Treatment of endometriosis

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Endometriosis

- Pain: 50% with, 50% without
- Infertility: 50% with, 50% without
- Gruppo Italo Belga 2017
THE SCIENTIST: ENDOMETRIOSIS

What is endometriosis – types
What is the prevalence – pain – infertility
Which treatment?

THE CLINICIAN treats women

- With pain
- With infertility
- Using research knowledge
  experience
  evidence

EBM: Evidence Based Medicine
## Basics of endometriosis lesions

<table>
<thead>
<tr>
<th></th>
<th>Prevalence</th>
<th>Pain</th>
<th>Infertility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtle</strong></td>
<td>80%</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td><strong>Typical</strong></td>
<td>25%</td>
<td>in 50% +</td>
<td>?</td>
</tr>
<tr>
<td><strong>Cystic</strong></td>
<td>10%</td>
<td>in 80% +++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Deep</strong></td>
<td>2-3%</td>
<td>in 95% ++++</td>
<td>??</td>
</tr>
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</table>

- Adenomyosis
- Peritoneal pockets – Müllerianosis - Choristoma
What is endometrosis?

Subtle and microscopic endometriosis
• Not associated with pain
• Not associated with infertility

Glands and stroma outside the uterine cavity
• Are not always pathology
• We need another definition of endometriosis
Bowel resection: 10-20% positive margins


- **27%** Roman Horace fertil Steril 2016

**Bowel occult microscopic endometriosis in resection margins in deep colorectal endometriosis specimens has no impact on short-term postoperative outcomes**

Horace Roman, MD PhD\(^1\), Clotilde Hennetier, MD\(^1\), Basma Darwish, MD\(^1\), Alexandra Badescu, MD\(^{1,3}\), Marie Csanyi, MD\(^4\)

Moutaz Aziz, MD\(^4\), Jean-Jacques Tuech, MD PhD\(^5\), Carole Abo, MD\(^1\)
SHOULD WE REVISE THE DEFINITION OF ENDOMETRIOSIS?

ENDOMETRIOSIS SURGERY AND ERADICATION OF ALL ENDOMETRIAL CELLS AND STROMA

CONCLUSION

A tentative conclusion might be that the occurrence of small, macroscopically invisible, nests of endometrial glands and stroma is much more frequent than we thought on the peritoneum, in pelvic lymph nodes, and inside the bowel walls, at least in women with endometriosis. It is also strongly suggested that most of these endometrial cell nests do not constitute a clinical pathology or develop into more severe lesions, nor do they cause pain or infertility.
Diagnosis and treatment during laparoscopy

- Is this a cause of infertility?
If no pain and no infertility

• Deep endometriosis nodule
  • If not growing >90% : no therapy
  • If growing : excise
  • Before IVF: excise

• Cystic ovarian endometriosis
  • If mobile – no pain : cystic corpus luteum ?
  • If young – persistent > 1 year
    ? THL + coagulation
Infertility and endometriosis

- We know: Infertility > 2 years
  - >80% have subtle and microscopic endometriosis
  - 50% have typical endometriosis
    Prevalence increases with duration of infertility
  - ... cystic ovarian endometriosis by ultrasound
  - Deep is a pain issue

- Mechanism of infertility ??
Infertility: when a laparoscopy?

- **Yes**
  - If associated symptoms of pain
  - If (big) cystic endometriosis

- **?** When infertility is the only symptom
  - Calculated risk: overtreatment
    - Missing treatable pathology
  - The exact place of THL is still unclear

- **No** when IVF is anyway indicated
During Diagnostic Laparoscopy (THL ?)

- If surgery is indicated
  - Perform surgery if skilled
  - Otherwise refer

- 3 Groups
  - **Surgery indicated** for reasons other than fertility
    - Very severe pain + deep endometriosis, cystic ovarian endo, frozen pelvis
    - Symptomatic myoma
  - **Surgery indicated** beyond reasonable doubt
    - Hysteroscopic polypectomy, small myomectomy, septum
    - Superficial endometriosis
    - Filmy peritubal-peri-ovarian adhesions
  - **Unclear** indications Surgery<->IVF
    - Ovarian drilling (under water) for PCO
    - Deep endometriosis without pain, asymptomatic adhesions
    - Smaller cystic ovarian endo
    - Tubal occlusion: hydrosalpinx, cornual block
Pelvic Pain

- Endometriosis pain is not very specific
- Know the other causes of pain
- For images see www.gynsurgery.org/pelvic-pain
Gynaecological Pain: Where?

- Below the umbilicus eventually radiating to the back
Gynaecological Pain: Where?

- Below the umbilicus eventually radiating to the back

Isolated back pain is not gynaecological
Gynaecological Pain: Radiation

- Below the umbilicus eventually radiating to the back.
- Ovarian pain can be lateralised and radiates up to the knee, anterior medial side.

Below the knee is not gynaecological.
Gynaecological Pain: Radiation

• Perineal radiation is **pathognomonic** for bowel pain ie rectum up to rectosigmoid not mentioned spontaneously !!!
Sacro ileac joint: Radiation

- Back pain and ipsilateral fossa pain
- Gets worse during rest eg at night

Isolated back pain is not gynaecological
Frequent cause of unnecessary surgery
Gynaecological Pain: Cyclicity

- Endometriosis pain typically increases during menstruation.
- Dyschesia in larger deep endometriosis, evt + blood.
- Mictalgia for bladder endometriosis.

But all pain increases during menses..... increase thus is not pathognomonic for endo.
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EBM: Evidence Based Medicine
Evidence in medicine (population)

- Laws of physics
- Observation can be biased or unclear
  - Patient: placebo effect **blinded**
  - Doctor: observer bias **double blinded**
  - Allocation bias **randomized**
  - Unclear: male or female?
- The pyramid of evidence
  - Therapy
    - RCT’s + meta-analysis
    - Cohort – case control
  - Opinions
- Diagnosis
  - Sensitivity and specificity (!!!! not significance)

The Evidence
EBM and Guidelines on endometriosis

- “EBM has become considered a movement in crisis with the realization that ....”
  - clinical guidelines have become unmanageable
  - that statistically significant may have little clinical relevance
  - that EBM poorly maps on complex multimorbidity
  - That EBM is not suited for rare events

Greenhalgh T, Howick J, Maskrey N. Evidence based medicine: a movement in crisis? Bmj 2014; 348:g3725

- How to interpret a not perfect RCT ??
  - Eg when blinding is impossible as medical treatment of endo
Evidence based medicine in endometriosis surgery: the double blind randomised controlled trial versus the consensus-opinion of experts.

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- Non-published evidence
- Experience
- Accidents
- In guidelines
EBM and guidelines for Endolethriosis

• J. Obstet Gynecol Canada guidelines 2017

The “Primary Dysmenorrhea Consensus Guideline” in this issue of the Journal is a nice review of the literature, but clinically a missed opportunity. The major problem is that evidence is limited to published evidence, and absence of evidence is not considered. Clinical practice is a compre-
http://www.gynsurgery.org/guidelines-by-surgeons/

The clinician

List of surgery guidelines - All surgeons invited to contribute

Endometriosis surgery
- Medical therapy before and after surgery for endometriosis
- Diagnosis and treatment of typical lesions
- Diagnosis and surgery of cystic ovarian endometriosis
- Diagnosis and surgery of deep endometriosis

General surgical guidelines
- Good surgical practice (GSP)
- Adhesion and pain prevention
- Antibiotics before and after surgery
- Electrosurgery
- Hysterectomy indications and technique

Reproductive surgery
- Hydrosalpinx and tubal occlusion
- Trans-hysteroscopy

Pelvic floor surgery
- Oncologic surgery
- Hysteroscopic surgery
The clinician

Medical therapy before and after endometriosis surgery

Guidelines by surgeons for surgeons

What is different in comparison with ESHRE guidelines below (1)

Medical therapy Before surgery

Facts

Medical therapy for endometriosis suppresses ovarian function. The lack of estrogens inactivates endometriosis lesions (as after menopause) or the high doses of progestogens will decidualize (as during pregnancy) them.

Subtle and probably other lesions (typical, smaller cystic or some deep) thus risk to be missed since less visible. Cystic ovarian endometriosis will sometimes decrease slightly in volume. Deep endometriosis will shrink and probably becomes less vascularized.

Potential Benefits

The absence of ovulation and of a corpus luteum can be a surgical advantage. A corpus luteum indeed bleeds easily when touched during ovarian surgery, with subsequent risks of ovarian damage by coagulation and later adhesion formation. There should be less confusion between a cystic corpus luteum and cystic ovarian endometriosis. Practically however, a cystic corpus luteum can persist for more than 6 months under oral contraception.

Adverse effects

Subtle and typical lesions risk to be missed during surgery. Thus the diagnosis is not made and so is the excision.

Cystic ovarian endometriosis. Smaller lesions might be missed. Surgical excision of is not facilitated by medical therapy.
The clinician

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Non surgeons: Lone Hummelshøj, www.endometriosis.org

Discussion

The ESHRE guidelines (1) for medical therapy before and after surgery for endometriosis are evidence based i.e. based on the published evidence only. These guidelines are biased and not that useful since they do not take into account observational medicine and surgical experience.

The ESHRE Guidelines 1 are published below for comparison

Hormonal therapy before surgery

Guideline: “Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis (A evidence)” There is insufficient evidence from the studies identified to conclude that hormonal suppression in association with surgery for endometriosis is associated with a significant benefit with regard to any of the outcomes identified. There may be a benefit of improvement in AFS scores with the pre-surgical use of medical therapy. (2)

Hormonal therapy after surgery

Guideline: “Clinicians should not prescribe adjunctive hormonal treatment in women with endometriosis for endometriosis-associated pain after surgery, as it does not improve the outcome of surgery for pain (A) GDG concluded that there is no proven benefit of post-operative hormonal therapy (within 6 months after surgery), if this treatment is prescribed with the sole aim of improving the outcome of surgery. The GDG states that there is a role for prevention of recurrence of disease and adjunctive treatment in women medically treated for endometriosis. (A) The choice of hormonal treatment is rig...
Medical therapy before/after endometriosis surgery

• Before surgery
  • Absence of a corpus luteum is an advantage  S-A
  • No advantage for outcome  S-A
  • Risk to miss lesions  S-A

• After surgery
  • could decrease recurrences  S-B
  • not indicated to replace complete surgery  S-A
Diagnosis and treatment of superficial endo

• Diagnosis
  – subtle endometriosis
    • A laparoscopy is needed
    • Clinical exam and Imaging are not useful
  – Typical endometriosis
    • A laparoscopy is needed
    • Imaging is not useful
    • Clinical exam is generally negative
    • Clinical exam sometimes reveals shots in uretersacra

• Treatment
  – Vaporisation or excision, not coagulation
    • S-A
  – Medical therapy
    • Is not recommended without a diagnosis
    • Can be given in order to decrease recurrences
    • S-A
    • S-V
Diagnosis and treatment during laparoscopy

- Is this a cause of pain ??? infertility ?
Surgery Results: typical: infertility

- Infertility
  - Surgical treatment: Endocan study (R. Maheux et al)
    Stage I and II and no other infertility factor

• Discussion
  - Patient not blinded to treatment
  - Increase in treatment or decrease in non-treatment?
  - LUF and stress
  - Trait anxiety and fertility
Results of treatment

• Infertility

• Surgical treatment: Gruppo Italiano per lo studio dell’Endometriosi (Hum Reprod 99,14,1332-1334)

Stage I and II and no other infertility factor

RCT

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Typical: Surgery Result of pain

• Half of them have less pain
  • Significant RCT (Sutton)
  • Strong placebo bias ??

• We cannot judge extend or depth without excision
Conclusions: surgery for subtle - typical

**The clinician**
- Is it acceptable not to treat during laparoscopy?
- If you treat: excision

**The Evidence**
- Infertility?
- Typical: pain decreased by 50%
- No good RCT

**Research**
- Subtle: not pathology
- Typical associated with infertility, LUF, pain
Diagnosis of cystic ovarian endometriosis

- Clinical suspicion of ovarian involvement when lateralized hypogastric pain with radiation to the anterior inside of the upper thigh
- A cystic corpus luteum can persist for at least 6 months during medical treatment
- Diagnosis by transvaginal ultrasound
  - Arguments pro cystic ovarian endometriosis
    - Specific characteristics
    - Associated with adhesions
  - Arguments contra
    - Acute onset of pain
    - Mobile without adhesions
- Diagnosis during laparoscopy
  - Chololate cyst with adhesions
  - The added value of ovarioscopy is unclear
The clinician

The Surgeons’ Club Jan-2017 Guidelines

Therapy of cystic ovarian endometriosis

- Medical therapy
  - Does not decrease the size of a cyst
  - Probably prevents progression

- A cystic ovarian endometriosis 4-5 cm
  - Excision of the cyst wall
  - Protection of the hilus

- A cystic ovarian endometriosis > 6 cm
  - Two step surgery or adnexitomy

- A cystic ovarian endometriosis 1-3 cm
  - Unclear

- Specific considerations
  - THL for Smaller cysts in young women
  - Early treatment to prevent oocyte damage

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2017
Cystic ovarian endometriosis

- > 6 cm = 2 step

- Smaller
  - Excise
  - Do not destroy the ovary
  - Fertility: CPR 60%

- The Questions are
  - Judgment without a laparoscopy?
  - During laparoscopy: is no treatment an option?
  - Unclear: smaller and recurrences
Vaporisation

- Slow
- Incomplete
- Depth?
- Too deep bleeding
Diagnosis and treatment during laparoscopy
Conclusion 3: Cystic ovarian endometriosis

Common sense suggests

• The bigger the cyst the more damage
  • > 6cm = destroys the ovary
• Oocyte damage
  • The size of the cyst
  • Already some damage before surgery
  • The surgeon
  • The CO2

Medical treatment

• After surgery decreases recurrences
Diagnosis of deep endometriosis

- Diagnosis of a deep endometriosis nodule
  - Clinical suspicion in all women with severe menstrual pain, especially dyschesia, mictalgia, deep dyspareunia and perineal radiation. The diagnosis is made during surgery
  - The diagnostic accuracy of Clinical exam, ultrasound and MRI varies with the size and the localisation
    - Larger nodules >2-3 cm
      - If situated low clinical exam diagnoses 50% n to 90%
      - If situated low ultrasound diagnoses >95%
      - MRI diagnosis >95% bot low and sigmoid
    - Smaller nodules less than 1 cm
      - If situated low clinical exam detects less than 30%
      - Accuracy of ultrasound is unknown but less than 90%
      - Accuracy of MRI is unknown but less than 90%
  - Nodule of sciatical nerve: No accurate diagnosis besides surgical exploration

- Diagnosis of depth of bowel infiltration
  - Low nodule: rectum or recto sigmoid
    - Transvaginal ultrasound: accuracy of 80%
    - Transrectal ultrasound: accuracy of 90%
    - MRI: accuracy of 80-90%
  - Sigmoid nodule: no accurate prediction

- Diagnosis of degree of bowel occlusion
  - Contrast enema: >90%
  - Ultrasound and/or MRI: not useful

- Diagnosis of hydronefrosis
  - Ultrasound ok if stenosis is low
  - IVP, Uro-CAT: 100% accuracy
Therapy of deep endometriosis

Asymptomatic: no therapy
Asymptomatic and infertility
  – If pregnancy planned: wise to perform surgery first in order to avoid complications during pregnancy
  – If IVF planned: surgical excision before IVF to avoid severe pelvic adhesions
Severe Pain: surgery

Preparation for surgery
  – Estimate size and localization of nodule
  – Estimate degree of bowel occlusion= contrast enema
  – Judge depth of bowel invasion
  – If hydronefrosis -> preoperative stent
  – Pre-operative bowel preparation

Medical therapy
  – Can be given to decrease pain until surgery

Surgery is the only therapy
  – Opinion 1: If occlusion of more than 50%: elective bowel resection; otherwise try to excise and do a discoid excision or a bowel resection if necessary
  – Opinion 2: a more liberal use of bowel resection if deep bowel invasion
  – A more liberal use of bowel resection for sigmoid lesions than for rectum lesions
  – Avoid low rectum resections
  – The difficulty increases exponentially with size
Deep endometriosis & infertility

• If severe pain (95%) : surgery needed

• If no pain and infertility
  • We suggest surgery since Frozen pelvis after IVF
  • Complications of pregnancy

• CPR after surgery : 25-50 % in 6-12 months

• Expertise required
  • to avoid unnecessary bowel resections, nerve damage and adhesions
Pregnancies in deep endometriosis

N=2500

50% without children

50% with children

full analysis with

age

diameter of lesion

duration of surgery

not done yet
Pregnancy rates

**Cox Regression**

- Duration I: 0.001
- rAFS: 0.06
- Deep: 0.057
- E-oma: 0.09
- Age: 0.04

**MODEL**

- Duration: 0.01
- Endometriosis: 0.02
- Volume (deep): 0.05
- E-oma: 0.09

age # duration

6 Months
Conclusions:

Deep Endometriosis and infertility

- Huge variability in techniques
- Poorly documented fertility explorations
- Series too small for meaningful analysis eg size
- Spontaneous pregnancy rates of 25-60%

- Prognostic factors?
- Indication for surgery is pain not fertility

- Data suggest a negative effect upon fertility-MFR:

The clinician
IVF with a rectovaginal nodule is a mistake

- Frozen pelvis
- Reactivation?
- Complications

Bowel complications of deep endometriosis during pregnancy or in vitro fertilization

António Setúbal, M.D., Zacharoula Sidiropoulou, M.D., Sc., Mariana Torgal, M.D., Ester Casal, M.D., Carlos Lourenço, M.D., and Philippe Koninckx, M.D.


- Surgery and IVF are obviously complementary
Conclusion 4: Deep endometriosis

A pain problem

Surgery needed before IVF (frozen pelvis-complications)

• Therapy = excision
  • Completeness: leave some fibrosis
  • Try and see: Bowel resection is rarely needed
    Excision - circular stapler

• Urinary tract
• Postoperative management
The clinician

http://www.gynsurgery.org/endometriosis-treatment-medical/

Mistakes

- **Medical treatment without a diagnostic laparoscopy** should never been done since the diagnosis is not made.

- **Medical therapy** because surgery has been incomplete because of a lack of experience

- **Medical treatment before surgery** should rarely be done since smaller lesions risk to be missed.

Useless

- Medical therapy for infertility and endometriosis
Types of Medical Therapy for endometriosis

Medical menopause: LHRH agonists (or antagonists)

LHRH agonists (e.g., Lupron Depot, Synarel, Zoladex, Decapeptyl) will suppress ovarian function, resulting in an artificial menopause with all its consequences such as hot flushes, night sweats, insomnia, vaginal dryness, loss of sexual interest, and depression. According to the FDA, LHRH agonists should not be taken for longer than six months in a lifetime because of the risk of osteoporosis. Can give excellent pain relief but the symptoms will come back after treatment has been stopped. Can be associated with add-back therapy (small doses of estrogens) enough to prevent the worst menopause symptoms.
Progestagens only and oral contraception

Higher doses of progestagens (e.g., orgametril, lutenyl, danazol) decidualise and grow the endometrium and endometriosis as occurs during pregnancy. Can give pain relief but the symptoms will come back after treatment has been stopped. Higher doses of these progestagens with some androgenic side effects, invariably are associated with weight gain and symptoms of androgenisation. Oral contraception probably remains the best choice. When given continuously, the recurrence of cystic ovarian endometriosis is less.

Experimental drugs

**Anti-progestin** primate experiments suggest they might be as effective as GnRH agonist without the side effects. Today no drugs are approved for endometriosis.

**Aromatase inhibitors**: since endometriosis lesions produce estrogens within the lesions it might be useful to prevent this activity. Today, there is no evidence of clinical superiority.
Conclusion medical therapy endometriosis

- Infertility: useless
- Pain: Not a single blinded RCT
  - Placebo effect on pain is likely
  - Most trials are not about endometriosis
- Prevent progression??
- Prevent recurrences
  - Probably yes for cystic during treatment
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A surgical disease