Added health benefits of the LNG-IUS and other delivery systems

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A long history

- attempts have been made to treat gynaecological disease with hormonal preparations for longer than they have been used for contraception;
- but somehow the therapeutic opportunities have steadily fallen behind the contraceptive vision;
- there is now substantial information to support the use of all contraceptive hormonal preparations for various therapeutic purposes, but grade A quality evidence is limited;
- two ICCR inventions now lead the way – the most effective reversible contraceptives and therapeutic leaders – the LNG-IUS and the subdermal implants;
Long recognised benefits of hormonal therapy, especially the COC, for treating benign gynaecological symptoms and disease

- 1957; marketing of ‘Enovid’ (for treatment of menstrual bleeding disturbances)
- Major reduction of menstrual bleeding (1960s)
- Major reduction of dysmenorrhoea (1960s)
- Reduction of acne and hirsutism (1970s)
- Reduction of endometrial cancer risk (1970s)
- Treatment of endometrial hyperplasias (1970s)
- Treatment of premenstrual symptomatology (1980s)
Progestogen-only methods

- depot medroxy-progesterone acetate was not far behind
- treatment of endometrial hyperplasia
- medical treatment of endometrial cancers
- treatment of dysmenorrhoea and endometriosis pain
- treatment of other cyclical symptoms (e.g., migraines and epileptic seizures)
- prevention of sickle-cell crises
- treatment and prevention of a number of other conditions
Hormonal delivery systems (long-acting) with added health benefits

- intrauterine: LNG-IUS
- subdermal: LNG systems; etonogestrel system
- injectable: depot medroxy-progesterone acetate

- [vaginal: combined or progestogen rings]
- [transdermal: combined patch]
Added health benefits of non-hormonal contraceptives

- many are now well researched

- non-hormonal methods:
  - copper IUDs: prevention of endometrial cancer
    (Beining et al, Ann Epidemiol 2008)
  - [ male condoms: prevention of transmission of STIs]
  - [hopes for good STI protection with new female barriers ± tenofovir]
So, why have we seen so little emphasis on this aspect of hormonal contraception?

- Society mesmerised by the concepts of negatives and ‘harm’ – “balance” has a low priority.
- Complications and disasters occupy the media, bureaucracies, politicians and the legal system.
- Side effects and potential complications occupy the regulatory agencies.
- Clinical studies address the minutiae of side-effects ("adverse events")
- "Fear of litigation"; "failure to warn".
- Minimal investment into "health benefits".
- Many indications are still "off-label".
Minimal investment into studying “added health benefits”

Yet, I believe that these “added health benefits” are becoming an integral part of the “contraceptive choice equation”

In many countries the younger women are starting to enquire about the “best pill” to manage any one of a range of potential conditions. Indeed, much of the evidence for “added health benefits” comes from COCP use
Survey about the desired frequency of menstruation

135 Australian women completed an on-line survey about their desired frequency of menstruation:

- Once-a-month: 8 (6%)
- Second monthly: 10 (7%)
- Every three months: 35 (26%)
- Every 6 months: 31 (23%)
- Never: 51 (38%)

Weisberg and Fraser; unpublished
Limited regulatory approvals for additional indications for COCs in individual countries

- most countries - no additional indications
- acne, seborrhoea (± “idiopathic” hirsutism)
- dysmenorrhoea
- heavy menstrual bleeding, “DUB”, “FUB”
- premenstrual tension, PMDD
- endometriosis
- urgent treatment of acute uterine bleeding
- “cyclical disorders” (menstrual cycle-related)
- such approvals appear “erratic”
Treatment benefits of COCP, LNG-IUS for which there is good research evidence

- heavy menstrual bleeding
  - endometrial molecular causes
  - coagulopathies
  - PCOS and other cycle irregularities (hyperplasias)
  - uterine myomas; adenomyosis
- iron deficiency ± anaemia
- pelvic pain (primary dysmenorrhoea; endometriosis)
- PMS and PMDD
- Acne, seborrhoea (other androgenic conditions)
LNG-IUS versus 20 μg EE/1 mg norethindrone acetate in the treatment of HMB – MBL

- Pictorial blood assessment chart used to assess MBL

p=0.002

OC1/20, 1 mg norethindrone acetate/20 μg ethinyl estradiol
LNG-IUS versus 20 μg EE/1 mg norethindrone acetate in the treatment of HMB – treatment success


12 months FAS Population *p=0.0095

Percent treatment success (MBL Score <100)

LNG-IUS: 80.0

OC1/20: 36.8

*
E_{2}valerate:dienogest

- Oestradiol valerate and dienogest
- First oestradiol-based oral contraceptive
- Four-phase regimen
- Highly effective oral contraceptive
- Also has a dramatic effect in reducing menstrual blood loss in women with HMB
- Good clinical trial evidence; suggests that this is not a COC class-effect
After 6 months, median MBL had decreased by **88%** from 142 mL to 17 mL in the E₂V/DNG group, compared with 24% from 154 mL to 117 mL in the placebo group.

Intention-to-treat population excluding patients with missing data

p<0.0001 for reduction in MBL between 90 days run-in and 90 days efficacy phase

Premenstrual disorders

Premenstrual dysphoric disorder (PMDD) is the most severe form of PMS.

Mild symptoms experienced by the majority of women during the late luteal phase.

Less severe symptoms: Premenstrual symptoms

More severe symptoms: Premenstrual syndrome

PMDD: Premenstrual symptoms that are severe enough to cause significant disability and impairment.
**Significant improvement in individual items with EE/DRSP**

<table>
<thead>
<tr>
<th>Item number</th>
<th>Change from baseline</th>
<th>EE/DRSP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-1.5</td>
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<td>9</td>
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<tr>
<td>10</td>
<td>-0.5</td>
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<tr>
<td>11</td>
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</tbody>
</table>

* *p<0.05 vs. placebo; decrease = improvement*


**Eleven items: Daily record of severity of problems**

<table>
<thead>
<tr>
<th>Item number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Depressed; Hopeless; Worthless/guilty</td>
</tr>
<tr>
<td>2</td>
<td>Anxious/tense</td>
</tr>
<tr>
<td>3</td>
<td>Mood swings; Feel sensitive</td>
</tr>
<tr>
<td>4</td>
<td>Angry/irritable; Conflicts</td>
</tr>
<tr>
<td>5</td>
<td>Diminished interest</td>
</tr>
<tr>
<td>6</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>7</td>
<td>Tired/fatigued</td>
</tr>
<tr>
<td>8</td>
<td>Increased appetite; Food cravings</td>
</tr>
<tr>
<td>9</td>
<td>Slept more; Trouble sleeping</td>
</tr>
<tr>
<td>10</td>
<td>Overwhelmed, lack of control</td>
</tr>
<tr>
<td>11</td>
<td>Breast tenderness; Breast swelling; Bloated sensation; Headache; Muscle pain</td>
</tr>
</tbody>
</table>
Effective reduction of all types of acne lesion with EE/DRSP

Change in mean number of acne lesions from baseline

EE/DRSP Placebo

Koltun et al. 2006; Lucky et al. 2006.
First proof of concept for non-contraceptive therapeutic benefits of intrauterine progestogen delivery

- Intrauterine Progesterone Contraceptive System (IPCS; Progestasert, Alza Corp)

  - 25 women with cystic endometrial hyperplasia; complete regression in 23.

  - 12 women with HMB; 65% reduction in measured menstrual blood loss at 12 months; much spotting and irregularity; all women experienced some intermenstrual spotting
Menstrual blood loss in women with HMB before and after LNG-IUS insertion

Andersson and Rybo, Br J Obstet Gynaecol 1990
LNG-IUS reduction in uterine volume and blood loss in women with adenomyosis over 36 months

LNG-IUS: Endometrial hyperplasias and cancer

- **High levels of regression of simple benign hyperplasia**
  - 96% full regression at 12 months (90% at 2 years; some reversion to hyperplasia during continued treatment)

- **Moderately high levels of regression (67%) of complex hyperplasias (± atypia)**

- **Hyperplasia with oestrogen replacement therapy**
  - (100% regression with LNG IUS)

- **Numerous case reports: small numbers; short duration**

- **Low grade endometrial carcinoma: small numbers of case reports; variable regression (some good)**
  - Not advised without sound reasons to avoid hysterectomy
  - Require very close monitoring

Therapeutic use of the IUS in women with endometriosis – a 3 year study

Lockhat et al. Hum Reprod, 2005
Use of LNG IUS in adolescents

- extensive anecdotal experience
- mostly straightforward insertions
- New Zealand post-marketing experience (n = 133)
  - contraception alone (n = 18)
  - heavy menstrual bleeding alone (n = 22)
  - contraception plus HMB (n = 21)
  - endometriosis (n = 27)
  - combinations (n = 24)
  - others [mainly menstrual management with disability] (n = 21)

The LNG-IUS:

- reduces fibroid-related problems with long-term use
- may reduce need for fibroid-related surgery
- may reduce fibroid and uterine size
- reduces menstrual blood loss in women with fibroid or adenomyosis-related heavy menstrual bleeding and pain
- may be a useful adjuvant to conservative surgery
- widely used in nullipara

Total number of hysterectomies vs. total LNG-IUS units sold in Finland 1997-2008

Heikinheimo O, 2012
Key areas of hormonal treatment benefits

- heavy menstrual bleeding
  - major reduction in total blood loss (± pain)
- endometriosis
  - control of pain and bleeding
- adenomyosis
  - control of pain and bleeding
- endometrial hyperplasia
  - control of endometrial proliferation
- PMS and PMDD (control of wide range of symptoms)
- others (acne and seborrhoea)
Prevention of medical conditions (1, 2) (by COCPs, LNG-IUS, implants, injectables)

- endometrial adenocarcinoma
- ovarian adenocarcinoma
- endometrial hyperplasia (endometrial protection)
- uterine myomas
- benign ovarian cysts
- acute episodes of pelvic inflammatory disease
- endometriosis
- endometrial polyps
- complaint of infertility
- sickle cell crises
Conclusions

- Many health benefits – both therapeutic and preventive - of low-dose hormonal therapy (esp. COCP & LNG-IUS) are now well demonstrated.
- These health benefits are not well known to the general public.
- These benefits should become an integral part of the treatment choice equation.
- Hence, there is a real need for investment into addressing the current risk-benefit knowledge imbalance (research; education).