Stress and endometriosis

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Endometriosis

Family demands

Social expectations

Infertility

Uncertainty

Pain

Sexual dysfunction

Work absenteeism

STRESS

Depression
Stress symptoms

Physical

Psychological

Nery et al., unpublished data
Stress intensity

Lazzeri et al., Gynecol Obstet Invest 2015; Fertil Steril 2015
Stress correlates with Pain

Coping

Donatti et al., *Einstein* 2017;15(1):65-70
Mindfulness

RCT, infertile women
Trial registration # RBR-7by76r

Nery et al., manuscript submitted
Mechanisms
Fig. 1. Alterations in plasma glucose and PRL levels induced by restraint (○), ether anaesthesia (●), laparotomy under ether anaesthesia (△), or acute haemorrhage (▲) in male rats. The first blood sample (0 min) was obtained from awake freely moving rats and all samples were withdrawn through a venous catheter chronically implanted. Restraint stress: the...
FIG. 1. The effects of ether inhalation on plasma PRL in male and female rats. Asterisks indicate significant differences between sham-operated (open circles) and pituitary-grafted (dark circles) rats ($P < 0.05$, t-test). Data are means ± SEM of 8–13 animals.
Prolactin in women with endometriosis

Table 3. Prolactin and cortisol concentrations in serum and peritoneal fluid of fertile women without endometriosis, of infertile women with stage I-II endometriosis and stage III-IV endometriosis.

<table>
<thead>
<tr>
<th>Parameters analyzed</th>
<th>Fertile women without endometriosis (N = 21)</th>
<th>Infertile women with stage I-II endometriosis (N = 18)</th>
<th>Infertile women with stage III-IV endometriosis (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactin in serum (ng/mL)</td>
<td>13.2 ± 2.1a</td>
<td>23.4 ± 3.7b</td>
<td>28.9 ± 2.1b</td>
</tr>
<tr>
<td>Prolactin in peritoneal fluid (ng/mL)</td>
<td>11.4 ± 1.3</td>
<td>13.5 ± 1.34</td>
<td>14.1 ± 1.56</td>
</tr>
<tr>
<td>Cortisol in serum (ng/mL)</td>
<td>10.5 ± 1.4a</td>
<td>14.8 ± 1.2a</td>
<td>20.1 ± 1.3b</td>
</tr>
<tr>
<td>Cortisol in peritoneal fluid (ng/mL)</td>
<td>4.4 ± 0.13</td>
<td>4.8 ± 0.21</td>
<td>4.4 ± 0.11</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD. Different letters indicate statistically significant differences between means. Absence of letters indicates that there is no significant difference between groups (P < 0.05, Kruskal-Wallis test, followed by Dunn test).


Bilibio et al. Gynecol Obstet Invest 2014
Cortisol in women with endometriosis

Inconsistent findings
No correlation with pain
Brain-derived neurotrophic factor in plasma of women with endometriosis

Authors
Andrea Giannini, Fiorella Bucci, Stefano Luisi, Vito Cela, Nicola Pluchino, Sara Merlini, Elena Casarosa, Marinella Russo, Alessandra Cubeddu, Diana Daino, Paolo G. Artini, Andrea R. Genazzani

Assessing brain-derived neurotrophic factor as a novel clinical marker of endometriosis

Authors
Jocelyn M. Wessels, Ph.D., Vanessa R. Kay, B.Sc., Nicholas A. Leyland, M.D., Sanjay K. Agarwal, M.D., and Warren G. Foster, Ph.D.

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Plasma brain-derived neurotrophic factor in women with pelvic pain: a potential biomarker for endometriosis?

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$r = 0.489$  
$p<0.0001$
Urocortins

Urocin 1

Florio et al, Obstet Gynecol 2007
Endometriosis
Swim Stress for 10 days before endometriosis induction

**Figure 3.** Prior stress increases implant frequency and severity.

Cuevas *et al.* Reprod Sci 2012
Swim Stress after endometriosis induction
Lesion size

Cuevas et al. Reprod Sci 2018

Appleyard et al. Reprod Sci 2015
Swim Stress after endometriosis induction
Mast Cells

Cuevas et al. Reprod Sci 2018

Appleyard et al. Reprod Sci 2015
Swim Stress after endometriosis induction
Nerve Growth Factor expression in the Uterus

Cuevas et al. Reprod Sci 2018
Psychological Stress
Psychological Stress

Cell proliferation

Lesion growth

VEGF

Macrophages

Microvessels

Stress: predator outside the cage for 24h
Model: suture of small uterine fragments from donor mice in the peritoneal wall

Guo et al. RBM Online 2016
Psychological Stress
Adrenergic activation of lesions
Effects of stress are prevented by propranolol

Stress: immobilization
Model: ip injection of endometrial fragments from donor mice

Long et al. Hum Reprod 2016
Psychological Stress
Adrenergic activation of lesions
Effects of stress are prevented by propranolol

Stress: immobilization
Model: ip injection of endometrial fragments from donor mice

Long et al. Hum Reprod 2016
Endometriosis

STRESS

Adrenergic output
Cell proliferation
Angiogenesis
Macrophage / mast cell infiltration
What is known

• Women with endometriosis have increased stress prevalence and severity
• Stress severity correlates with pain, disease extension, coping and depression
• HPA axis and adrenergic pathways are dysregulated in endometriosis
• Stress before and/or after endometriosis onset promotes disease mechanisms and accelerates lesion growth in rodents
What is unknown

• Is chronic stress a cause of endometriosis?
• Can we reduce the risk of developing endometriosis by avoiding or treating chronic stress?
• Are anti-stress therapies helpful to reduce symptoms and lesions in women with endometriosis?
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