ENDOMETRIOSIS AND OVARIAN CANCER

Shara Borgato
ENDOMETRIOSIS

• Endometriosis is a common gynecological disorder that is characterized by ECTOPIC GROWTH OF ENDOMETRIAL GLANDS AND STROMA

• The estimated PREVALENCE in the general population is about 4%

• The etiology is not fully understood but the predominant hypotheses are:
  1. RETROGRADE MENSTRUATION
  2. METAPLASIA: mesothelium turns into endometrial tissue
  3. LYMPHATIC SPREAD: endometrial cell may spread through lymphatic and vascular channels and gain capacity for implantation in various sites in the pelvic cavity

• Endometriosis might cause pelvic inflammation, adhesion, chronic pain, and infertility.

• Epidemiological studies have consistently shown that endometriosis is associated with an increased risk of ovarian cancer.
SAMPSON AND SCOTT’S CRITERIA

- Already in 1925, SAMPSON proposed criteria for the diagnosis of ovarian cancer arising from endometriosis:
  1. evidence of endometriosis near the tumor,
  2. demonstration of cancer arising within ovarian endometriosis and not elsewhere
  3. presence of tissue similar to the endometrial stroma surrounding characteristic epithelial glands.

- In 1953, SCOTT added a fourth criterion:
  4. histologic demonstration of transition of endometriosis to neoplasm

This has raised the question of whether endometriosis is a premalignant condition.
EPIDEMIOLOGY: quantification of the risk

- OMEGA cohort (hormone stimulation in IVF-treated women) linked with PALMA (all citological and histological diagnosis) linked with NCR (data on invasive malignant neoplasm).
- 3657 endometriosis group
- 5247 comparison group
- Follow up 15.2 years

1. First analytic group: diagnosis of CO and BOT at the same time of endometriosis
2. Second analytic group: diagnosis of endometriosis occurred before CO

- 3 to 8 fold increased risk of ovarian tumors associated with endometriosis
- when excluded the info from pathology database the risk is lower → studies using this method may have a too low risk assessment
Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies

<table>
<thead>
<tr>
<th>Subtype</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>3.73 (1.04-12.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2.32 (1.94-2.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.09 (0.76-1.58)</td>
<td>0.63</td>
</tr>
<tr>
<td>High-grade serous</td>
<td>1.11 (0.96-1.29)</td>
<td>0.16</td>
</tr>
<tr>
<td>Low-grade serous</td>
<td>2.02 (1.38-3.97)</td>
<td>0.13</td>
</tr>
<tr>
<td>Borderline</td>
<td>1.26 (1.05-1.50)</td>
<td>0.012</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1.17 (0.97-1.47)</td>
<td>0.24</td>
</tr>
<tr>
<td>Serous</td>
<td>1.31 (1.01-1.63)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Sensitivity analyses suggest that the risk is increased even among women whose endometriosis was diagnosed many years before ovarian cancer.

Self reported endometriosis was associated with a significantly increased risk of:

- CLEAR CELL
- LOW-GRADE SEROUS
- ENDOMETRIOID
Women with histologically verified endometriosis have an increased risk of epithelial ovarian cancer predominantly of the CLEAR-CELL and ENDOMETRIOID subtypes.
Epithelial ovarian cancer: composed of a diverse group of tumors

Type I (low-grade serous, endometrioid, clear cell, mucinous, Brenner)
- Genetically more stable
- Distinctive pattern of mutations in specific cell type
- TP53 mutation very rare

Type II (high grade serous, carcinosarcoma)
- Genetically unstable
- High frequency of TP53 mutation

Endometriosis is commonly linked to the tumorogenesis of **TYPE I** ovarian carcinomas and precisely to **ENDOMETRIIOD** and **CLEAR CELL** subtypes
Endometrial tissue, by a process of RETROGRADE MENSTRUATION, implants on the ovarian surface to form an endometriotic cyst.

- Eutopic endometrium in women with endometriosis exhibit molecular abnormalities including ACTIVATION OF ONCOGENIC PATHWAYS.

- LOW GRADE ENDOMETRIOID or CLEAR CELL CARCINOMA can develop.

Evidence: protective effect for tubal ligation was seen only for endometrioid and clear cell carcinoma of the ovary.
PATHOGENESIS: what makes the connection?

Histologic evidence

Immunologic evidence

Genetiche ed epigenetic evidence
PATHOGENESIS: what makes the connection?

“ABNORMAL ENDOMETRIUM”

EUTOPIC ENDOMETRIUM in women with endometriosis has intrinsic molecular abnormalities including activation of oncogenic pathways. These changes presumably enable implantation, survival, and invasion of the endometrial tissue in the ovary and in the peritoneal surfaces.
**PATHOGENESIS:** what makes the connection?

“ABNORMAL ENDOMETRIUM”

1. High COX2 and AROMATASE levels
   \[ \rightarrow \] increased PGE2 and ESTRADIOL

2. Decreased progesterones receptors levels in stroma cell
   \[ \rightarrow \] DISRUPTION OF THE PARACRINE PATHWAY
   that inactivates estradiol and PROGESTERONE RESISTANCE

Originate from overexpression of SF1 and ESTROGEN RECEPTOR β in endometriotic stromal cells.
**PATHOGENESIS:** what makes the connection?

**Immunologic evidence**

- **↑ PROINFLAMMATORY CYTOKINES**
- **↑ PERITONEAL MACROPHAGES**
- **↓ CITOTOXICITY OF NATURAL KILLER and T-CELL**

Defective system with altered NK and PM activities:
- Increased local production of factors promoting **ANGIOGENESIS** and **IMPLANTATION OF ENDOMETRIAL CELL**
- Reduced killing of **ECTOPIC ENDOMETRIUM**
- Reduced killing of **DENDRITIC CELLS**
- Reduced secretion of **REGULATORY CYTOKINES** that control autoimmunity
PATHOGENESIS: what makes the connection?

**Immunologic evidence**

**REGULATORY T LYMPHOCYTES** (suppress the activation of immune system)

**↑** FOXP3-POSITIVE LYMPHOCYTES has been observed in the eutopic endometrium of patients with endometriosis during the secretory phase of the menstrual cycle

**↑** FREQUENCY OF TREGS in the peritoneal fluid in women with endometriosis → compensatory anti-inflammatory mechanism and may account for abrogated local cellular immune responses

ENDORMETRIOSIS and OVARIAN CANCER share similar immune aspects such as increased levels of Foxp3 and Tregs, resulting in malfunction of the immune system and creating conditions for disease establishment.
PATHOGENESIS: what makes the connection?

Values of LYMPHOVASCULAR DENSITY are observed in the endometriotic tissues compared with adjacent healthy tissue.

Expression of VEGF C and D, both important factors in lymphovascular growth produced by endometriotic epithelial cells, suggests the presence of lymphangiogenesis in deep endometriosis.
Several studies have shown evidence of MONOCLONALITY in endometriosis, a characteristic of malignant lesions, with a positive frequency in 60% to 100% of the samples studied. Can contribute to development of endometriosis alone and no doubt represent important mutagenic events detected in 12 samples of ovarian tumors associated with endometriosis and in 12 samples of ovarian endometriosis only (9p, 11q, 22q) → OVARIAN ENDOMETRIOSIS AND OVARIAN TUMORS MAY HAVE SIMILAR GENETIC ORIGIN.
PATHOGENESIS: what makes the connection?

Mutation genes frequently occurred in endometrial and ovarian carcinomas.
PATHOGENESIS: what makes the connection?

- MicroRNA expression signature differentiates ovarian cancer tissues from normal ovary
- **MiR-200 family** is the most significantly overexpressed group in ENDOMETRIOID and CLEAR CELL CARCINOMAS
- **miR-17-5p and miR-20** involved in angiogenesis are DOWN-REGULATED IN OVARIAN ENDOMETRIOMAS compared with eutopic endometrium
- **miR-222** are significantly increased in endometriomas

In ovarian carcinogenesis MUTATION OF MICRORNA have been identified
PATHOGENESIS: malignant transformation of endometriosis
DIAGNOSIS: biomarkers - a way to detect CO earlier

**ENDOMETRIOSIS**

- CA 125
- HE 4
- RO MA

**OVARIAN CANCER**

- CA 125, elevated in 47% of early disease and in 80% to 90% of advanced case
- HE 4
- RO MA, Overexpressed in endometrioid and serous tumors
- Risk of ovarian malignancy algorithm

Panel of 5 biomarkers in suspected ovarian masses:
1. CA-125,
2. b2 microglobulin,
3. apolipoprotein A1,
4. Prealbumin,
5. transferrin

There are NO BIOMARKERS that identify patients with endometriosis at elevated risk of ovarian cancer.
DIAGNOSIS: biomarkers - a way to detect CO earlier

Found 4 miRNAs (miR-15b, 16, 21, and 195) differentially expressed in human EAOCs from healthy controls

circulating miRNAs may serve as promising biomarkers with high sensitivity and specificity FOR EARLY DETECTION and DIAGNOSIS OF ENDOMETRIOSIS AND EAOCS
**DIAGNOSIS:** ultrasound

Sonographic characteristics of MALIGNANT TRANSFORMATION in endometrioid cyst:

- Presence of solid tissue
- Heterogeneous cystic content
- Solid tissue with positive Doppler signals
- Papillary projection more frequent
ENDOMETRIOSIS ASSOCIATED OVARIAN CANCER has a much better survival rate than OVARIAN CANCER

EAOC patients were more likely to have:

- Low grade
- Early stage tumors
TAKE HOME MESSAGE

There is a **connection** between endometriosis and OC but **ENDOMETRIOSIS IS NOT A PRECANCEROSIS**

Pre-operative counselling and work-up is **CRUCIAL** in the clinical management of women with endometriosis

Pay attention to **SUSPICIOUS SITUATION:**

- Women > 40 years
- Suspicious ultrasound
- CA 125 very high