Evaluation of an Adnexal Mass

Reviewed by Bill Rooney MD
VP/Medical Director
SCOR Global Life

Agenda

- Case examples
- Adnexal anatomy/physiology
- Incidence
- Ovarian cancer with mortality data
- Common cystic and non-cystic adnexal masses
- Imaging
- Biomarker exams, in particular use of CA-125
- Genetic abnormalities associated with ovarian cancer, in particular BRCA1 and BRCA2
- Putting it all together in underwriting.

- The differential diagnosis for adnexal masses is extensive.
- Some of the conditions have tremendous mortality implications.
- The goal today is to make the subject applicable to what we do as medical directors performing underwriting functions

"Hate is too great a burden to bear. It injures the hater more than it injures the hated"

Coretta Scott King (American civil rights activist; widow of the Rev. Martin Luther King, Jr. Died at age 78)

Cases to Consider

Case #1

33 y/o female applying for $450,000 insurance.

- A recent US showing a 4.5 cm left adnexal ovarian cyst.
- Cyst is described as a “simple cyst”

Questions:

- What if it had been a mixed solid/cystic mass?
- What if it had been a 62 y/o?
- What other tests would you like to see to make a mortality risk assessment judgment?
- What if it had been discovered 1 year ago and f/u imaging showed a stable exam?

Case #2

52 y/o postmenopausal female with a recent finding of an adnexal mass.

- US shows a cystic structure with multiple and thick septations. Radiologist’s report mentions clinical correlation needed.
- CA-125 value of 322 (normal range on lab report 0-35)
- Family hx. of breast cancer in two first degree relatives.

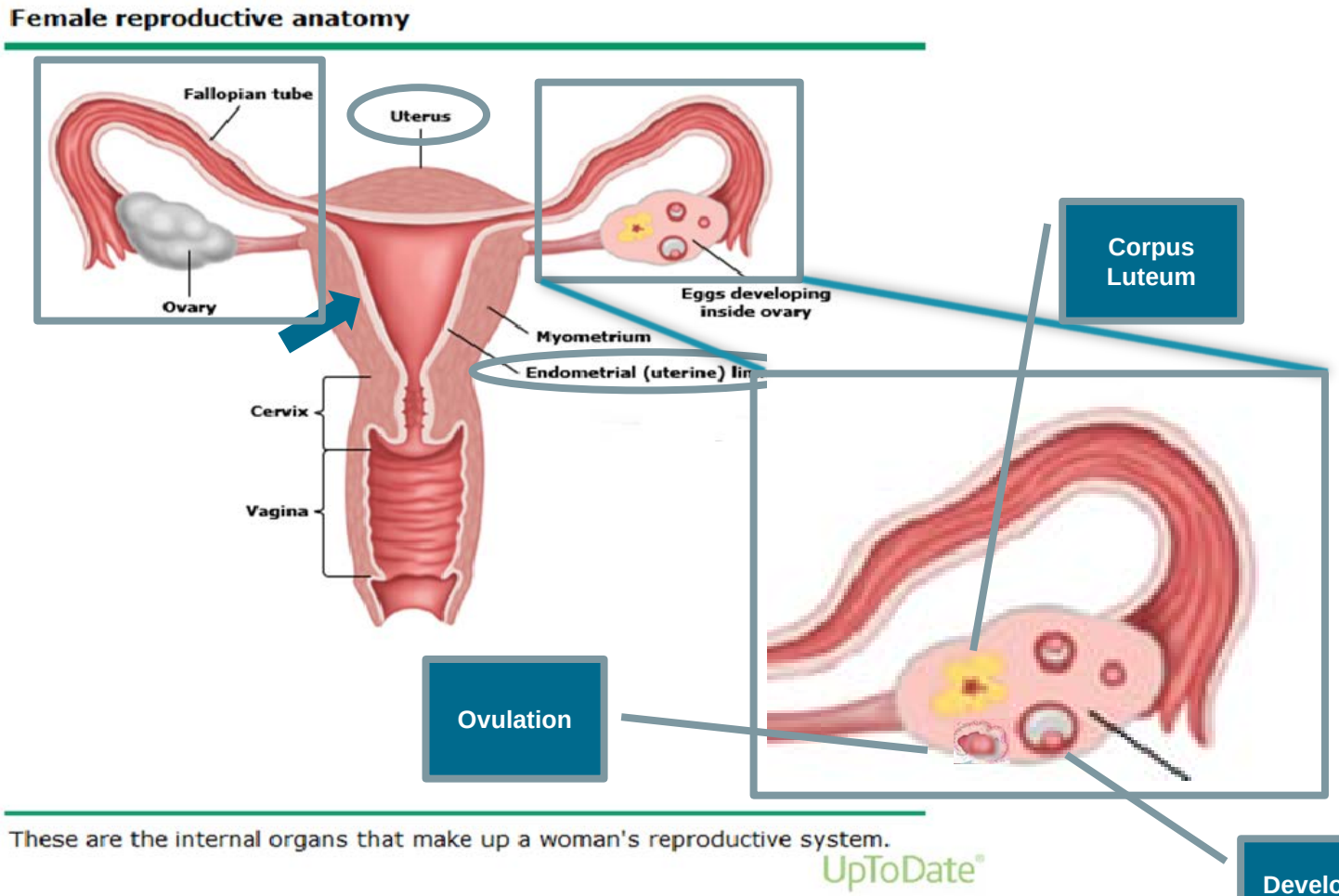
Questions:

- What is the role of CA-125?
- Is it a good screening test for ovarian cancer. Great sensitivity? Great specificity?
- Is the family history important?

First a review of the anatomy

Adnexa

The area next to the uterus that contains the ovary, fallopian tubes, vessels, ligaments, and connective tissue



"There is a recent history of an adnexal mass, how concerned should we be?"

- Very common---Most are benign.
- However, it is very important to determine benign from malignant.
- More common in premenopausal women but can be found at any age.
- Characteristics that increase the chance of malignancy
  - If found in children, adolescents, or postmenopausal women
  - A complex or solid appearing mass on US/MRI
  - Genetic predisposition
  - History of non-gynecological cancer such as breast or stomach cancer (either metastatic or primary ovarian)
- In the US approximately 5-10% lifetime risk for a woman to have a surgery for a suspected ovarian cancer

Adnexal Masses
(Some examples)

Non-Ovarian Lesions	
Ectopic pregnancy	Hydrosalphinx
Para-ovarian cyst	Lymphocele
Endometrioma which is extra-ovarian	Lymphangioma
Fallopian tubal carcinoma	Leiomyoma
Appendiceal mucocele	Malignant mesothelioma

Cystic type non-ovarian lesions	
Ascites	Bowel
Diverticulitis	Iliac aneurysm
Hematoma	Peritoneal and omental cysts

Ovarian Lesions	
Ovarian cysts Follicular cyst Corpus luteum cyst	Cystic teratoma
Tubo-ovarian abscess	Endometrioma
Cystadenoma (serous and mucinous)	Cystadenocarcinoma
Ovarian torsion	

Common Benign Ovarian Neoplasms

Cystadenomas
Serous and mucinous types
Thin-walled
Uni- or multilocular
5-20 cm in size typically
Occur bilaterally at times (especially serous types at 20-25% of the time)

Mature Cystic Teratomas (Dermoid Cyst)
Benign germ cell tumor
Most common ovarian tumor in 2nd and 3rd decades
Contains elements of all three germ cell layers (teeth and hair are common)

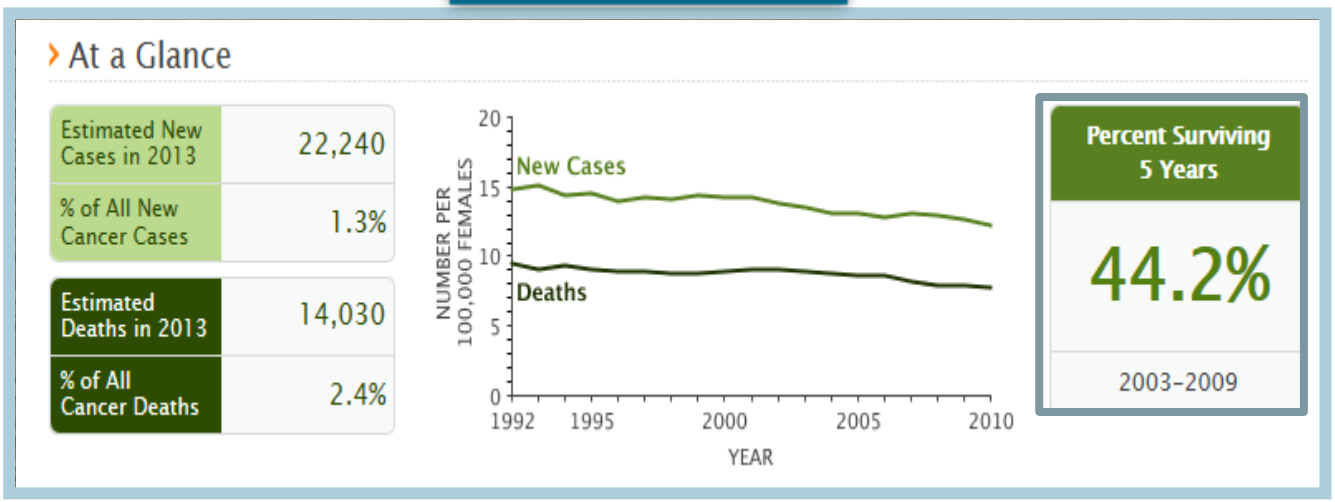
Leiomyoma
Benign neoplasm typically arising from the uterus—not a true ovarian neoplasm
May be found in the broad ligament
Can be confused with an ovarian mass especially when • Pedunculated • Present in the fundus or posterior cul-de-sac

What is the significance of an Adnexal mass in underwriting?

- Ovarian cancer: (not counting low malignant potential ovarian tumors)*
  - Is diagnosed in ~22,240 women each year.
  - Will kill 14,230 women each year
  - 9th most common cancer in women
  - 5th most common cause of cancer death
  - Will occur in 1 in 72 women in their lifetime
  - Will cause the death of 1 in 100 women
  - Impacts women over age of 63 about ½ of the time
  - Is found in an early stage only 15-20% of the time

The disorder that has the largest mortality concern is cancer of the ovary, so let's talk about it first.

Ovarian Cancer Statistics



*http://www.cancer.org/cancer/ovariancancer/detailedguide/ovarian-cancer-key-statistics
**http://seer.cancer.gov/statfacts/html/ovary.html

Ovarian cancer presentation—Common symptoms and findings

Ovarian Cancer Common Symptoms
Pain (Pelvic/Abd)
Increased abdominal size/Bloating
Difficulty eating/Early satiety
Urinary urgency/frequency

Of Note
Symptoms that are more severe and/or frequent are of concern
Symptoms of recent onset are of concern
Combination of bloating/increased abdominal size/urinary symptoms found in 43% of those with cancer but only 8% in control

Ovarian Cancer Common Findings	
Adnexal mass	Pleural Effusion
Bowel Obstruction	DVT
Incidental finding at surgery	Incidental finding on imaging

Goff, BA et al. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA. 2004;291(22):2705

Risk factors for ovarian cancer

The big box is supposed to represent a person.
The circle sort of helps

Age

Genetic factors

- F.H.
- BRCA gene mutations
- Lynch Syndrome

Reproductive/Hormonal Factors

- Early menarche
- Late menopause
- Nulliparity
- Polycystic ovarian syndrome

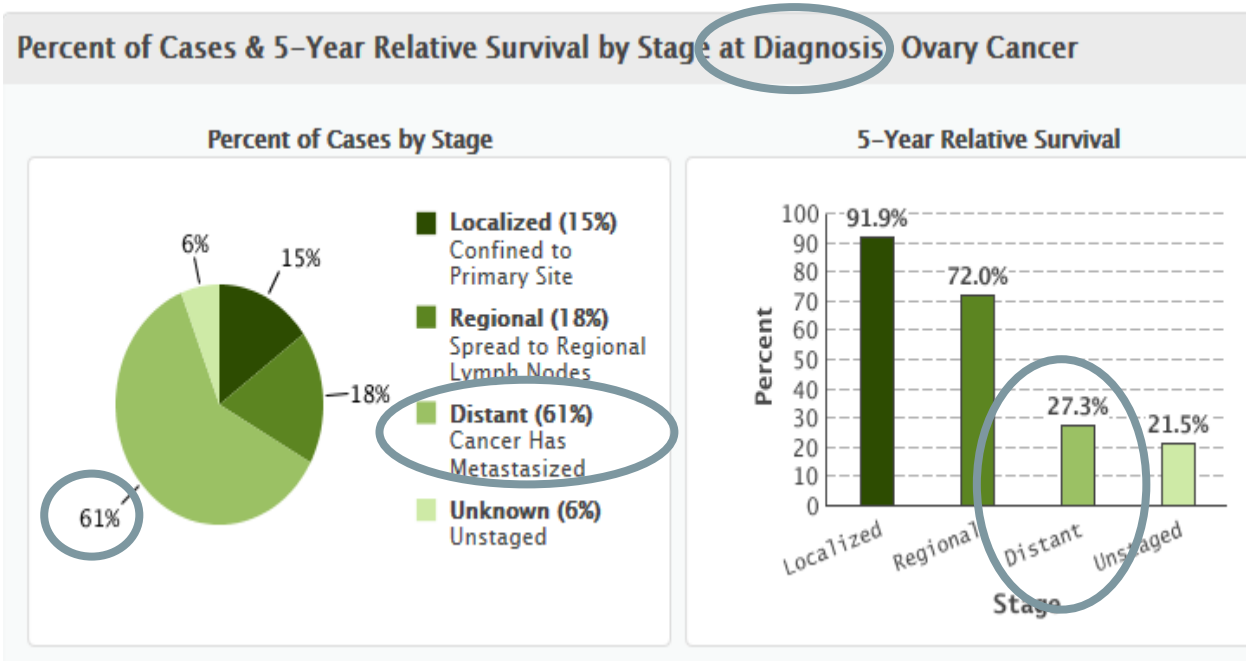
Cigarette smoking

Obesity

Protective factors

- OCP's
- Breastfeeding
- GYN surgery

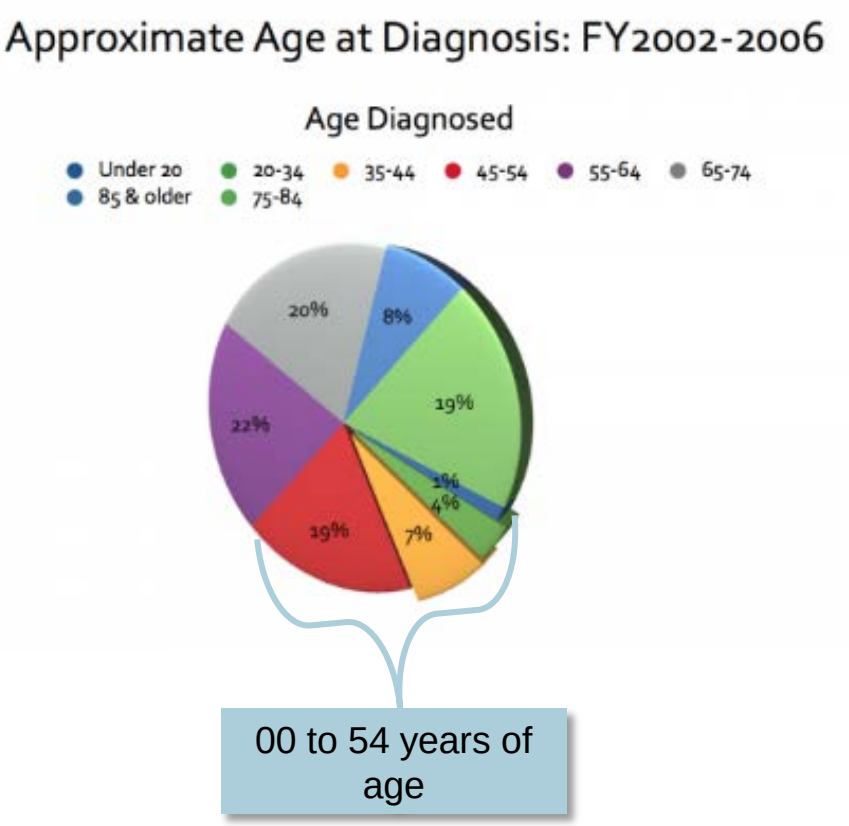
Mortality Statistics



http://seer.cancer.gov/statfacts/html/ovary.html

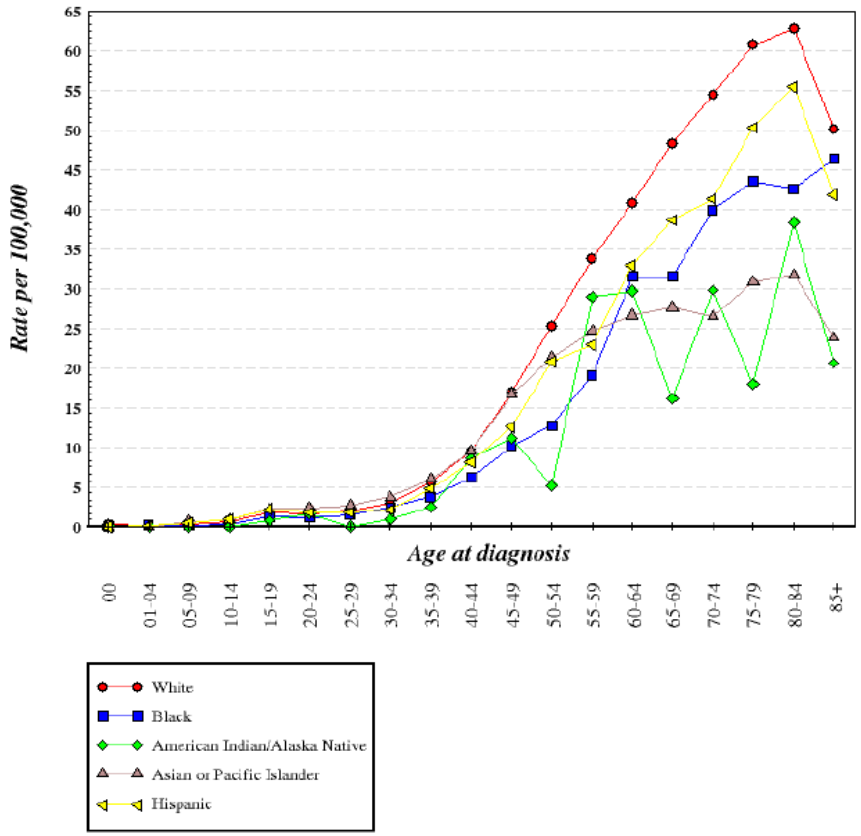
Staging Tumor characteristics	
I	Confined to the ovary
II	Beyond the ovary but confined to pelvis
III	Beyond the pelvis (throughout the peritoneal cavity or involves the paraaortic nodes or inguinal nodes
IV	Distant metastasis

Ovarian Cancer—Age at Diagnosis



http://www.ovariancancer.org/about-ovarian-cancer/statistics/
Accessed 1/28/14

Figure 1. U.S. ovarian cancer incidence by age and race, 1992-2002



Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov).[2]

Screening for Ovarian cancer

We have seen that ovarian cancer:

- ❑ **Can occur at almost any age**
- ❑ **Typically presents in an advanced stage**
- ❑ **Has poor mortality characteristics**

So, what about screening?

- ❑ Historically many experts have established a goal of a positive predictive value of 10% for screening tests for ovarian cancer* (i.e. no more than 9 healthy women with false-positive tests would undergo unnecessary procedures for each case of ovarian cancer found)
- ❑ Predictive value of a screening test depends on the prevalence of the disease in the population.
- ❑ A screening test that targets all women over age 50 for ovarian cancer would need to have a specificity of 99.6% assuming an 80% sensitivity to achieve a 10% positive predictive value.

*Moore, RG, et al. Current state of biomarker development for clinical application in epithelial ovarian cancer. Gynecol Oncol. 2010;116(2): 240

Screening for Ovarian cancer

Interest in screening has grown with the discovery of serum tumor markers and with improved US diagnostic abilities.

Women with average risk:

Previous studies[1] have shown

- **No reduction in mortality from ovarian cancer screening**
- **Increased harm from f/u testing/surgery**
  - **(15% of women undergoing surgery for falsely + screening tests had a serious complication in the PLCO study involving over 78,000 women).**

However, two large trials are in progress to evaluate blood testing and/or US for screening.

The NCI states "There is solid evidence to indicate that screening for ovarian cancer with the serum marker CA-125 and TVU does not result in a decrease in ovarian cancer mortality, after a median follow-up of 12.4 months"[2].

Currently consensus is that screening should not be done for women of average risk.

This includes:

- The US Preventative Services Task Force (USPSTF)
- The Society of Gynecologic Oncology
- The American College of Obstetrics and Gynecologists.

Women at high risk:

Risk reducing salpingo-oopherectomy (RRSO) has been shown to be a reliable method of decreasing mortality.

Studies on those not undergoing RRSO and obtaining transvaginal US and CA-125 have had mixed results.

- Some studies showed decreased stage of cancer when detected
- Other studies have not shown this.

The National Comprehensive Cancer Network (NCCN) has recommended screening every six months with CA-125 and TVUS beginning between age 30-35 in women with identified hereditary ovarian cancer syndromes.

1:Buys, SS et al. Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011;305 (22) 2295
2:http://www.cancer.gov/cancertopics/pdq/screening/ovarian/healthprofessional/allpages#3 Accessed 1/27/14

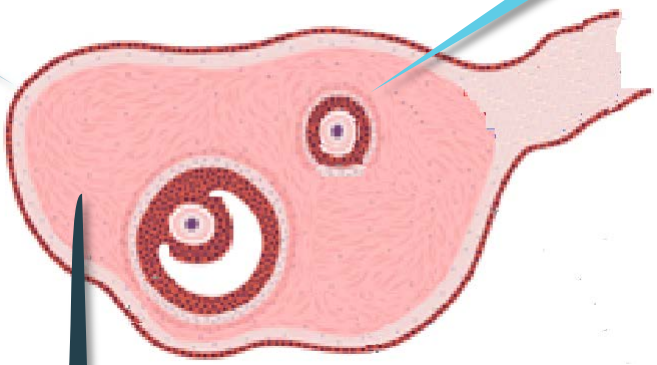
Types of Ovarian Cancer

Epithelial Cancers

~90% of all ovarian cancers

Types:
Serous
Mucinous
Endometroid
Clear Cell
Transitional
Undifferentiated

OVARY



Germ Cell Cancers

~5 % of all ovarian cancer

~80 % are in women <30 y/o

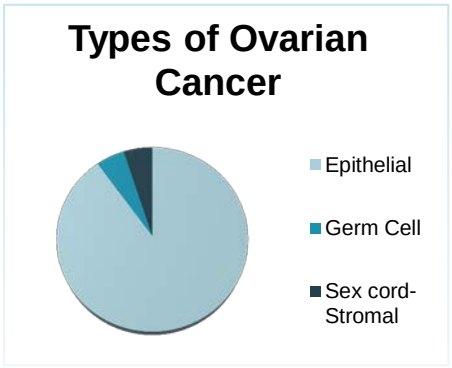
Types:
Teratomas
Dysgerminoma
Choriocarcinoma
Endodermal (Yolk sac)

Sex Cord-Stromal Cancers

~5 % of all ovarian cancers

Most are in older women

Types:
Granulosa
Granulosa-theca
Sertoli-Leydig cell



Note:
The ovary can have a non-ovarian primary tumor metastasize to the ovary as well---
The most common types are GI cancers and breast cancer:

- Colon cancer 15-32%
- Breast cancer 8-28%
- Stomach cancer 6-22%
- Appendix cancer 2-20%

http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-types/ovarian-cancer/index.html

Ovarian tumors of low malignant potential ("borderline tumors")

- Account for 10-20% of ovarian epithelial tumors
- Average age of dx. is 40-60 y/o but is not uncommon in the 15-69 y/o group
- BRCA gene mutations don't seem to increase the risk for these types of cancers

Tumors have a variety of histologies

Serous borderline tumors

- Majority of borderline tumors
- 75% dx as stage I
- 25-50% are bilateral

Mucinous borderline tumors

- Another common histological type
- 90% dx as stage I
- 10% are bilateral

Other types of borderline tumors

- Endometriod
- Transitional cell
- Clear-cell

Commonly present with an asymptomatic adnexal mass

Mortality data is more favorable

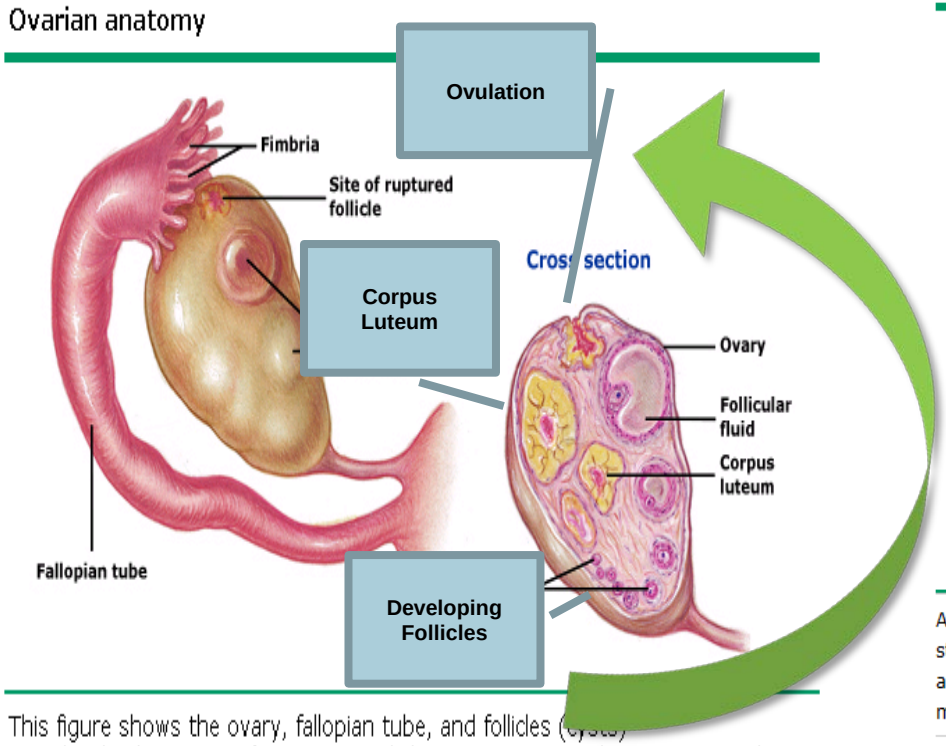
Stage	10 yr survival
I	97%
II	90%
III	88%
IV	69%

Underwriting Notes

- So, screening is not universally recommended but it is occasionally done.
- At times US and/or CA-125 tests are ordered for suspicious symptoms or abnormal exams and so we do see the results of abnormal imaging and lab testing at times.
- Possibly the most common abnormality we see are cysts on the US. The questions that come up are
  - Should there be cysts on the ovaries?
  - If present, how large are they before there should be concern?
  - What typically happens to a cyst once formed? How long does it last?
  - Are cysts common in all women, regardless of age or menopausal status?
- To answer these questions let's look at the ovary again.

"I never wanted to set the world on fire. So I never had to burn any bridges behind me"
Dinah Shore (Actress/singer who died at age 77)

Ovarian anatomy



This figure shows the ovary, fallopian tube, and follicles (cysts)

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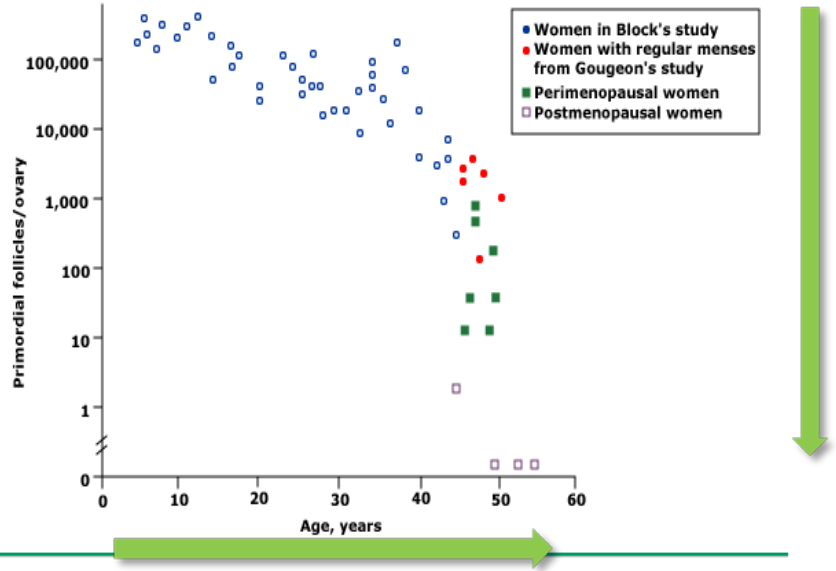
Declining follicle number with age



A comparison of the relationship between age and primordial follicle number in Block's study of 44 girls and women aged 7 to 44 years with that of Gougeon's study of women aged 45 to 55 years. Follicle depletion appears to accelerate in the decade preceding menopause.

Data from:

1. *Block E. Quantitative morphological investigations of the follicular system in women; variations at different ages. Acta Anat 1952; 14:108*
2. *Gougeon A. Caractères qualitatifs et quantitatifs de la population folliculaire dans lóvaire humain adulte. Contr Fert Sex 1984; 12:527.*

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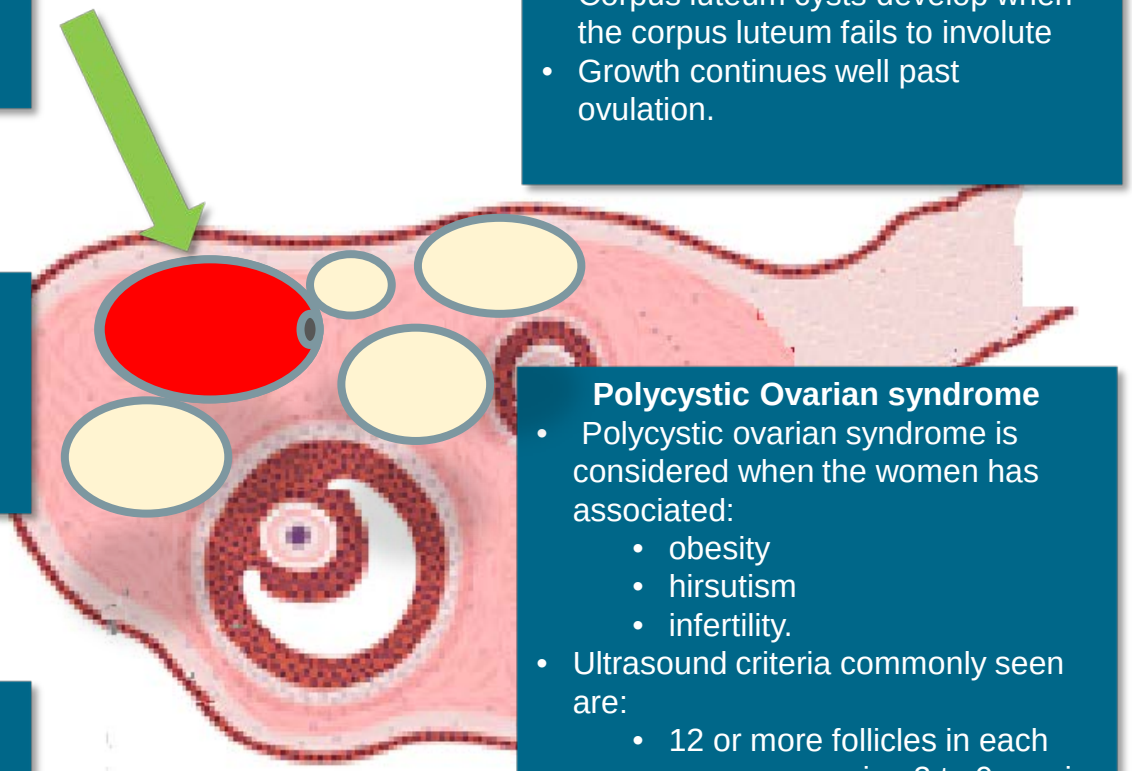
Common types of cysts

Follicular cysts
- Follicular cysts develop when the developing follicle does not rupture
- The ovum is not released.
- The follicle then continues to grow

Corpus luteum cysts
- Corpus luteum cysts develop when the corpus luteum fails to involute
- Growth continues well past ovulation.



Hemorrhagic cysts
- Hemorrhagic cysts can be follicular cysts or corpus luteum cysts
- They occur when there is hemorrhage into the cyst.

Polycystic Ovarian syndrome
- Polycystic ovarian syndrome is considered when the women has associated:
  - obesity
  - hirsutism
  - infertility.
- Ultrasound criteria commonly seen are:
  - 12 or more follicles in each ovary measuring 2 to 9 mm in diameter
  - and/or increased ovarian volume (>10 ml).

Endometriomas
- A growth of ectopic endometrial tissue within the ovary.
- Called a “chocolate cyst” since it frequently has a thick brown fluid

Important facts

- **30% of ovarian masses in women over age 50 are malignant.[1]**
- **8.75% of ovarian masses in premenopausal women are malignant.[1]**

Simple cysts are common in premenopausal women.

- Study of 335 asymptomatic between 25-40 y/o showed:
- 6.6% had an ovarian cyst.[2]
- 80% resolved spontaneously at 3 months.

Simple cysts are common in postmenopausal women.

- Study of 15,000 asymptomatic women over 55 y/o with annual US exams showed:
- 14% had simple cysts on first US.
- 8% had a new simple cyst with F/U US one year later

1 Kinkel, K et al; Indeterminate ovarian mass at US: Incremental value of second imaging test for characterization-meta-analysis and Bayesian analysis. Radiology. 2005;236(1):85
2 Borgfeldt C et al; Transvaginal sonographic ovarian findings in a random sample of women 25-40 years old. Ultrasound Obstetrics Gynecology. 1999;13 (5): 345.

Ovarian cysts and neoplasms in children and adolescents

- We won't discuss neonatal and infant cysts/tumors in great detail today. That is probably a whole different discussion. Relatively uncommon for us to encounter this in our day to day work.
- Fewer than 5% of all ovarian malignancies occur in children and adolescents.
- However 10-20% of all ovarian masses are malignant in adolescents. (80% are malignant in girls <9 y/o)[1]
- 35-45% of ovarian cancers in children are germ cell tumors.[2]

1 Laufer, Marc et al. UpToDate.com accessed 2/6/14.
2 You, W. et al. Gynecologic malignancies in women aged less than 25 years. Obstetrics and Gynecology. 2005;105(6):1405

Evaluation of adnexal masses---Looking at it with the help of imaging. Typically US evaluation

- The next few slides will describe common US findings and have a few US images to review

US

Sensitivity of 86-91%[1]
Specificity of 68-83%[1]
Good at differentiating between cystic and solid masses.
Good at detecting ascites which is frequently associated with benign and malignant tumors

MRI and CT scans

While US is commonly the initial test, MRI and CT scanning do play a role,
MRI is frequently used for equivocal US findings. It can differentiate malignancy from benign or normal findings.
CT scanning can be helpful in finding metastasis and many feel it is helpful in evaluation of the retroperitoneum.

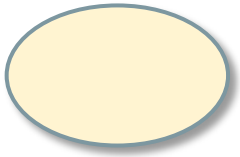
PET scans

Studies suggest the sensitivity and specificity are not as good

Myers ER, Bastian LA, Havrilesky LJ, et al. Management of Adnexal Mass. Evidence Report/Technology Assessment No.130 AHRQ Publication No. 06-E004, Agency for Healthcare Research and Quality, Rockville, MD February 2006.

Asymptomatic Adnexal cysts—Management in those otherwise at low risk Society of Radiologists in Ultrasound

Simple Cyst
- Round/oval
- Smooth thin walls
- Posterior acoustic enhancement
- No solid component or septation
- No internal flow with color Doppler US



Premenopausal Age	
<3 cm	Normal finding. Typically not mentioned in report
>3 cm and <5 cm	No need for f/u
>5 cm and <7 cm	Yearly f/u recommended
>7 cm	Imaging with MRI or surgical evaluation should be considered

Postmenopausal Age	
<1 cm	Not an unusual finding. No need for f/u
>1 cm and <7 cm	Yearly f/u with US recommended
>7 cm	Imaging with MRI or surgical evaluation should be considered

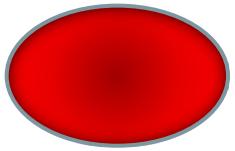
I color coded the charts.

Green: Typically a benign finding which would be considered low risk

Yellow: Intermediate underwriting risk. Serial results would be very helpful in establishing risk

Red: Typically a finding of concern. Additional evaluation is typically planned.

Hemorrhagic Cyst
- Complex cystic mass
- Reticular pattern of internal echoes (spiderweb or lacy appearance)
- Can be a solid-appearing area with concave margins
- No internal flow with color Doppler

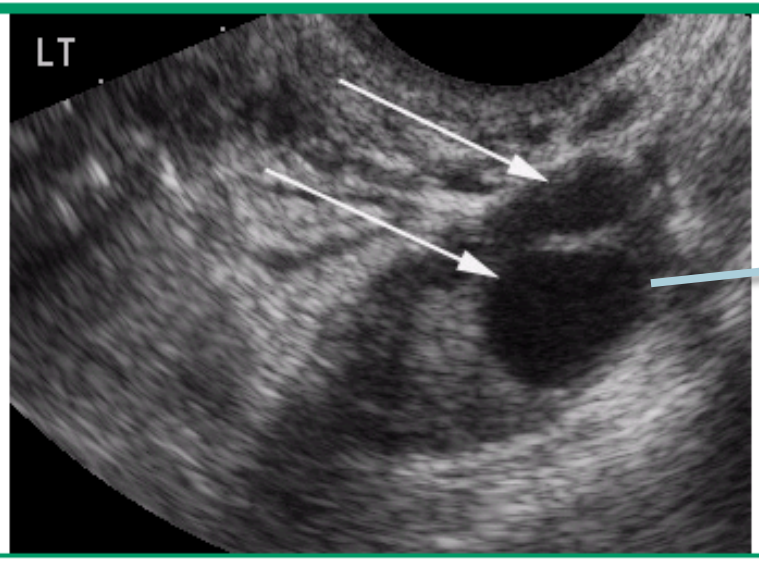


Premenopausal Age	
<3 cm	Common finding. No need for f/u
>3 cm and <5 cm	No need for f/u
>5 cm	Short-interval f/u (6-12 weeks) with US

Postmenopausal Age	
Early postmenopausal Any size	Short-interval f/u (6-12 weeks) with US to ensure resolution
Late postmenopausal Any size	Surgical evaluation should be considered

Management of Asymptomatic Ovarian and other Adnexal Cysts Imaged at US: Society of Radiologists in Ultrasound Consensus Conference
Levine, Deborah, et al, September 2010 Radiology, 256, 943-954

Follicular ovarian cyst



Transvaginal ultrasound of the left adnexa. Normal left ovary with two follicles that are shown by the arrows. The follicles are circular anechoic structures within the substance of the hypoechoic ovarian tissue.

Courtesy of Thomas D Shipp, MD.

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Simple Cyst

- Round/oval
- Smooth thin walls
- Posterior acoustic enhancement
- No solid component or septation
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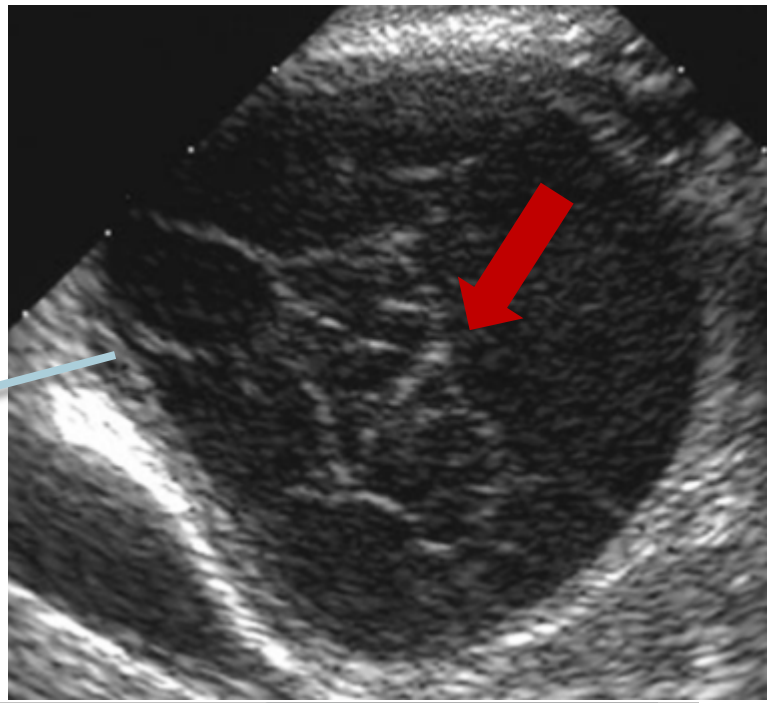
Hemorrhagic ovarian cyst



Hemorrhagic Cyst

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- Reticular pattern of internal echoes (spiderweb or lacy appearance)
- Can be a solid-appearing area with concave margins
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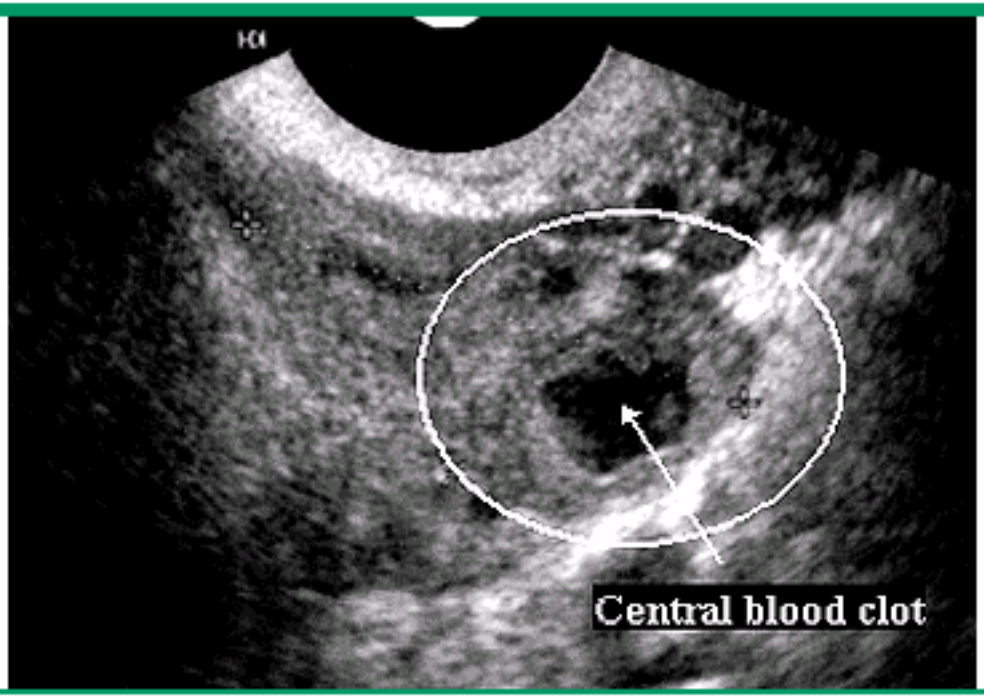
Corpus luteum cyst



Corpus luteum cysts can look more complex than follicular cysts. In this case, ultrasonography reveals a central blood clot within the cyst.

Courtesy of Jorge Londono, MD.

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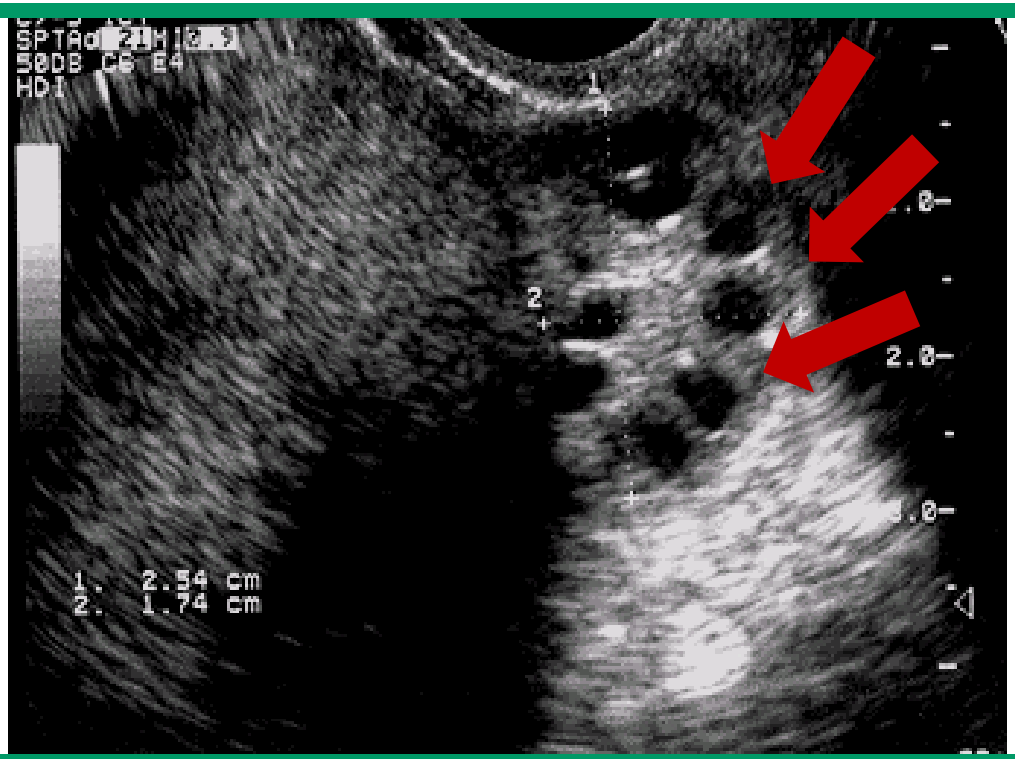
Polycystic ovary



Pelvic ultrasonography shows multiple ovarian cysts (ring of black circles on right) that are suggestive, although not diagnostic, of polycystic ovary syndrome.

Courtesy of Jorge Londono, MD.

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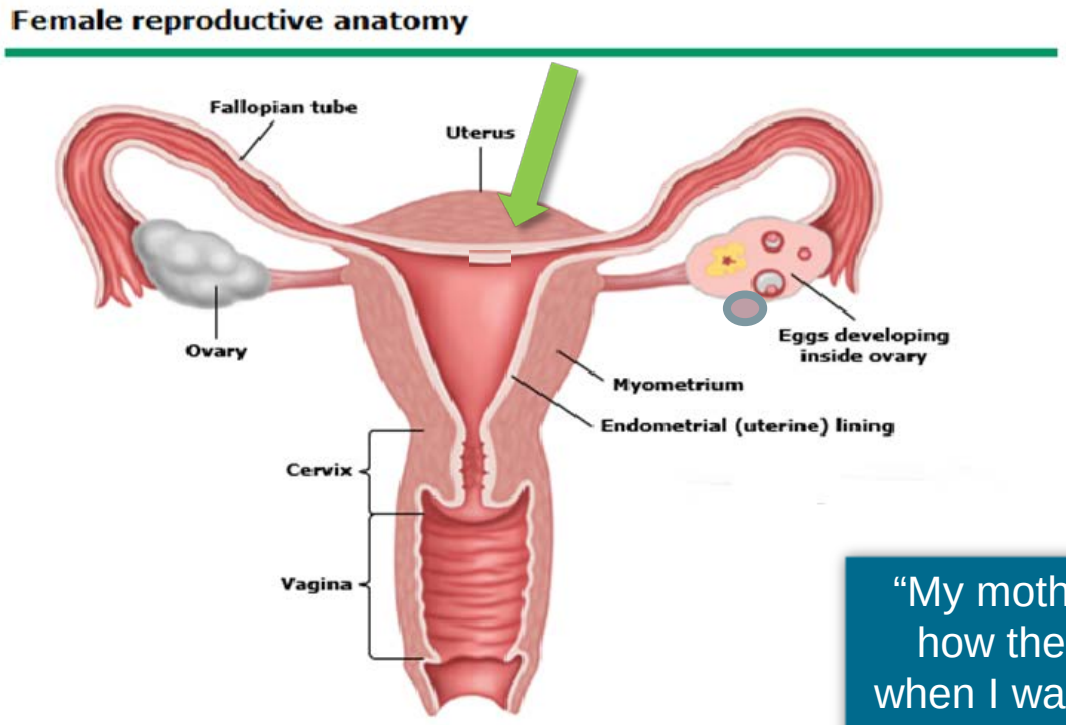
Endometrioma



"My mother used to tell this corny story about how the doctor smacked me on the behind when I was born and I thought it was applause, and I have been looking for it ever since"

Kathy Bates (Oscar winning actress--survivor)

Teratoma

Teratomas
- Mature (Dermoid Cyst)
- Immature (malignant)

- Most common type of germ cell neoplasm
- Most are benign
- Most are cystic

Composed of 3 types of tissue

Ectodermal tissue
- Skin
- Hair follicles
- Sebaceous glands

Mesodermal tissue
- Muscle
- Urinary

Endodermal tissue
- Lung
- Gastrointestinal

Asymptomatic Adnexal cysts—Management in those otherwise at low risk Society of Radiologists in Ultrasound

Endometrioma

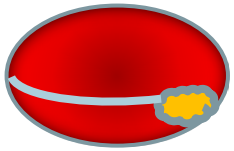
- Internal Homogenous and hypoechoic mass
- Diffuse low-level echoes (ground glass)
- No internal flow with color Doppler
- No enhancing nodules or solid masses
- Echogenic foci seen within cyst wall (30% of the time)
- **1% undergo malignant transformation**
  - Uncommon if <6 cm
  - Typically >45 y/o

Premenopausal Age	
Any size without echogenic foci	6-12 week F/U with US
Any size with echogenic foci	Yearly F/U with US or surgical excision

Postmenopausal Age	
Early postmenopausal—Any size Without echogenic foci	Short-interval f/u (6-12 weeks) with US to r/o hemorrhagic cyst
Late postmenopausal—Any size Without echogenic foci	Surgical evaluation should be considered or MRI
With echogenic foci	Yearly FU with US or surgical excision

Mature cystic Teratoma (Dermoid Cyst)

- Hypoechoic mass with hyperechoic nodule
- Usually unilocular (90%)
- May contain calcifications (30%)
- May contain hyperechoic lines—floating hairs
- May contain a fat-fluid level
- No internal flow with color Doppler
- **.17% to 2% undergo malignant transformation**
  - Typically >50 y/o
  - Typically >10 cm



Any Age	
Any size	F/U US every 6 months to 1 year if not excised

Endometrioma

Endometrioma

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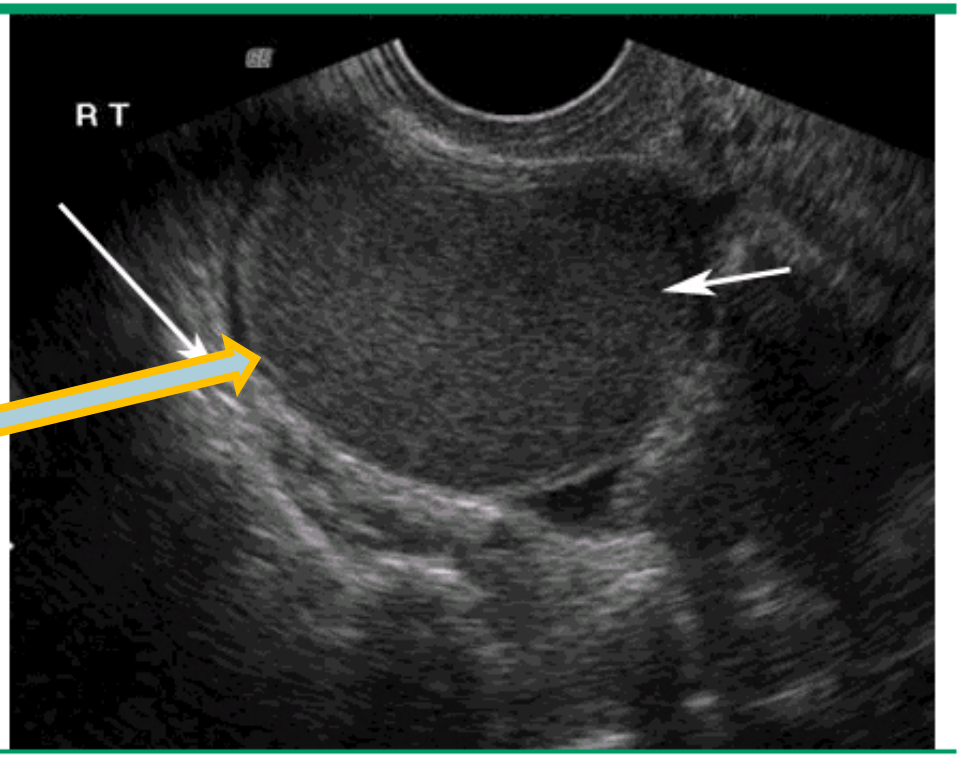
  - Uncommon if <6 cm
  - Typically >45 y/o



Transvaginal ultrasound image of the right adnexa showing an endometrioma of the right ovary. The homogeneous echo-pattern of the cyst contents (ie, "ground-glass" appearance) is characteristic of an endometrioma (short arrow).

Reproduced with permission from: Thomas D Shipp, MD. Copyright © Thomas D Shipp, MD.

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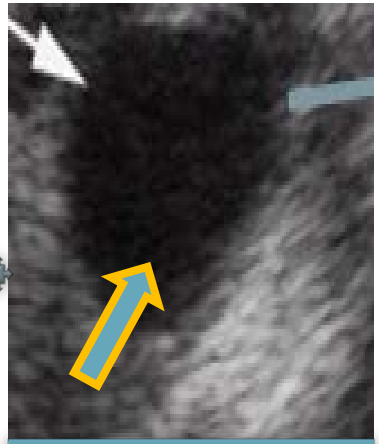


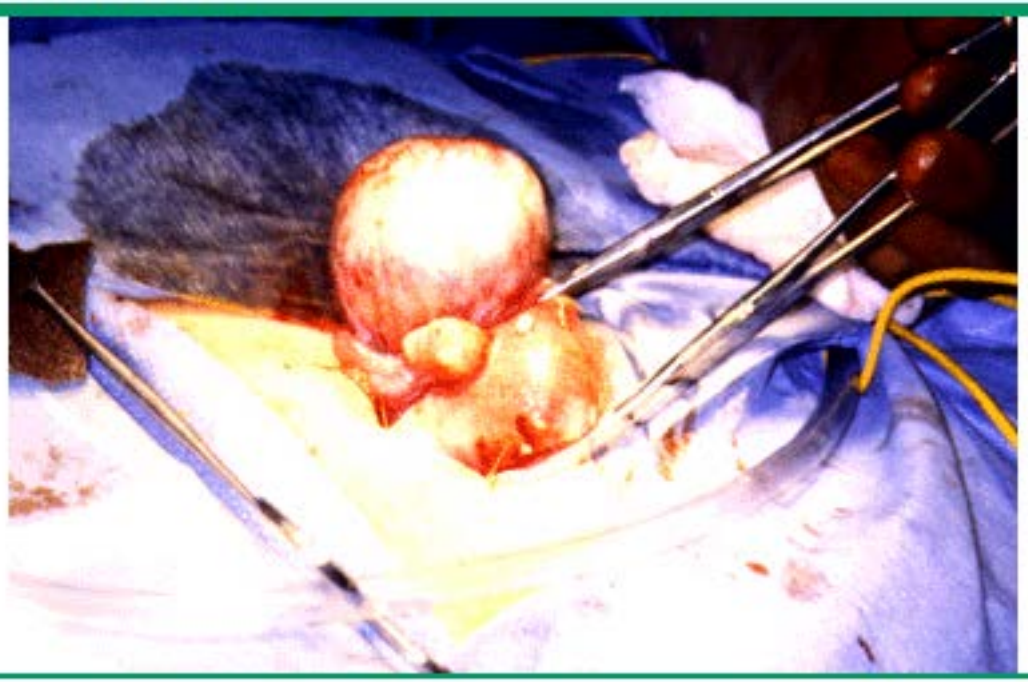
For comparison
This is the simple cyst from the previous slide

WARNING:

The next 2 slides have graphic photographs.

If you are squeamish look away now!!

Endometrioma



Gross intraoperative photograph of a left endometrioma in a patient with endometriosis.
Courtesy of Mitchel Hoffman, MD.

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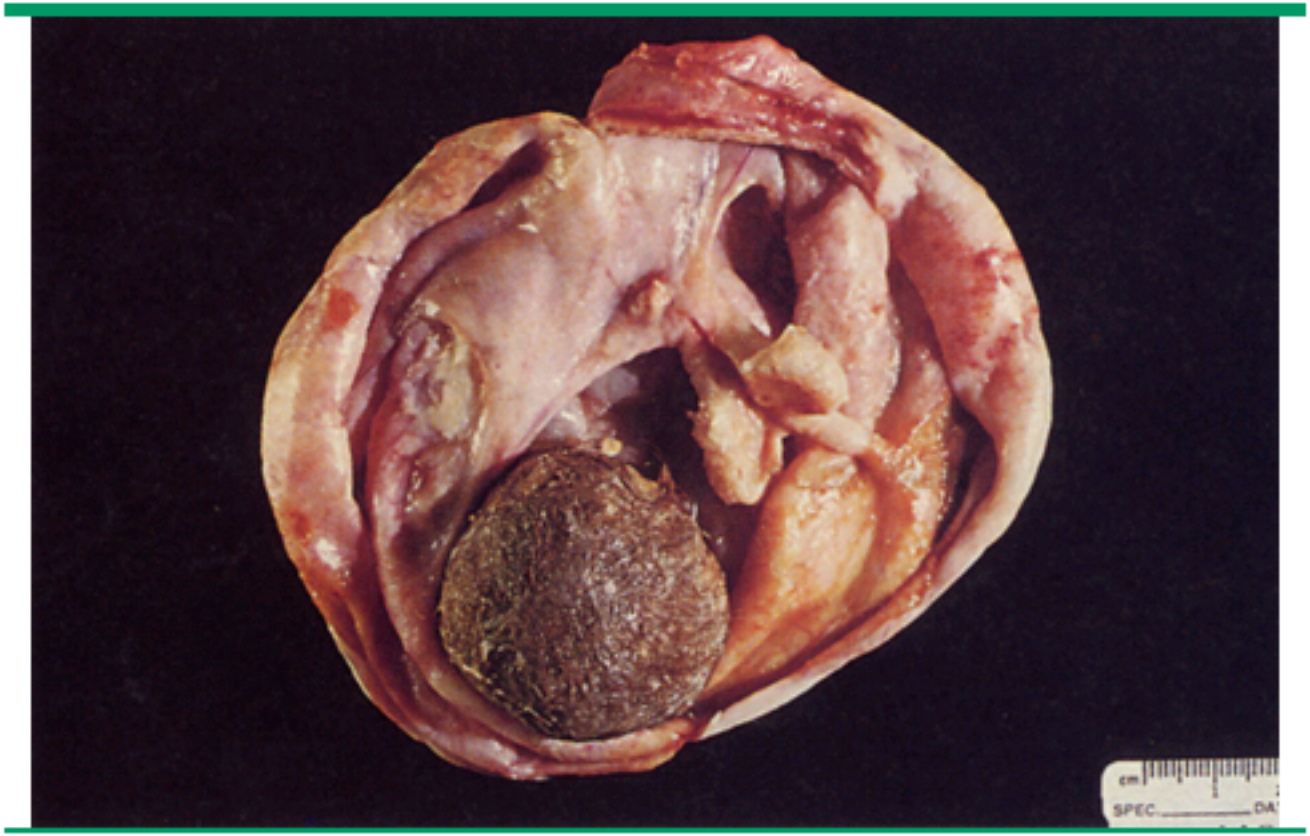
Opened mature cystic teratoma (dermoid cyst) of the ovary



Hair (bottom) and a mixture of tissues are evident.

Reproduced with permission from: Crum CP. The Female Genital Tract. In: Pathologic Basis of Disease, 6th ed, Cotran RS, Kumar V, Collins T (Eds), WB Saunders Company, Pennsylvania 1999. Copyright © 1999 Elsevier.

http://www.lww.com

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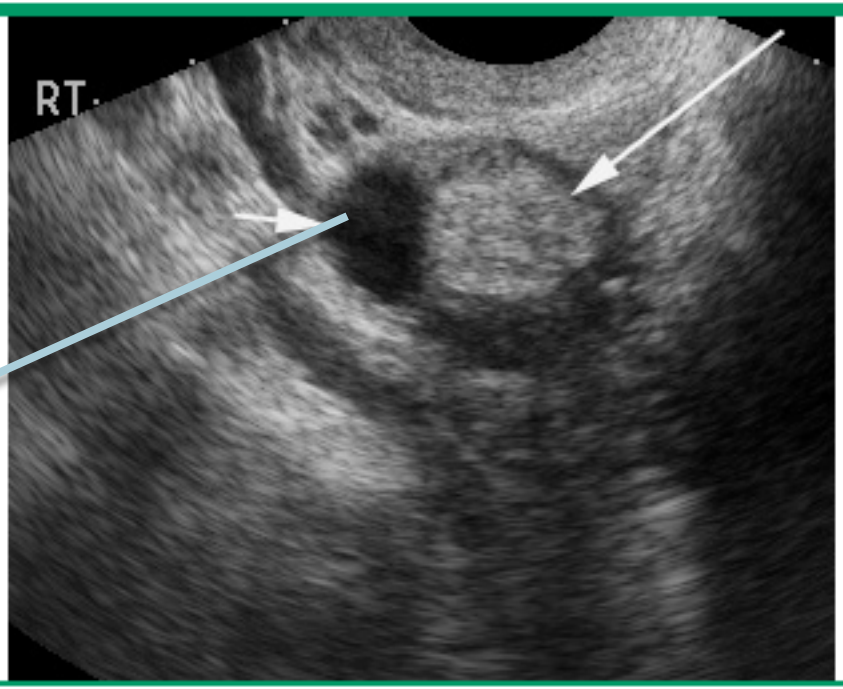
OK, it is safe to look again!

Transvaginal image of the right adnexa



Benign cystic teratoma (dermoid tumor) of the right ovary. The complex nature of this small tumor is demonstrated. The long arrow indicates the solid hyperechoic echogenic portion with shadowing of the ultrasound beam distal to the echogenic portion. The short arrow demonstrates the anechoic cystic portion with post cyst enhancement of the ultrasound beam.

Courtesy of Thomas D Shipp, MD.

Mature cystic Teratoma (Dermoid Cyst)

- Hypoechoic mass with hyperechoic nodule
- Usually unilocular (90%)
- May contain calcifications (30%)
- May contain hyperechoic lines—floating hairs
- May contain a fat-fluid level
- No internal flow with color Doppler
- **.17% to 2% undergo malignant transformation**
  - Typically >50 y/o
  - Typically >10 cm

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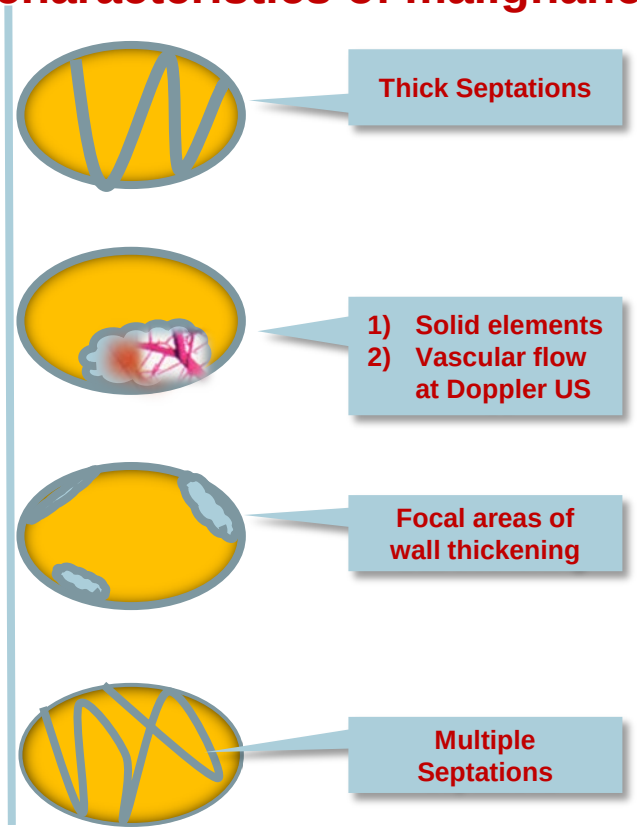
Asymptomatic Adnexal cysts—Management in those otherwise at low risk Society of Radiologists in Ultrasound

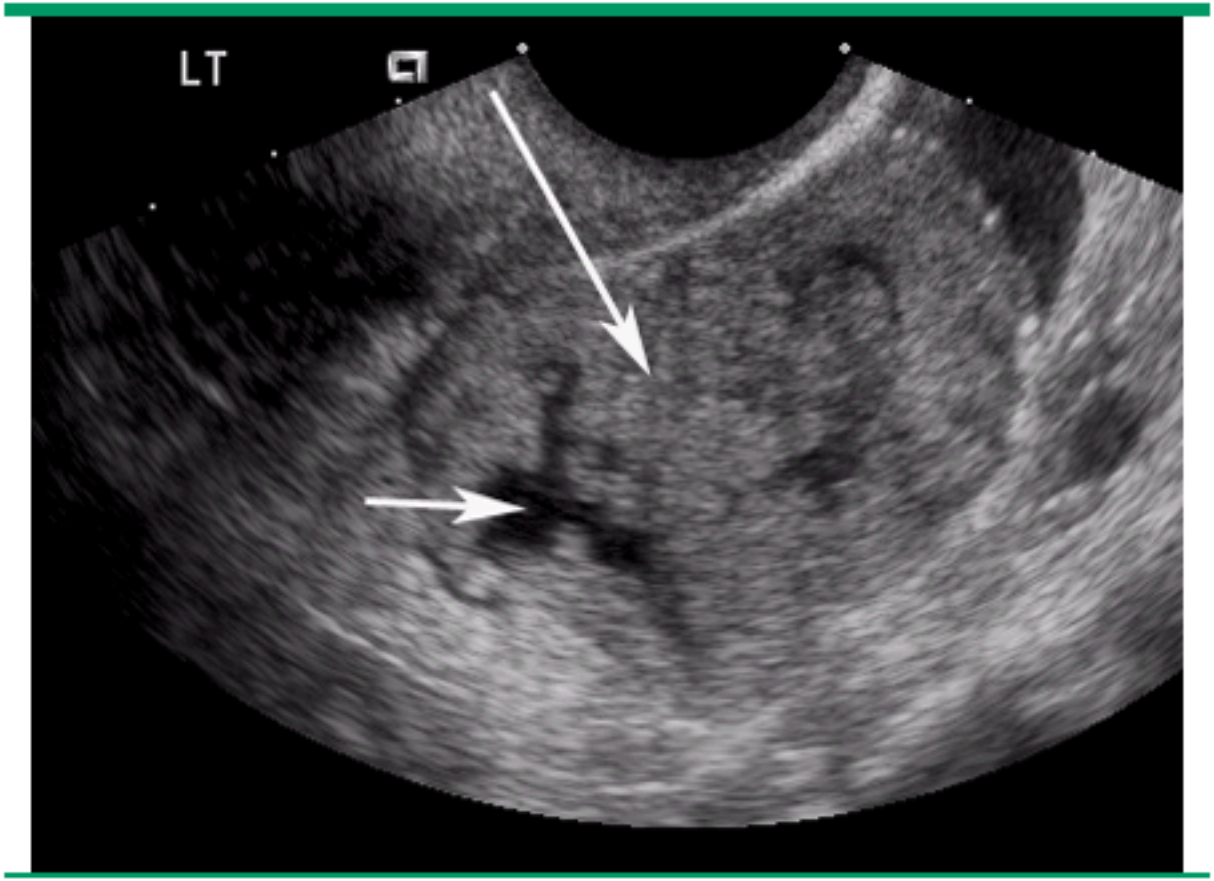
US characteristics of malignancy

High Risk US Findings	
Thick septations	>3 mm
Solid elements with flow at Doppler US	Any
Focal areas of wall thickening	>3 mm
Multiple septations	>1



Any Age	
All cases	Consider surgical evaluation

Ovarian cancer



Transvaginal ultrasound image of the left ovary showing ovarian cancer. The left ovarian mass is primarily solid as indicated by the long arrow. A small cystic portion is demonstrated by the short arrow.

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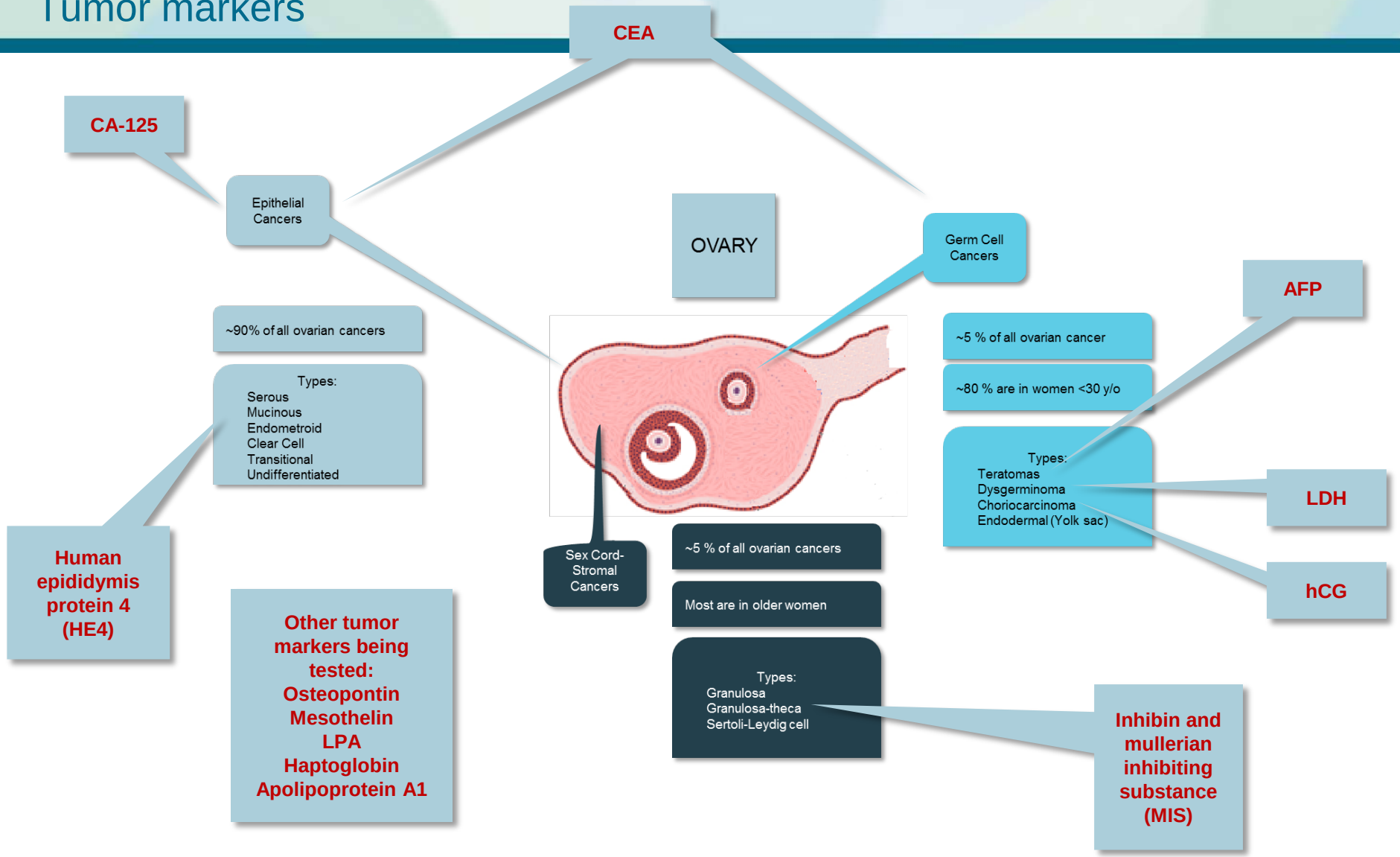
Tumor markers



CA-125 information

- FDA approved for the monitoring of women with ovarian cancer for response to therapy.
- Used off label at times for evaluation of adnexal masses
- Two different assays (CA 125 and CA125 II).
- Normal values lacks consensus. Some suggest <30, others <200 U/ml. There are some that feel normal may range from 20-200 in premenopausal women.

Human epididymis protein 4 (HE4) information

- FDA approved for the monitoring of women with ovarian cancer for response to therapy.
- Normal values are </= 150 p/M.

"Science, for me, gives a partial explanation of life. In so far as it goes, it is based on fact, experience, and experiment."

Rosalind Franklin (British physical chemist, linked with the discovery of the shape of the double helix of DNA who died at age 37)

There is a history of an abnormal CA-125. As far as underwriting, how worried should one be?

- Three common scenarios.
  - CA-125 in screening
  - CA-125 in evaluation of someone with pelvic pathology
  - CA-125 in evaluation of someone after ovarian cancer
    - This test is frequently performed prior to surgery to be able to monitor the woman after definitive treatment for signs of recurrence.

Meta-analysis of 77 studies
- Sensitivity of 78%
  - Sensitivity lower in premenopausal women as compared to postmenopausal women
  - Sensitivity lower in early stage cancer
    - Some studies as low as 25% for stage I (25-75%) and 61% for stage II (61-96%)
  - Not all epithelial ovarian cancers produce CA-125.
    - Mucinous, clear cell, and mullerian ovarian tumors
- Specificity of 78%

Another Meta-analysis involving 6 studies of postmenopausal women
- Sensitivity 50-74%
- Specificity 81-93%

CA-125

Conditions associated with an elevated serum CA 125 concentration

Gynecologic malignancies
Epithelial ovarian, fallopian tube, and primary peritoneal cancers
Endometrial cancer
Benign gynecologic conditions
Benign ovarian neoplasms
Functional ovarian cysts
Endometriosis
Meig syndrome
Adenomyosis
Uterine leiomyomas
Pelvic inflammatory disease
Ovarian hyperstimulation
Pregnancy
Menstruation

Nongynecologic conditions
Cirrhosis and other liver disease
Ascites
Colitis
Diverticulitis
Appendicular abscess
Tuberculosis peritonitis
Pancreatitis
Pleural effusion
Pulmonary embolism
Pneumonia
Cystic fibrosis
Heart failure
Myocardiopathy
Myocardial infarction
Pericardial disease
Renal insufficiency
Urinary tract infection
Recent surgery
Systemic lupus erythematosus
Sarcoidosis
Nongynecologic cancers
Breast
Colon
Liver
Gallbladder
Pancreas
Lung
Hematologic malignancies

Data from:

1. *Buamah P. J Surg Oncol 2000; 75:264.*
2. *Miralles C, et. al. Ann Surg Oncol 2003; 10:150.*
3. *Moss EL, et al. J Clin Pathol 2005; 58:308.*

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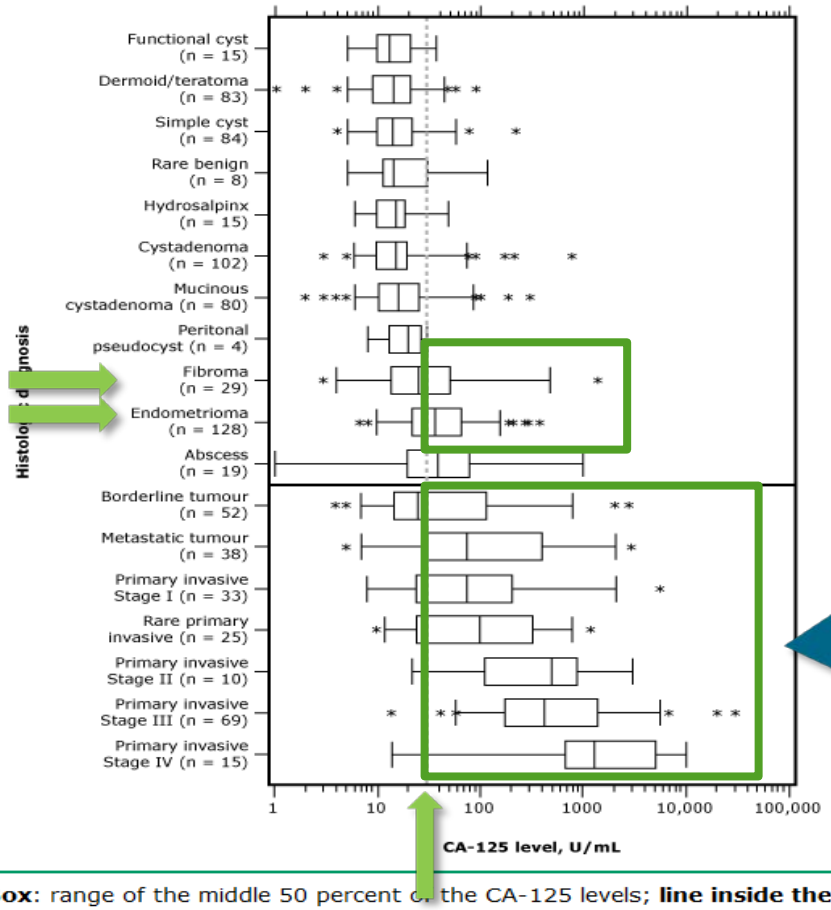
Several important points here:

- There are many causes of elevated CA-125
- Some of the causes are serious diseases
- However, some of the causes have no long term mortality concerns.

CA-125

Underwriting Pearl
Beware of a rising CA-125 in an individual with a history of ovarian cancer

Box plots showing CA-125 serum levels by histologic diagnosis of adnexal masses.



Box: range of the middle 50 percent of the CA-125 levels; **line inside the box**: median; **whiskers**: the 5th and 95th percentile; *: data points that lie outside the whiskers.

Reproduced with permission from: Van Calster, B, Timmerman, D, Bourne, T, et al. Discrimination between benign and malignant adnexal masses by specialist ultrasound examination versus serum CA-125. J Natl Cancer Inst 2007; 99:1706. Copyright ©2007 Oxford University Press.

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Several points here:

- Hard to say exactly what the definition of a high CA-125 should be.
- Some studies have used 30 U/ml. Others 200. Some just discuss markedly elevated values.
- Higher values tend to be down in the higher stage ovarian cancer area.

OVA1

- Is a test with five serum biomarkers
- Approved in 2009 by the FDA to assess likelihood of malignancy in women preparing for surgery for an adnexal mass. Used to help decide:
  - What type of surgery is needed
  - If a gynecological oncologist is needed
- 5 biomarkers are:
  - CA 125
  - Beta 2 microglobulin
  - Transferrin
  - Transthyretin
  - Apolipoprotein A1

OVA1 algorithm using OvaCalc software		
Premenopausal women		
OVA1	<5.0 > or = to 5.0	Low probability of malignancy High probability of malignancy
Postmenopausal women		
OVA1	<4.4 > or = to 4.4	Low probability of malignancy High probability of malignancy
Additional Considerations		
High triglycerides OR High rheumatoid factor titer		Can interfere with assay results

Some observed strategies clinicians deploy for evaluating adnexal masses

- Some suggest surgery for cysts >10 cm. in postmenopausal women[1]
- Some will do CA-125 testing or other tumor marker testing.
- Some classify the mass as low risk, intermediate risk, or high risk based upon US findings. This depends on the age of the patient.
  - High risk—Surgical exploration
  - Intermediate risk—Proceed based upon risk factors, tumor marker results, and symptoms
  - Low risk—Surveillance with serial pelvic ultrasounds

Questions:

What do you expect to find with serial pelvic ultrasounds?
Do they all resolve?
How quickly?

1 Muto, Michael et al. UpToDate.com accessed 1/29/14

A large prospective study[1] to evaluate surveillance

- 39,000 asymptomatic women
- followed by annual US for 25 years
- Average duration of follow up was 7.3 years
- Inclusion criteria:
  - 50 y/o and older
  - 25 y/o and older if with F.H. of ovarian cancer
- 17.3 % found to have an ovarian abnormality on one of the annual US exams
- 42% of the abnormalities resolved within 1 year
- Prevalence of abnormalities highest in premenopausal women (~35% to 17%)
- Low risk abnormalities more common than high risk
- Low-risk abnormalities resolved less frequently in 1 year compared to high risk (33-44% versus 77-81% of the time)
- Bilateral solid masses resolved more quickly than cysts with a solid component
- Surgery was performed on 557 women (85 malignancies/472 nonmalignant)

70% of premenopausal women will have resolution of the cyst within several menstrual cycles[2]

1. Pavlik, EJ et al Frequency and disposition of ovarian abnormalities followed with serial transvaginal ultrasonography Obstetrics and Gynecology. 2013 Aug;122;210-7
2. Curtin JP et al Management of the adnexal mass Obstetrics and Gynecology. 1994;55

BRCA1 and BRCA2 and risk for ovarian cancer

- Of course BRCA1 and BRCA2 refer to the presence of a mutation on one of two susceptible genes breast cancer susceptible gene 1 (17q21) or breast cancer susceptible gene 2 (13q12-13). Even though the BRCA is an abbreviation for breast cancer there are several other cancers associated with this mutation including ovarian cancer
- A meta-analysis of 10 studies showed the risk of ovarian cancer by age 70 years[1]:
  - 40% for BRCA1
  - 18% for BRCA2
- In addition to ovarian cancer both BRCA1 and BRCA2 are associated with an increased risk of fallopian tube cancer and possibly uterine cancer.
- Interestingly there is some suggestion that even short term use of modern oral contraceptives decreases the chance for breast cancer.
- For completeness sake be aware that ovarian cancer and other adnexal type cancers can be associated with other genetic mutations (eg. Cowden, Peutz-Jeghers syndromes)

1) Chen S. et al Meta-analysis of BRCA1 and BRCA2 penetrance. J. Clin. Oncol. 2007;25(11): 1329

BREAKING NEWS!!!!
Feb 2014 Article

- Article in Journal of Clinical Oncology Feb, 2014
- 5,783 women with BRCA1 or BRCA2 mutations observed for dx. of ovarian, fallopian tube or peritoneal cancer as well as death.
- Followed for 5.6 years.
- Preventative oophorectomy showed:
  - 80% reduction in risk of ovarian, fallopian tube or peritoneal cancer
  - 77% reduction in all-cause mortality.
- 186 women developed one of the cancers. 68 died.
  - 108 diagnosed while with intact ovaries
  - 46 diagnosed with occult cancer at time of oophorectomy
    - 27 ovarian
    - 18 fallopian tube
    - 1 peritoneal
  - 32 diagnosed with peritoneal cancer after oophorectomy
    - On average 6.1 elapsed years since oophorectomy at time of dx.

The risk of peritoneal cancer in the 20 years after oophorectomy was estimated to be:
3.9% BRCA1
1.9% BRCA2

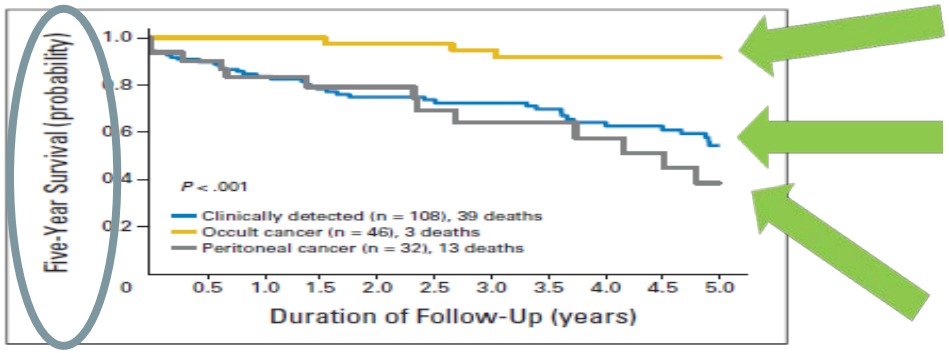


Fig 1. Five-year survival after cancer in *BRCA1* or *BRCA2* mutation carriers by type of cancer.

Occult cancer

Clinically detected

Peritoneal cancer

1) Finch, Amy et al Impact of Oopherectomy on Cancer Incidence and Mortality in Women with a BRCA1 or BRCA2 Mutation.
J. Clin. Oncol. 2014. Downloaded 2/25/14

The final outcome for those that have surgery for an adnexal mass

2001 study of 656 complex pelvic masses (30% postmenopausal)

Histopathology in 656 women with a persistent adnexal mass

Pathology	Number
Endometrioma	152
Serous cystadenoma	101
Mature teratoma	76
Hemorrhagic cyst	44
Mucinous cystadenoma	34
Paraovarian cyst	25
Cystadenofibroma	22
Follicular cyst	13
Ovarian fibroma	12
Hydrosalpinx	12
Tuboovarian abscess	8
Peritoneal cyst	8
Leiomyoma	4
Granulosa cell tumor	2
Fibrothecoma	2
Malignant ovarian neoplasm	122
Ovarian tumor of low malignant potential	19

From Guerriero, S, Alcazar, JL, Ajossa, S, et al. Gynecol Oncol 2001; 83:299.

Back to our cases

Case #1

33 y/o female applying for $450,000 insurance.

- A recent US showing a 4.5 cm left adnexal ovarian cyst.
- Cyst is described as a “simple cyst”

Simple Cyst

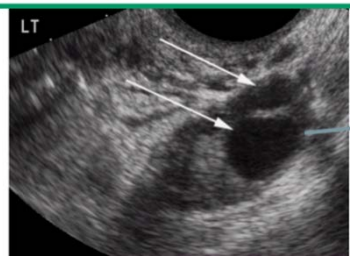
- Round/oval
- Smooth thin walls
- Posterior acoustic enhancement
- No solid component or septation
- No internal flow with color Doppler US

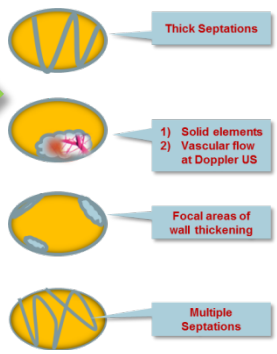
Premenopausal Age	
<3 cm	Normal finding. Typically not mentioned in report
>3 cm and <5 cm	No need for f/u
>5 cm and <7 cm	Yearly f/u recommended
>7 cm	Imaging with MRI or surgical evaluation should be considered

Postmenopausal Age	
<1 cm	Not an unusual finding. No need for f/u
>1 cm and <7 cm	Yearly f/u with US recommended
>7 cm	Imaging with MRI or surgical evaluation should be considered

Underwriting Risk

Follicular ovarian cyst





Individual Risk

Age

Genetic factors
- F.H.
- BRCA gene mutations
- Lynch Syndrome

Reproductive/Hormonal Factors
- Early menarche
- Late menopause
- Nulliparity
- Polycystic ovarian syndrome

Protective factors
- OCP's
- Breastfeeding
- GYN surgery

Cigarette smoking

Obesity

CA-125
(+/- other biomarkers)

Conditions associated with an elevated serum CA 125 concentration

Gynecologic malignancies	Nongynecologic conditions
Epithelial ovarian, fallopian tube, and primary peritoneal cancers	Cirrhosis and other liver disease
Endometrial cancer	Ascites
Benign gynecologic conditions	Colitis
Benign ovarian neoplasms	Diverticulitis
Functional ovarian cysts	Appendicular abscess
Endometriosis	Tuberculosis peritonitis
Meig syndrome	Pancreatitis
Adenomyosis	Pleural effusion
Uterine leiomyomas	Pulmonary embolism
Pelvic inflammatory disease	Pneumonia
Ovarian hyperstimulation	Cystic fibrosis
Pregnancy	Heart failure
Menstruation	Myocardiopathy
	Myocardial infarction
	Pericardial disease
	Renal insufficiency
	Urinary tract infection
	Recent surgery
	Systemic lupus erythematosus
	Sarcoidosis
	Nongynecologic cancers
	Breast
	Colon
	Liver
	Gallbladder
	Pancreas
	Lung
	Hematologic malignancies

Premenopausal Age	
<3 cm	Normal finding. Typically not mentioned in report
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Postmenopausal Age	
<1 cm	Not an unusual finding. No need for f/u
>1 cm and <7 cm	Yearly f/u with US recommended
>7 cm	Imaging with MRI or surgical evaluation should be considered

Results of serial testing
(If available)

Estimated Risk

Back to our cases

Case #2

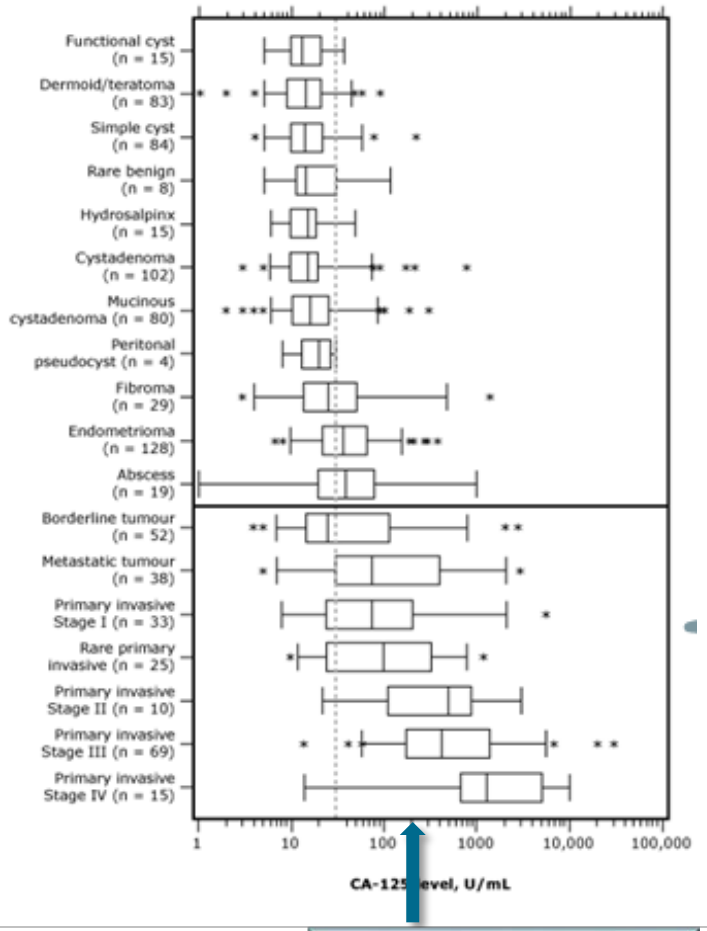
52 y/o postmenopausal female with a recent finding of an adnexal mass.

- US shows a cystic structure with multiple and thick septations. Radiologist's report mentions clinical correlation needed.

High Risk US Findings	
Thick septations	>3 mm
Solid elements with flow at Doppler US	Any
Focal areas of wall thickening	>3 mm
Multiple septations	>1

- CA-125 value of 322 (normal range on lab report 0-35)

- Family hx. of breast cancer in two first degree relatives.



MMDA Presentation
May, 2014

In summary …Pertinent Underwriting Pearls

Abnormal symptoms, physical exams, imaging results and/or biomarker test results are common. We in the underwriting department will see them.

Risk evaluation is similar to the clinical team in that the medical history, PE, imaging results and any biomarker results should be inspected carefully

When dealing with an adnexal mass

The history is important

- Menopausal status
- Symptoms
- Risk factors and the presence of any metastatic disease

US appearance is typically very helpful

Biomarker results can be helpful

The risk of cancer is significantly higher in postmenopausal women as well as those with a genetic predisposition.

Intermediate risk individuals are sometimes followed by serial images
This can be somewhat reassuring at times.

An abnormal finding, such as an adnexal mass without full evaluation, that could have tremendous mortality ramifications deserves close scrutiny

In summary …Pertinent Underwriting Pearls

Ovarian cancer:

- Is common
- Occurs typically in postmenopausal women
- Presents frequently in an advanced stage
- Has a poor prognosis

Screening for ovarian cancer

- Has not been found to be of benefit in the average risk individual
- Is seen however especially in women who have a genetic predisposition for ovarian cancer

Adnexal masses

- Common in women of all ages
- Most are benign
- Small, anechoic, thin-walled, unilocular fluid-filled cysts are typically benign

Genetic markers

- The presence of either the BRCA 1 or BRCA 2 mutations increases the chance of ovarian cancer

Biomarkers (e.g. CA-125)

- Useful in certain situations
- Not as sensitive or specific as desired unfortunately

Thank You

Evaluation of Adnexal Masses

Questions?

"While we have the gift of life, it seems to me the only tragedy is to allow part of us to die – whether it is our spirit, our creativity or our glorious uniqueness"

Gilda Radner (Actress/comedian who died at age 42)

Ovarian tumors of low malignant potential ("borderline tumors")
Slide for questions----Slide seen earlier

- Account for 10-20% of ovarian epithelial tumors
- Average age of dx. is 40-60 y/o but is not uncommon in the 15-69 y/o group
- BRCA gene mutations don't seem to increase the risk for these types of cancers

Tumors have a variety of histologies

Serous borderline tumors

- Majority of borderline tumors
- 75% dx as stage I
- 25-50% are bilateral

Mucinous borderline tumors

- Another common histological type
- 90% dx as stage I
- 10% are bilateral

Other types of borderline tumors

- Endometriod
- Transitional cell
- Clear-cell

Commonly present with an asymptomatic adnexal mass

Mortality data is more favorable

Stage	10 yr survival
I	97%
II	90%
III	88%
IV	69%

Ovarian tumors of low malignant potential ("borderline tumors") Slide for questions

Histological presentation
- Defined histologically by atypical epithelial proliferation without stromal invasion

Presentation
- Presents typically with an adnexal mass on exam or as an incidental finding on imaging
- Symptoms can occur however

US appearance
- No sonographic features that can reliably diagnosis this condition
- Appearance on US can range from unilocular cyst to solid and fluid filled masses as well as having papilla present
- Most common finding however is papillae within a cyst

Biological Markers
- CA 125 is not very helpful in predict ing the presence of this condition
- CA 125 may be high in over half of patients with BOT
- One study[1] showed
  - CA-125 to be high in 24% of pts
  - CEA to be high in 9% of pts
  - CA19-9 to be high in 46% of pts.

Surgical consideration
- Frozen section typically identifies this condition and frequently dictates the surgical procedure
- A 2007 study found under-diagnosis in 30% of cases and over-diagnosis in 6.6%[2]

Staging/Prognosis
- Staging is done the same as with other ovarian tumors
- Invasive implants and residual disease are the two major prognostic indicators (when considering age/peritoneal implants/CA-125 values etc)

Link to Ovarian Cancer
- Progression to invasive cancer is unclear. Some differing beliefs regarding this include:
  - True transformation
  - De novo development of ovarian cancer
  - De novo development of peritoneal cancer

Treatment
- Frequently treated conservatively in women who desire future childbearing
  - Unilateral salpingo-oopherectomy
  - Ovarian cystectomy
- Chemotherapy typically not done for early stage, completely resected disease
- F/u is recommended for 15 years after the initial diagnosis

[1]Engelen, MJ et al. Serum CA 125, CEA, and CA 19-9 as tumor markers in borderline ovarian tumors. *Gynecol Oncol* 2000 Jul; 78(1): 16-20

[2]Tempfer, CB et al. Acurracy of intraoperative frozen section analysis in borderline tumors of the ovary: a retrospective analsysis of 96 cases and review of the literature. *Gynecol Oncol* 2007 Nov; 107(2): 248-52

Long Term Mortality data in ovarian tumors of low malignant potential

200 patients			
Age range 6 to 98 years (median 34 years)			
Stage	**I**	**II**	**III**
%	67.5%	12%	20.5%

Mortality by stage			
Stage	I	II	III
%	0.7%	4.2%	26.8%

All Stage Mortality				
Years	5	10	15	20
% survival	97%	95%	92%	89%

Leake JF et al. Long-term follow-up of serous ovarian tumors of low malignant potential. *Gynecol Oncol* 1992 Nov; 47(2): 150-8

Borderline carcinoma of the ovary: Five-year survival by stage (1993-95)

FIGO Stage	Tumors of low malignant potential	
	Patients, number	Five-year survival, percent
IA	296	95.6
IB	28	95.9
IC	90	96.3
IIA	6	100.0
IIB	7	85.7
IIC	14	59.5
IIIA	14	71.4
IIIB	22	62.0
IIIC	25	45.0
IV	18	-

Modified from J Epidemiol Biostat 2001; 6:116.

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