Medical Management of Endometriosis in Patients with Pain and/or Infertility

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Disclosure

- Dr. Luciano serves as advisory board member, speaker or principal investigator of clinical research for the following pharmaceutical companies:
  - Baxter, Covidien, AbbVie, Bayer, Boehringer Ingelheim, Intuitive

- Neither Dr. Luciano nor any member of his family own stocks or have direct financial interest in any pharmaceutical companies

- Dr. Luciano will not discuss the use of any off-labeled products

- This CME activity has no commercial support
Endometriosis: Management Dilemma

- Pain
- Ovarian cyst
- Deep endometriosis

Infertility
- Asymptomatic
- Recurrences and Sequelae
Hormonal Treatment of Endometriosis is based on the fact that Estrogen stimulates the growth and function of endometriosis lesions.

Goals of hormonal therapy should:

- Suppress estrogen production
  - GnRH-a, GnRH-ant,, Arom. Inhib. SERMS
- Oppose estrogen action
  - Progestins (MPA, NETA)
  - Androgens (Danazol, Gestrinone)
Medical Management of Endometriosis-Related Infertility

• Medical treatment does not improve fertility.

• Women with endometriosis may benefit from:
  • O. C. for 6-8 weeks treatment prior to IVF

• GnRH-a for 3-6 months before IVF
Nafarelin VS Danazol for Endometriosis


% with severe symptoms

Months on treatment
Placebo-Controlled Comparison of Danazol and MPA in the Treatment of Endometriosis

![Graph showing the comparison of Endo. Score and Pain between Baseline, Placebo, MPA 100 mg/d, and Danazol 600 mg/d.](graph.png)
Oral MPA in Endometriosis-Related Pain


[Bar chart showing changes from baseline in Endo. Scores, Pain, Dysm., Dyspar., E-2 Levels for Baseline and End of Therapy]

AFS-Classification
DMPA-SC Versus Leuprolide for the Treatment of Endometriosis-Associated Pain: Study Designs

- Two 18-month, randomized, evaluator-blinded, comparator-controlled Phase 3 studies
  - Study 1: United States and Canada
  - Study 2: Europe, Latin America, and Asia

<table>
<thead>
<tr>
<th>6 Months Treatment</th>
<th>12 Months Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA-SC</td>
<td>Off medication</td>
</tr>
<tr>
<td>104 mg/0.65 mL every 3 months</td>
<td></td>
</tr>
<tr>
<td>Leuprolide</td>
<td></td>
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<tr>
<td>11.25 mg IM every 3 months</td>
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</tbody>
</table>
% of Patients that Improved at the End of Therapy (6 M) and 12 Months after Therapy

DMPA-SC: Less BMD Decline at Month 6 and 12 Months Follow-up (ITT), Study 1


*Statistically significantly greater decline observed in the leuprolide group vs DMPA-SC group.
Median Average Daily Number of Hot Flushes by Month (ITT)

**Study 1***
- DMPA-SC
- Leuprolide

**Study 2***
- DMPA-SC
- Leuprolide

*Differences between groups significant from Month 1 through Month 6, \( P < .001 \).
PT = pretreatment.
Medical Management of Endometriosis-Associated Pain

GnRH-a; Progestins; Danazol

1. All medical therapies seem to be effective
2. No treatment is more effective than the others
3. Preference of any one therapy should be based on tolerability, degree of adverse effects (bone loss), and (when everything else is equal) cost.
Pelvic Pain and Suspected Endometriosis

NSAID or OC’s

Failure

Success

Continue RX

HST = Hormonal Suppressive Therapy [GnRH-a, MPA, O.C.; Danazol; etc.]
### Recurrence Rates of Endometriosis According to Phase of the Menstrual Cycle when Laparoscopy Was Done

<table>
<thead>
<tr>
<th>Phase</th>
<th>Macroscopic</th>
<th>6 Months</th>
<th>12 Months</th>
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<tbody>
<tr>
<td>Follicular</td>
<td>3.2%</td>
<td>8.1%</td>
<td></td>
</tr>
<tr>
<td>Periovulatory</td>
<td>2.2%</td>
<td>6.6%</td>
<td></td>
</tr>
<tr>
<td>Luteal</td>
<td>14.9%</td>
<td>20.9%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Microscopic</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>1.6%</td>
<td>8.1%</td>
<td></td>
</tr>
<tr>
<td>Periovulatory</td>
<td>1.1%</td>
<td>6.6%</td>
<td></td>
</tr>
<tr>
<td>Luteal</td>
<td>9%</td>
<td>14.9%</td>
<td></td>
</tr>
</tbody>
</table>

Pain Recurrence

Endometriosis: Absence of recurrence in patients after endometrial ablation.

- 28 patients with symptomatic endometriosis underwent laparoscopic conservative surgery;
- 14 underwent endometrial ablation and 14 did not
- 2 years later all patients underwent second look laparoscopy
- Endometriosis recurrence was found in none of the ablation and in 9 of 14 non-ablation patients.
- 13/14 ablation patients reported resolution or significant improvement of symptoms; while only 3/14 non-ablation patients experienced significant improvement.

In one small RCT*, 40 symptomatic patients with stages III or IV disease were randomized to either LNG-IUS insertion or control after conservative laparoscopic surgery. There was a significant ($p = .012$) reduction in pain recurrence in the LNG-IUS group compared to the control group (10% vs 45%). 75% vs 50% satisfied or very satisfied with treatment.

Progestin-IUD and Menorrhagia

- Levonorgestrel-releasing intrauterine system (Mirena) releases 20 mcg/day of L-norgestrel directly to the endometrium inducing decidualization and atrophy of the endometrium.
- Serum levels of L-norgestrel reach 0.1-0.2 ng/mL (compared to 3-6 ng/ml when taking Alesse which has 100 mcg of L-norgestrel per pill).
- Mirena reduces menstrual blood loss by 80% at 3 months and nearly 100% at 1 year, comparable to endometrial ablation.
- Mirena has been reported to reduce the volume of fibroids and uterus, as well as MBL in women with menorrhagia. May be particularly useful in younger, symptomatic women who wish to delay childbearing.

Postoperative oral contraceptive exposure and risk of endometrioma recurrence

After laparoscopic excision of endometriomas, 239 women were randomized to no therapy or to cyclic or continuous oral contraceptives for 24 months and followed semiannually. Serracchioli R et al. Fertil Steril 2010;93:52-56
IN CONCLUSION

• Although we cannot yet prevent endometriosis, we have the tools that allow us to minimize the risk of recurrence and prolong the disease-free interval in the majority of women afflicted by the disease.