

Intrauterine delivery of progestogen in the peri- and postmenopausal women

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Outline of the presentation

- Intrauterine delivery of progestins
 - Introduction to LNG-IUS
 - Other options...
- Studies assessing the use of LNG-IUS during peri- and postmenopause
 - Acceptability
 - Bleeding patterns
 - Safety
 - Endometrium
 - General health
- Long-term use of LNG-IUS
- 'Clinicians view...'
- Future prospects

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Levonorgestrel releasing IUS - Mirena®

- Intrauterine release of 20µg LNG/d
- Approved for up to 5 years
- Pearl-index ~ 0.1
 - 12% of Scandinavian women used Mirena® in 2007
- Effective in the treatment of heavy menstrual bleeding
 - Rate of oligo-amenorrhea ~ 20%
 - Reduces the need for hysterectomy
- Local progestin delivery as a part of HRT

Current use and approval status of Mirena®

- Currently >7.5 million Mirena® users

Indication	# countries
Contraception	122
Heavy menstrual bleeding	115
Endometrial protection during ET	106

Current status of LNG-IUS use in Finland

- Mirena® on the market since 1990
 - 15% Finnish women use Mirena®
- Effects on ob&gyn speciality
 - Rate of hysterectomy ↓
 - Rate of surgical sterilization ↓
- Increasing use as a part of HRT
 - How much ??

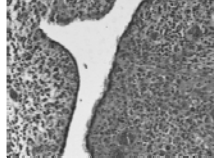
Other alternatives...

Wildemeersch, Contraception 2007

- **Frameless FibroPlant LNG-IUS**
 - 3 or 4.5 cm long, Ø 1.6 device, releasing 14 or 20µg of LNG/day
 - Anchored to uterine fundus
- **Femilis™ and Femilis™ slim LNG-IUS**
 - 2.4 x 3cm or 2.0 x 3cm devices
 - 20µg of LNG/day
- Manufactured by Contrel Research, Belgium
- Both tested also in HRT
 - Similar results as those with Mirena®

How does LNG-IUS work?

1. Endometrial effects most important
2. Viscosity of cervical mucus increased
3. Inhibition of sperm motility
4. In addition, some
 - Foreign body reaction
 - Effects on ovarian function



Endometrial effects of Mirena

1. Atrophy of the glands
 - Inactivation of IGF-1 -system
 - Steroid receptors ↓
2. Decidualization of the stroma

Local is logical

- LNG concentrations during the use of LNG-IUS (*Nilsson et al., 1982*)

- Endometrium 470- 1500 ng/g
- Myometrium 1.8-2.4 ng/g
- Plasma 0.1-0.2 ng/ml

Search strategy

- PubMed search using the terms
 - LNG-IUS/IUD and menopa^s*
 - LNG-IUS/IUD and HRT
 - LNG-IUS/IUD and hormone replacement therapy
- Personal knowledge of the field
- Cross referencing

Summary of the different studies

- **Perimenopausal women**
 - Suhonen et al., Acta Ob&Gyn Scand, 1997
 - Hampton et al., Hum Reprod, 2005
- **Postmenopausal women**
 - Suvanto-Luukkonen et al., F&S, 1999
 - Raudaskoski et al., BJOG, 2002

Practical points - Insertion at peri- or postmenopause

- **Hampton et al., 2005**
 - Insertion successful in 98% (80/82)
 - Easy 77%
 - Difficult 23%
 - Dilatation in 30%
 - Pain
 - No pain 24%
 - Mild 56%
 - Moderate 16%
 - Severe 3%
- **Varila et al., 2001**
 - n=40
 - Easy 65%
 - Difficult 35%
 - 'Facilitating intervention' in 30%
 - Pain
 - No pain 48%
 - Mild 33%
 - Moderate 18%
 - Severe 3%

Effects on endometrial histology

Ref	Estrogen used	Baseline	1-5 years
Suhonen et al., 1997	E ₂ releasing implants, 50µg E ₂ patch OR 2mg E ₂ valerate		Glandular atrophy, decidualized stroma. Weak E2 effect in 24%
Suvanto-Luukkonen et al., 1999	1.5 mg E ₂ gel		Epithelial atrophy, decidualized stroma in 100%
Varila et al., 2001	50µg E ₂ patch OR 2mg E ₂ valerate		'Strong' progestin effect in 97%
Hampton et al., 2005	1.25 - 0.625 mg CEE orally	Proliferative in 45% Inadequate sample 26%	Non-proliferative in >95%

LNG-IUS + systemic estrogens - rates of amenorrhea

Ref	Comment	1 year	3 years	5 years
Suhonen et al., 1997	Peri- and postmenopausal women	76%	79%	N.A.
Suvanto-Luukkonen et al., 1999	Post-menopausal women	80%	80%	80%
Varila et al., 2001	Symptomatic perimenopausal women	90%		
Hampton et al., 2005	Symptomatic perimenopausal women >40y and FSH >15 IU/L, OR >47y. n=82	54%		93%

Patterns of bleeding & spotting *Suhonen et al., 1997*

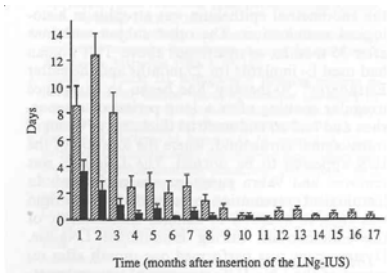


Fig. 3. Number of days of bleeding (solid bars) and spotting (hatched bars) in periods of 30 days up to the first evaluation; means \pm SD are shown.

Continuation rate is high

Reference	Continuation rate at 5 years
Suvanto-Luukkonen et al., 1999	60%
Hampton et al., 2005	80%

Long-term use of LNG-IUS

Rönnerdag et al. Acta Obst Gyn Scand 1999

- European Multicentre Trial (LNG-IUS vs NovaT)
 - Swedish participants of the offered to continue the use of the LNG IUS

1. Mirena 2. Mirena 3. Mirena



↑	↑	↑	↑
	5y	7y	12y
300	100	82	69

High rate of amenorrhea during long-term use of LNG-IUS

Rönnerdag et al. Acta Obst Gyn Scand 1999

Bleeding pattern	End of 1 st LNG-IUS	During 2 nd LNG-IUS
Regular	70%	28%
Infrequent	4%	12%
Amenorrhea	26%	60%

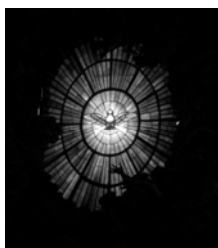
Clinicians view...

- **HRT with systemic E₂ and intrauterine progestin administration often ideal**
 - High rate of amenorrhea
 - Tailored administration of E₂
- **Long term patient-doctor relationship important**
 - Start the transition to intrauterine contraception during late reproductive years

Practical points...

- **How to diagnose menopause in LNG-IUS user with scanty / no bleeding?**
 - Symptoms
 - FSH measurements rarely needed
 - Ovarian US (?)
 - Trial of E₂ therapy
- **Does the use of LNG-IUS alleviate menopausal symptoms?**

Intrauterine progestin in HRT - long term health consequences?

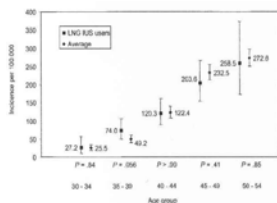


- No data on the risk of
 - Breast cancer
 - Cardiovascular disease
- Registry based studies on-going in
 - Denmark
 - Finland

Contraceptive use of LNG-IUS vs. the risk of breast cancer

Backman et al., Ob&Gyn, 2005

- Postmarketing study of 17,360 LNG-IUS users
- Finnish Cancer Registry data on breast cancer
- **No difference in the incidence of breast cancer in LNG-IUS users vs general female population**



Effects of LNG-IUS on breast density and proliferation

Lundström et al., F&S, 2006

- 20 postmenopausal women receiving 2mg E₂ and LNG-IUS for 18 mo
- Mammographic density & breast proliferation in FNB specimens evaluated
- Effect on breast density
 - Increase in 15% (3/20)
 - No increase in 85%
- No increase in MIB-1 positive breast cells in FNB specimens

Effect of LNG-IUS on serum lipids (Raudaskoski et al., BJOG 2002)

- 55 postmenopausal women using LNG-IUS and 2mg E₂ orally for 18 months

	Baseline	6 mo	12 mo
Total chol	5.89 mmol/l	↓ 9%	↓ 8%
LDL	3.64 mmol/l	↓ 14%	↓ 11%
HDL	1.64 mmol/l	↔	↔
Triglycer	1.12 mmol/l	↔	↔

Use of LNG-IUS in endometrial hyperplasia (Varma et al., 2008)

- **Prospective study on LNG-IUS treatment of endometrial hyperplasia**
 - n=105 women
 - 35% pre- and 65% postmenopausal
 - Histological sampling at regular intervals
 - Outcome based on histology at 1 and 2 years
- **Results**
 - Non-atypical hyperplasia - regression in 92% (88/96)
 - Atypical hyperplasia - regression in 67% (6/9)
- **LNG-IUS is an alternative to oral progestin / hysterectomy in cases on endometrial hyperplasia**

Future prospects - smaller devices releasing lower doses of LNG

- **Randomized comparison of 10µg vs 20µg releasing LNG-IUS** (Raudaskoski et al., BJOG 2002)
 - Similar rates of amenorrhea and endometrial suppression

	10µg IUS	Mirena®
Dimensions	2.8 x 2.8 cm	3.2 x 3.2 cm
Diameter	2.3 mm	3.2 mm
Insertion easy	70 %	46 %

Conclusions

- **Combination of systemic E₂ and intrauterine release of LNG is a often an ideal option for HRT**
 - Effective suppression of endometrium
 - High rate of amenorrhea
 - High continuation rate
- **Long-term effects on general health still unknown**

Thank you!