Contraception and the treatment of medical disorders - Endometriosis

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Treatment for endometriosis in 2016

**Surgical**
- Removal of the lesions
- Adhesiolysis

**Medical**
- To destroy the lesion
- To prevent the lesion

The Patient Experience Matters

The "Pragmatic Approach" to treatment of endometriosis

Treat the Patient

**NOT THE LESIONS**


Treatment Options

**Medical management**
- COCs*
- Progestin only (oral, IM, SC)
- GnRH agonist + addback
- LNG-IUS*
- Danazol
- Aromatase inhibitors*
- NSAIDs, other analgesics

**Surgical management**
- Excision vs ablation
- Conservative vs Definitive

But – expertise & resources are not always available & recurrence is common

When is medical treatment required?

First-line treatment
After surgery to reduce recurrence
When surgery is not possible or refused

"Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures"
Estrogen in COCs may stimulate disease progression

**Rationale for the Use of Progestins**

- Progestins may be a rescue factor for regurgitated endometrial glands that would otherwise undergo necrosis and resorption during the physiologically hypoestrogenic menstrual milieu.

**Studies of long-term hormone therapy after surgery to treat endometriosis**

<table>
<thead>
<tr>
<th>Study and results</th>
<th>Study design</th>
<th>Treatment group</th>
<th>Median VAS score (at 24 months)</th>
<th>Follow-up, years</th>
<th>Primary outcome measures</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nettleton et al 2006</td>
<td>RCT</td>
<td>LNG-IUS</td>
<td>15</td>
<td>12</td>
<td>Median VAS score reduction 37.10</td>
<td>P = 0.01</td>
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Studies of long-term hormone therapy after surgery to treat endometriosis

<table>
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<tr>
<th>Study</th>
<th>Year</th>
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<th>No of patients</th>
<th>Primary outcome</th>
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<tr>
<td>Vercellini et al. 2008</td>
<td></td>
<td>Cyclo-OC</td>
<td>78/73/70</td>
<td>Median 100% score reduction</td>
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Occlusion: Nonsurgical outcomes

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</tr>
</thead>
<tbody>
<tr>
<td>Seracchioli et al.</td>
<td></td>
<td>IUS/EM</td>
<td>127</td>
<td>VAS score</td>
<td>ns</td>
</tr>
<tr>
<td>Seracchioli et al.</td>
<td></td>
<td>Cyclo-OC</td>
<td>93/45/43</td>
<td>VAS score</td>
<td>ns</td>
</tr>
<tr>
<td>Vercellini et al. 2010</td>
<td></td>
<td>Cyclo-OC</td>
<td>125/109</td>
<td>VAS score</td>
<td>ns</td>
</tr>
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Efficacy of postoperative use of COC for more than 6 months on pain recurrence

<table>
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<tr>
<th>Author</th>
<th>Year</th>
<th>Dysmenorrhea</th>
<th>Ovulatory pain</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Soosairaj et al.</td>
<td>2010</td>
<td>--</td>
<td>--</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitas et al.</td>
<td>2013</td>
<td>--</td>
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</tbody>
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Efficacy of postoperative use of LNG-IUS for more than 6 months on pain recurrence

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<tr>
<td>Seracchioli et al.</td>
<td>2003</td>
<td>--</td>
<td>--</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitas et al.</td>
<td>2012</td>
<td>--</td>
<td>--</td>
<td>0.04</td>
</tr>
</tbody>
</table>

OC after surgery: efficacy in prophylactic recurrence

- Randomize research, 311 pts
- Placebo: 184, Cyclo-OC: 187, no break: 185
- Duration of observation 24 months
- Evaluate pain recurrence

The use of COCs in continuous mode reduces only frequency of return dysmenorrhea

Application COC in the postoperative period does not affect the return of chronic pelvic pain and dyspareunia

Studies of long-term hormone therapy after surgery to treat endometriosis

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<th>Intervention</th>
<th>No of patients</th>
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<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vercellini et al. 2008</td>
<td></td>
<td>Serum</td>
<td>126/86</td>
<td>8.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Talamonti et al. 2010</td>
<td></td>
<td>Serum</td>
<td>36/39</td>
<td>3.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bommel et al. 2010</td>
<td></td>
<td>Serum</td>
<td>75/73/68</td>
<td>15.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loo et al. 2010</td>
<td></td>
<td>Serum</td>
<td>175/147</td>
<td>7.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Guazzetti et al. 2015</td>
<td></td>
<td>Serum</td>
<td>124/118</td>
<td>8.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Efficacy of postoperative medication for more than 6 months on endometrioma recurrence (RCT)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Intervention</th>
<th>No of patients</th>
<th>Median</th>
<th>Overall recurrence rate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soosairaj et al.</td>
<td>2010</td>
<td>Cyclo-OC/Ocrelone OC/GYN</td>
<td>74/35/36</td>
<td>24</td>
<td>25/5 (OC/OC/OC) vs (26/5) (Ocrelone)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Wang et al. 2010</td>
<td></td>
<td>LNG/IUS + EMPA depot</td>
<td>15/15</td>
<td>36</td>
<td>No recurrence was detected in both groups</td>
<td>NS</td>
</tr>
<tr>
<td>Curry et al. 2013</td>
<td></td>
<td>OC with desogestrel/OC with desogestrel/OC with Ocrelone</td>
<td>73/40/36</td>
<td>24</td>
<td>25/5 (OC/OC/OC) vs (26/5) (Ocrelone)</td>
<td>&lt;0.05</td>
</tr>
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<td>Curry et al. 2013</td>
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</table>
LNG-IUS vs. Depot MPA as a long term maintenance therapy for patients with moderate and severe endometriosis

• randomized controlled trial
• 30 patients after conservative surgery
• 15 LNG-IUS / 15 Depot MPA (3 years)
• improvement of symptoms in both groups
• compliance: LNG-IUS (13/15) better vs. Depot MPA (7/15)
• BMD (after 3 years) (hip and lumbar regions)
  LNG-IUS: +0,023 / + 0,071 g/cm²
  Depot-MPA: –0,030 / –0,017 g/cm²

Conclusions: LNG-IUS better compliance and no bone loss

Efficacy of postoperative medication for more than 6 months on endometrioma recurrence (Cohort Studies)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Follow-up period, (months)</th>
<th>Results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takamura et al.</td>
<td>2009</td>
<td>OC for 24 months/EM</td>
<td>34/36</td>
<td>36</td>
<td>OC (2.9%)/EM (8.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Law et al.</td>
<td>2010</td>
<td>GnRHa (3 or 6 months)+OC followed by OC</td>
<td>175/107</td>
<td>35</td>
<td>GnRHa+OC (4.7%)/GnRHa alone (28.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vlahos et al.</td>
<td>2013</td>
<td>Cyclic OC/continuous OC at least 6 months</td>
<td>147/185</td>
<td>31/3</td>
<td>Cyclic OC (7.4%)/continuous OC</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Visanne long term experience during 5 year for endometrioma prevention after surgery

568 women (32.8 ±7.7 yrs);
151 Placebo
417 Visanne
Duration of observation-5 year
Visanne usage - 60 months

DNG in women with persistent endometriosis related pelvic pain during NETA treatment

• 25 women with symptomatic rectovaginal endometriosis with persistence of pain after 6 months NETA
• change treatment to 2 mg DNG treatment
• after 6 months: improvement of VAS (pelvic pain, dyspareunia), increase of QoL-score
• no significant change of endometriotic nodules
• “NETA-resistant” patients with rectovaginal endometriosis symptoms have benefits from a DNG-treatment

POP (DSG) vs. Vaginal ring in treatment of rectovaginal endometriosis infiltration the rectum

• 143 patients with rectovaginal endometriosis infiltrating the rectum
• 12 months POP vs. ring
• rate of satisfied patients higher in POP treated group
• gastrointestinal symptoms: improvement: 50 % (POP) 31 % (Ring)
Postoperative use of Depot MPA vs. continuous COC in the treatment of endometriosis associated pain

- 48 patient after conservative surgery
  → DMPA (150 mg) every 12 weeks or COC (EE 0.03 mg/Gestoden 0.075 mg) for 24 weeks
- satisfaction rate after:
  12 weeks: 93 vs. 90 %
- pain score improvement in both groups
- dysmenorrhoea score higher in COC group
- no differences in side effects
- both treatments are effective

Cheewadhavenaraks et al. (2012)

POP vs. COC in treatment of endometriosis – pain in patient with migraine without aura

- 6 months treatment in women with symptomatic rectovaginal endometriosis and migraine without aura
- satisfied with treatment: POP: 61.2 % (38/62) COC: 37.8 % (21/56)
- significant reduction of pelvic pain and dyspareunia in both groups
- number of migraine attacks was lower than at baseline in POP group
- no reduction in COC group
- also the intensity of migraine attacks was reduced in POP group
- Conclusion: POP should be preferred in patients with migraine

Morotti et al. (2014)

Treatment of endometriosis: COC vs. POP

<table>
<thead>
<tr>
<th></th>
<th>COC</th>
<th>Progestin (POP, Depot MPA, Implanon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy - Contraception</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td>Thrombotic Risk</td>
<td>higher</td>
<td>lower</td>
</tr>
<tr>
<td>Bleeding disorders</td>
<td>lower</td>
<td>higher</td>
</tr>
<tr>
<td>Efficacy - Endometriosis</td>
<td>lower</td>
<td>higher</td>
</tr>
</tbody>
</table>

Walch et al. (2009)

Implanon vs. MPA: effects on pain scores in patients with symptomatic endometriosis

- randomized trial: 41 patients with histological proven endometriosis and pain or/and dyspareunia
- 1 year treatment. Implanon (n=21) vs. Depot MPA (n=20)
- improvement of pain in both groups
- reduction of VAS-Score: Implanon: 68 %, DMPA: 53 %
- no difference in satisfaction and side effect profiles

Walch et al. (2009)

ESHRE Endometriosis Guidelines 2013
Treatment of Pain

Clinicians are recommended to use progestagen (medroxyprogesterone acetate (oral or depot) dienogest, norethisterone acetate or danazol) or anti-progestagen (gestrinone) as one of the options to reduce endometriosis-associated pain (Morotti et al., 2014)

A

The GDG recommends that clinicians take the different side effect profiles of progestagens and anti-progestagens into account when prescribing these drugs especially irreversible side effects (e.g. thrombosis, androgenic side effects).

GPP

Clinicians can consider prescribing levonorgestrel-releasing intrauterine system as one of the options to reduce endometriosis-associated pain (Morotti et al., 2014, Seccareccia et al., 2017, Fafak et al., 2016)

B
**ESHRE Endometriosis Guidelines 2013**

**Treatment of Pain**

In women operated on for endometriosis, clinicians are recommended to prescribe postoperative use of a levonorgestrel-releasing intrauterine system (LNG-IUS) or a combined hormonal contraceptive for at least 18-24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia (Aboulkheir et al., 2006; Seracchioni et al., 2009).

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**Possible mechanisms for the treatment of Adenomyosis**

- Decidualization and subsequent atrophy of endometrium
- Direct action of the hormone on the foci of adenomyosis
- Down regulation of ER in glandular and stromal tissue
- Shrinkage of adenomyosis foci
- Reduction of PG production within the endometrium
- Relieve of dysmenorrhea pelvic pain

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**Intrauterine System (IUS)**

- Concept invented by Prof T. Luukkainen
- Releases the progesterone
- levonorgestrel at 20µg/day
- Provides 5 years reliable contraception
- Has other non-contraceptive health benefits

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**What is Mirena®**

- Intrauterine System (IUS)
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- Releases the progesterone
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- Has other non-contraceptive health benefits

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**Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before insertion</th>
<th>30 days</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound volume (ml)</td>
<td>11.3 ± 1.6</td>
<td>10.5 ± 1.5</td>
<td>9.8 ± 1.4</td>
<td>9.2 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>Total intramuscular</td>
<td>10.1 ± 1.5</td>
<td>9.4 ± 1.3</td>
<td>8.7 ± 1.2</td>
<td>8.1 ± 1.1</td>
<td></td>
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**Possible mechanisms for the treatment of Adenomyosis**

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**Mirena® and Adenomyosis**

- 29 patients MRI-diagnosed adenomyosis suffering from metrorrhagia and dysmenorrhoea (age: 24-46 years)
- Mirena®-insertion
- MRI-monitoring after 6 months

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**Mirena® and Adenomyosis**

- 29 patients MRI-diagnosed adenomyosis suffering from metrorrhagia and dysmenorrhoea (age: 24-46 years)
- Mirena®-insertion
- MRI-monitoring after 6 months
Mirena® and Adenomyosis

Results:
• significant reduction of junctional zone thickness (MRI) = 24%
• no significant reduction of uterus volume (142 → 136 ml)
• significant reduction of VAS (pelvic pain) (6 patients without improvement)
• reduction of metrorrhagia (33% spotting after 6 months)

Bragh et al (2007)

Contraception and the treatment of medical disorders - Endometriosis
• COC and LNG-IUS after surgery
  - significant reduction of recurrence rate for dysmenorrhea
  - no significant effects for improvement of dyspareunia and nonmenstrual pain
• COC after surgery of endometriosis
  - significant reduction of recurrence rate (anatomical relapses)
  - continuous use of COC is more effective than cyclic use of COC
  - in selected studies COC containing demegos are more effective than COC containing other progestins
• LNG-IUS is effective in reduction of recurrence of rectovaginal endometriosis and in treatment of adenomyosis
• Depot MPA is also effective the treatment of endometriosis

Clinical symptoms and Localization of endometriosis

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>Localisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>dysmenorrhea</td>
<td>peritoneal endometriosis</td>
</tr>
<tr>
<td>dyspareunia</td>
<td>rectovaginal endometriosis</td>
</tr>
<tr>
<td>recurrent cystitis</td>
<td>peritoneal bladder endometriosis</td>
</tr>
<tr>
<td>cyclic scar pain</td>
<td>scar endometriosis</td>
</tr>
<tr>
<td>cyclic upper abdominal pain</td>
<td>diaphragm endometriosis</td>
</tr>
<tr>
<td>bladder pain</td>
<td>bladder endometriosis</td>
</tr>
<tr>
<td>cyclic bowel bleeding</td>
<td>bowel endometriosis</td>
</tr>
<tr>
<td>bowel pain (often constipation)</td>
<td></td>
</tr>
</tbody>
</table>

Different localizations of endometriosis

ENDOMETRIOSIS – Medical Treatment Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDS</td>
<td>In primary dysmenorrhea, NSAIDs have been shown to be effective compared to placebo. Limited data is available for pain related to endometriosis.</td>
</tr>
<tr>
<td>COCs</td>
<td>Widely used off-label for endometriosis. Effective in primary dysmenorrhea. Lack of RCT evidence in endometriosis.</td>
</tr>
<tr>
<td>GnRH</td>
<td>Considered ‘standard’ treatment for endometriosis due to high efficacy. Limited to short-term use (6 months) due to adverse effects.</td>
</tr>
<tr>
<td>Synthetic Androgens</td>
<td>Not widely used anymore due to poor tolerability with many androgenic side effects (weight gain, acne, oily skin, hirsutism, deepening of voice).</td>
</tr>
<tr>
<td>Progestins</td>
<td>Most were not developed for treatment of endometriosis.</td>
</tr>
</tbody>
</table>
Medical therapy – COCs

Non-specific therapies – not approved in endometriosis

- Widely used off-label for endometriosis
- Effective in primary dysmenorrhea
- Lack of RCT evidence in endometriosis
- Only 1 study included in Cochrane review
- Not all types of pain respond equally to COCs use (e.g., dyspareunia, chronic pelvic pain)
- May cause estrogenic AEs (nausea, weight gain, water retention, increased thromboembolic risk)

Relevant factor: Progestins in COC

Exposure to ethinyl estradiol

- Lowest effective dose of COCs given
- The closer each tablet is to a poor indicator of the systemic exposure
- E2 levels vary widely among COC formulations
- Between 0 differences between current & older COCs
- Different route of administration with E2 also contribute to pharmacokinetics
- Dose-response relationship with gender systemic exposure

Medical therapy – Progestins

Specific therapies – approved in endometriosis
- e.g., gonadotrophin-releasing hormone agonists, danazol and some progestins

Summary of Activities for Various Progestogens

<table>
<thead>
<tr>
<th>Progestogens</th>
<th>Androgenic</th>
<th>Estrogenic</th>
<th>Glucocorticoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>(+)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gestodene</td>
<td>(+)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Norgestrelide</td>
<td>(+)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cypochlomide</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

- Hirt and colleagues (2009): + indicates activity; (+) indicates negligible activity at pharmacologically relevant levels.
- Hirt et al. (2009): + indicates activity; (+) indicates negligible activity at pharmacologically relevant levels.

Conclusions Progestins

- Progestins effective in treatment of endometriosis, but a lack of evidence in the most of progestins
- Evidence available for DNG, limit evidence for DSG, NETA and MPA
- Evidence for LNG-IUS and treatment of adenomyosis
- Important for clinical use: selection of progestins (different efficacy and side effects)
Comparison of different progestins

<table>
<thead>
<tr>
<th></th>
<th>DNG</th>
<th>MPA</th>
<th>NETA</th>
<th>DNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval for contraception</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Approval for long term treatment</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antiandrogenic effect</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Endometrium effect</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Negative side effects</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Guidelines for Progestins

- ESHRE guideline: 
  - Progestins "...can be considered as a first choice for the treatment of endometriosis because they are as effective in reducing [laparoscopy] scores and pain as danazol or GnRH agonists, and have a lower cost and a lower incidence of adverse effects."

- Other expert comment: 
  - "Given their good tolerability, minor metabolic effects and low cost, progestogens must therefore be considered the drugs of choice."

- Recent Canadian clinical practice guidelines include dienogest as an effective long-term treatment option.

- German guidelines stated that dienogest is equally effective as GnRH agonist.

Medical therapy – Progestins

- Synthetic hormones with progestosterone-like activity.
- Most were not developed for treatment of endometriosis.
- Adverse events include irregular bleeding and (especially with older agents) weight gain, headaches, acne, and adverse lipid changes.
- Newer types selectively bind progesterone receptors specifically.

Specific therapies – approved in endometriosis:
- e.g. gonadotropin-releasing hormone agonists, danazol and some progestins.

Minimize androgenic, estrogenic or glucocorticoid side-effects.

Disadvantages of systemic progestins

- different efficacy (no approval for many progestins)
- side effects
  - bleeding disorders (depend on the endometrium effect)
  - depression in long term use possible
  - androgenic effect (skin, hair)

Gestagen applications

1. systemic
   - oral
   - injections
   - implants
2. local
   - LNG-IUS (Mirena®)

NETA in treatment of colorectal endometriosis: a pilot study

- 40 patients with symptomatic colorectal endometriosis
- 2.5 mg NETA / 12 months
- dosage increased (5 mg NETA) in cases of breakthrough bleedings
- significant improvement of symptoms during treatment (pelvic pain, dyspareunia, dyschezia)
- no significant effect to gastrointestinal symptoms (constipation) (patients with gastrointestinal symptoms related to the menstrual cycle has a greater benefit)
Hormonal treatment of endometriosis (state of the art)

**OC**
- treatment of mild endometriosis

**Progestins**
- treatment of severe endometriosis
- treatment of recurrence of endometriosis (long term treatment of endometriosis with high risk of surgery)

**GnRH-analogue**
- severe progestin-resistant endometriosis
- IVF pretreatment in severe endometriosis

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Progestagen for pain associated with endometriosis

Cochrane Review (2012)

- MPA (10 mg) more effective than placebo (12 months follow up)
- significant more side effects (acne, oedema)
- no evidence between dydrogesterone and placebo
- no evidence of a benefit with Depot progestin vs. other treatments (COC, GnRH-a)
- more side effects

Conclusions: Limited evidence for the most progestins

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Comparison LNG-IUS and GnRH-analogue for treatment of chronic pelvic pain in women with endometriosis

1) both treatments effective in CPP-associated endometriosis (Petta et al. 2005; Bayoglu Tekin et al. 2011)

Clinical problems:
- LNG-users: higher bleeding scores (satisfaction rate lower)
- GnRH-analogue: hypoestrogenismus (side effects)

2) limited evidence showing that postoperative LNG-IUS use reduces the recurrence of painful periods in women with endometriosis (Abou-Setta et al. 2013)