Non-contraceptive Uses of the Levonorgestrel Intrauterine Device

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Progestin levels with LNG-IUS

- Lower plasma levels
  - Mirena – 150-200 pg/ml
  - Norplant – 400 pg/ml
    - 250-300 at 5 yrs
  - Levlen (.15mg per tab)
    - 700-800 pg/ml
- Ovulation not suppressed
- Higher endometrial concentrations
- Measurable levels in pelvic tissues

Endometrial effects

- Atrophic and inactive
- Scanty glands
- Minimal mitotic activity
- Decreased response to estradiol
- Thin stripe on ultrasound assessment
- No change in HIV shedding (Keikinheimo 2006)
Non-contraceptive benefits of LNG-IUS

- Menorrhagia
- Leiomyomas
- Endometriosis
- Adenomyosis
- Estrogen replacement therapy
- Tamoxifen therapy
- Endometrial hyperplasia
- Endometrial carcinoma

Potential advantages of LNG-IUS

- Office procedure for insertion
- Little skill required
- Five year duration of action
- Reversible contraception provided
- Favorable side effect profile
- Relatively low cost

LNG-IUS for menorrhagia

- v. oral progestins
- v. hysterectomy
- v. endometrial resection
- v. balloon ablation

- Bleeding outcomes
- Quality of life outcomes

Menstrual Blood Loss after LNG-IUS

LNG-IUS v. hysterectomy

- 236 women referred for hysterectomy for menorrhagia
- Randomized:
  - 119 to LNG-IUS
  - 117 to hysterectomy
- By 12 months:
  - 20% in LNG-IUS group had hyst
  - 91% in routine care group had hyst
  - Transient ovarian cysts more frequent in IUS group
    - 14 v. 4

At 5 years
- 119 LNG-IUS group
  - 57 (48%) remained with LNG-IUS
  - 50 (42%) had hysterectomy
- LNG-IUS “failures”
  - 42 (70%) intermenstrual bleeding
  - 19 (32%) heavy bleeding
  - 18 (30%) hormonal symptoms

Quality of life measures improved in both groups
- Outcomes similar for general health, depression, sexual function in both groups
- Improvement maintained at 5 years

Direct and indirect costs lower in IUS group
- Even with half of LNG-IUS group moving to hysterectomy

LNG-IUS v. endometrial resection

- Reduction in bleeding in both groups
  - Marginally better in the ablation group
- Reduction in dysmenorrhea in both groups
- Similar rates of amenorrhea
- Similar range of bleeding patterns short term
- Similar levels of satisfaction
- More progestin symptoms in IUS group
**LNG-IUS v. endometrial resection**

- Crossignani 1997 LNG-IUS dots, Resection circles

**LNG-IUS v. Balloon Ablation**

- Randomized trials
- Equivalent improvement in bleeding at a year
- Longer followup (Busfield) favored IUS
- More side effects in LNG-IUS group
- Health related quality of life better in ablation group
- Short term follow-up

**LNG-IUS for menorrhagia: choice of treatment**

- **Bourdrez 2004**
  - IUD group
    - 40% No hospital admission
    - 26% No general anesthetic
    - 22% No hysterectomy
  - Ablation group
    - 22% No IUD
    - 19% No hysterectomy
    - 15% Short hospitalization

**LNG-IUS for menorrhagia: choice of treatment**

- **Bourdrez 2004**
  - Hysterectomy group
    - 85% No complaints any more
    - 16% No oral contraceptives
    - 12% No IUD
  - 70% of the women would opt for ablation or a levonorgestrel-releasing IUD over hysterectomy if the presumed success rate were 50%. 
LNG-IUS is an effective treatment for menorrhagia

- Level of evidence: I
- Strength of conclusion: A
  - Resection more effective short term
  - Balloon ablation probably equivalent
  - LNG-IUS reversible
  - LNG-IUS more side effects
  - Hysterectomy definitive

LNG-IUS and Uterine Fibroids

- Cohort studies, up to 1 yr follow-up
- Included those with uterine size <12 weeks
- Reduction in bleeding unless
  - very excessive at baseline
  - Significant intracavitary lesion
- Expulsion rate >10%

LNG-IUS and Uterine Fibroids
Soysal 2005

- Prospective trial, 32 pts, matched historical controls with balloon ablation (TBA)
- Myomas <5cm, minimal intracavitary involvement.
- Better control of bleeding with TBA at 3 months, equalized by 6
- No change in uterine volume
- No difference in satisfaction or hysterectomy rates

LNG-IUS and Uterine Fibroids
Magalhaes 2007

- Prospective cohort study, 87 women
  - 32 idiopathic menorrhagia
  - 27 menorrhagia with leiomyomata
  - 28 contraceptors as controls
- Bleeding improved in all groups
  - Menorrhagia persisted in 11% of those with fibroids
  - 0% in other 2 groups
- Mean uterine volume decreased most in fibroid group, second in menorrhagia group, no change in controls
- NO significant decrease in size of the fibroids themselves by 36 months
LNG-IUS and Uterine Fibroids

- LNG-IUS decreases bleeding in women with fibroids
  - <12 week size
  - Minimal submucous component

- Level of evidence: II-2
- Strength of recommendation: B
  - Moderate effect
  - Less effective as bleeding becomes heavier

LNG-IUS for endometriosis pain

- 2007 Cochrane review did not find evidence for significant benefit from pre/post op medical therapy in association with surgery (Yap 2007)

- 2007 Cochrane review on post-surgical use more positive, but found only one acceptable study (Abou-Setta 2007)

LNG-IUS for Endometriosis

- 40 women with disabling dysmenorrhea over 6 months duration
- Randomized to LNG-IUS v. expectant mgmt immediately after conservative surgery
- No other hormonal treatment

- At 12 months:
  - 10% with LNG-IUS with dysmenorrhea
  - 45% in expectant mgmt group
  - Absolute risk reduction 35%

- Satisfied or very satisfied at 12 months
  - 75% in LNG-IUS group
  - 50% in expectant mgmt group
LNG-IUS for Endometriosis
Lockhat 2004
- Prospective cohort of 34 women
- Laparoscopically confirmed endometriosis
  - Minimal to moderate
- LNG-IUS inserted for 6 months
- Repeat laparoscopy at 6 months
- AFS staging improved in 31%
> 80% of those continuing with device had maintained pain relief at 1 and 3 years.

LNG-IUS v. GnRH analog for pain of endometriosis
Petta and Bahamondes 2005
- RCT of 82 women
- Histologically confirmed endometriosis
- Mirena or monthly Lupron 3.75mg
- Six month assessment
- No discontinuation due to side effects

Both treatments were equally effective in
- Reducing pelvic pain
- Reducing bleeding
- Faster onset, greater reduction in bleeding with GnRH
  - Amenorrhea 98% v. 70% with IUS.

Pain score - endometriosis
Values are mean VAS (visual analogue scale, 0-10 ± SEM)
Endometriosis

LNG-IUS is effective in treating pain in women with endometriosis

- Level of evidence: Ib
- Strength of recommendation: B
  - Moderate benefit
  - Side effects common

LNG-IUS as a component of HT


- Uniform endometrial suppression
  - Thin endometrial stripe
  - Well suppressed histologically
- High rates of amenorrhea after first year
- Minimal progestin side effects
- High continuation rates – followed up to 5 years.

Low dose LNG-IUS as a component of HRT

Raudaskoski 2002, Wildemeersch 2004

- Raudaskoski RCT of 163 postmenopausal women
  - 20mcg v. 10mcg IUS, 2mg E2 valerate
  - 98% and 96% amenorrhea
  - Suppression on biopsy at 12 months
- Wildemeersch prospective cohort
  - 24 women using 14mcg device
  - Estradiol 1.5mg daily
  - Endometrial suppression in all, stripe <5mm

LNG-IUS and Tamoxifen

Gardner 2000

- Randomised controlled trial, 122 women
  - 64 with LNG-IUS and Tamoxifen
  - 58 Tamoxifen alone
- Baseline endometrial assessment benign in all women
- Benign decidual response in all women with IUS on followup
- No new polyps in these women
- Initial bleeding in IUS group, which resolved.
LNG-IUS as a component of HRT

LNG-IUS provides an acceptable bleeding profile

Level of evidence I
Strength of recommendation A

Endometrial Hyperplasia

Wildermeersch D 2003

- 12 women, hyperplasia on pipelle
  - 7 simple hyperplasia
  - 5 hyperplasia with atypia

- 14mcg frameless LNG-IUS placed
- Pipelle at 12 months - resolution of hyperplasia in all
- Endometrial stripe <5mm in all

LNG-IUS as a component of HRT

LNG-IUS provides adequate endometrial suppression when used with ERT

Level of evidence I
Strength of recommendation A

Endometrial Hyperplasia

LNG-IUS is an effective treatment for endometrial hyperplasia, with or without atypia

Level of evidence II-2
Strength of recommendation I
LNGIUS in Women with Bleeding Disorders

- Menorrhagia is most common presenting symptom - ¾ with VWD have menorrhagia
- Risk of VTE minimal with progestin only oral contraceptives or injectibles
- Increased risk seen with progestins is with higher doses used for menstrual disorders - 10mg provera, for example.
- LNG IUS has lowest plasma levels

LNG-IUS in bleeding disorders  
Kingman, 2004

- Prospective pilot study, 16 women
- Initial irregular spotting in all – 30-90 days.
- 9 became amenorrheic, 7 others with resolution of menorrhagia.
- Hemostatic cover controversial
  - DDAVP for VWD pts
  - Tranexamic acid for Factor XI

LNG-IUS with anticoagulation  
Pisoni 2006

- Case review of 23 pts receiving oral anticoagulation in their antiphospholipid antibody syndrome clinic
- 17 responded to questionnaire
- Mean age 41.6
- Bleeding reduced in 10 (58%) and amenorrhea occurred in 4 (23.5%)
- 8 (47%) very satisfied, 4 (23.5%) satisfied

Summary

- Menorrhagia        A
- Uterine fibroids   B
- Endometriosis     B
- Component of HRT   A
- Hyperplasia       I
Endometrial Carcinoma

Bahamondes L. 2003

- 2 women with grade 1 adenocarcinoma
- Poor surgical candidates
- LNG-IUS placed and hyst deferred
- Grade 1 adenocarcinoma persisted
  - One 1A, one IB

Endometrial Carcinoma

Dhar 2005

- Four women with stage 1 grade 1 endometrial adenocarcinoma
- All ASA risk IV - major co-morbidities
- One had complete histological regression at 6 months
- One had myometrial invasion at 6 months (hyst for persistent bleeding)
- Two with persistent grade 1 on EMB

Endometrial Carcinoma

Giannopoulos 2005

- Single elderly pt with BMI 58, angioplasty x 3, bleeding
- Endometrial adenocarcinoma with myometrial involvement on MRI
- Rx LNG-IUS and MPA 200mg bid
- Pipelle at 5, 9, 13 months with no neoplasia
- Bleeding resolved
END OF PRESENTATION