Endometrial changes in endometriosis: do they affect implantation?

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I declare no conflict of interest

What is endometriosis?

- Estrogen-dependent inflammatory disease
- Affects 5-10% of women in reproductive age
- Symptoms: pelvic pain, chronic bleeding, inflammation and infertility

Endometrial tissue outside the uterine cavity

ECTOPIC ENDOMETRIUM

Estrogen-dependent inflammatory disease

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Endometrial tissue outside the uterine cavity

ECTOPIC ENDOMETRIUM
Pathogenesis of endometriosis

- THE MOST ACCEPTED retrograde menstruation
- coelomic metaplasia theory
- endometrial tissue travelling through veins or lymphatic vessels
- stem cells from bone marrow differentiate into endometriotic tissue in different sites
- new concept embryological origin alterations in female genital tract organogenesis

Endometriosis and infertility

- The role of oocyte
- The role of the endometrium
Endometriosis

- Endometriosis is associated with affected implantation and clinical pregnancy rates.
  - Due to poor oocyte/embryonic quality
  - Due to endometrial receptivity problems

Ovarian quality and endometriosis

- Retrospective study: Oocytes from donors with endometriosis are associated with lower implantation but not clinical pregnancy rates compared to oocytes from normal donors

Prospective study

Group 1: control
Group 2: donor with endometriosis/healthy recipient
Group 3: healthy donor/recipient with endometriosis

Pregnancy and implantation rates were significantly (2-fold) reduced in Group 2
Ovarian quality and endometriosis

Granulosa cells

- A decreased number of granulosa cells in the G2/M phase and an increase in both the S phase and apoptotic cells were documented in women with endometriosis

Granulosa cells

- Granulosa cell apoptosis increased proportionally with the severity of disease and resulted in poor oocyte quality and a reduction in fertilization and pregnancy rates
- A higher percentage of granulosa cell apoptosis was associated with significantly reduced pregnancy rates in patients with endometriosis or tubal factor infertility undergoing IVF

Granulosa cells

- Oxidative stress markers were significantly elevated in granulosa cells of patients with endometriosis
The new trend: endometrial receptivity in infertile patients with endometriosis

EUTOPIC VS ECTOPIC ENDOMETRIUM

- Steroid hormone responsiveness and receptor content
- Growth factor responsiveness and receptor content
- Protein production
- Expression of enzymes and their inhibitors

Eutopic endometrium, Endometriosis and implantation
Eutopic endometrium and implantation markers (1)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Metastatic secretary phase</th>
<th>Normal</th>
<th>Eutopic endometrium</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GJA</td>
<td>No difference among stages</td>
<td>2.57±0.73</td>
<td>2.60±0.79</td>
<td>0.931</td>
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<tr>
<td>CA125</td>
<td>No difference among stages</td>
<td>12.3±4.81</td>
<td>12.1±4.85</td>
<td>0.951</td>
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<tr>
<td>TNFα</td>
<td>No difference among stages</td>
<td>5.3±2.32</td>
<td>5.2±2.34</td>
<td>0.941</td>
</tr>
<tr>
<td>LTA</td>
<td>No difference among stages</td>
<td>3.1±1.19</td>
<td>3.1±1.17</td>
<td>0.951</td>
</tr>
<tr>
<td>VEGF</td>
<td>No difference among stages</td>
<td>2.5±1.19</td>
<td>2.6±1.17</td>
<td>0.931</td>
</tr>
<tr>
<td>IL-6</td>
<td>No difference among stages</td>
<td>1.5±0.51</td>
<td>1.4±0.50</td>
<td>0.941</td>
</tr>
<tr>
<td>IL-8</td>
<td>No difference among stages</td>
<td>1.2±0.41</td>
<td>1.2±0.39</td>
<td>0.951</td>
</tr>
<tr>
<td>MDA5</td>
<td>No difference among stages</td>
<td>1.8±0.61</td>
<td>1.8±0.60</td>
<td>0.931</td>
</tr>
</tbody>
</table>

Note: *N=20 in each group.

Eutopic endometrium and implantation markers (2)
Eutopic endometrium and implantation markers (3)

- RT-PCR for LIF and IL-11
- Endometrial flushings
- There is no receptivity defect with regard to LIF and IL-11 secretions by eutopic endometrium in infertile women with endometriosis.


Eutopic endometrium and implantation markers (4)

- Integrin AvB3 is down-regulated in eutopic endometrium of patients with endometriosis

Changes in eutopic endometrium of women with endometriosis

- Structure and histology
- Proliferation and growth factors
- Angiogenesis
- Apoptosis and cell cycle
- Immunology
- Cell adhesion molecules
- Steroids and cytokines
- Protein production and gene expression

Structure changes of eutopic endometrium in women with endometriosis

- Increased heterogeneity in surface epithelium, reduced glandular and stromal raises, basal vacuolated cells
- Reduced endometrial thickness
- Altered neuroendocrine cells
- Nerve fibres identified

A: Preovulatory stage healthy women
B: Secretory stage healthy women
C: Preovulatory stage endometriotic women
D: Secretory stage endometriotic women

Changes in eutopic endometrium of women with endometriosis

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Increased proliferation of endometrial epithelial, stromal and endothelial cells
No differences in endometrial cell proliferative activity

Controversial theories

Proliferation – growth factors
changes of eutopic endometrium in women with endometriosis

- Increased proliferation of endometrial epithelial, stromal and endothelial cells
- No differences in endometrial cell proliferative activity
- Lower TGFβ1
- Higher activin, IGF, IGF-BP3, HGF, annexin-1
- Reduced cripto

Changes in eutopic endometrium of women with endometriosis

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VEGF elevated in secretory phase, some studies during the proliferative phase
- VEGF-A elevated
- Reduced VEGF receptor-1
- Controversy concerning VEGFR-2
- VEGF – C reduced
- Increased angiopoietin-1 and -2 in the secretory phase
- Higher endoglin positive vessels
- Decreased platelet growth factor – A
- Controversy for thrombospondin – I and prokineticin- I (angiogenetic factors)

Angiogenesis
changes of eutopic endometrium
in women with endometriosis

Changes in eutopic endometrium
of women with endometriosis

- Structure and histology
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Reduced number of apoptotic cells or increased apoptosis in secretory phase CONTROVERSY

Increased or unchanged Bcl-2 CONTROVERSY

Reduced caspase-1 levels

Increased or reduced p53 levels CONTROVERSY

TNF-α suppresses proliferation of endometrium in healthy women BUT enhances proliferation of endometrium of women with endometriosis

Increased MCL-1

Reduction of Bak, some others increased Bax and Bak ratios → anti-apoptotic environment

Increased proteins for cell survival (p21 activated kinase-1, pERK1/2, cyclin D1)

Increased levels of c-myc promoting cell growth and proliferation
Changes in eutopic endometrium of women with endometriosis

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- Immunology
- Cell adhesion molecules
- Steroids and cytokines
- Protein production and gene expression

Immunology
changes of eutopic endometrium in women with endometriosis

- Increased secretion of complement component C3
- Decreased mitogenicity for autologous lymphocytes
- Fewer T-suppressor/cytotoxic cells and endometrial granulated lymphocytes
- More T helper/inducer cells
- Increased resistance to cytotoxic effect of heterologous lymphocytes
- Increased endometrial IgG and HLA-DR, HLA class I

Changes in eutopic endometrium of women with endometriosis

- Structure and histology
- Proliferation
- Angiogenesis
- Apoptosis and cell cycle
- Immunology
- Cell adhesion molecules
- Steroids and cytokines
- Protein production and gene expression
Cell adhesion implantation

Controversial data concerning the alterations of integrins, E-Cadherin, ECM molecules, Matrix Metalloproteinase family proteins

Changes in eutopic endometrium of women with endometriosis

- Structure and histology
- Proliferation
- Angiogenesis
- Apoptosis and cell cycle
- Immunology
- Cell adhesion molecules
- Steroids and cytokines
- Protein production and gene expression
Hormones in endometrium of healthy women

Steroids and Cytokines
changes of eutopic endometrium
in women with endometriosis

- No difference in estrogen nor progesterone receptor expression
- Elevated production of IL-1β, IL-13, IL-15, macrophage-stimulating protein
- Controversial data for IL-6, IL-8, MCP-1

Changes in eutopic endometrium of women with endometriosis

- Structure
- Proliferation
- Apoptosis
- Immunity
- Cell adhesion molecules
- Proteases
- Steroids and cytokines
- Protein production and gene expression
Proteins and genes
changes of eutopic endometrium
in women with endometriosis

- Elevated production of CA-125
- Absence of HOX gene expression
- Increased production of CRH, UCN

Impaired CRH and Urocortin expression and function in eutopic endometrium of women with endometriosis  
(Novembri R. et al, 2011)
OVEREXPRESSION OF CRH, UCN, CRHR1 AND CRHR2 IN ECTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS (Vergetaki A. et al., in process)

**A:** eutopic endometrium  
**B:** ectopic endometrium

**CRH** expression

**UCN** expression

E: endometrial tissue, P: placental tissue, M: myometrial tissue  
Ishii: Ishikawa cell line, JEG3: human choriocarcinoma cell line, - : negative control

OVEREXPRESSION OF CRH, UCN, CRHR1 AND CRHR2 IN ECTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS (Novembri R. et al., 2011)
OVEREXPRESSION OF CRH, UCN, CRHR1 AND CRHR2 IN ECTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS (Vergetaki A. et al., in process)

A: eutopic endometrium
B: ectopic endometrium

A

B

C

D

E

THE EFFECT OF CRH ON GALECTIN-1 PATTERN IN ENDOMETRIOSIS AND GALECTIN-1 EXPRESSION IN ECTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS (Jeschke U. et al., in process)

Dowregulation of galectin-1 in endometriotic tissue

Normal endometrium

Endometriosis

THE EFFECT OF CRH ON GALECTIN-1 PATTERN IN ENDOMETRIOSIS AND GALECTIN-1 EXPRESSION IN ECTOPIC ENDOMETRIUM OF WOMEN WITH ENDOMETRIOSIS (Jeschke U. et al., in process)

Ishikawa cells

A

B

C

D

E
Conclusions

- The association of endometriosis and infertility can be attributed to both ovarian and endometrial etiologies.
- Ovarian dysfunction can lead to bad quality oocytes and thus embryos.
- Both ectopic and eutopic endometria from patients with endometriosis differ from normal endometrium.

Endometriosis is inducing a microenvironment against implantation and early fetal development.
- The role of local stress in the endometrium of endometriosis patients may substantially explain the increased rate of IVF failures.
- Further experiments using animal models could elucidate the role of CRH in endometriosis.
CONCLUSION

Abnormal eutopic endometrium

Decidualization – Implantation problems

Infertility

ACKNOWLEDGEMENTS

Department of Obstetrics and Gynecology, Medical School University of Crete – Human Reproduction Laboratory:

- Irini Taliouri, BSc, PhD,
- Aikaterini Vergetaki, BSc, PhD student

First Department of Obstetrics and Gynecology, Medical School, LMU Munich – Laboratory of Gynecologic Oncology and Placental Research:

- Prof Dr. Udo Jeschke

Department of Obstetrics and Gynecology, Medical School University of Ioannina:

- Prof Sophia Kalantaridou MD, PhD
- Ass. Prof Thomas Vrekoussis, MD, PhD

THANK YOU
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