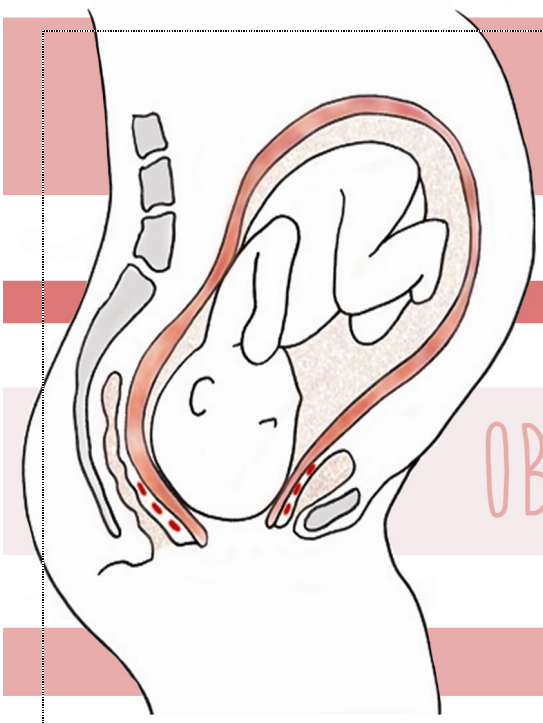

OBSTETRICS AND GYNECOLOGY

(23) Ovarian Cancer

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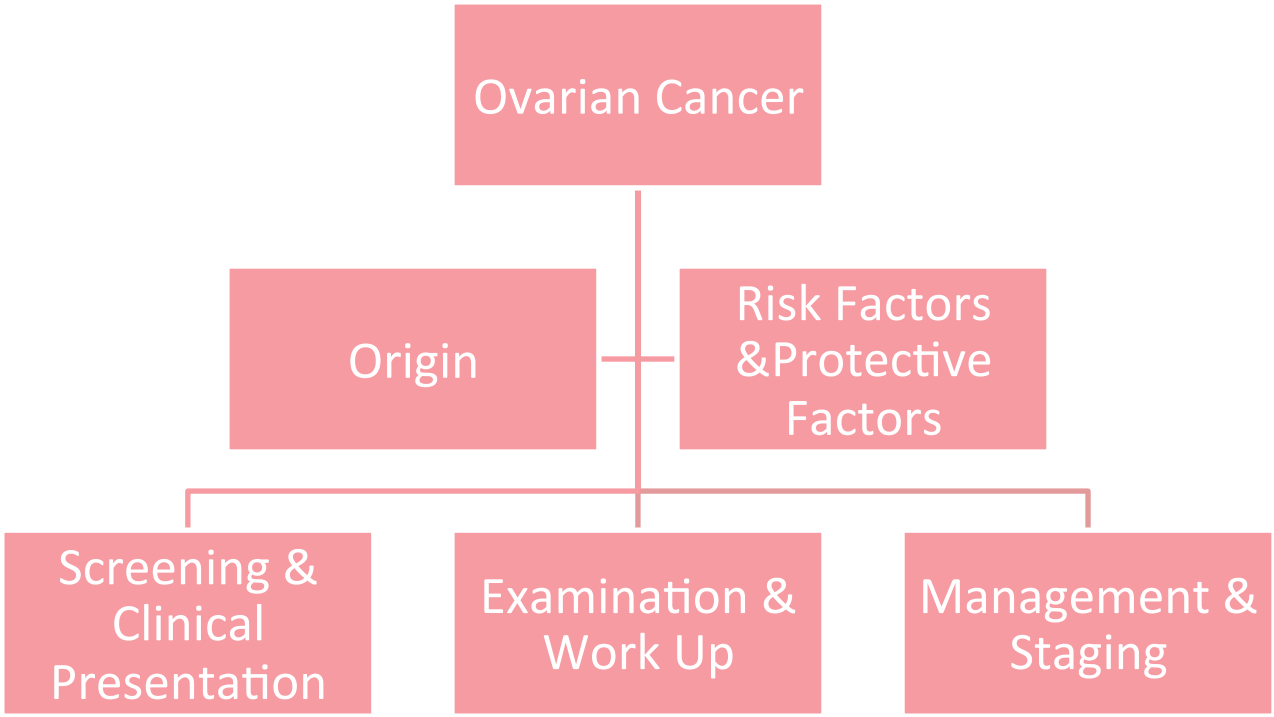
Doctor's note Team's note Not important Important 431 teamwork

Objectives:

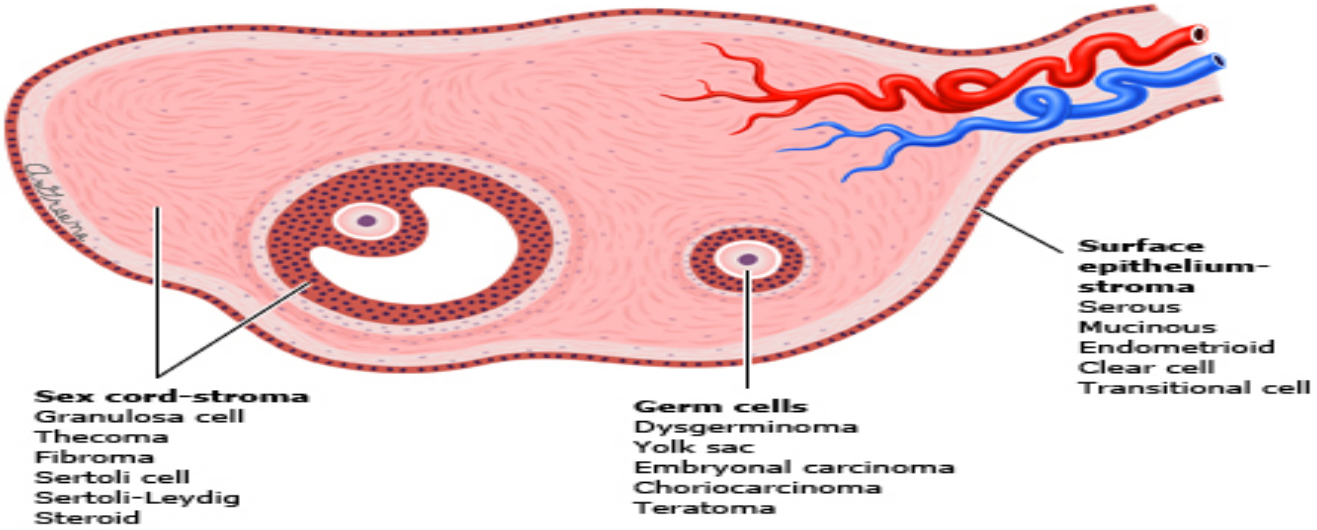
Not given



Introduction:

- Second most common gynecologic malignancy after endometrial cancer.
- In developed countries, the incidence of 9.4 per 100,000 women and a mortality rate of 5.1 per 100,000.
- In developing countries, it is the third most common gynecologic malignancy (cervical cancer is the most common), with an incidence of 5.0 per 100,000 and a mortality rate of 3.1 per 100,000.

Origin Of Ovarian Cancer:



Random Notes:

The granulosa -theca cell neoplasms are commoner compared to Sertoli-leydig cell tumors and they release estrogen while Sertoli-leydig cell tumors release testosterone. Rarely lipid cell tumors release adrenal corticoids and clinical cushingoid syndrome.

Teratomas are very common and they are composed of ectodermal tissue mainly, some mesodermal and rarely endodermal tissue.

Epithelial tumors are derived from the mesothelial cells lining the peritoneal cavity and also lining the surface of the ovary. The commonest type is serous which resembles fallopian tube epithelium and the second most common is mucinous which resembles endocervial tissue

A) Coelomic epithelial origin (80 – 85%)

- Serrous 70%
- Mucinos 25%
- Endometrioid 20%
- Clear cell 5%
- Brenner tumor 2 – 3% (Mainly benign)
- Undifferentiated.
- Carcinosarcoma

B) Germ cell origin (10 – 15 %)

- Teratoma
    - Mature teratoma.
    - Dermoid cyst.
    - Stroma ovarii.
    - Malignant neoplasm arising from teratomas.
    - Immature teratoma.
- Dysgerminoma: children and young adult are affected and 10% are bilateral.
- Endodermal sinus tumor.
- Embryonal carcinoma.
- Choriocarcinoma.
- Gonadoblastoma.

C) Specialized gonadal stromal origin (3 – 5 %)

- Granulosa – Theca cell tumors.
    - Granulosa cell tumor.
    - Thecoma (rarely malignant)

- Sertoli – leydig tumor only 3 – 5% are malignant and classically associated with masculinization due to release of testosterone.
    - Arrhenoblastoma.
    - Sertoli cell tumor
- If Ovarian cancer occurred at a young age it would be germ cell tumor or stromal in origin.

Pathognomonic pathological features:

- Serous tumor:
  - Psammoma bodies
- Mucinous (Large 10 – 20 % bilateral) can be gastric or ovarian in origin:
  - Gastric origin is always associated with segnet ring.
- Endometrioid:
  - Arise in association with endometrial cancer in 20% of cases.
- Clear cell:
  - 25% occur in association in patients with endometriosis.
- Granulosa cell tumor:
  - Call – exner bodies (Oval in shape with colonies of nuclei)

Protective Factors and Risk Factors:

Risk Factors:

- The cause of ovarian cancer is unknown.
- Western countries.
- Patients with multiple associations. (Like the use of asbestos contaminated talic powder and ovulation induction methods due to recurrent trauma to the ovaries).

1. White race
2. Late age at menopause
3. Nulliparity
4. Infertility
5. Advanced age
6. Genetics and positive family history

5) Age

- The incidence of ovarian cancer increases with age.
- In women 50 to 75 years of age, the annual incidence is 50 per 100,000, which is approximately twice the rate found in younger women.
- The likelihood that a case of ovarian cancer is attributable to a gene mutation decreases with increasing age at diagnosis

6) Genetics and positive family history

- 5 -10 % in women with hereditary predisposition.
- Occur in younger age especially if the patient has first-degree relatives with ovarian / Breast cancer. Usually breast cancer arises first before ovarian cancer.
- If the patient presented at a young age with germ cell or stromal tumor this is less likely related to genetic mutations. Usually they present with epithelial type at a young age.
- If the patient presented with breast cancer and she's young screen for ovarian cancer by U.S. and CA125 or CEA tumor marker level in the serum.
- Life time probability:
  - General population … 1.4
  - BRCA**1**…. 35 – 46 (located on chromosome 17)
  - BRCA **2**… 13 – 23 (located on chromosome 13)
  - Lynch syndrome…3 – 14 (Lynch syndrome type two which is associated with mutation in the mismatch repair gene)

- A meta-analysis of pooled case-control studies calculated an odds ratio of 3.1 for developing ovarian cancer in women with one first- or second-degree relative. Based upon these data, it was estimated that a family history of ovarian cancer in one relative increased the lifetime probability of ovarian cancer in a 35-year-old woman from 1.6 to 5.0 percent.
- In contrast, women with hereditary ovarian cancer syndromes have a lifetime probability of ovarian cancer of 25 to 50 percent.

Protective Factors:

1.Pregnancy (no ovulation) 2. The use of OCPs (The use of OCPs for 5 consecutive years decreases the risk of ovarian cancer by 50% cause of decreased ovulation)

3.Breastfeeding (no ovulation) 4.Tubal ligation or hysterectomy

Screening and Clinical Presentation:

Screening:

- The potential benefit of screening is its ability to identify ovarian cancer at a more localized and curable stage, leading to reduced mortality from the disease.
- Although ovarian cancer is an important cause of cancer death, its incidence and prevalence in the general population are relatively low. So no screening for ovarian cancer is done in general population.
- The problem of false-positive screening tests becomes critically important in diseases with low prevalence. Unless the test or sequence of tests is extremely accurate.

Clinical Presentation:

- It's a silent disease and patients usually present late (Average age is 61- 62).
- Non-specific symptoms.
- 80% of patient present in metastatic stage of disease (stage III and more)
- May be present with:
  - Weight loss, fatigue, generalized illness.
  - Abdominal pain or fullness.
  - Nausea vomiting.
  - Urinary frequency.
  - Constipation.
  - Abnormal uterine bleeding.

Examination and Work up:

Examination:

- General examination:
    - Pallor (due to anemia), jaundice (due to obstruction of biliary tract).
    - Chest dullness because of pleural effusion.
    - Abdominal distention due to ascites.
    - Lower limb edema due to obstruction of lymphatic drainage.
- Internal exam:
    - Solid irregular pelvic or adnexal mass.
    - Nodularity of recto-vaginal septum. (The most common site of metastasis for ovarian cancer is pouch of douglas).

Work Up:

a. Lab work:

1. CBC
2. Liver function
3. Renal function
4. Coagulation profiles.
5. Tumor markers (Sensitive but not Specific):
    - CA125: Epithelial tumor
    - AFP: Endodermal sinus tumor
    - LDH: Dysgerminoma
    - Inhibin: Granulosa cell tumor
    - HCG: Choriocarcinoma.
    - Testosterone: Sertolilyding tumor
    - Both HCG & AFP: Embryonal carcinoma

- CA 125:

- Measurement of the serum concentration of the CA 125 glycoprotein antigen is the most widely studied biochemical method of screening for ovarian cancer. Serum CA 125 values are elevated in approximately 50 percent of women with early stage disease and in over 80 percent of women with advanced ovarian cancer.

- However, the specificity of CA 125 is limited. CA 125 levels are elevated in approximately 1 percent of healthy women and fluctuate during the menstrual cycle. CA 125 is also increased in a variety of benign and malignant conditions, including:

  Any thing that causes epithelial irritation

  - Endometriosis
  - Uterine leiomyoma
  - Cirrhosis with or without ascites
  - Pelvic inflammatory disease
  - Cancers of the endometrium, breast, lung, and pancreas
  - Pleural or peritoneal fluid due to any cause

b. Imaging:

➢ Ultrasound (gold standard for any ovarian mass)

- Trans-vaginal ultrasonography (TVUS) allows better visualization of the ovaries (independent of body habitus) and shorter examination times.

- The upper limit of ovarian volume is considered to be 20 cc in premenopausal women and 10 cc in postmenopausal women. In addition to size, morphologic characteristics (presence of septae , cyst wall irregularity, solid components, papillary projections, turbid fluid, thick wall and hyper-vascularity) are considered in the interpretation of an ultrasound study and if they are present the mass is more likely malignant than benign according to the risk malignancy index.

Staging:

Mode Of Spread:

- Trans-coelomic: exfoliating cells that disseminate and implant throughout the peritoneal cavity.
  - Commonly seen: cul – de – sac, para-colic gutter, liver surface and omentum.
- Lymphatic spread: pelvic and paraortic lymphnodes.
- Hematogenous (not common): Liver and lungs.

Management:

a) Staging: No macroscopic disease suggestive of metastasis.
b) Cytoreduction (debulking): removal of all gross disease to reach a residual disease less than 1cm.
   - Primary
   - Interval

Example: If the patient underwent U.S. for gallstones and they found an ovarian mass as an incidental finding you would go for staging. However, if the patient presented with severe disease, abdominal mass and ascites you would go for cyto-reduction and the use of neo-adjuvant chemotherapy maybe indicated.

c) Chemotherapy: Can be given either as adjuvant therapy (post surgery) or neo-adjuvant (before surgery to reduce the size). Also it can be given as multiple agents or single agent if the patient can't tolerate multiple agents. Chemotherapy can be administered intra-peritoneal with minimal residual disease.

- Adjuvant and Neo-adjuvant
- Multiple agents
  - Platinum base
  - Paclitaxel.
- Single agent
- Intra-peritoneal

Special regimen: Germ cell tumor

B leomycin
E toposide
P latinum or Cisplatin

5 yrs. survival 90 – 95% and good prognosis

Staging:

- Surgically staged disease.
    - Pelvic wash for cytology.
    - Total abdominal hystrectomy
    - Bilateral salpengo-oophrectomy
    - Omentectomy
    - Pelvic and para aortic lymphadenectomy
    - Multiple peritoneal biopsies.

- If the patient was in reproductive age and you want to preserve her fertility you would go for fertility preserving concept in surgical staging which includes:
    - Pelvic wash for cytology.
    - Unilateral salpengo-oophrectomy
    - Biospy of the other ovary or fallopian tube
    - Omentectomy
    - Pelvic and para aortic lymphadenectomy
    - Multiple peritoneal biopsies.

FIGO Staging:

- Stage I
    - Tumor confined to the ovaries or fallopian tubes, negative peritoneal fluid and intact surface and capsule.
        - IA tumor limited to one ovary or one fallopian tube
        - IB both ovaries and both tubes.
        - IC one or both ovaries or tubes with
            - Surgical spill
            - Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
            - Malignant cells in the ascites or peritoneal washings
            - Usually chemotherapy is given from stage IC and beyond

- Stage II
  - Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer
    - IIA: Extension and/or implants on uterus and/or tube(s) and/or ovaries.
    - IIB: Extension to other pelvic intra-peritoneal tissues.

- Stage III
  - Tumor involves one or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
    - IIIA: Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond pelvis.
    - IIIB: Macroscopic peritoneal metastasis beyond pelvis up to 2 cm in greatest dimension, with or without positive retroperitoneal lymph nodes.
    - IIIC: Macroscopic peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ), with or without positive retroperitoneal lymph nodes.

- Stage IV
  - Distant metastases excluding peritoneal metastases
    - IVA: Pleural effusion with positive cytology.
    - IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity).

Prognosis:

FIGO staging	1yrs. Survival	2 yrs. Survival	3yrs. Survival
IA	98.4	96.2	89.6
IB	100	93.9	86.1
IC	96.3	91.4	83.4
IIA	93.0	87.2	70.7
IIB	93.4	84.5	65.5
IIC	93.6	85.6	71.4
IIIA	88.1	72.6	46.7
IIIB	85.7	70.6	41.5
IIIC	84.8	64.5	32.5
IV	72.4	48.4	18.6

Summary

- Ovarian neoplasms may be divided generally by cell type of origin into three main groups: epithelial, stromal, and germ cell. Taken as a group, the epithelial tumors are by far the most common, although the single most common is the benign cystic teratoma (dermoid cyst), which is a germ cell tumor.

- Most women with ovarian cancer are in the fifth or sixth decade of life.

- The cause of ovarian tumors is unknown.

- Risk factors: white race, late age at menopause, family history of ovarian/breast/ bowl cancer, prolonged periods of ovulation uninterrupted by pregnancy, infertility and being nulliparous.

- The pattern of inheritance if present is autosomal dominant.

- Population screening for ovarian cancer is not feasible.

- There are no specific symptoms for ovarian cancer.

- The diagnosis requires laparoscopy or laparotomy.

- Most common form of spread is by exfoliating cells.

- Remember that the most common **malignant** germ cell tumor is dysgerminomas and the second most common is immature teratoma.

MCQ's (Pretest):

1) The patient is very anxious regarding her risk of developing ovarian cancer because of her grandmother's history. You counsel her that all of the following are risk factors for ovarian cancer except

a. Use of combination oral contraceptive therapy

b. One first-degree relative with ovarian cancer

c. Nulliparity

d. Increasing age

e. Ovulatory drugs

2) Which of the following neoplasms has been associated with the use of oral contraceptives?

f. Breast cancer

g. Ovarian cancer

h. Endometrial cancer

i. Hepatic cancer

j. Hepatic adenoma

Answers:

1) **The answer is a.** Oral contraceptive use, multiparity, breast-feeding, and early menopause are all factors believed to decrease the risk of developing ovarian cancer because they reduce the number of years a woman spends ovulating. The use of combination oral contraceptives decreases the risk of developing ovarian cancer by about 40%. Nulliparity, increasing age, and fertility drugs all increase ovulatory cycles and therefore are risk factors for developing ovarian cancer. In the general population, the risk of developing ovarian cancer is about 1 to 1.5%. This risk increases to about 5% if a woman has one first-degree rel- ative with ovarian cancer and to about 7% if she has two or more first- degree relatives with ovarian cancer.

2) **The answer is e.** Beginning with high- dose combination contraceptive pills used over 20 years ago, pills have been studied extensively for a possible association with neoplasia. There is only scant evidence from this experience that use of oral contraceptives increases the risk of any type of cancer. Actually, the progestational com- ponent of combination pills (or progestin-only minipills) may confer a pro- tective effect against carcinoma of the breast and endometrium, and avoiding ovulation may decrease the risk of developing ovarian carcinoma. A slightly higher risk of cervical carcinoma was observed in some studies of users of oral contraceptives. These studies were not controlled, however, for confounding variables such as multiple partners or age at onset of sex- ual intercourse, and it is generally believed now that any increased risk in contraceptive pill users would be attributable to these other factors and not the steroids themselves. Although the risk of developing benign liver adenomas is increased somewhat in users of oral contraceptives, the risk of hepatic carcinoma is not increased.