International Federation of Gynecology and Obstetrics
Endometriosis:  
Medical and Surgical Management of Pain and Infertility

FIGO  
2016

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A disease characterized by the presence of endometrium-like epithelium and stroma outside the endometrium and myometrium.

Intrapelvic endometriosis can be located superficially on the peritoneum (peritoneal endometriosis), can extend 5 mm or more beneath the peritoneum (deep endometriosis) or can be present as an ovarian endometriotic cyst (endometrioma).
Endometriosis Symptoms

- severe dysmenorrhoea
- deep dyspareunia
- chronic pelvic pain
- ovulation pain
- cyclical or perimenstrual symptoms (e.g. bowel or bladder associated) with or without abnormal bleeding
- infertility
- chronic fatigue.

The predictive value of any one symptom or set of symptoms remains uncertain as each of these symptoms can have other causes (and a significant proportion of affected women are asymptomatic)

Impact on quality of life in the last 12 months

- Activities negatively impacted by symptoms (n=2,753 in eight countries)

  - Sexual life: 50%
  - Relationship: 36%
  - Family: 35%
  - Performance at work/school/university: 35%
  - Housekeeping: 34%
  - Attendance at work/school/university: 32%
  - Social activities: 29%
  - Sports: 21%
  - Other: 9%

Endometriosis affects an estimated **1 in 10 women** during their reproductive years.

Rogers et al, Reprod Sci 2009;16:335-346

1,761,687,000 women in the world aged 15 - 49

World Bank Population Projection Tables by Country and Group for 2010

**176 million women worldwide during the prime years of their lives**

Hummelshoj. 02/2010
## Socio-economic burden

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>DIAGNOSTICS</th>
<th>SURGERY</th>
<th>HEALTH CARE</th>
<th>OTHER</th>
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Consensus on current management of endometriosis

Neil P. Johnson¹,²,³,* and Lone Hummelshoj¹, for the World Endometriosis Society Montpellier Consortium†

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World Endometriosis Society Consensus on the Classification of Endometriosis

• Accepted for publication July 28, 2016, Human Reproduction

World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype data collection in endometriosis research

Christian M. Becker, M.D., a,b Marc R. Laufer, M.D., c,d,e Pamela Stratton, M.D., f Lone Hummelshøj, g Stacey A. Missmer, Sc.D., d,e,h,i Krina T. Zondervan, D.Phil., a,b,i and G. David Adamson, M.D., a,k for the WERF EPHect Working Group

For a **definitive diagnosis** of endometriosis visual inspection of the pelvis at **laparoscopy is the gold standard** investigation, unless disease is visible in the vagina or elsewhere.


The **diagnostic delay** is on average **7 years** depending on health care settings.

Positive histology confirms the diagnosis of endometriosis; negative histology does not exclude it. Whether histology should be obtained if peritoneal disease alone is present is controversial: visual inspection is usually adequate but histological confirmation of at least one lesion is ideal.

In cases of ovarian endometrioma (>4 cms in diameter), and in deeply infiltrating disease, histology should be obtained to identify endometriosis and to exclude rare instances of malignancy.
Endometriosis Investigations (i)

Compared to laparoscopy, trans-vaginal ultrasound (TVS) has no value in diagnosing peritoneal endometriosis, but it is a useful tool both to make and to exclude the diagnosis of an ovarian endometrioma.

TVS may have a role in the diagnosis of disease involving the bladder or rectum.

At present, there is **insufficient evidence** to indicate that magnetic resonance imaging (**MRI**) is a useful test to diagnose or exclude endometriosis compared to laparoscopy.

**MRI reserved** for **equivocal ultrasound** results in cases of **rectovaginal** or **bladder** endometriosis.

Serum CA-125 levels may be elevated in endometriosis. However, measuring serum **CA-125** levels has **no value** as a diagnostic tool.

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MANAGEMENT OF PELVIC PAIN ASSOCIATED WITH ENDOMETRIOSIS
Comprehensive Management Approach

- Life-altering disease for many patients
- Comprehensive evaluation/plan/treatment
  - NSAID’s (+/-), analgesics (1)
  - Healthy lifestyle: diet, exercise, mind-body
  - Self-help organizations, personal counseling
  - Referral as necessary (e.g. pain clinic, other)
  - Anxiolytics, antidepressants
- Empathetic approach
- Focus on objective activities of daily living

**Results of Ovarian Suppression**

- Initial pain relief ~ 75-90% (1)
- Ovarian suppression drugs equivalent (1-7)
- GnRHa more effective if initial failure (1)
- Median time pain recurrence ~ 6 months (8, 9)
- ? Recurrence related to stage
  - Minimal recurrence higher than mild or moderate (10)
  - Pain relief at 5 years: minimal 65%, severe 33% (11)

Add-back Therapy

• **Purpose**
  – Eliminate or **reduce bone loss**
  – Ablate side effects of **hypoestrogenism**
  – Maintain or enhance therapeutic efficacy

• **Multiple regimens**
  – **Estrogen (CEE) 0.625 mgm plus norethindrone acetate 5 mgm daily** (1)

Duration of Treatment With GnRHa

- **Initial** Treatment
  - 6 months generally recommended
  - 3 months equivalent to 6 months (1)

- **Retreatment**
  - 6 months generally recommended
  - 3 months equivalent to 6 months (2)

- **Continuous**
  - With add-back?

Other Medical Treatments

• Pentoxifylline (1)
  – No benefit for pain or infertility

• Complementary Alternative Medicine, Chinese Herbal Medicine (2)
  – ? Comparable to gestrinone for pain relief, with fewer side effects
  – May be more effective than danazol:
  – More rigorous research is required

• Anti-TNF-alpha (3)
  – Insufficient evidence to use for pain

• Continuous vs. cyclic oral contraceptives
  –

• Levonorgestrel Intrauterine System (5)
  – Growing evidence useful

• Aromatase inhibitors (e.g. letrozole) (6)
  – Promising effect on pain, but dearth of evidence

• Rosiglitazone or valproic acid weak evidence

• Anti-angiogenesis research only

• ? GnRH antagonists (e.g. elagolix)

• ? Antiprogestins (e.g. mifepristone)

Results of Laparoscopic Treatment: Summary

- Pain-free: 37-100% “Estimate”
- Improved: 18-80% 80%
- No change: 0-36% 15%
- Worse: 0-13% 5%

- Recurrence
  - 1 year: 10-15%
  - 5 years: 20-40%

- Laparoscopy
  - Beneficial (1)
  - OR = 7.72 (2)

Severe Endometriosis and Pain: Results of Laparoscopic Treatment

- **Severe Disease**
  - Initial relief superior to minimal/mild
  - Higher risk of recurrence
  - Recurrence rates 10-20% per year

- **Deep rectovaginal lesions**
  - Postoperative relief 70%
  - Recurrence of pain 33%
  - Severe pain at 5 years 5%

- **“Primum non nocere”**

Chronic Pain and Adhesions: What is the relationship?

• Role of adhesions unclear
  – ? Distortion of anatomy
  – ? Other

• No documented relationship with
  – Pain severity and/or duration (1)
  – vs. adhesion location and/or extent

• Staging systems not helpful

• Adhesions in 25 % of CPP vs. 17 % of non-CPP (2)

Chronic Pain and Adhesions: Results of Adhesiolysis

- Role of adhesiolysis **unclear**
  - Uncontrolled studies
  - Pain relief 60-90% (1)
  - Randomized clinical trials Not effective (2)

- Incidence of reformation of adhesions (3)
  - Initially minimal/mild 33%
  - Initially severe 67%
  - Initially extensive 90%

- Adhesion barriers (non-resorbable) may help (4)

Endometriosis and Pain: Role of LUNA

- LUNA + Endo Ablation (1,2)
  - RCT laser vs. no treatment
  - Diagnostic laparoscopy only 22.6%
  - Endometriosis laser ablation 62.5%
  - Mild and moderate (excl. minimal) 73.7%
  - Long term (88.6 mos: 77-104 mos) 60%

- Cochrane review 1999: Insufficient evidence (3)
- Nerve interruption for dysmenorrhea: Limited evidence (4)
- RCT: no reduction in recurrence by adding LUNA (5)
- Reasonable if already operating &/or uterosacral nodules

(2) Jones et al. JSLS. 2001;5:111-5.
Presacral Neurectomy: Results and Indications

- Results of published studies
  - PCRT: effective for midline dysmenorrhea (1)
  - PCRT: not effective (2)
  - Cochrane review: insufficient evidence (3)
  - PCRT: relief at 1 year (4)
    - Stage I-III 85%
    - Stage IV 75%
    - Deep rectovaginal 57%

- Indications for use of presacral neurectomy
  - Highly selected patients
  - Primarily midline dysmenorrhea
  - Excellent surgeons
  - Success rate 37-89% (5)

Endometriosis and Pain: Role of Appendectomy

• Incidence (1-3)
  – Involved in 17% of patients with bowel endo
  – Pathology in 50-80% of “endo + pain” patients

• Results of appendectomy (4)
  – Complete relief in up to 97% of patients

• Indications
  – Chronic right-sided pain and endometriosis

(2) Lyons et al. JAAGL. 2001;8:522-4.
(3) Harris et al. JAAGL. 2001;8:536-41.
Hysterectomy and/or Oophrectomy

- **Indications**
  - Severe symptoms + failure other treatment + no fertility desires (1)
  - 20% of chronic pain patients (2)
- **Hysterectomy benefits**
  - Retrograde menstruation
  - Adenomyosis
  - Other (e.g. myomas)
- **Oophrectomy benefits**
  - Endometriomas
  - Hypoestrogenism
  - Retrograde menstruation
  - ? Improve outcome for bladder/bowel endometriosis(3)

Endometriosis and Pain: Results of Hysterectomy +/- Oophrectomy

- Hysterectomy alone
  - Pain relief 80%
  - Persistent pain 22% (1)
  - Symptom recurrence 15-30%
  - Additional surgery 5-10%
- Hysterectomy with oophrectomy
  - Symptom recurrence 10%
  - Additional surgery 3-4% (2)
  - Hormonal replacement appropriate (3)
- If pain recurs, consider
  - Ovarian suppression
  - Re-operation for resection of residual disease
  - Re-operation for oophrectomy if not already performed
  - Ovarian remnant (4)

Pain Outcomes: Surgery vs. Ovarian Suppression

• Initial surgery
  – Superior to ovarian suppression
  – in patients with more severe disease

• Not different with
  – Minimal/mild disease
  – Chronic pelvic pain
  – Previously resected disease
Management of Endometriosis: Combined Therapy

Medical therapy prior to surgery
  – Possibly useful: pain management prior to scheduled surgery in more severe cases

• Medical therapy following surgery
  – If known or suspected implants remain
  – For pain management
    • OC’s first choice in most cases
    • GnRHa for persistence/recurrence
    • Danazol, progestogens as necessary

• Insufficient evidence for benefit before or after (2)
• Experimental medical interventions (2)
  – Aromatase inhibitors, gestrinone, antiprogestins, SPRM’s (RU-486), GnRH antagonists, TNF alpha inhibitors, angiogenesis inhibitors, pentoxifyline & other immunomodulators, MMP’s, E receptor beta agonists

MANAGEMENT OF INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS
Biologic Mechanisms That Might Link Endometriosis and Infertility

• Distorted pelvic anatomy
• Altered peritoneal function
• Altered hormonal & cell-mediated function
• Endocrine and ovulatory abnormalities
• Impaired implantation
• Oocyte and embryo quality
• Abnormal uterotubal transport

**Ovarian Suppression For Fertility**

- No evidence of fertility benefit from ovarian suppression: 25 RCTs (1)
  - Costs and delay time to pregnancy
- GnRHa treatment before IUI is not recommended
  - 1 RCT suggesting benefit IVF and IUI
  - Insufficient evidence to determine benefit in IUI alone (2)

Infertility Outcomes: Ovarian Suppression and Surgery

- Adjunct to Surgery (16 RCTs)
  - Preoperative
    - No data conclusively show benefit (1)
  - Postoperative
    - No data show benefit (1)
    - Does not improve fertility (A. Level 1b)(2,3)
- Delay in attempting pregnancy, costs, side effects render *ovarian suppression not appropriate*

(3) RCOG. Guideline No XX. 2005.
# Endometriosis Treatment

## Stage I and II

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Unexplained infertility</th>
<th>Endometriosis-associated infertility</th>
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</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Guzik et al. (27)</td>
<td>Deaton et al. (28)</td>
</tr>
<tr>
<td>No treatment or intracervical insemination</td>
<td>0.02</td>
<td>0.033</td>
</tr>
<tr>
<td>IUI</td>
<td>0.05&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Clomiphene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene/IUI</td>
<td></td>
<td>0.095&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.066</td>
</tr>
<tr>
<td>Gonadotropin/IUI</td>
<td>0.09&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.129&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>IVF</td>
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<tr>
<td></td>
<td></td>
<td>0.222&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

<sup>a</sup> P<.05 for treatment vs. no treatment.


**OS + IUI Appropriate BEFORE Laparoscopy**
Laparoscopy Prior to OS/IUI

- Insufficient data to recommend laparoscopic surgery prior to OS/IUI
- Unless
  - History
  - Evidence of anatomic disease
  - Sufficient to justify the physical, emotional, financial and time costs

When To Do Laparoscopy?

- Younger women (<37 years of age)
- Short duration of infertility (<4 years)
- Normal male factor
- Normal or treatable uterus
- Normal ovulation, or
- Easily treatable ovulation disorder
- Limited prior treatment
- Appropriate candidate for laparoscopy
  - “Treatable” disease reasonably suspected (NNT)
  - OR= 1.66 (1)
  - No contraindications to laparoscopy
  - Patient accepts 9-15 months attempting before IVF

Infertility Outcomes: Surgery

- Moderate/Severe Disease
  - Severe anatomic distortion
  - Very low background pregnancy rate
  - Numerous uncontrolled trials show benefit
  - L/S > laparotomy: RR 1.87; p=0.031 (1)
  - Surgery indicated for invasive, adhesive, cystic endometriosis (Evidence level 3) (2,3)
  - Conservative surgical therapy with laparoscopy and possible laparotomy are indicated. (4)
  - Repeat surgery rarely indicated (4)

(2) RCOG Guideline No. 24. 2006.
(3) ESHRE Endometriosis Guideline. HR 2014;29(3):400-12.
ESTIMATING POST-OPERATIVE PREGNANCY RATES
Fecundity (f) Following Treatment of Endometriosis

Endometriosis Fertility Index (EFI) Surgery Form

Endometriosis fertility index surgery form.

ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

<table>
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<tr>
<th>Score</th>
<th>Description</th>
<th>Left</th>
<th>Right</th>
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<tr>
<td>4</td>
<td>Normal</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3</td>
<td>Mild Dysfunction</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2</td>
<td>Moderate Dysfunction</td>
<td>☐</td>
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<tr>
<td>1</td>
<td>Severe Dysfunction</td>
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<tr>
<td>0</td>
<td>Absent or Noninvasive</td>
<td>☐</td>
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</table>

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If a uterus or adnexa is absent or noninvasive, that side should be scored the same as the side that was present. The LF score is calculated by dividing the lowest score on one side by the score on the other side.

ENDOMETRIOSIS FERTILITY INDEX (EFI)

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<th>Factor</th>
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<td>L.F. Score ≤ 7 or ≤ 8 (high scores)</td>
<td>3</td>
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<tr>
<td>If age is 36 to 39 years</td>
<td>1</td>
<td>L.F. Score ≤ 4 to ≤ 6 (medium score)</td>
<td>2</td>
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<tr>
<td>If age is ≥ 40 years</td>
<td>0</td>
<td>L.F. Score &gt; ≤ 3 (low scores)</td>
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<tr>
<td>Hydrosalpinx</td>
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<td>Presence</td>
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<tr>
<td>Hydrosalpinx ≥ 5 mm</td>
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<tr>
<td>Hydrosalpinx ≥ 10 mm</td>
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<td>Hysterosalpinge</td>
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<td>Presence</td>
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<td>Hysterosalpinge ≥ 5 mm</td>
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<td>Light Peritoneal Adherence</td>
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MANAGEMENT OF ENDOMETRIOMAS
Endometriomectomy: Surgical Principles

• In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart et al., 2008).

• The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery. GPP

Endometriomas: Results of Treatment

- Initial pain relief: 60-100%
- Recurrence rates (1-5):
  - Following cyst stripping: <10%
  - Following cyst drainage: ~20%
  - Ultrasound recurrence: 12%
- If cyst recurs, pain present: 73% (5)

Management Summary (1)

- **Pelvic Pain**
  - Initially analgesics, NSAID’s, OC’s
- **Infertility** with other factors normal
  - CC 100mg CD 3-7 + IUI for 3-6 cycles, depending on age
  - Other ovarian stimulation regimen
- **Persistence of pain and/or infertility** without other significant infertility factors
  - Laparoscopy, diagnostic & operative
Management Summary (2)

• Surgery well performed is effective treatment
  – All stages endometriosis & endometriomas
  – Infertility and Pain
• Ovarian suppression generally effective for pain
• Repeat surgery
  – Limited benefit for fertility, some for pain
• Pre-IVF treatment ONLY
  – Suppression: reasonable extensive disease
  – Surgery: ? large > 3-4 cm endometriomas
• Endometriosis NO effect on IVF LBR except
  – Extensive disease +/or endometriomas

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THANK YOU!