

Harvard-MIT Division of Health Sciences and Technology
HST.071: Human Reproductive Biology
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Here is another common incidental finding: a benign paratubal cyst. Sometimes such simple cysts are found adjacent to ovary and are called parovarian cysts. They are filled with clear serous fluid and lined by flattened cuboidal epithelium.

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This is an adult ovary with two corpora lutea. The larger one at the top is a hemorrhagic corpus luteum of menstruation, and the smaller one at the bottom is involuting from a previous menstrual period. If implantation of a fertilized ovum occurs, then the corpus luteum will persist because of HCG from the placenta. Of 400,000 ovarian follicles present at birth, only about 400 will mature to the point of ovulation during childbearing years.

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A normal adult ovary has been sectioned here to reveal a hemorrhagic corpus luteum. Note the dark red-black hemorrhagic region surrounded by a thin rim of yellow corpus luteum.

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Here is the microscopic appearance of a hemorrhagic corpus luteum lined by luteinized granulosa cells next to the hemorrhagic area at the right.

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Here is a benign cyst in an ovary. This is probably a follicular cyst. Occasionally such cysts may reach several centimeters in size and, if they rupture, can cause abdominal pain.

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This is a benign theca lutein cyst in an ovary. Note the luteinized cells forming the inner cyst lining at the left, with adjacent surrounding theca cells. These cysts are rarely more than a few centimeters in diameter.

Ovarian cancer

- Fifth most common cancer in women
- Fifth most frequent cause of cancer death
- In the year 2000
 - 23,100 new ovarian cancer cases
 - 14,000 patients died of it
- In the year 1993
 - About 23,000 cases were diagnosed
 - 14,000 women died
- Approximately 1 in 70 newborn girls will develop ovarian cancer during her lifetime
- Disease of
 - Postmenopausal woman
 - Prepubescent girl
 - Documented to occur in females of all ages.

Risk of Ovarian Cancer

- Advancing age is the most significant risk factor
- The risk increases from 15.7 to 54 per 100,000 as one ages from 40 to 79 years
- Mean age at diagnosis is 59.4
- In the United States approximately one woman in 70 develops ovarian cancer
- Other than age, the strongest risk factor for the development of ovarian cancer is a familial history of the disease.
- 5% to 10% of all epithelial ovarian cancers result from a hereditary predisposition in which germ line inheritance of a mutant gene confers autosomal dominant susceptibility with high penetrance
- Average age of onset for ovarian cancers thought to be familial in origin is up to 10 years lower than that of general population

Groups at High Risk for OC

- Women with a strong family history of breast and/or ovarian cancer (two or more first degree relatives and/or a relative with cancer before menopause)
 - May carry a mutation of the *BRCA1* and *BRCA2* genes
 - Have a risk of ovarian malignancy of up to 50%.
- Women with a strong family history of colon cancer (at least three affected family members in at least two successive generations, with one case below age 50 years)
 - At increased risk for endometrial and ovarian malignancy because they carry a mismatch repair gene mutation.
 - Have a risk of up to 10% for ovarian cancer
 - 50% for endometrial cancer

ETIOLOGY OF OVARIAN CANCER

- Unknown
- Predisposing risk factors
 - Repeated ovulation is causally related
 - Ovulation is accompanied by disruption of the germinal epithelium
 - Activation of cellular repair mechanisms
 - May provide ample opportunity
 - Somatic gene deletions
 - Mutations to occur
 - Contribute to tumor initiation and progression
 - Protective
 - Chronic anovulation
 - Multiparity
 - History of breastfeeding
 - Pregnancy - risk reduction of 13-19% per pregnancy
 - Oral contraceptives - 50% for users of 5 years and longer
 - Increased
 - Infertility treatment
 - Polycystic ovarian syndrome (PCOS) - 2.5-fold increased risk
 - Unopposed estrogen therapy
 - No change in risk
 - Hormone replacement therapy

ETIOLOGY OF OVARIAN CANCER

- **Dietary factors**
 - High in saturated animal fats seem to confer an increased risk - unknown mechanisms
 - Japanese women who move to the United States - increased ovarian cancer risk
 - Alcohol and milk product consumption ??
- **Exposure to talc**
 - Talc granulomas in the ovaries
 - Never been previously operated on
 - Continuity of the introitus and peritoneal cavity
 - Talc and asbestos - carcinogenic substances

ETIOLOGY OF OVARIAN CANCER

- **>90% of ovarian cancer develops sporadically**
- **10% of epithelial ovarian cancers based on genetic predisposition**
- **Chromosomal abnormalities: Turner's syndrome (45,XO)**
 - Increased risk of dysgerminoma and gonadoblastoma
- **Two first-degree relatives with ovarian cancer have a 50% likelihood of developing ovarian cancer until age 70.**
- **Hereditary ovarian cancer**
 - Breast and ovarian cancer syndrome (BOC)
 - Less common Lynch II syndrome (hereditary nonpolyposis colorectal cancer syndrome (HNPCC syndrome))
- **Breast and Ovarian Cancer Gene (BRCA)**
 - Germ line mutations in the *BRCA1*
 - Located on chromosome 17
 - Less commonly with *BRCA2*
 - Chromosome 13
- **Frequency of *BRCA1* mutation carriers in the United States**
 - Approximately 1 in 800 women
 - Greater mutation frequencies
 - Ashkenazi Jews
 - Icelandic women
 - Autosomal dominant fashion
 - Lifetime risk of ovarian cancer as high as 28-44%.

ETIOLOGY OF OVARIAN CANCER

- **HNPCC syndrome**
 - Combination of familial colon cancer
 - High rate
 - Ovarian
 - Endometrial
 - Breast cancer
 - Other gastrointestinal malignancies
- **Genes involved**
 - Mainly DNA mismatch repair genes
 - *hMSH2*
 - *hMLH1*.
- **Molecular mechanisms related to ovarian cancer**
 - Allelic loss and mutations of the p53 tumor suppressor gene
 - Found in about 55% of all ovarian cancers
 - HER2/*neu* proto-oncogene is activated
 - 30% of ovarian cancers
 - Providing the potential for increased proliferation and metastasis
- **Other molecular pathways**
 - *bcl-2*
 - *k-ras*
 - Ki67
 - interleukin-6.
- **Therapeutic approaches (???)**
 - Replacing missing p53 tumor suppressor gene function
 - Blocking the activation of HER2/*neu*.

Major Histopathologic Categories of Ovarian Cancer

Epithelial

- Serous, mucinous, endometrioid, clear cell, transitional cell (Brenner), undifferentiated

Germ Cell

- Dysgerminoma, endodermal sinus tumor, teratoma (immature, mature, specialized), embryonal carcinoma, choriocarcinoma, gonadoblastoma, mixed germ cell, polyembryona

Sex Cord and Stromal

- Granulosa cell tumor, fibroma, thecoma Sertoli-Leydig cell, gynandroblastoma

Neoplasms Metastatic to the Ovary

- Breast, colon, stomach, endometrium, lymphoma

Epithelial Neoplasms

- Derived from the ovarian surface mesothelial cells
 - **Serous**
 - **Mucinous**
 - **Endometrioid**
 - **Clear cell**
 - **Transitional cell**
 - **Undifferentiated**
- Account for over 60% of all ovarian neoplasms
- > than 90% of malignant ovarian tumors

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Benign epithelial tumors of the ovary can reach massive proportions.
The serous cystadenoma seen here fills a surgical pan and dwarfs the 4 cm ruler.

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Here is a benign serous cystadenoma that demonstrates multiloculation. Note that the inner surface is, for the most part, smooth, with only a solitary papillation at the upper right.

Serous Neoplasms

- **Serous Cystadenocarcinoma**
 - Most common - 35-50% of all epithelial tumors
 - Bilateral in 40-60%
 - 85% are associated with extraovarian spread at the time of diagnosis
 - >50% of serous tumors exceed 15 cm in diameter
- Cut section
 - Solid areas
 - Areas of hemorrhage
 - Necrosis
 - Cyst wall invasion
 - Adhesions to adjacent structures
 - Cysts often contain coarse papillae - project into the cystic lumen

Serous Neoplasms

- Exhibit mild to moderate **nuclear atypia**
- **Occasional mitotic figures** of the stratified squamous epithelium
- Often forms **budding tufts**
- **Psammoma bodies** (irregular calcifications)
- Grade of differentiation based on the degree of **preservation of the papillary architecture**
- Most serous carcinomas - poorly differentiated with trabecular and solid growth patterns
- Serous neoplasms of low malignant potential
 - Histologic features suggestive of both carcinoma and benignity
 - Marked cellular pleomorphism
 - Mitotic figures are often present
 - No stromal invasion
 - Psammoma bodies are often present
 - Prognosis and therapy of serous carcinoma of low malignant potential are different from invasive serous carcinoma
 - Accurate diagnosis is essential

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Microscopically, a borderline serous cystadenoma is seen here with papillary projections of epithelium extending into the lumen of the tumor. There is no invasion of the stroma or capsule.

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Here is a serous cystadenocarcinoma in which there is more pronounced papillary growth with more hyperchromatic cells.

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Ovarian papillary serous cystadenocarcinomas may contain small concretions called **psammomma bodies**, seen here as purplish rounded and laminated objects. They are essentially just a form of dystrophic calcification in neoplasms.

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This is a papillary serous cystadenocarcinoma. Note the many papillations on the inner surface. Between benign cystadenomas and malignant cystadenocarcinomas lies the grey zone of "borderline" lesions that are not clearly malignant, but are treated as though they could be.

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This ovarian papillary cystadenocarcinoma is mostly composed of solid tissue and has invaded outside of the ovary, with papillations seen over the surface. Because there are no early signs or symptoms with masses in the ovary, many of these ovarian tumors have metastasized by the time they are detected with abdominal enlargement. These neoplasms characteristically spread by "seeding" along peritoneal surfaces.

Mucinous Neoplasms

- 10-20% of all epithelial ovarian tumors
- Second most common type of epithelial ovarian cancer
- Mucinous tumors are bilateral in less than 10% of cases.
- Notable for the large size
- Neoplasms over 150 pounds have been reported
- Average size of these lesions is 16-17 cm.
- Cut sections
 - Multilocular cysts
 - Filled with viscous mucin
 - The lining of these tumors is composed of atypical cells
 - Numerous mitotic figures
- Histologically
 - Intestinal-like cells
 - Invade the surrounding stroma
 - Large hyperchromatic nuclei
 - Prominent nucleoli
 - Marked histologic variability from area to area
 - Extensive sampling required.
- **Mucinous tumors of low malignant potential**
 - Several cell types
 - Endocervical-like columnar cells
 - Intestinal-like columnar cell
 - Goblet cells
 - Cellular atypia may be mild to moderate
 - Cellular stratification does not exceed 2-3 layer
 - Stromal invasion is absent.

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This is a tumor of ovarian surface epithelium. These are the most common ovarian neoplasms. Such neoplasms may be lined by epithelium that is serous or mucinous. Pictured here is a serous cystadenoma. It was filled with pale yellow serous fluid in only a single cavity. Mucinous tumors are filled with sticky mucin and tend to be multiloculated. Benign epithelial ovarian tumors are bilateral in about 20% of cases.

Pseudomyxoma Peritonei

- Described by Karl F. Rokitansky in 1842, is an enigmatic, often fatal intra-abdominal disease characterized by dissecting gelatinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin.

Pseudomyxoma Peritonei

- Unusual condition
- May occur in association with mucinous neoplasms of the ovary
- Resulting from the progressive accumulation of mucin in the abdominal cavity
 - Following its slow leakage from a neoplasm
- Most commonly occurs in association with lesions of low malignant potential
 - Also reported to occur in association with cystadenocarcinoma of the ovary and appendix
- Histologically benign in appearance
- Protracted and potentially morbid course
 - Repeated bowel obstruction
 - Mortality rate that approaches 50%.

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Pseudomyxoma peritonei

Pseudomyxoma Peritonei

- Pseudomyxoma peritonei is a disease of MUC2-expressing goblet cells. These cells also express MUC5AC but the latter mucin is not specific for pseudomyxoma peritonei. MUC2 expression accounts for the voluminous deposits of extracellular mucin (mucin:cell ratios exceeding 10:1) and distinguishes pseudomyxoma peritonei secondarily involving the ovary from primary ovarian mucinous tumors with peritoneal implants. Because mucinous tumors of the appendix similarly express MUC2, the MUC2 expression profile also supports an appendiceal rather than ovarian origin for pseudomyxoma peritonei.
- Extracellular mucin accumulates dramatically in pseudomyxoma peritonei because the number of MUC2-secreting cells dramatically increase and because this MUC2 has no place to drain. These studies suggest that pseudomyxoma peritonei should be regarded as a disease of MUC2-expressing goblet cells whose MUC2 expression might be susceptible to pharmacological targeting

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Appendiceal pseudomyoma peritoneii

Endometrioid Neoplasm

- Exhibits an adenomatoid pattern
- Resembles endometrial adenocarcinoma
- Bilateral in 30-50% of cases
- Rarely arises in foci of endometriosis (less than 10% of cases)
- Degree of differentiation is based on extent of retained glandular architecture
- 30% of patients also have a synchronous endometrial carcinoma
 - Second primary rather than a metastatic focus of disease.

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Endometriod carcinoma

Primordial Germ Cell Migration

Interfering with SDF-1 signaling results in severe migration defects. For example, when the activity of SDF-1 or its receptor, CXCR4, is reduced, the PGCs maintain their motile behavior but are unable to detect directional cues and they end up dispersed throughout the embryo. The ability of SDF-1 to direct PGC migration was demonstrated by its ability to attract PGCs towards positions where they are normally not found. In experiments where the endogenous SDF-1 activity was inhibited, introduction of SDF-1 at random sites within the embryo redirected PGC migration towards these abnormal positions.

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Germ Cell Tumors

- **Mature teratomas** or dermoids are common ovarian neoplasms, occurring primarily in women aged 20-30 years. They represent the most common neoplasm diagnosed during pregnancy. Rarely, the squamous component undergoes malignant transformation (less than 2%) in women over the age of 40.
- **Embryonal carcinoma** of the ovary is a very rare germ cell tumor in pure form, although foci may occasionally be found admixed with other germ cell neoplasms. Histologically, this neoplasm consists of solid sheets of large polygonal cells with pale, eosinophilic cytoplasm that appear to merge together as a syncytium because the cell membranes are poorly defined. Serum human chorionic gonadotropin (hCG) and AFP values are usually elevated.
- **Choriocarcinoma** of the ovary is another rare germ cell tumor that is unrelated to pregnancy. Unlike gestational choriocarcinoma, primary ovarian choriocarcinoma is associated with somewhat lower elevations of hCG. The endocrine activity of this neoplasm may cause precocious puberty, uterine bleeding, or amenorrhea. Microscopically, this neoplasm is composed of cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts.
- **Gonadoblastoma** of the ovary is a rare neoplasm composed of nests of germ cells and sex cord derivatives that are surrounded by connective tissue stroma ([Fig 49-7](#)). These tumors are more common in the right ovary than in the left and usually occur during the second decade of life. Gonadoblastomas are found in patients with abnormal gonadal development in the presence of a Y chromosome.
- **Mixed germ cell tumors** of the ovary account for approximately 10% of germ cell neoplasms. As implied by the name, these neoplasms contain two or more germ cell elements. A dysgerminoma and endodermal sinus tumor occur together most frequently. These neoplasms must be meticulously evaluated by the pathologist to identify all elements correctly, since different components may require treatment with different chemotherapeutic regimens.

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Here are bilateral mature cystic teratomas of the ovaries. These are a form of ovarian germ cell tumor. Histologically, a variety of mature tissue elements may be found. These tumors are often called "dermoid cysts" because they are mostly cystic.

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There is a large unilateral mature cystic teratoma seen here at the right (in left ovary--the uterus is opened anteriorly). The uterus has an intramural and a subserosal leiomyoma. The other ovary is replaced by a fibroma.

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Dermoid

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X-ray of dermoid

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X-ray of tooth

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Microscopically, this teratoma has cartilage, adipose tissue, and intestinal glands at the right, while at the left is a lot of thyroid tissue. This condition can be termed struma ovarii. Rarely, a struma ovarii can even be a cause for hyperthyroidism.

Teratoma With Teeth

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Teratoma with teeth

Teratoma

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Benign Teratoma

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Germ Cell Neoplasms

- Arise from the germ cell elements of the ovary

Include

- Dysgerminoma
 - Endodermal sinus tumor
 - Embryonal cell carcinoma
 - Choriocarcinoma
 - Teratoma
 - Polyembryona
 - Mixed germ cell tumors
- Tends to occur during the second and third decades
 - Associated with a better prognosis
 - Many produce biologic markers - can be monitored

Immature Teratomas

- Malignant counterpart of the mature cystic teratoma
- 20% of germ cell neoplasms
- Bilateral in less than 5% of cases
- Contralateral ovary commonly contains a **dermoid** cyst
- Serum AFP is usually elevated in patients with an immature teratoma.

- Microscopic examination
 - Disordered collection of tissues
 - Derived from the three germ layers
 - Some of the components having an immature, embryonic appearance
- Immature elements - commonly neuroectodermal
 - Small round malignant cells
 - May be associated with glia formation
 - Stain positive for AFP.
 - Graded from 1 to 3 based on the amount of immature neural tissue

Dysgerminoma

- Female counterpart of the seminoma
- Occurs primarily in young females
- Accounts for about 30-40% of germ cell tumors
- Grossly
 - Rubbery in consistency
 - Smooth
 - Rounded
 - Thinly encapsulated
 - Brown or grayish-brown color
- Unilateral in 85-90% of cases. It is a solid neoplasm, which may contain areas of softening due to degeneration.
- Mimics the pattern seen in the primitive gonad
 - Nests of germ cells
 - Appear as large, rounded cells with central nuclei
 - One or two prominent nucleoli
 - Surrounded by undifferentiated stroma
 - Lymphocytic infiltrate is considered a favorable prognostic indicator

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This is an ovarian dysgerminoma that has been sectioned into two halves. Note the pale brown appearance of the parenchyma, along with some central collagenous scar. The gross and microscopic appearance of an ovarian dysgerminoma is essentially the same as a seminoma of the testis in a male.

SEX CORD-STROMAL TUMORS OF THE OVARY

- **Granulosa cell tumors**
 - Represent 1-2% of all ovarian neoplasms
 - Most common malignant tumors of the sex cord-stromal tumor category
 - Associated with hyperestrogenism
 - May cause precocious puberty
 - Adenomatous hyperplasia and vaginal bleeding in postmenopausal women
- **Thecoma**
 - Often associated with hyperestrogenism
 - Benign ovarian tumor
 - Consists of lipid-laden stromal cells
 - Yellow color on cut section
- **Ovarian fibroma**
 - Benign tumor
 - Association with Meigs' syndrome
 - Ovarian fibroma, ascites, and pleural effusion,
 - Collectively mimic the presentation of ovarian cancer
- **Sertoli-stromal cell tumors**
 - Rare
 - Consist of testicular structures
 - Usually virilizing
 - Occur most commonly during the third decade of life.
 - Rarely bilateral

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Here is an ovarian stromal tumor that is hard and white and is a fibroma.

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Here are bilateral benign ovarian tumors. These proved to be fibrothecomas. The thecoma component of the neoplasm gives the tumor a yellowish cast because of the lipid content and can also produce estrogen. These are tumors that arise from the ovarian stroma. They are bilateral in only about 10% of cases. A right-sided hydrothorax in association with this tumor is known as Meig's syndrome.

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This is a granulosa cell tumor of ovary with a variegated cut surface. These tumors are derived from the ovarian stroma and often have a component of thecoma. They are often hormonally active and can produce large amounts of estrogen such that the patient may initially present with bleeding from endometrial hyperplasia.

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Microscopically, the granulosa cell tumor attempts to form structures that resemble primitive follicles, as seen at the left. Most of these tumors are histologically benign, but some are malignant.

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At higher magnification, an ovarian granulosa cell tumor has nests of cells which are forming primitive follicles.

NEOPLASMS METASTATIC TO THE OVARY

- As many as 25% of all ovarian malignancies
- Often mimic primary ovarian cancer
- Usually present as bilateral adnexal masses
- Unilateral mass occurs in as many as 25% of patients
- Usually smooth and bosselated, solid, and mobile
- Most common primary cancers that metastasize
 - Breast
 - Stomach
 - Colon
 - Endometrium
- Ovarian metastases with breast cancer found in up to 40% of cases

- Microscopically presents a variety of potentially confusing patterns
- Gastrointestinal carcinoma simulates a primary mucin-secreting adenocarcinoma of the ovary
- Presence of characteristic signet ring cells
- Krukenberg tumors by definition represent carcinomas of the stomach metastatic to the ovary. However, the eponym is commonly used to denote any gastrointestinal carcinoma metastatic to the ovary.

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Metastatic tumors to ovary are uncommon, but there is one situation in which a metastatic adenocarcinoma to ovary appears as a large mass and resembles a primary tumor: a so-called "Krukenberg" tumor of ovary which has a signet ring histologic pattern and usually is metastatic from a primary in gastrointestinal tract. Seen here extending out of the pelvis at autopsy is a **large right ovarian mass**. Metastases are also present in the **lower right portion of liver**.

Ovarian Cancer

- **Insidious disease**
- **Few warning signs or symptoms**
- **Few symptoms until the disease is widely disseminated**
 - History of nonspecific gastrointestinal complaints common
 - Early satiety
 - Abdominal distention
 - Ascites
 - Change in bowel habits
 - Constipation
 - Decreased stool caliber
 - Large tumors may cause a sensation of pelvic weight or pressure
 - Menstrual abnormalities - in as many as 15% of reproductive age patients
 - Rarely, excess androgens or estrogens may be present
- Prognosis of ovarian cancer is significantly improved when the disease is detected while still confined to the ovary
- **Detection**
 - Routine pelvic examination has limited sensitivity and specificity
 - Significant percentage of tumors are missed
 - Ultrasonographic evaluation can detect the majority of ovarian neoplasm
 - Poor specificity
 - CA-125.
 - Antigen from fetal amniotic and coelomic epithelium
 - Level can be detected in serum using immunoassay.
 - CA-125 might have a role in screening of high-risk patients
 - Other currently studied markers include TAG 72, M-CSF and OVX1.

US – Pelvic Mass

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U/S Scan showing a pelvic mass.

US – Multiloculated Mass

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US showing multiloculated pelvic mass.

C-T Scan – Omental Cake

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C-T Omental cake.

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Increased blood flow to pelvic mass – solid areas shown by arrows.

C-T Scan – Liver Metastases

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CT showing liver metastases.

C-T Scan – Metastatic Ovarian Cancer

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CT showing metastatic ovarian cancer.

C-T Showing Residual Cancer

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CT showing residual cancer after three cycles of chemotherapy.

MR – Large Cystic Mass

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MR T1 axial image showing large cystic pelvic mass.

MR – Pelvic Mass

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MRI T2 sagittal image showing the same pelvic mass.

Ovarian Cancer

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Large ovarian cancer

Plain Radiograph

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Plain film with pelvic mass.