IUD-Levonorgestrel: when and how to use it?

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What is Mirena®?

- Intrauterine system (IUD) 32 mm long
- **T-shaped polyethylene frame** (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem
- The reservoir consists of a **white cylinder**, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a **total of 52 mg Levonorgestrel**
- Releases **Levonorgestrel (20 µg/die)**
- **Up to 5 years contraceptive cover** (after 5 years the release of Levonorgestrel decrease to 11 µg/die, so that the average release is about 14 µg/die)
- The T-shaped frame is impregnated with **barium sulfate**, which makes it **radiopaque**
Mirena: a local action

The continuous and constant release of LNG avoids “peaks and trough” concentrations

The plasmatic concentrations of LNG achieved by Mirena are 10 times lower than those seen with the combined oral contraceptive and 5 times lower than those of mini-pill

Indications

1. Contraception
2. HRT
3. Abnormal Uterine Bleeding

When?
Contraception with Mirena®

- Inhibition of endometrial proliferation
  - Silverberg et al. Int J Gynecol Pathol 1986
- Inhibition of sperm movement
  - Videla-Rivero et al. Contraception 1987
- Thickening of the cervical mucus
  - Barbosa et al. Contraception 1997
- Interference with ovarian function
  - Scholten et al. 1989
  - Xiao et al. Contraception 1990
- Reduction of secretory activity
- Low-level inflammatory response

Serum levels of LNG, after insertion of Mirena are 300 pg / mL, but gradually reduced up to 100 pg / mL after 2 years. So, immediately after insertion of Mirena, inhibition of ovulation occurs in 70% to 85% of cases, while 12 months after insertion physiological ovulatory cycles occur in 80% of cases.
### THE EFFICACY OF CONTRACEPTIVE METHODS

<table>
<thead>
<tr>
<th>METHOD</th>
<th>% PREGNANCY (PERFECT USE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No method</td>
<td>85</td>
</tr>
<tr>
<td>Combined oral Contraceptive</td>
<td>0.1</td>
</tr>
<tr>
<td>POP</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>LNG-IUD</strong></td>
<td><strong>0.1</strong></td>
</tr>
<tr>
<td>Copper IUD</td>
<td>0.8</td>
</tr>
<tr>
<td>Progestin injection</td>
<td>0.3</td>
</tr>
<tr>
<td>Norplant</td>
<td>0.05</td>
</tr>
<tr>
<td>Condom</td>
<td>3-5</td>
</tr>
<tr>
<td>Diaphragm + spermicide</td>
<td>6</td>
</tr>
<tr>
<td>Ogino-Knaus</td>
<td>9</td>
</tr>
<tr>
<td>Sympto-thermal method</td>
<td>2</td>
</tr>
<tr>
<td>Female sterilization</td>
<td>0.05</td>
</tr>
<tr>
<td>Male sterilization</td>
<td>0.1</td>
</tr>
</tbody>
</table>
The efficacy and safety of Mirena® allows its use in special categories of patients

- **Deep Vein Thrombosis**
  - Familiarity: class OMS 1
  - Past: class OMS 2

- **Uterine Fibroid**
  - Without distortion of the cavity: class OMS 1
  - With distortion of the cavity: class OMS 4

- **Cigarette Smoking**
  - Class OMS 1

- **Obesity (BMI ≥30 kg/m²)**
  - Class OMS 2

- **Age**
  - <20: Class OMS 2
  - >20: Class OMS 1

- **PID**
  - Past PID followed by pregnancy: class OMS 1
  - Past PID without pregnancy: class OMS 2
  - Current PID: class OMS 4

- **Sexually trasmitted diseases**
  - High risk: class OMS 3
  - Current: class OMS 4

- **HIV**
  - Class OMS 2

- **Diabetes Mellitus**
  - Class OMS 2 (gestational diabetes → class OMS 1) *

* Women with diabetes type 1 and type 2 in the presence of vascular complications, renal or retinal can use Mirena
Mirena® is an effective treatment and contraception in lactating women and does not negatively influence breast-feeding or the growth and development of breast-fed infants.

Mirena appears to have no effects on lactation and child development when placed 6 weeks after labour.

The milk levonorgestrel concentration is 0.03µg/24h (0.1%) in 600 ml.

**OMS Guide-lines**

Breastfeeding or non-breastfeeding women, including caesarean section:

- < 48 hours: OMS class 3
- > 48 hours to < 4 weeks: OMS class 3
- > 4 weeks: OMS class 1
- Puerperal sepsis: OMS class 4

*Heikkila. Contraception 1 982
Shaamash. Contraception 2005*
Reversibility

- The menstrual cycle restarts within 30 days
- Rapid return to fertility (independently of duration of use)
- 96% of women become pregnant within 12 months Mirena’s removal
## Cost- benefit evaluation

<table>
<thead>
<tr>
<th>Product cost (€)</th>
<th>Mirena</th>
<th>Ring</th>
<th>Patch</th>
<th>Pill</th>
<th>Progestin-only pill</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 12 months</td>
<td>198,07</td>
<td>186</td>
<td>159</td>
<td>171,36</td>
<td>178,8</td>
</tr>
<tr>
<td>After 24 months</td>
<td>198,07</td>
<td>372</td>
<td>318</td>
<td>342,72</td>
<td>357,6</td>
</tr>
<tr>
<td>After 36 months</td>
<td>198,07</td>
<td>558</td>
<td>477</td>
<td>514,08</td>
<td>536,4</td>
</tr>
<tr>
<td>After 48 months</td>
<td>198,07</td>
<td>744</td>
<td>636</td>
<td>685,44</td>
<td>715,2</td>
</tr>
<tr>
<td>After 60 months</td>
<td>198,07</td>
<td>930</td>
<td>795</td>
<td>856,8</td>
<td>894</td>
</tr>
</tbody>
</table>

- Mirena is an optional contraceptive with a favorable cost-benefit index for the women who desire a longer than 1 year contraception.
- After the first year of use the cost of Mirena is equal to zero for the next four years.
- €3,3/month (not including costs for its insertion)
- €5,8/month (including costs for its insertion)
When?

Indications

2

HRT
Why choosing Mirena?
Continuous combined scheme

“...women can switch from the contraceptive use of LNG-UIS to its use as a part of their HRT...”.

HRT in PERIMENOPAUSE

Estrogens:
Oral continuous administration

Levonorgestrel:
Local continuous administration

Inhibits endometrial proliferation

↓ Abnormal uterine bleeding

Suvanto-Luukkonen et al. Maturitas 1997
Varila et al. Fertil Steril 2001
Continuous intrauterine compared with cyclic oral progestin administration in perimenopausal HRT

Oral HRT

Oral E + LNG-IUD

MIRENA = BETTER COMPLIANCE

Boon, Maturitas 2003
Abnormal uterine bleeding

When?

Indications
Efficacy of Mirena® in menorrhagia

- Mirena® effectively reduces menstrual blood loss (MBL)

* p<0.001

(≥80mL MBL = menorrhagia)
Percent reduction in menstrual bleeding with medical therapies

Haider Z., D’Souza R. Best Practice & Research Clinical Obstetrics and Gynecology, 2009
## Reduced cost (5 years)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction of bleeding (%)</th>
<th>Medium monthly cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirena</td>
<td>74-97%</td>
<td>3,16</td>
</tr>
<tr>
<td>Combined oral contraceptive</td>
<td>43%</td>
<td>4,6-13,20</td>
</tr>
<tr>
<td>Oral progestogen for 21 days</td>
<td>32-50%</td>
<td>2,25-10,3</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>47-54%</td>
<td>2,5-5</td>
</tr>
<tr>
<td>Mefenamic Acid</td>
<td>20-50%</td>
<td>3,20</td>
</tr>
<tr>
<td>Danazol</td>
<td>49,7%</td>
<td>5-20</td>
</tr>
<tr>
<td>GnRh Analogues</td>
<td>&gt; 90%</td>
<td>50-150</td>
</tr>
</tbody>
</table>
Reduction of bleeding with endometrial ablation (thermal balloon) and Mirena®
Surgery is statistically more effective than the LNG-IUD in reducing menstrual bleeding.

LNG-IUD has the same efficacy of hysterectomy in improving the quality of life.
Cost-effectiveness

- “The comparative analysis of costs between hysterectomy, ablation and Mirena® reveals that it is cheaper and more effective”
  
  *Fattore G., Lazzaro C., PharmacoEconomics, 1999*

- “119 women treated with Mirena® vs. 117 women undergoing hysterectomy: cost 3 times greater in the hysterectomy group”

  *R.Hurskainen, et al., Lancet, 2001*
The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia


Contraception, 2003
MIRENA and MYOMAS

Unsolved issues

- Lack of randomized trials
- Effect on size and volume of myomas
- Increased incidence of expulsion rate
  (number of myomas? location? size?)
New indications

- Menorrhagia in bleeding disorders
- Dismenorrhea
- Endometriosis / Adenomyosis
- Prevention and treatment of endometrial hyperplasia
- Treatment of endometrial cancer (early stage)
- Prevention of endometrial pathology induced by tamoxifen
Mirena reduce the size of endometriotic lesions in patients with endometriosis of the recto-vaginal septum.

LGN-IUD Mirena®
ENDOMETRIOSIS (after surgery)

At the moment there is only limited evidence on the efficacy of LNG-IUD in reducing pelvic pain in patients undergoing surgery for endometriosis.

Future randomized and controlled studies are needed on this subject.
The role of Mirena in the treatment of the endometrial hyperplasia...

Hyperplasia regression in > 95% of cases in a 12 months follow-up
Our cases:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis (1)</th>
<th>Treatment (2)</th>
<th>Treatment response (3)</th>
<th>Follow up (24 months) (4)</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>APA</td>
<td>HS+LIIG-IUS</td>
<td>CR</td>
<td>Free of disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>AEH</td>
<td>REA+LIIG-IUS</td>
<td>CR</td>
<td>Free of disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>APA</td>
<td>HS+LIIG-IUS</td>
<td>CR</td>
<td>Free of disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>AEH</td>
<td>REA+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease Ilo Medical Treatment</td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>EC</td>
<td>REA+LIIG-IUS+ GnRH-a</td>
<td>SD</td>
<td>Stable Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 6</td>
<td>EC</td>
<td>REA+LIIG-IUS</td>
<td>PR</td>
<td>Stable Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 7</td>
<td>AEH</td>
<td>REA+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 8</td>
<td>AEH</td>
<td>REA+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 9</td>
<td>APA</td>
<td>HS+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease Ilo Medical Treatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 10</td>
<td>APA</td>
<td>HS+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 11</td>
<td>AEH</td>
<td>REA+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease Ilo Medical Treatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient 12</td>
<td>EC</td>
<td>REA+LIIG-IUS+ GnRH-a</td>
<td>SD</td>
<td>Stable Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 13</td>
<td>EC</td>
<td>REA+LIIG-IUS+ GnRH-a</td>
<td>PR</td>
<td>Stable Disease LIIG-IUS</td>
<td></td>
</tr>
<tr>
<td>Patient 14</td>
<td>AEH</td>
<td>REA+LIIG-IUS</td>
<td>CR</td>
<td>Free of Disease LIIG-IUS</td>
<td></td>
</tr>
</tbody>
</table>

A 24 months followup:
- 9 patients free of disease
- 5 patients without progression

1. Atypical polypoid adenomyofibroma (APA), atypical endometrial hyperplasia (AEH), endometrial cancer (EC).
2. Hysteroscopic Surgery (HS); Resectoscopic endometrial ablation (REA); levonorgestrel releasing intrauterine system (LNG-IUD), GnRH analogues (GnRH-a).
3. Complete response (CR), Partial response (PR), stable disease (SD).
4. Patients 1, 3, 7, 8, 10, 14: LNG-IUD is still inserted for contraceptive purpose; patients 6, 5, 12, 13: LNG-IUD is still inserted for medical treatment.
The Mirena LNG-IUS appears to prevent the development of benign endometrial polyps in breast cancer patients taking tamoxifen, over a one-year period.
There is no clear evidence from the available randomised controlled trials that LNG-IUS prevents endometrial hyperplasia or adenocarcinoma in these patients.

Analysis 1.3. Comparison 1 Mirena versus control, Outcome 3 Endometrial hyperplasia.
How?

Counselling

Insertion

Follow-up
Is a critical step for use “Mirena”

- Discussion of treatment options
- Focus on local action and reversibility of Mirena®
- Describe cyclic events associated with hormonal changes (subjective criteria reassuring: ovulatory cervical mucus, breast tenderness, no flushing, …)
- Information on menstrual disorders reduction (benefits)
- For women with bleeding disorders exclude those with intrauterine malignancy, endometrial polyps or cavity distorting fibroids
- Information on potential side effects (spotting, amenorrhea, device expulsion)

Proper counselling improves the continuation rate for Mirena
LGN-IUD Mirena®

ADVERSE EFFECTS

EARLIER MONTHS

No problems 45-49,8 %
Menstrual disorders 20-30
Pelvic pain 7,5-10,5
Acne 2,5-3,5
Breast tenderness 2-3,3
Headache 2-2,8

AFTER 3-6 MONTHS

No problems 80-85,4 %
Menstrual disorders 5-6,3
Pelvic pain 0,5-2,0
Acne 1-1,8
Breast tenderness 0,5-1
Headache 0,6-1,5
Potential difficulties with insertion in perimenopausal women are caused by:

- Narrowing of the cervical canal
- Shrinking of the uterus
- Drying up of the mucosa

... however, in clinical practice insertion is easy in most perimenopausal women!!
LGN-IUD Mirena®

ADVERSE EFFECTS

TOTAL EXPULSION RATE
5%

I-II YEAR
4.2%

III-V YEAR
1.3%

Expulsion risk factors:
- parity
- age < 25 years
- previously IUD expulsion

Sivin et al, Contraception 1991
LNG-IUD Mirena®: conclusions

- Contraceptive efficacy
  - Preserves fertility
  - Easy to use
  - High satisfaction rate
  - Effective in reducing blood loss
  - Well tolerated
  - Enhanced cost-effectiveness
  - Effective alternative to surgery