Medical Management of Endometriosis: Novel Targets and Future Treatments

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Objectives

■ Etiopathogenesis: Relation with the treatment
■ Medical Treatments
  ■ Established
  ■ New Modalities?
■ Experimental Treatments
■ Research
Current areas of research in the etiopathogenesis of endometriosis

- Immunology
- Environmental Science
- Genetics
- Cancer Biology
- Hormonal factors
- Steroidogenesis

Pelvic Endometriosis
Proposed Etiopathogenesis:

- Genetical Susceptibility
- Environmental Factors
  - Toxins: DIOXIN
  - Epigenetical Mechanisms
- Immunological & Cellular Alterations
- Angiogenesis
  - VEGF
- Retrograde Menstruation
- Endometrium
- Aromatase E2
- TNF-α
- IL8
- MCP1

Link between the genetics and immune system

*In Viva*, 2010 May-Jun;24(3):297-301.

**Genetic variants of vascular endothelial growth factor and risk for the development of endometriosis.**

Attar R¹, Agachan B, Kuran SB, Toptas B, Eraltan IY, Attar E, Isbir T.


**DNA repair genes in endometriosis.**

Attar R¹, Cacina C, Sozen S, Attar E, Agachan B.


**Association of interleukin 1beta gene (+3953) polymorphism and severity of endometriosis in Turkish women.**

Attar R¹, Agachan B, Kucukhuseyin O, Toptas B, Attar E, Isbir T.


**Increased concentration of vascular endothelial growth factor in the follicular fluid of patients with endometriosis does not affect the outcome of in vitro fertilization-embryo transfer.**

Attar E, Genc S, Bulgurcuoglu S, Topuz S, Serdaroglu H.
Peritoneal Macrophages

TNF-α

TNF-α induces apoptosis in Mesothelial Cells.

VEGF/IL-8/MCP-1

MMPs

Endometrial Stromal Cells

Implantation & Angiogenesis

Proliferation
IL-1 & TNF-α induced IL-8 mRNA Expression in Mesothelial Cells

Epigenetic Mechanisms in relation to Endometriosis

- CpG dinucleotide methylation of the CYP19 I.3/II promoter modulates cAMP-stimulated aromatase activity
  Masashi Demura & Serdar E. Bulun

- Epigenetic mechanisms regulating CYP19 transcription in human breast adipose fibroblasts
  K C. Knower, SQ. To, ER. Simpson, C D. Clyne
Genetics and Hormonal Causes

Prostaglandin E2 via steroidogenic factor-1 coordinately regulates transcription of steroidogenic genes necessary for estrogen synthesis in endometriosis.
Attar E¹, Tokunaga H, Imir G, Yilmaz MB, Redwine D, Putman M, Gurates B, Attar R, Yaegashi N, Hales DB, Bulun SE.

Steroidogenic factor-1 and endometriosis.

Upstream stimulatory factor-2 regulates steroidogenic factor-1 expression in endometriosis.
cAMP

Aromatase

COX-2

VEGF

IL1-β

GROWTH

Epithelial Cell

Arachidonic Acid

INFLAMMATION

PGE$_2$

Cholesterol

StAR

Adrenal Ovary

Endometriotic Cell

Cholesterol

StAR

Aromatase

A

E$_2$

E$_1$

Attar E and S.E. Bulun, Hum Reprod Update. 2005; 0: 341
Progesterone Resistance in Endometriosis


**Progesterone resistance in endometriosis: link to failure to metabolize estradiol.**


**Estrogen receptor-beta, estrogen receptor-alpha, and progesterone resistance in endometriosis.**

Pelvic Endometriosis

Defence Mechanisms

Retrograde Cell Amount
Environmental Factors
Genetic Susceptibility
Hormonal Factors
Immune Alterations
The goal of the treatment of endometriosis is to achieve successful pregnancy in infertile patients and/or relieve pain.
There is **NO** medical treatment for endometriosis associated infertility, except ultralong protocol in IVF.
Endometriosis Treatment: Pain

- Medical Treatment
  - Established Medical Treatments
  - Experimental Treatments
Endometriosis is an estrogen dependent disorder
Established Medical Treatments

- NSAIDs
- Oral Contraceptives
- Progestins
  - MPA
  - Dianogest
  - LNG-IUD
- Danazol
- GnRH analogues
Established Medical Therapy for Total Pain

- These drugs are equally effective in reducing the endometriotic implant mass/severity of the disease as well as reducing pelvic pain associated with endometriosis.
- **Initial treatment the choice should be based on cost and side effect profile of the drug**
- NSAID’s appropriate and successful in many cases
- GnRH agonists have been proved effective after the failure of a prior medical hormonal therapy
The optimal medical treatment

- No menopausal symptoms
- No proliferation

Menopausal Symptoms

Therapeutic Window

Proliferation of implants

Estradiol level (pg/ml)
Protocols for OCS: Cyclic- Continuous (Pseudopregnancy)

1. Low dose OC
   
   4w cycle
   bleeding

2. Low dose OC (monophase)
   
   3 sheets (9w)
   bleeding


3. Mid dose OC
   
   7-15 w cycle
   bleeding
Continuous treatment is more effective?

50 women with endometriosis with persistent dysmenorrhea on cyclic OCPs started on continuous monophasic OCPs

Mean VAS at baseline was 75
At 2 years it was 31

Vercellini Fertil Steril 2003
GnRHa Treatment-duration

- GnRHa for 3 mo or longer with add-back
Protocols for GnRH-a Therapy Followed by Low-dose Danazol, Mid/Low-dose EP or dienogest

- **GnRH agonist**
  - Danazol 300 mg/day
  - 200 mg/day
  - 100 or 150 mg/day
  - 6 Mo

- **GnRH agonist**
  - Mid-dose EP
  - 12 w cycle
  - Withdrawal bleeding

- **GnRH agonist**
  - Low-dose EP
  - 4-10 w cycle
  - Withdrawal bleeding

- **GnRH agonist**
  - Dienogest 1-2 mg/day
  - 4-6 Mo


Maintenance Therapy with Danazol or mid/low doses of OC after GnRH-a Treatment for Endo-associated Pelvic Pain

(A) Dysmenorrhea
(B) Non-menstrual pelvic pain
(C) Dyspareunia

a P<0.01 vs. before treatment of corresponding group, b P<0.05 vs. after GnRH-a treatment, and c P<0.05.
Analyzed by the Kruskal-Wallis test followed by multiple comparison using the nonparametric Dunn’s test.

Non-steroid anti-inflammatory ilaçlar

NSAİ’lerin endometrioziste kullanımına ilişkin yeterli kanıt bulunmamaktadır, yalnızca ağrıın azaltılması amacıyla önerilebilirler.

Öneri düzeyi: İyi klinik özellikleri

Oral kontraseptifler

Oral kontraseptiflerin endometrioziste kullanımına ilişkin sınırlı düzeyde kanıt bulunmaktadır.

Endometrioziste kullanımları düşünülebilir.

Öneri düzeyi: B

Progestinler
(dienogest, vd.)

Progestinlerin endometriozise bağlı ağrıın giderilmesindeki etkililikleri kanıtlanmıştır, tedavi amacıyla önerilebilirler.

Öneri düzeyi: A
Experimental Treatments

- RU486 (mifepristone) and SPRMs
- GnRH antagonists
- TNF-α Inhibitors
- Angiogenesis Inhibitors
- MMP Inhibitors
- Immunomodulators
- Estrogen Receptor-β Agonists
- Aromatase Inhibitors
TNF-α antagonists: A novel treatment for endometriosis?

- It was suggested 12 years ago
- More specific TNF-α antagonists were evaluated
- One potential mechanism by which anti-TNF-α therapies may elicit their effect is through the inhibition of MMP transcription
TNF-α Inhibitors

- There are currently scarce data in humans regarding the use of immunomodulators acting on TNF-α in the treatment of endometriosis.
Aromatase inhibitors: the next generation of therapeutics for endometriosis?

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COUP-TF
WT-1
COX2

COUP-TF
WT-1
SF-1
StAR?
Aromatase
COX2

COUP-TF
WT-1
SF-1
StAR
Aromatase
COX2

ENDOMETRIUM
(NORMAL)

ENDOMETRIUM
(ENDOMETRIOSIS)

ENDOMETRIOTIC
TISSUE

PGE$_2$

E$_2$
PGE$_2$

E$_2$
PGE$_2$

Attar E and S.E. Bulun, Hum Reprod Update. 2005; 0: 341
The effect of aromatase inhibitors in four critical body sites.

**Hypothalamus**
- Postmenopausal on Al
- Premenopausal on Al (Hypothetical)
- Premenopausal on Al + P or OC

**Ovary**
- No Follicular Aromatase
- Follicle Development

**Endometriosis**
- Aromatase

**Peripheral Tissues**
- Peripheral Aromatase

Pretreatment and posttreatment disease stages, based on American Society for Reproductive Medicine (ASRM) scores, for individual patients (n = 10). (A) Baseline: first-look laparoscopy, 1 month before treatment. (B) Second-look laparoscopy 1 month after treatment. Determinations for each patient before and after treatment are interconnected (49). Mean pretreatment ASRM score: 44.1 ± 29.7; mean posttreatment ASRM score: 5.4 ± 5.64 (P = .013).
Pain scores before and after treatment in two recent trials.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>L+NEA</th>
<th>A+OC</th>
<th>L+NEA</th>
<th>A+OC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Baseline</td>
<td>6 mo</td>
<td>Baseline</td>
<td>6 mo</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>19</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.22 ± 2.07</td>
<td>8.24 ± 1.76</td>
<td>2.34 ± 2.11</td>
<td>4.24 ± 2.70</td>
</tr>
</tbody>
</table>

Note: L+NEA = letrozole+norethindrone acetate; A+OC = anastrozole+oral contraceptive.

\( P < .01 \) (L+NEA, baseline vs. 6 mo).

\( P < .0001 \) (A+OC, baseline vs. 6 mo).

Kaplan-Meier curves for pain-free (recurrence-free) periods in patients treated with goserelin-only (dotted line) vs. goserelin plus anastrozole (solid line) (50).
## Current Clinical Trials of AIs in Endometriosis

### The use of aromatase inhibitors in endometriosis: current clinical reports.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Study type</th>
<th>Indication</th>
<th>Medication</th>
<th>Length (mo)</th>
<th>Sample size</th>
<th>Outcome (6 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Takayama et al.</td>
<td>Case report</td>
<td>Postmenopausal endometriosis not responding to surgical or medical treatment</td>
<td>A</td>
<td>9</td>
<td>1</td>
<td>Pain relief, reduced lesion size</td>
</tr>
<tr>
<td>2004</td>
<td>Razzi et al.</td>
<td>Case report</td>
<td>Postmenopausal endometriosis not responding to surgical or medical treatment</td>
<td>L</td>
<td>9</td>
<td>1</td>
<td>Pain relief, reduced lesion size</td>
</tr>
<tr>
<td>2004</td>
<td>Ailawadi et al.</td>
<td>Pilot prospective</td>
<td>Premenopausal endometriosis not responding surgical or medical treatment</td>
<td>L+NEA</td>
<td>6</td>
<td>10</td>
<td>90% pain relief, 100% reduced lesion size</td>
</tr>
<tr>
<td>2004</td>
<td>Soysal et al.</td>
<td>Randomized Case report</td>
<td>Premenopausal endometriosis</td>
<td>A+GnRH-a</td>
<td>6</td>
<td>80</td>
<td>100% pain relief</td>
</tr>
<tr>
<td>2004</td>
<td>Shippen et al.</td>
<td>Case report</td>
<td>Premenopausal endometriosis not responding surgical or medical treatment</td>
<td>L+P</td>
<td>6</td>
<td>2</td>
<td>Pain relief, reduced lesion size</td>
</tr>
<tr>
<td>2005</td>
<td>Amsterdam et al.</td>
<td>Pilot prospective</td>
<td>Premenopausal endometriosis not responding surgical or medical treatment</td>
<td>A+OC</td>
<td>6</td>
<td>10</td>
<td>93% pain relief</td>
</tr>
</tbody>
</table>

Note: A = anastrozole; L = letrozole; L+NEA = letrozole+norethindrone acetate; A+GnRH-a = anastrozole+gonadotropin-releasing hormone analogue; L+P = letrozole+P; A+OC = anastrozole+oral contraceptive.

Conclusion

■ AIs administered in combination with an ovarian suppressant represent promising and novel treatments.
■ Patients with endometriosis who do not respond to existing treatments appear to obtain significant pain relief from AIs.
■ Most of the AI regimens are fairly simple, consisting of taking one or two tablets a day.
■ Finally, the side-effect profiles of the AI regimens (including a progestin or OC add-back) are more favorable compared with treatments using GnRH-a or danazol.
■ Some of these regimens may potentially be administered over prolonged periods of time.
New Drugs?

- Local aromatase gene expression and enzyme activity were demonstrated in endometriotic implants
- Recently, we showed that aromatase enzyme inhibitors treat endometriosis successfully
- However, current aromatase inhibitors cause total body estrogen deprivation regardless of promoter use
Aromatase and other steroidogenic genes in endometriosis: translational aspects

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P11 regulates aromatase synthesis in endometriotic cells

COX-2 → PGH₂ → PGE₂ → cAMP → Co-Act (1) → C/EBP → Enh → SF-1 → Co-Act (2) → CRS → NRHS → P11 II AROMATASE

- Placenta
- Skin/Adipose
- Brain
- Bone
- Adipose/Cancer
- Ovary/Endometriosis

I.1 I.2a I.4 I.7 I.f I.6 I.3 ATG Coding region

COMMON SPLICE SITE

AG/GACT

PGH₃ → COX-2

CYP19

TELOMERE CENTROMERE
What is NaBu?

- A natural compound
- A four carbon fatty acid
- Inhibits histone deacetylase activity
- Inhibits growth arrest and induces cell differentiation
- Induces apoptosis in vitro in cancer cells

**MECHANISM** of anti-neoplastic activity?
Why it is important to test this compound in endometriosis?

- orally administered
- clinically evaluated in a phase I study for a solid tumor
- inhibits aromatase expression
- A NEW DRUG for the treatment endometriosis?
Endometriotic Cells 24h Treatment

![Bar chart showing PMol/mg values for Control, 5 mM/mL, 10 mM/mL, and 15 mM/mL treatments. There are asterisks indicating statistical significance: *p<0.01 and **p<0.01.]
The effect of NaBu on JEG-3 Cells (Choriocarcinoma cell line)

![Graph showing the effect of NaBu on cAMP in JEG-3 Cells]
Endometriotic Cells
24h Treatment

![Bar graph showing PMol/mg for different treatments](chart.png)

- Control
- PGE$_2$
- PGE$_2$+NaBu
- cAMP
- cAMP+NaBu

* $p<0.001$
Endometriotic Cells
12h pretreatment + 24h treatment

Control NaBu PGE\(_2\) PGE\(_2\)+NaBu cAMP cAMP+NaBu

*p<0.05 **p<0.01 ***p<0.001
NaBu inhibits ATF-2 binding to Promoter II

A: ATF-2
B: IgG
C: Input

NaBu (mM/mL) 0 5 10 15

A

B

C
Animal Models of Endometriosis
NaBu use in an animal model
Vitamins, Food intake and Prevention

- Vitamin D (ongoing study)
- Diet
- & More...
Thank You…

Northwestern Group

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