Ovarian, Peritoneal, and Fallopian Tube Epithelial Cancer (OPT)
ACOG District II
Learning Objectives

At the end of this clinical presentation, obstetrician-gynecologists and other women’s health care providers will be able to:

1. Interpret updated clinical guidance on the etiology, risk assessment and mitigation, and management of ovarian, fallopian tube and peritoneal cancer*

2. Outline the assessment and comprehensive management of adnexal masses as set forth in current clinical guidelines

3. Recommend guidance on appropriate timing for when to refer to a gynecologic oncologist

We will refer to epithelial ovarian cancer as EOC from this point forward.
Background

Disease Burden
Disease Classification
Risk Factors
U.S. Disease Burden

• American Cancer Society annual statistics
  • 22,000-25,000 incidence
  • 14,000 mortality rate

• 1 in 70 lifetime incidence of US women
  • 5-year survival rate for localized ovarian cancer - 92%
  • 5-year survival rate for advanced ovarian cancer - 30%
Disease Classification

- Epithelial ovarian cancer is the most common type
- Accounts for approximately 90% of ovarian cancers

NOTE: Other* refers to mixed or transitional carcinomas where it is not possible to categorize to a single subtype.

Source(s): Alvarez RD, Karlan BY, Strauss JF. Ovarian Cancer: Evolving Paradigms in Research and Care: Report from the Institute of Medicine, Gynecologic Oncology, 141: 413-415, 2016.
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<tr>
<th>Established</th>
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<td>Hormone replacement therapy</td>
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<td>Infertility</td>
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<td>Family history</td>
<td>Late age at menopause</td>
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<td>Obesity</td>
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<td>Nulliparity</td>
<td>Sedentary lifestyle</td>
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<td>Tobacco use</td>
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Risk Status

- **Average risk**: Risk reported for the general population

- **High risk**: Women with a genetic predisposition
  - Deleterious mutation associated with ovarian, peritoneal, and fallopian tube (OPT) cancers
  - Women with a significant family history but no known deleterious mutation, are also considered high risk.
Assessment of Hereditary Predisposition

• Assess risk based on both **paternal and maternal** family history and personal history of cancers, particularly those related to deleterious mutations
  • Consider performing genetic testing
  • Refer to a genetics professional (geneticist or genetic counselor) when appropriate
• If a deleterious mutation is found, a patient is considered high risk
• If patient declines testing or counseling, history dictates risk level
Primary Protective Factors

- Oral contraceptive use
  - >5 years of OCP use reduces risk by ~50% in both low and high risk women
- Pregnancy
- Risk-reducing bilateral salpingo-oophorectomy (RRSO)
  - RRSO reduces incidence in high-risk women by ~90%
  - Not recommended for women at average risk
- Other factors that are associated with a decreased risk of developing ovarian cancer:
  - Tubal ligation
  - Hysterectomy
  - Breastfeeding
Performance Metrics for Screening Tests: 

*Four Key Measures*

**Sensitivity** - % of people who are affected that the test correctly identifies as positive

**Specificity** - % of people who are not affected that correctly test negative

**Positive predictive value (PPV)** - % of people with positive test who are affected

**Negative predictive value (NPV)** - % of people with negative test who are not affected

The higher the sensitivity, the fewer false negative tests.
The higher the specificity, the fewer false positive tests.
Principles of Screening: Types of Testing

• **Screening**
  - Tests do not provide a definitive answer; provide only odds of a given condition
  - Offered to a much wider population to define the level of risk, starting with the *a priori* baseline risk modified by screening parameters
  - Based on adjusted level of risk, appropriate patients will be offered diagnostic testing

• **Diagnostic**
  - Developed to provide definitive answer
  - May be invasive, expensive, and potentially risky
  - Typically reserved for “at risk” patients based on screening, symptoms, or physical findings

*Only 1 in 5 ovarian cancer cases are localized when diagnosed*
OPT Cancer Screening: Challenges

• Low prevalence of disease causes even a poor test to have high NPV, thus limiting meaning of the result

• High numbers of false positive results of current screening tests in average risk women may result in an unacceptable number undergoing invasive procedures

• Screening has not been shown to reduce mortality from ovarian cancer even in high-risk patients

• No tests currently available have adequate sensitivity, specificity, or positive predictive value (PPV) to effectively screen for ovarian cancer
FDA Statement on Ovarian Cancer Screening

FDA Statement, September 7, 2016:
“There are no ovarian cancer screening tests that have been cleared or approved by the FDA and information in the medical literature, including published clinical trial data, do not demonstrate that currently available ovarian cancer screening tests are accurate and reliable, particularly for asymptomatic women.”

ACOG and the USPSTF recommend AGAINST routine screening for ovarian cancer
Current methods are not adequately effective
Screening Strategies

• Currently recommended screening tests (for high risk individuals) include CA125 and transvaginal ultrasound (TVS)

• A multimodal approach is more effective, but does not achieve adequate sensitivity, specificity, or positive predictive value (PPV)
  • CA125:
    • Not sensitive for early disease
    • Elevated in a number of benign conditions, even in older women
  • TVS:
    • Not reliable in distinguishing benign from malignant tumors
    • Its use in the asymptomatic patient leads to unnecessary surgery
Risk Reducing Strategies

Medical
Surgical
Risk-Reducing Bilateral Salpingo-Oophorectomy

**High-Risk Population**

- **Timing:**
  - Age 35-40 when childbearing completed for women with *BRCA1* mutation
  - Age 40-45 for women with *BRCA2*

- **Preventive benefit:**
  - Risk of gynecologic malignancy (85-90%)
  - Risk of breast cancer when performed prior to menopause

- **Surgeon’s responsibility:**
  - Peritoneal cytology, inspection of the abdomen, adequate margin, and 2-3mm sectioning by a pathologist
  - Awareness of rising risk of occult malignancy with increase in woman’s age (4-10%)
  - Patient counseling on potential extent of surgery
  - Surgical preparation to treat malignancy if identified

*Source(s):*
Estimated Benefits of Risk-Reducing Surgeries in BRCA Carriers

• 2,482 women in Europe and North America from 1974 to 2008 with median follow up of 3.65 years

• Approximately half of the women had risk-reducing surgery
  • Breast cancer mortality reduced by 56% (2% vs. 6%) and ovarian cancer mortality by 79% (0.4% vs. 3%)
  • Mastectomy
    • 0 breast cancers vs. 7% in those without risk-reducing mastectomy
  • RRSO
    • 86% reduction in “ovarian” cancer (1% v. 6%)
    • 37% reduction in breast cancer in BRCA1 (14% v. 20%)
    • 64% reduction in breast cancer in BRCA2 (7% v. 23%)

Source(s): Domcheck SM et al. “Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality.” JAMA 2010;304(9):967-75.
Serous Tubal Intraepithelial Carcinoma (STIC): Ovarian Cancer Precursor

Type II Tumors:

- 70% of sporadic (non-hereditary) ovarian and peritoneal high-grade serous carcinomas demonstrated mucosal tubal involvement including STIC

- Nearly all STICs overexpress p53 similar to high-grade serous carcinoma.

RRSO Controversies

• Balancing increased risk of cardiac disease, bone loss, adverse affect on cognitive function, and other quality of life issues with the timing of RRSO
• Performing a hysterectomy at the time of RRSO
• Will risk-reducing salpingectomy provide similar benefit as RRSO?
  • STIC (serous tubal in situ carcinoma) tumors – fallopian tube in situ lesions that may predispose to ovarian cancer
  • Evidence suggests that a majority of serous ovarian tumors arise in fallopian tube
Opportunistic Salpingectomy

**ACOG Committee Opinion #620**

- Surgeon should discuss the following with women at population risk of ovarian cancer:
  - Benefits of removal of the fallopian tubes during a hysterectomy with ovarian preservation
  - Bilateral salpingectomy can be considered a method that provides effective contraception
Summary of Recommendations for High-Risk Women

• Medical
  • Oral contraceptive use

• Surgical
  • RRSO when childbearing completed
    • All cause mortality increased if hormone replacement not provided
    • Risks of breast, ovarian, and fallopian tube cancer decreased; greatest impact in younger women

• “Screening”
  • Has not been shown to be effective
    • TVS every 6 months
    • CA125 every 6 months
    • Cancer mortality not reduced
Symptomatic Women

Symptoms or Presence of Suspicious Physical Findings
Previously called the "silent killer," most women experience cancer-related symptoms months before a diagnosis is made.

<table>
<thead>
<tr>
<th>10 SYMPTOMS</th>
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<tr>
<td>- abdominal pain + bloating</td>
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<tr>
<td>- weight loss</td>
</tr>
<tr>
<td>- feeling full without having eaten much</td>
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<tr>
<td>- needing to urinate frequently</td>
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<tr>
<td>- a feeling of fullness in the pelvis</td>
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<tr>
<td>- clothes fitting tightly around the belly</td>
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<tr>
<td>- nausea + vomiting</td>
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<tr>
<td>- lower back pain</td>
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<tr>
<td>- fatigue</td>
</tr>
<tr>
<td>- changes in bowel habits, especially constipation</td>
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</table>

Recognizing that the new onset or increased severity of symptoms can represent ovarian cancer provides an important diagnostic opportunity for ob-gyns.

Women with ovarian cancer report that symptoms are persistent and represent a change from normal for their bodies.

The frequency and/or number of such symptoms are key factors in the diagnosis of ovarian cancer. Several studies show that even early stage cancer can produce these symptoms.

Women who have these symptoms almost daily for more than a few weeks should see their ob-gyn. Early stage diagnosis is associated with an improved prognosis.

For more info, visit acogny.org
Evaluation:
Symptomatic Patient/Suspicious Physical Findings

• Personal and/or family history of:
  • Breast, ovarian, endometrial, and/or colorectal cancer
  • Known hereditary cancer syndrome, and/or
  • Ashkenazi (Eastern European) Jewish ancestry

• Complete physical examination, including an abdominal/pelvic exam with a rectovaginal exam

• TVS as the imaging modality of choice for initial evaluation

• If no gynecologic pathology is identified, consider referral to gastroenterologist
Evaluation of an Ovarian Mass: Symptomatic Patient/Suspicious Physical Findings

• Key TVS findings:
  • Size
  • Consistency (cystic, solid, mixed)
  • Presence of septations, mural nodules or papillary projections
  • Presence of ascites
  • Abnormal vascularity

• The majority of simple cysts <10 cm are benign.
  • May be treated conservatively with serial TVS if asymptomatic and not increasing in size

Complex lesions, abnormal vascularity, or ascites are highly concerning for malignancy
Evaluation:
Symptomatic Patient/Suspicious Physical Findings

- Biomarkers
  - CA125
    - Elevated in 80% of women with ovarian cancer but only 50% of women with stage I disease
    - Normal CA125 does not rule out cancer and is of limited value in pre-menopausal women
  - OVA-1, ROMA
    - Combined testing associated with higher sensitivity

- CT Scan
  - Evaluate if symptoms are persistent when initial work-up is negative
  - Evaluate the extent of abdominal spread when pelvic malignancy is suspected

- MRI
  - May distinguish lesions indeterminate on TVS
Additional Tests Available for Symptomatic Patients

• Single marker assay (CA125, HE4)
• Combination of markers & algorithms:
  • Multivariate Index Assay (MIA)
  • Risk of Malignancy Algorithm (ROMA)
  • Risk of Malignancy Index (RMI)
## Assessment of Women with Adnexal Masses

**Malignant or Not?**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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<td>74-96%</td>
<td>75-95%</td>
<td>34-74%</td>
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<tr>
<td>Clinical Assessment</td>
<td>75%</td>
<td>86%</td>
<td>65%</td>
<td>91%*</td>
</tr>
<tr>
<td>MIA** + Clinical Assessment</td>
<td>95%</td>
<td>44%</td>
<td>36%</td>
<td>97%*</td>
</tr>
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</table>

+ Algorithm utilizing single marker assay, range of results based on menopausal status.
* Source: Li AJ, New biomarkers for ovarian cancer. Contemporary OB/GYN, April 2012
** MIA = Ova-1

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Consulting with a Gynecologic Oncologist

Organizations that support gynecologic oncologist involvement:

- Meta-analysis of 18 studies confirmed survival benefit with a gynecologic oncologist:
  - Complete surgical staging with early disease
  - Optimal cytoreductive surgery with advanced disease
  - **Improved median and overall survival**
- Performance of comprehensive and appropriate surgery is significantly more likely in a teaching hospital
- The rate of comprehensive surgery is significantly higher in hospitals in urban settings
  - <50% of patients received comprehensive surgery at small rural hospitals
- Adjuvant chemotherapy/follow-up and supportive care may often be administered locally

Laparoscopy for “Benign” Adnexal Masses

• Preferred surgical approach
• Unexpected ovarian cancer discovered in adnexal masses
  • Must be considered preoperatively and discussed with the patient
  • Effort should be made to avoid cyst leakage to prevent seeding of the peritoneal cavity with potentially malignant cells
  • Consultation and potential expeditious referral to gynecologic oncologist
Evaluation: When to Refer
ACOG/SGO Referral Guidelines for a Newly Diagnosed Pelvic Mass

Refer if one or more of the following indicators:*

- Very elevated CA125 level
- Ultrasound findings suggestive of malignancy
- Ascites
- A nodular or fixed pelvic mass
- Evidence of abdominal or distant metastasis (by exam or imaging study)
- Elevated score on a formal risk assessment test such as the multivariate index assay or the Risk of Ovarian Malignancy Algorithm or one of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis group
- Significant family history of breast or ovarian cancer (in a first-degree relative)

* For additional information, please refer to the ACOG District II website at acogny.org

Management of an Unsuspected Malignancy

• Staging is essential to:
  • Define the extent of disease
  • Determine subsequent treatment recommendation

• Complete surgical staging is performed by:
  • Gynecologic oncologists: 97% of the time
  • Ob-gyns: 52% of the time
  • General surgeons: 36% of the time

• Removal of uterus and adnexa is one step in the staging process
  • Exceptions include fertility preservation, particularly for early stage disease and non-epithelial subtypes

Management of Malignancy

Surgical Staging
Cytoreductive Surgery
Adjuvant or Neoadjuvant Chemotherapy
Complete Surgical Staging Steps

• Evaluation of any free fluid for cytology; peritoneal washings
• Intact removal of the adnexal mass, if possible
• Systematic inspection of all intra-abdominal surfaces, biopsy or removal of any suspicious areas or adhesions
• Biopsies of peritoneum of the posterior and anterior cul-de-sac, both paracolic gutters, and the intestinal mesenteries and diaphragm (or scraping) if no suspicious areas seen
• Omentectomy
• Bilateral pelvic and para-aortic lymphadenectomy
• Removal of the uterus and the adnexa
Fertility-Sparing Surgery

- Women with apparent early stage disease (clinical stage IA, grade 1 or 2), may be considered for conservative surgical staging which includes:
  - Desire for fertility sparing
  - Unilateral salpingo-oophorectomy
  - Biopsy assessment of the contralateral ovary
  - Pelvic washings
  - Pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal and diaphragmatic biopsies

- **Genetic risk assessment is warranted**
Primary Cytoreductive Surgery

• Maximal cytoreduction (debulking) is the most significant predictor of survival

• **Cytoreductive surgery for advanced stage disease**
  • Purpose - to remove macroscopic disease evident at the time of initial surgery
  • Goal - to remove bulky disease as identified at the time of initial surgery

• “**Optimal” debulking**
  • Removal of bulky disease so that largest single residual tumor nodule is ≤ 1cm
  • Bulky Stage IIIC disease → no residual disease at the completion of surgery
    • Median survival of 106 months
    • The five-year survival for this group was over 70%

Diaphragmatic and Liver Capsular Disease
Optimal Debulking Surgery - Benefits

• Patients with low-volume residual disease (≤1cm) after surgery have:
  • Significantly improved rates of response to adjuvant chemotherapy
  • Lower rates of platinum resistance
  • Improved survival compared to patients with bulky residual disease
  • Improved quality of life by reducing symptoms caused by the increased tumor burden

Chemotherapy

- Post-operative (adjuvant) chemotherapy is a mainstay in the treatment of patients with a significant risk of recurrence.
- Ovarian cancer is highly chemosensitive.
- 70-80% of women will achieve complete clinical remission with initial chemotherapy following optimal debulking.
- ~20% of women with advanced ovarian cancer will remain free of disease for at least 5 years.

Source: PMID: 19224846
Chemotherapy Recommendations

Combination of Taxane and Platinum

• Adjuvant therapy options for Stages IA & IBIII, IC, II and higher
  • “Dose dense” chemotherapy
  • IV/IP treatment

• Neoadjuvant chemotherapy recommended for non-resectable Stage IIIC and Stage IV
  • SGO and ASCO statement (August 2016)
  • Interval cytoreductive surgery if tumor responds to chemotherapy

• Best outcomes for advance stage disease to date
  • IV/IP chemotherapy in women who had optimal cytoreduction

# Intraperitoneal Chemotherapy

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Survivorship
Counseling: Quality of Life Issues

- Cancer diagnosis and subsequent treatment can significantly affect woman’s quality of life and may impact the physical, psychosocial, spiritual, and sexual aspects of her life

- The role of the primary ob-gyn is important to:
  - Establish the diagnosis and provide referral based on regional expertise
  - Assist in conveying information about the diagnosis and endorsing treatment plan
  - Provide support during treatment, assist in addressing gynecologic symptoms, and be involved with follow-up care, including survivorship
Genetic Counseling, Testing, and Cascade Screening

• All women with a pelvic malignancy should be offered genetic counseling and testing
  • Approximately 20% are due to BRCA 1/2 and/or other deleterious mutations
  • Referral to a genetic counselor should be considered
  • Ob-gyns are uniquely positioned to promote genetic testing in affected individuals
    • Initiate or encourage cascade screening of 1st, 2nd, and 3rd degree relatives, including males
    • Assist in mitigating their risk or offering risk reducing services

Note: Consult ACOG District II’s genetics education/resources for additional information on this subject.
Conclusion

Future Directions
Role of Obstetrician-Gynecologists & Women’s Health Providers
Future Directions

• Identify new methods of effective screening and early detection

• Promote identification of high-risk populations and risk-reducing surgical interventions
  • Clarify the role of opportunistic and/or risk-reducing salpingectomy

• Identify potential molecular targets and support development of therapeutic agents

• Encourage and support increased funding for research and participation in clinical trials
  • Highest quality of clinical care
  • Critical in helping advance knowledge
Role of Obstetrician-Gynecologists

• Identifying women at risk
• Avoid ineffective screening testing and encourage women at high risk to proceed with risk-reducing strategies
• Practice evidence-based evaluation of symptomatic women and those with suspicious physical findings
• Refer to a gynecologic oncologist when appropriate
• Understand and support patient’s treatment options
• Support enrollment in cancer clinical trials
• Be involved in cancer survivorship plan
• Provide or assist with cascade testing of family members

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