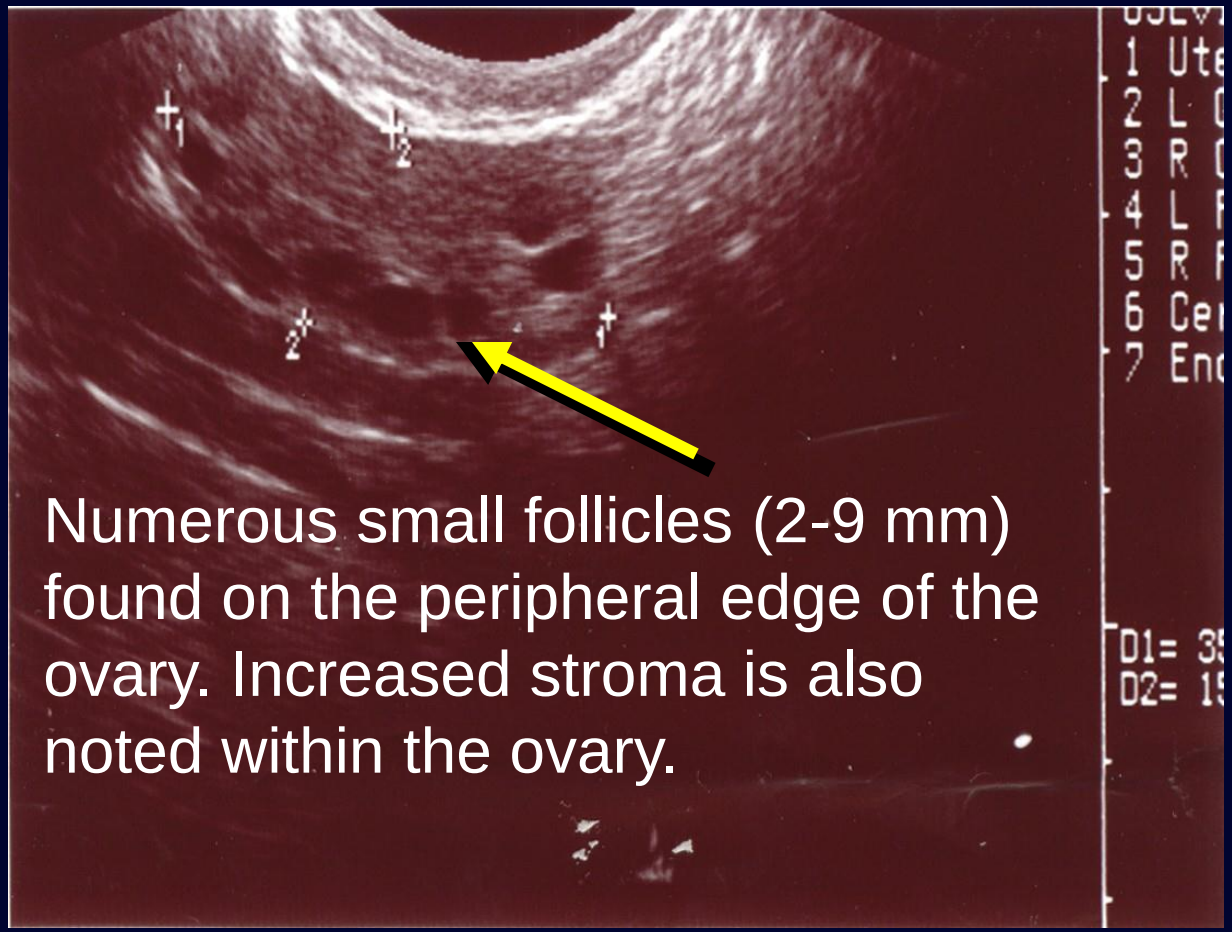
Polycystic Ovary Syndrome (PCO)

- There have been a couple of consensus conferences to agree on the criteria to use to make the diagnosis of PCO.
- The Rotterdam Consensus Statement was a joint agreement with European and US panels:
  - Anovulation or amenorrhea
  - Hirsutism or evidence of hyperandrogenemia
  - PCO-appearing ovaries
  - No other underlying disorder that can give the same appearance is present (ie, hypothyroidism, late-onset congenital adrenal hyperplasia, Cushing, exogenous androgen use, etc).

PCO-Appearing Ovaries

- An ovarian volume of 10 cm^3 or greater
- An AFC count of >12 follicles in one or both ovaries without a dominant follicle
- These follicles should be between 2-9 mm in size.

PCO Syndrome:
Ovary With "Pearl Necklace" Sign



Numerous small follicles (2-9 mm) found on the peripheral edge of the ovary. Increased stroma is also noted within the ovary.

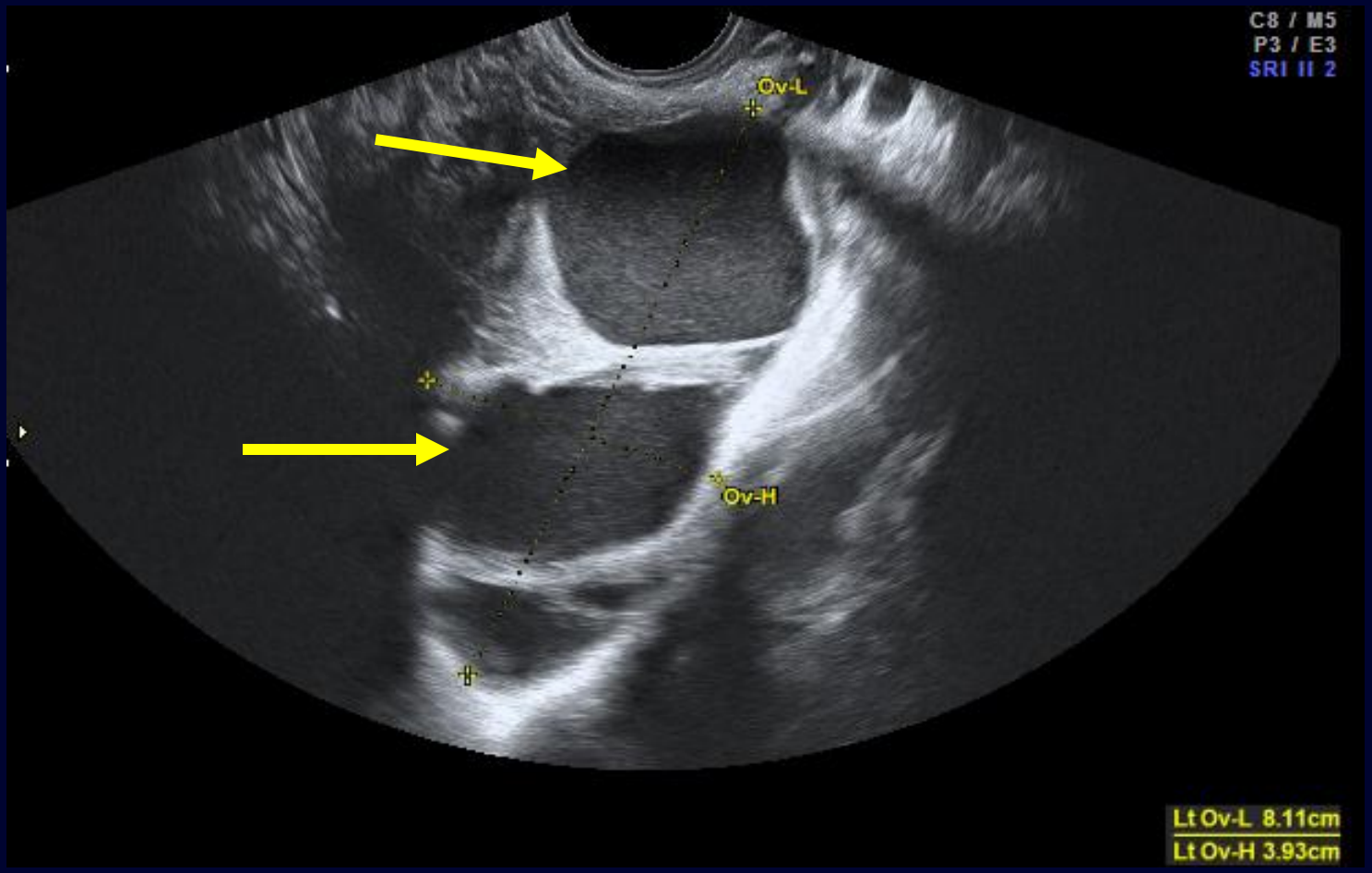
Endometriosis

- Endometriosis is endometrial glands and stroma located outside the uterus. These implants usually cannot be seen by ultrasound.
- Endometriosis is staged by the extent of the disease from stage I (minimal) to stage IV.
- Stage III usually includes an endometrioma (an ovarian cyst caused by an invaginating endometrial implant into the ovary), and stage IV indicates pelvic obliteration with adhesions.
- Endometriomas can be seen on ultrasound.

Endometriomas

- On ultrasound, the endometrioma typically has uniform, low-level echoes that some have described as a “ground glass” appearance and smooth borders. Those with these characteristic ultrasound findings are 90% accurate.
- There is no Doppler flow into the cyst since it is created from hemolyzed blood.

Endometrioma



Typical endometriomas have low-level echoes described as a “ground glass” appearance and smooth edges. Size varies.

Fibroids

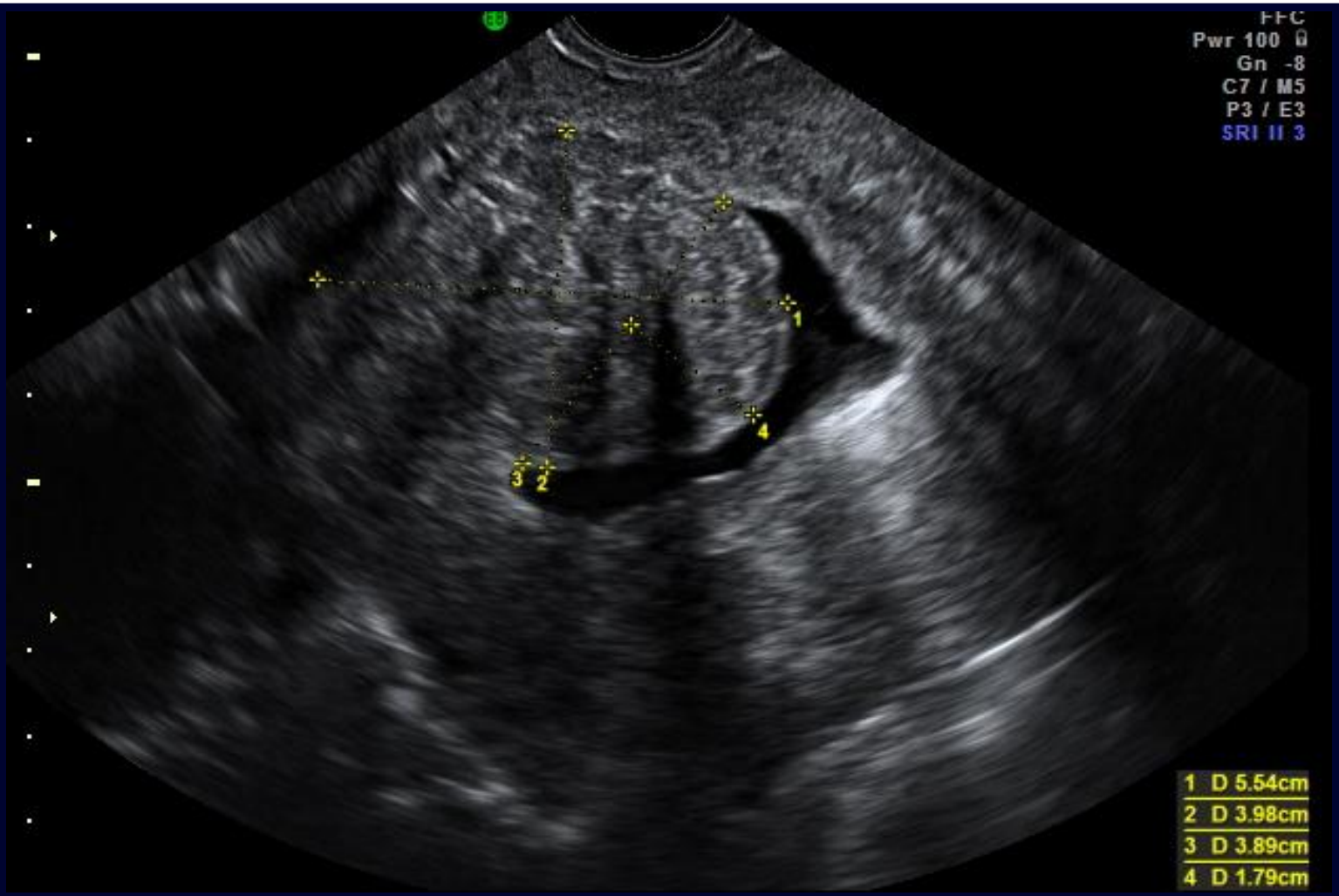
- Fibroids are very common.
- About 30% of all women have fibroids, and up to 50% of African American women may have fibroids.
- Fibroids typically don’t cause infertility but can be associated with increased miscarriages, preterm labor, abnormal lie, and increased abruption. Submucosal fibroids are much more likely to cause these problems.

Fibroids May Be Difficult to See

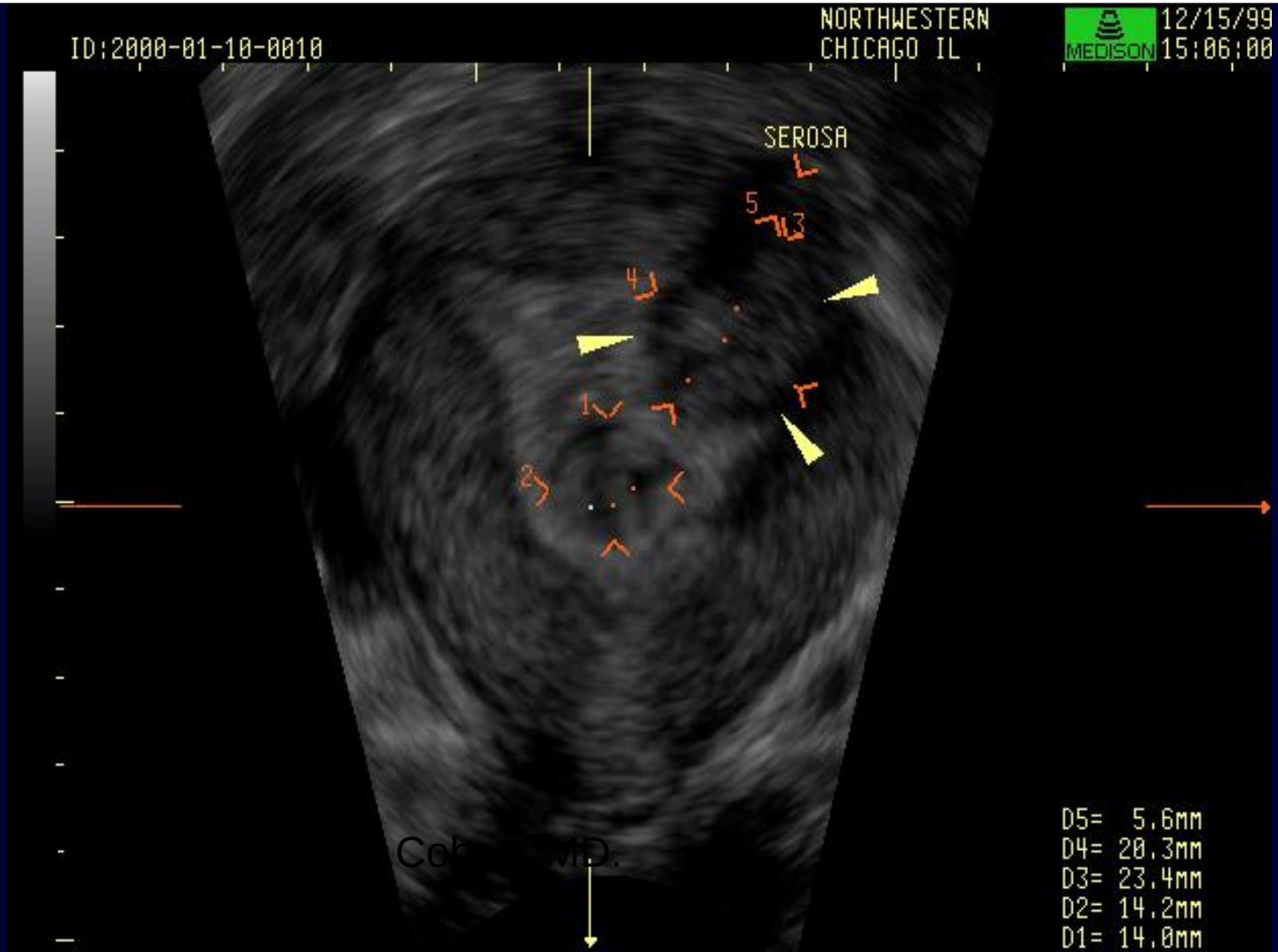
Fibroid With Power Doppler

Power Doppler enables the vessels of the fibroid to be seen, and it appears that this fibroid is located submucosally. Sonohysterography can confirm this finding.

Fibroid Impacting the Endometrial Cavity Shown Well With Sonohysterography



3D Ultrasound in the Luteal Phase Also Reveals Fibroid Locations Noninvasively



Coh[illegible] M.D.

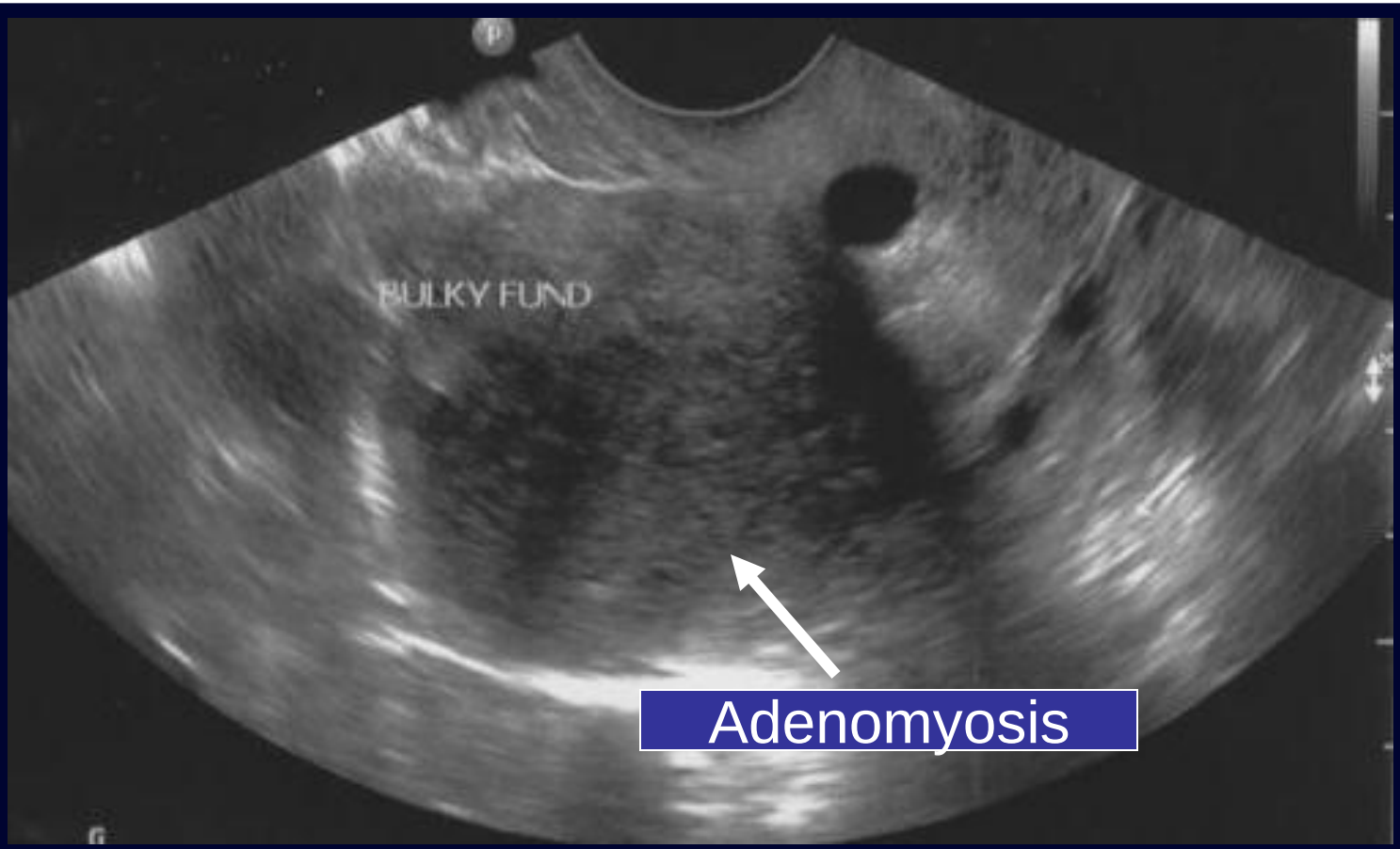
Adenomyosis

- Defined as endometriosis (both endometrial glands and stroma on histology) located deep in the myometrium. Typically, there is an indistinct endomyometrial junction suggesting where the endometrium and stroma migrated through to the myometrium.
- Classic triad of symptoms: uterine enlargement, dysmenorrhea, and dysfunctional bleeding.
- These are difficult to remove surgically because they tend to be soft with ill-defined borders.
- On magnetic resonance imaging (MRI), these areas tend to light up like endometrium.

Adenomyosis: Ultrasound Characteristics

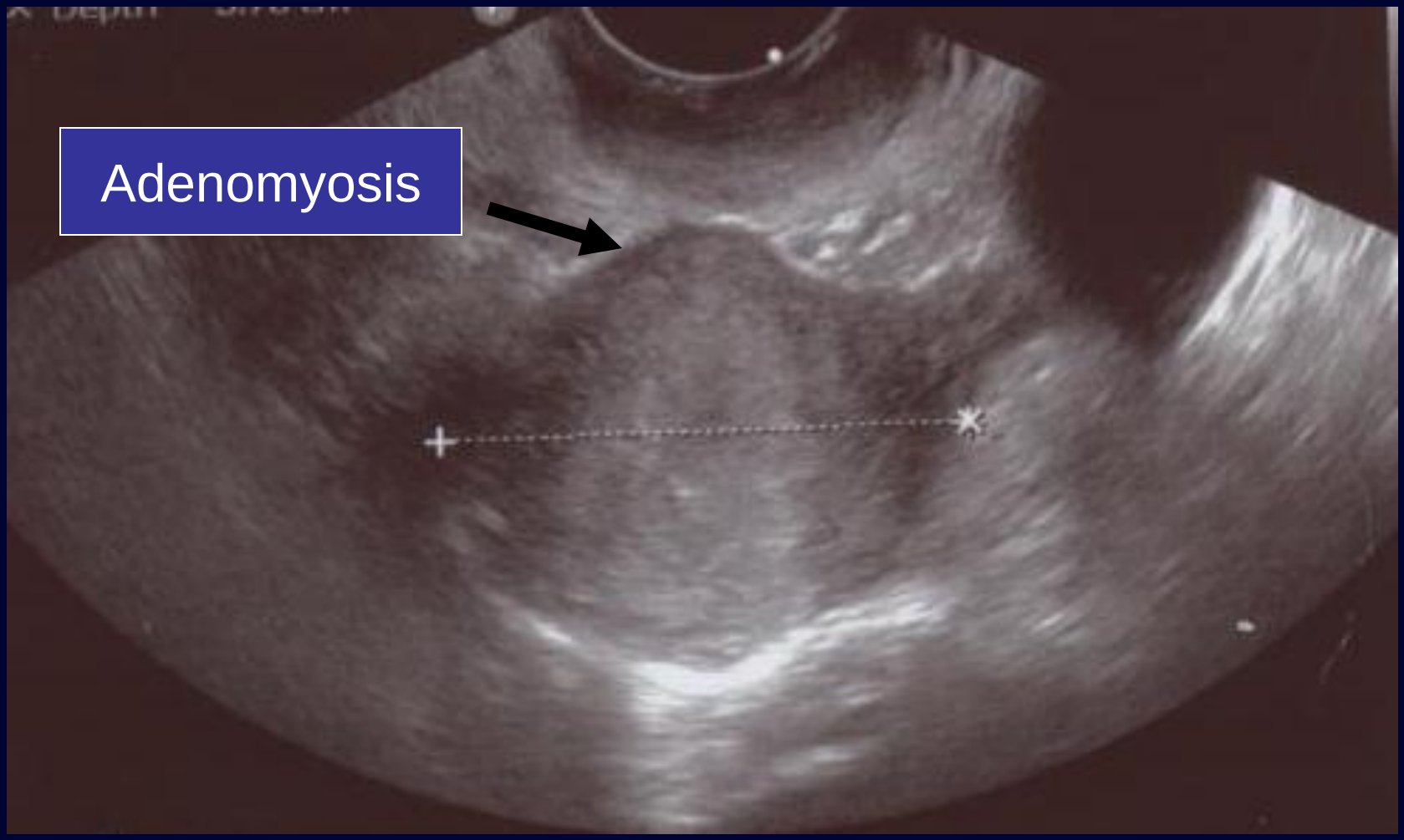
- A mottled inhomogeneous myometrial texture or nonuniform echo texture
- A globular-appearing uterus
- Small cystic spaces scattered throughout the myometrium
- An indistinct endometrial stripe in which the border between the more echogenic endometrium was blurred with respect to the myometrium.
- Using the above criteria, 82%-95% of prospectively identified cases were accurately diagnosed on pathology as adenomyosis. (Bromley et al. J Ultrasound Med 2000; 19:529-534.)

Adenomyosis



Small cystic spaces scattered throughout the myometrium

Adenomyosis



Ultrasound-Guided Procedures in Infertility

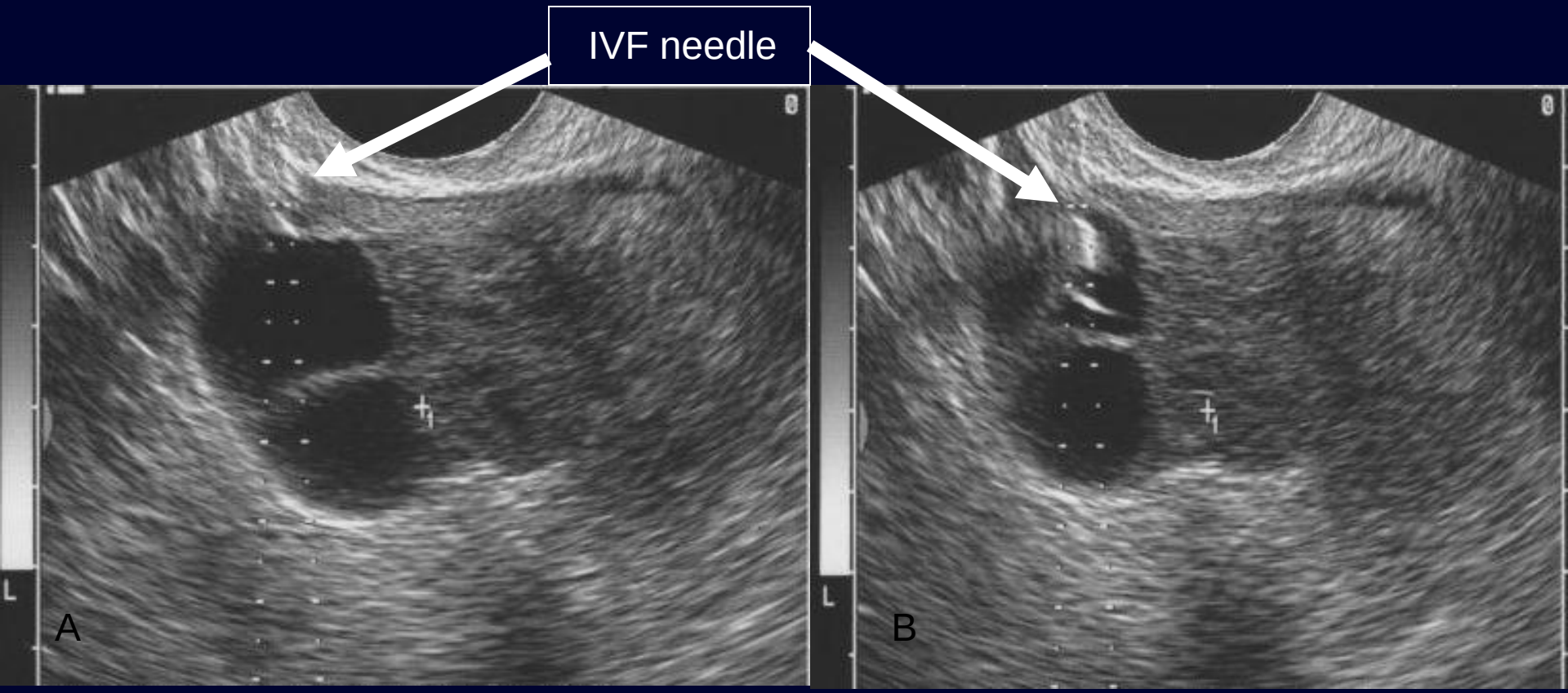
IVF procedures have benefited dramatically from ultrasound guidance for

- Oocyte retrieval
- Embryo transfer

Oocyte Retrieval

- Routinely, IVF is done with TV ultrasound guidance.
- The ultrasound probe is covered with a sterile sheath with gel, and a needle guide is attached directly over this sheathed probe. The needle has a suction tube attached to it on one end and a test tube trap to collect the follicular fluid (containing oocytes) on the other end.
- TV ultrasound-guided oocyte retrievals result in greater numbers of oocytes recovered than transabdominal ultrasound or laparoscopic approaches.
- Other advantages:
  - Easier procedure, more accurate
  - Shorter duration of the procedure
  - Less anesthesia

Oocyte Aspiration

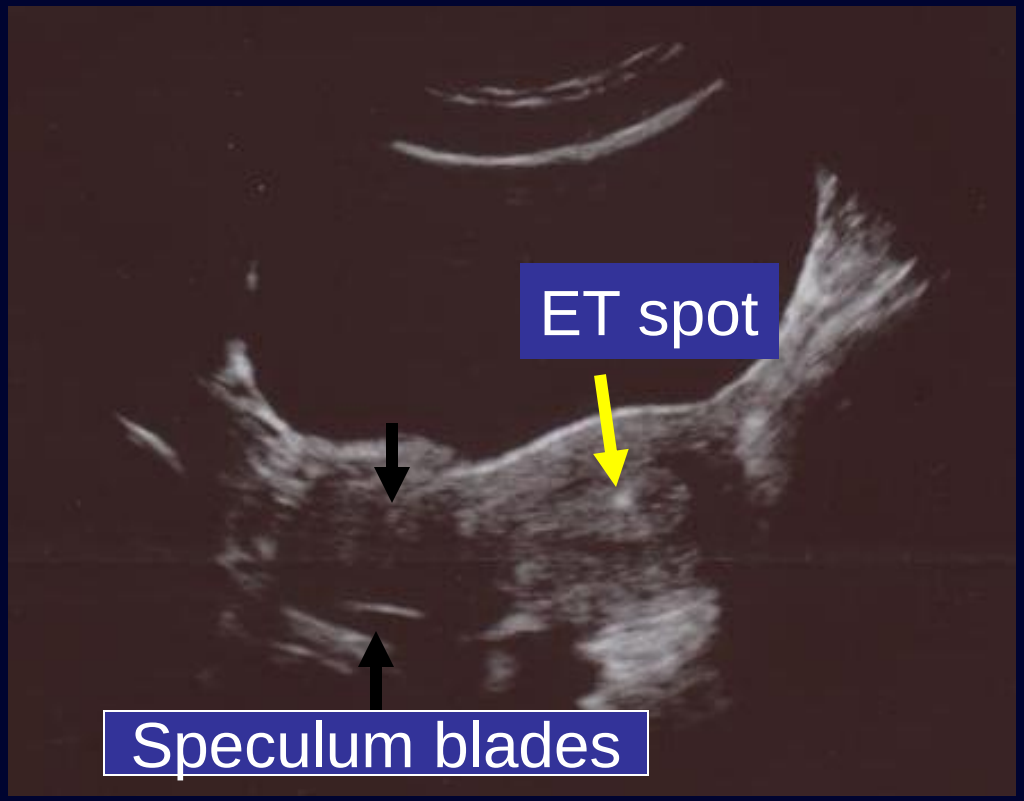


Transvaginal ultrasound is used to identify follicles to aspirate, and the biopsy guide shows the path that the IVF needle will take.

Ultrasound Guidance: Embryo Transfer (ET)

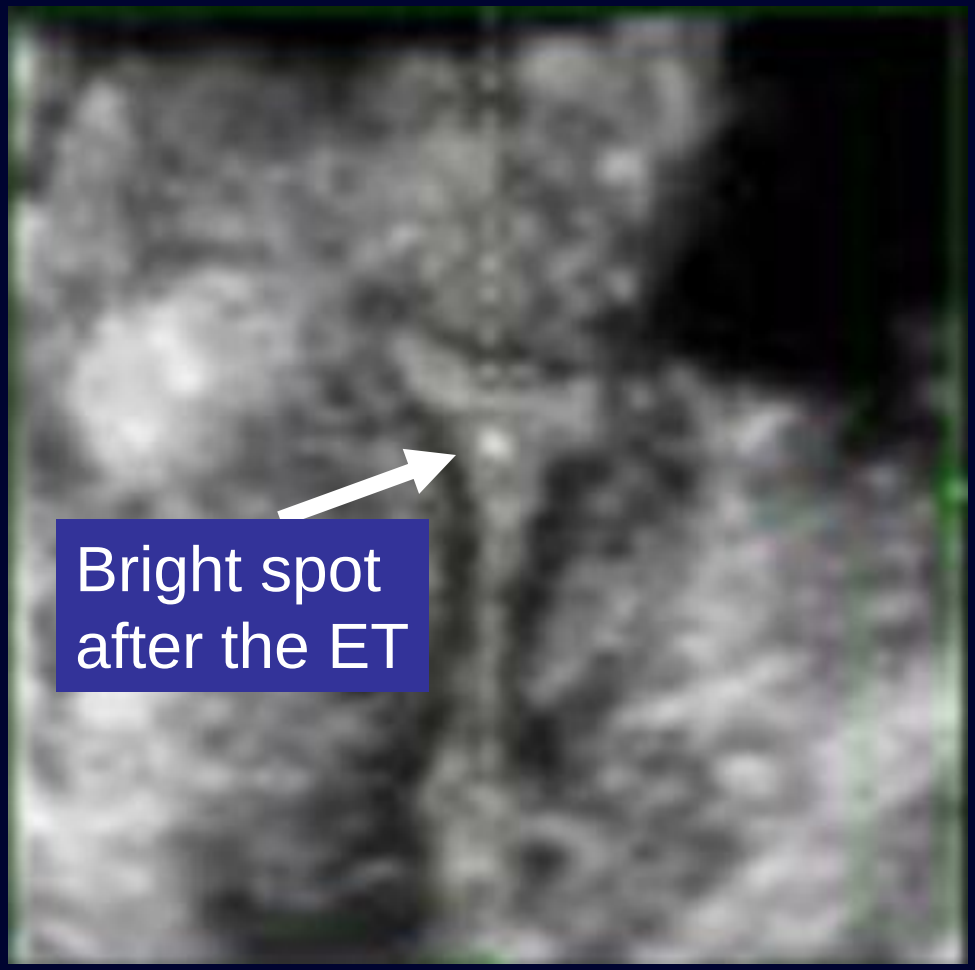
- Transabdominal ultrasound guidance began to be used for embryo transfers in the latter 1990s, and several studies show it improves pregnancy rates.
- The bladder should be full to allow for better visualization, plus it naturally straightens the uterus
- A speculum is placed. The cervix is cleaned and freed of mucus.
- Then the catheter containing the embryos for transfer is placed through the cervical canal and into the uterine cavity without touching the fundus. Appropriate placement is thought to be about 1.5-2 cm from the fundus.

Embryo Transfer



2D transabdominal ultrasound is used to guide the ET catheter to the appropriate place within the endometrial cavity. This image shows the full bladder with the speculum in place. The cervix is between the speculum blades and the uterus, with the endometrium visualized in the longitudinal plane. After ET, a small white spot can be seen within the middle of the endometrium consistent with good placement of the embryos.

3D Image of ET



- **At the end of the ET, the one white spot indicates the small fluid/air collection within the endometrium.**
- **Ideal location has not been proven, but we know that gentle placement with ultrasound guidance and without touching the fundus increases pregnancy rates. About 1-2 cm from the top and bottom of the endometrial cavity is thought to be the best placement.**

Common Congenital Uterine Anomalies (CUA)

- Septum
- Arcuate
- Unicornuate
- Bicornuate

CUA Pathophysiology

- In early development, the uterus is formed from 2 Müllerian ducts that fuse and then undergo resorption of the inside wall of the 2 ducts to make 1 cavity.
- CUA occur when there has been a problem with the fusion or resorption of the Müllerian ducts, or 1 duct just does not form.
- These abnormalities may lead to an increased miscarriage rate, preterm labor/delivery, and an abnormal lie.

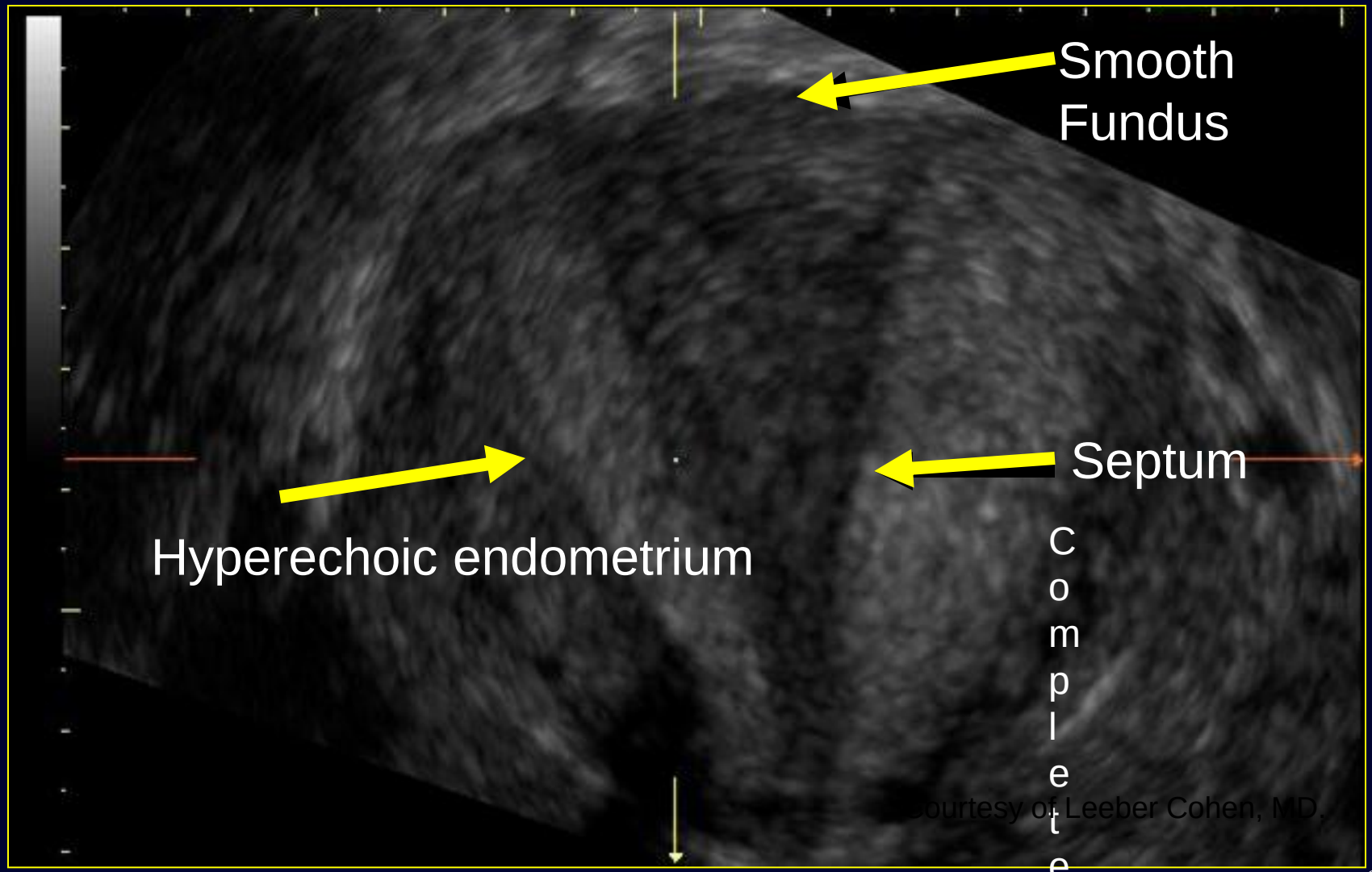
CUA Pathophysiology

- **Septum: The Müllerian ducts fused, but there is incomplete resorption of the inside walls. So the fundus is smooth and there is an indentation of the inside cavity by >1 cm. It may be complete (down to the cervix) or subseptate (incomplete or partial septum).**
- **Arcuate: Only a minimal portion of the Müllerian ducts have not undergone resorption. There is a a smooth fundus and a small indentation of the cavity (<1 cm). This is thought to be more likely a variant of normal.**
- **Unicornuate: Failure of one Müllerian duct to form.**
- **Bicornuate: Incomplete fusion of the 2 ducts so there is an indentation in the uterine cavity as well as the fundus.**

CUA

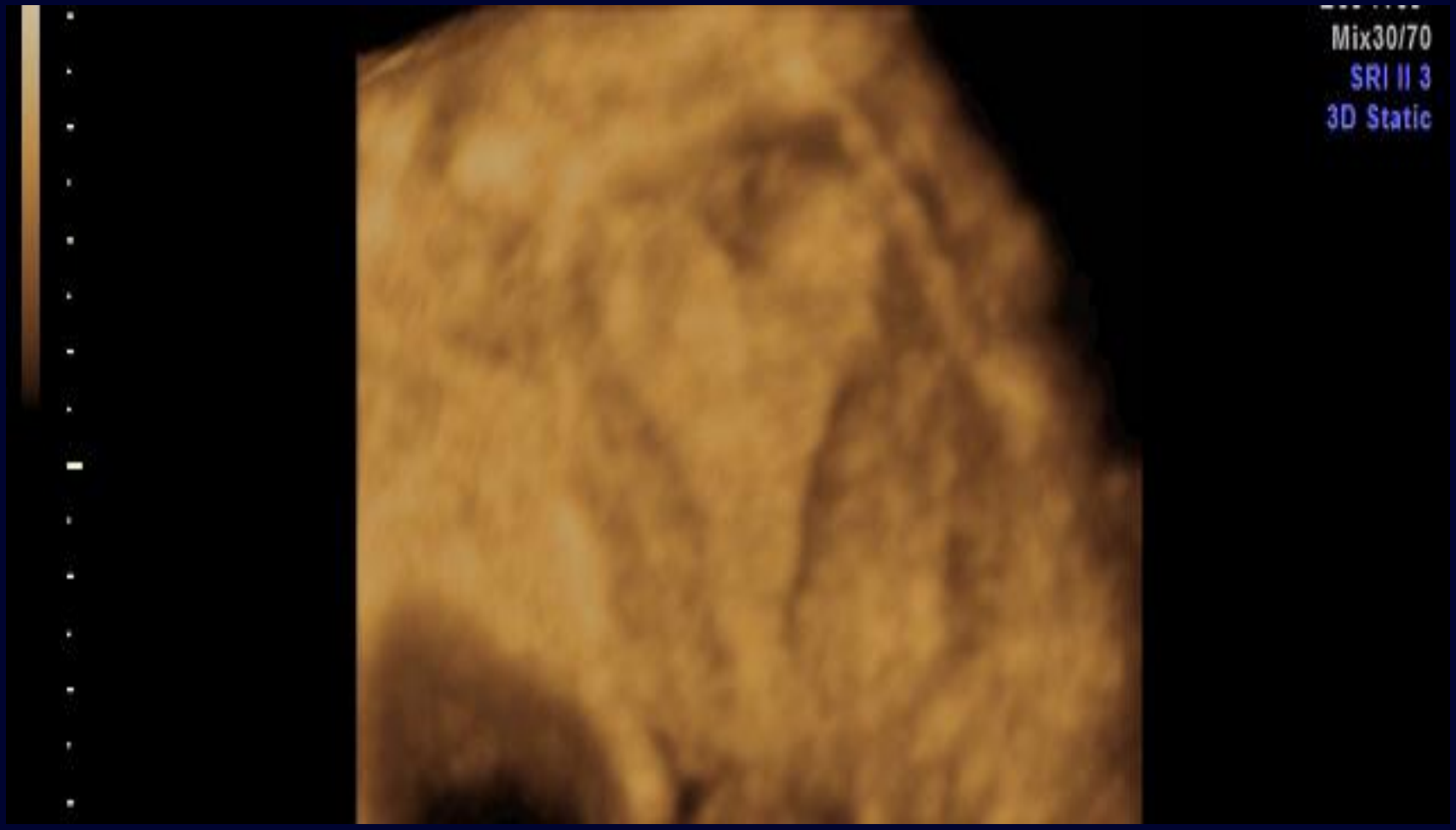
- 3D ultrasound is critical to making the correct diagnosis of a CUA.
- Unlike 2D ultrasound, the fundus of the uterus can be seen on the coronal view in 3D. On 2D ultrasound, only the saggital and transverse views are seen, which do not include the fundus.
- 3D ultrasound and MRI are equivalent technologies for diagnosing CUA. Ultrasound is much cheaper and takes less time to perform.

Complete Septum 3D, Rendered View

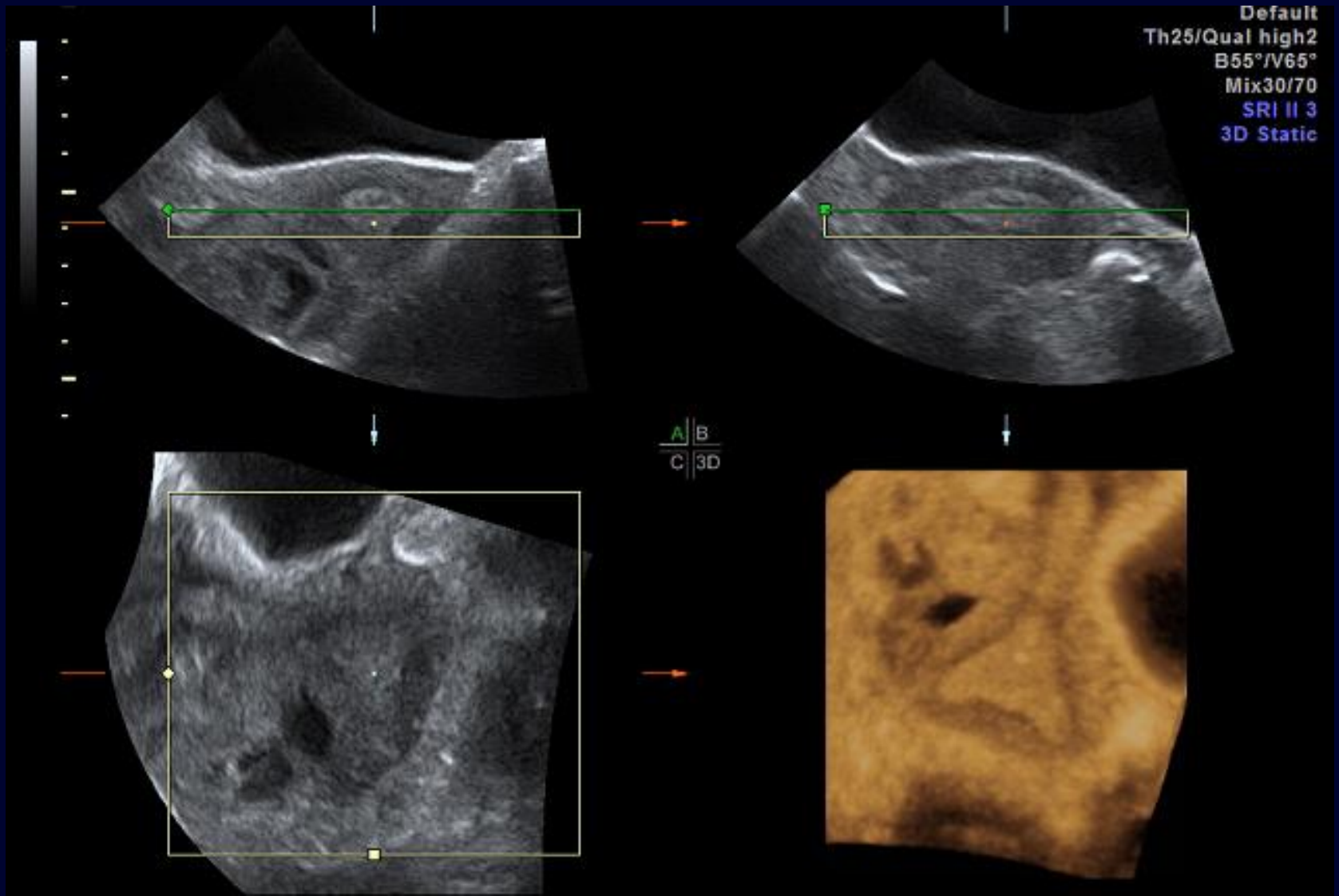


Wide Subseptate Uterus

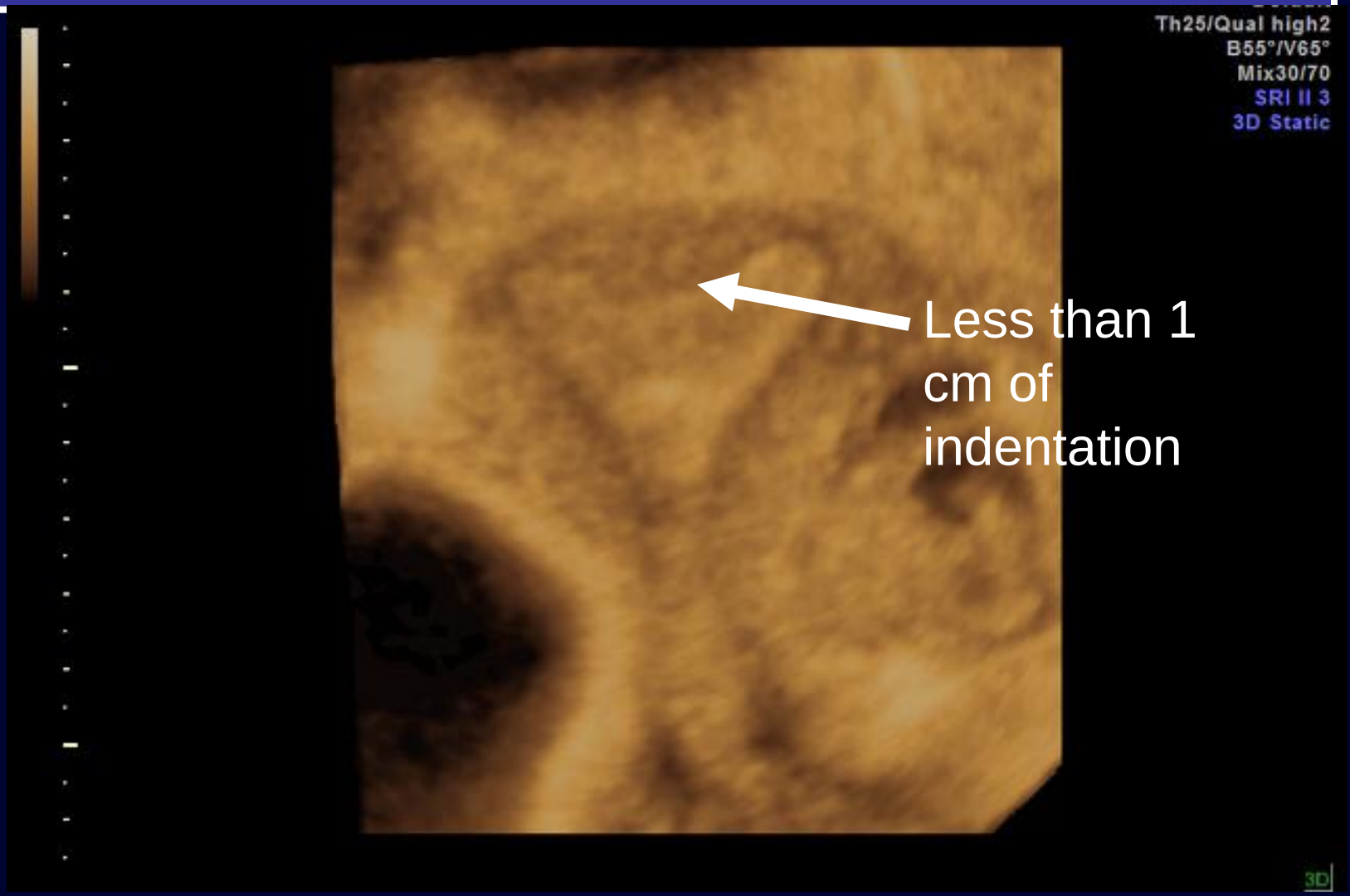
Small Subseptate Uterus



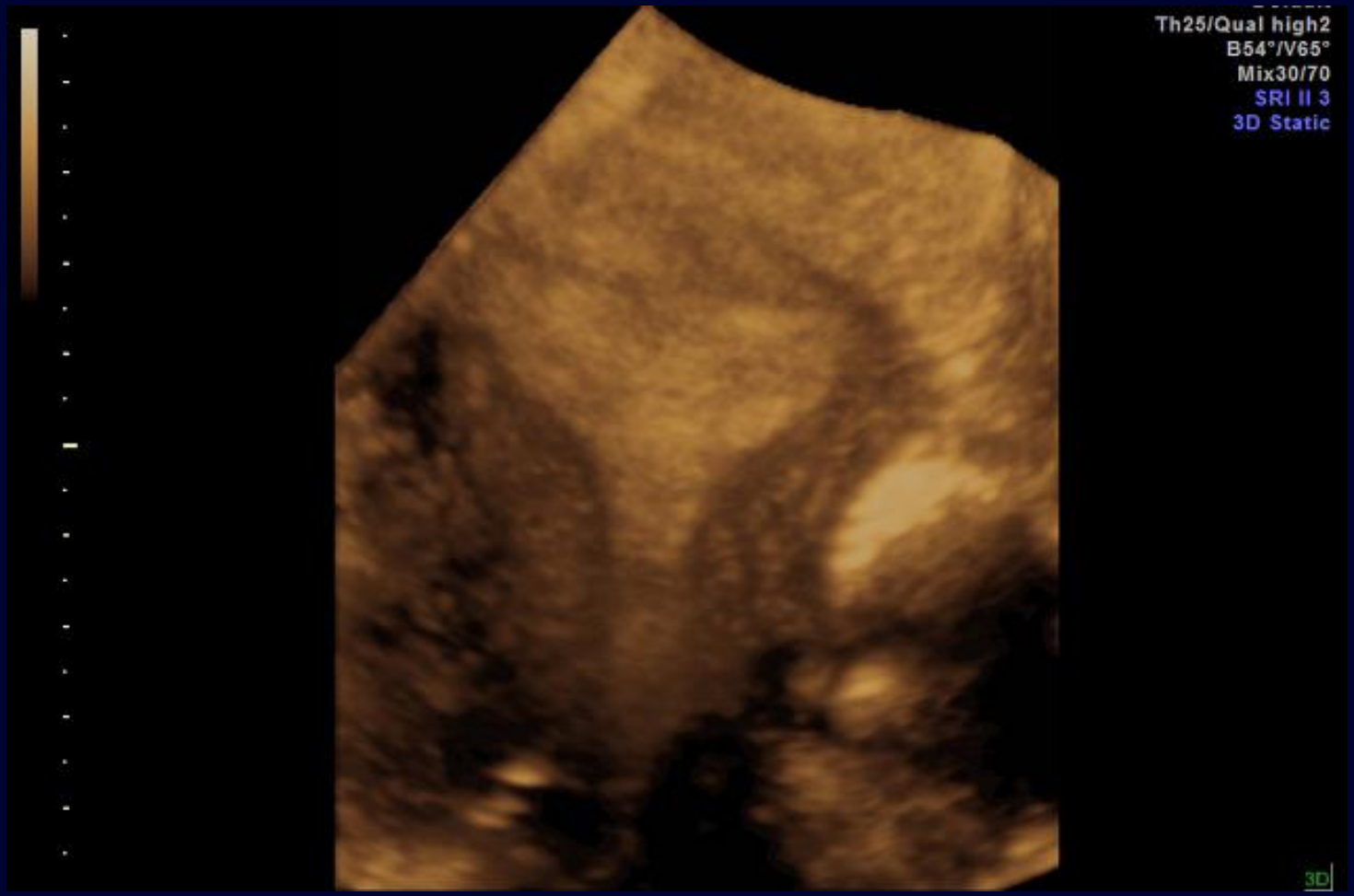
3D View of Arcuate Uterus



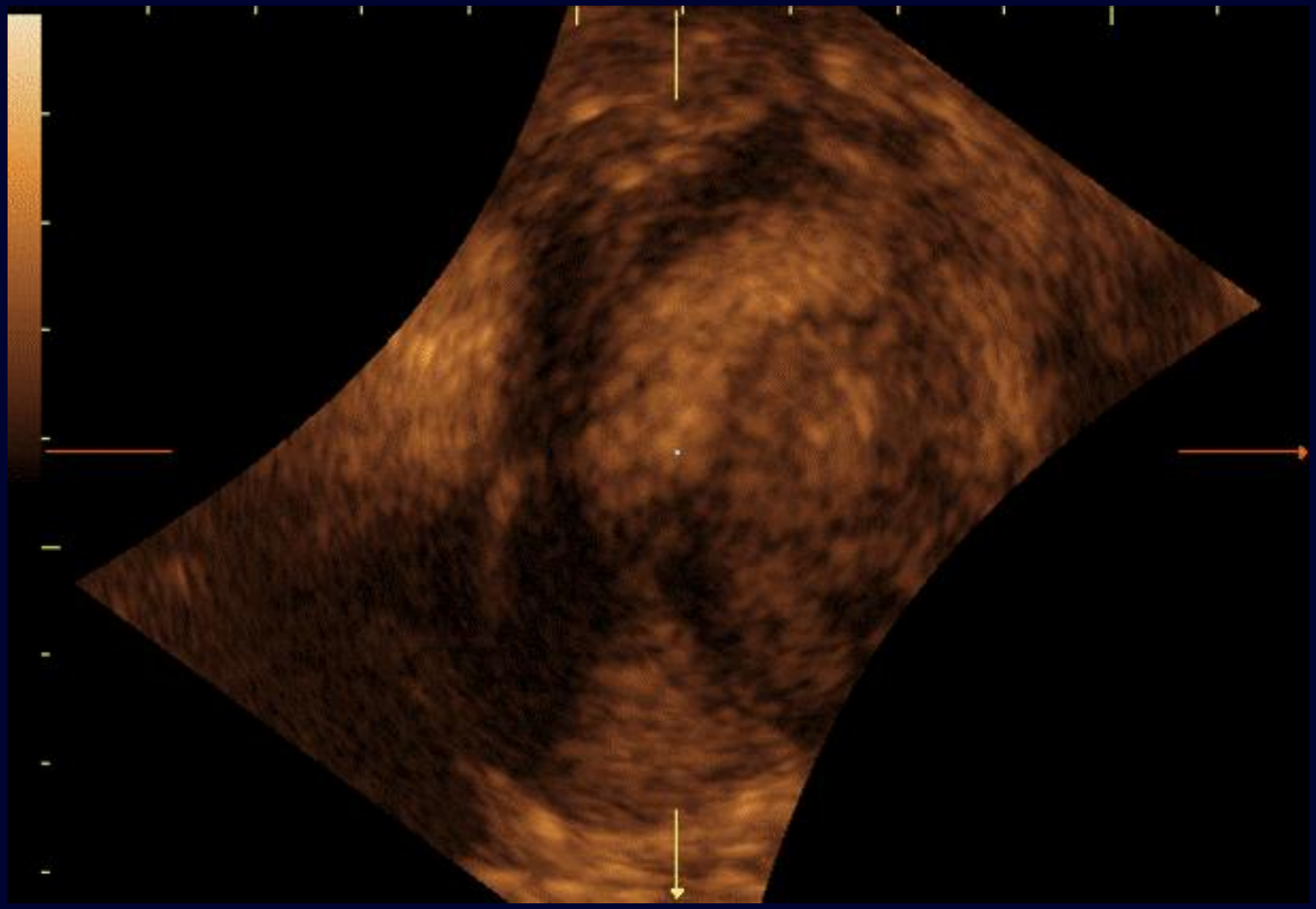
Arcuate Uterus: 3D Coronal View



Normal Uterus



Unicornuate Uterus



Note: this uterus curves to one side due to only 1 Müllerian duct forming . This is very difficult to detect on 2D ultrasound but is easy to diagnose with 3D.

Bicornuate Uterus

Courtesy of Leeber Cohen, MD

Summary

- Ultrasound plays a critical role in the evaluation and treatment of infertility.
- Ultrasound detects abnormalities in the uterus, ovaries, and tubes that can impact fertility.
- Ultrasound is critical in the monitoring of ovulation induction and IVF/ET procedures. In addition, ultrasound-guided transfers have been shown to improve pregnancy rates.

References

- Chang HJ, Han SH, Lee JR, et al. Impact of laparoscopic cystectomy on ovarian reserve: serial changes of serum anti-Müllerian hormone levels. Fertil Steril 2009 (epub).
- Puscheck EE, Cohen L. Congenital malformations of the uterus: the role of ultrasound. Semin Reprod Med 2008; 26:223-231.
- Wallace WH, Kelsey TW. Ovarian reserve and reproductive age may be determined from measurement of ovarian volume by transvaginal sonography. Hum Reprod 2004; 19:1612-1617.