Medical Treatment of Endometriosis Associated Pain in Confirmed Disease

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ES has no conflict of interest to declare related to this talk

Overview

- ESHRE Guidelines 2005
- Revised guidelines 2007
- Supporting documentation
- NSAIDs
- Hormonal treatment
  - COC
  - Progestagens
  - Danazol
  - Gestrinone
  - GnRHa
- Conclusions

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ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy[1,10], Agneta Bergqvist[2], Charles Chapron[3], Thomas D'Hooghe[4], Gerard Dunselman[5], Robert Greb[6], Lone Hummelshoj[7], Andrew Prentice[8] and Ertan Saridogan[9] on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

NSAIDs

Treatment of endometriosis-associated pain in confirmed disease

Non-steroidal anti-inflammatory drugs

A	Non-steroidal anti-inflammatory drugs (NSAID) may be effective in reducing endometriosis-associated pain (Kauppila *et al.*, 1979; Ylikorkala and Viinikka, 1983; Kauppila and Ronnberg, 1985).	Evidence level 1b

Revised guidelines, 2007

Non-steroidal anti-inflammatory drugs

A	There is inconclusive evidence to show whether NSAIDs (specifically naproxen) are effective in managing pain caused by endometriosis (Allen et al., 2005).	Evidence Level 1a

NSAIDs

Supporting documentation

- Endometriosis is an inflammatory process
- Significantly more complete or substantial pain relief with Naproxen compared to placebo (Kauppila and Ronnberg 1985)
- Local anti-nociceptive effect and reduced central sensitisation
- NSAIDs and opiates may have synergistic effects

NSAIDs for pain in women with endometriosis

Allen et al 2009

Kauppila 1979 *(published data only)*

* Kauppila A, Puolakka J, Ylikorkala O. Prostaglandin biosynthesis inhibitors and endometriosis. *Prostaglandins* 1979;**18**(6):955–61. Ylikorkala O, Viinikka L. Postaglandins and endometriosis. *Acta Obstetricia et Gynecologica Scandinavica* 1983;**113 Suppl**:105–7.

Kauppila 1985 *(published data only)*

Kauppila A, Rosenberg L. Naproxen sodium in dysmenorrhea secondary to endometriosis. *Obstetrics and Gynecology* 1985;**65**(3): 379–83.

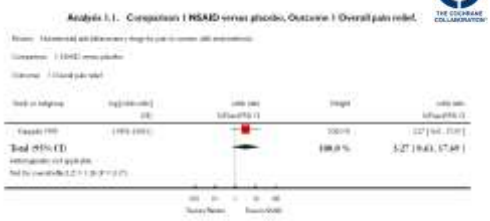
NSAIDs for pain in women with endometriosis

Allen et al 2009

- Kauppila 1979, 24 patients
  - Indomethacin 25 mg tds or Acetylsalicylic acid 500 mg tds vs
    - Tolfenamic acid 200 mg tds
    - Indomethacin
    - Acetylsalicylic acid
    - Placebo
- Kauppila 1985, 24 patients
  - Naproxen sodium 275-550 mg qds vs placebo

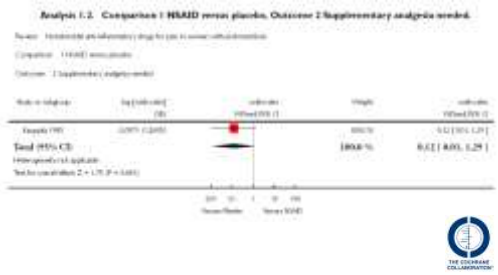
NSAIDs for pain in women with endometriosis

Allen et al 2009



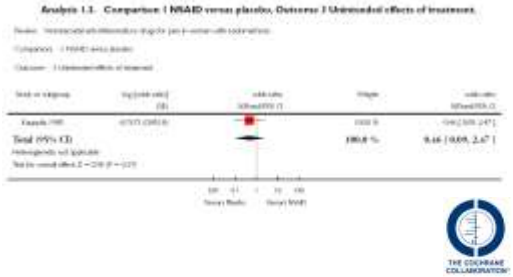
NSAIDs for pain in women with endometriosis

Allen et al 2009



NSAIDs for pain in women with endometriosis

Allen et al 2009



NSAIDs for pain in women with endometriosis

Allen et al 2009

- Conclusion
  - Inconclusive evidence that NSAIDs are effective for pain in women with endometriosis
  - No evidence to suggest any NSAIDs more effective than others

Hormonal treatment

A	Suppression of ovarian function for 6 months reduces endometriosis-associated pain. The hormonal drugs investigated—COC, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists—are equally effective but their side-effects and cost profiles differ (Moore *et al.*, 2004; Prentice *et al.*, 2004a,b; Selak *et al.*, 2004).	Evidence level 1a

Revised guidelines, 2007

Hormonal treatment

A	Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone, medroxyprogesterone, acetate and GnRH agonists - are equally effective but their side-effect and cost profiles differ (Davis et al., 2007 ; Prentice et al., 1999; Prentice et al., 2000; Selak et al., 2007).	Evidence Level 1a

Historical Context

- Long considered that pregnancy improves endometriosis
  - Does not resolve endometriosis
  - Hypothesised that improvement was a consequence of hormonal environment of pregnancy
  - Decidual transformation and necrobiosis of ectopic endometrium
    - Kistner, 1958

Pseudopregnancy

- Combination of oestrogens and progestagens
- 12 patients – 9 objectively and subjectively improved
- Duration of treatment 2-7 months
- Endometrial biopsy - decidual reaction
- 1 subject – decidual reaction in ectopic endometrium
  - Kistner, 1959

Other Early Medical Therapies

- Stilboestrol
- Methyl testosterone
- Effectiveness either debatable or side effect profile unacceptable
  - Thromboembolism and endometrial hyperplasia
  - Androgenic side effects and liver dysfunction

Combined oral contraceptives - continuous administration
Supporting documentation, 2007

- E+P combination to induce pseudopregnancy with resultant amenorrhoea due to endometrial decidualisation
- Low dose COC with 30-35 mcg EE can be effective in 60-95% patients with recurrence rates of 17-18% first year and 5-10% annual recurrence rates (Moghishi 1999)
- Low cost

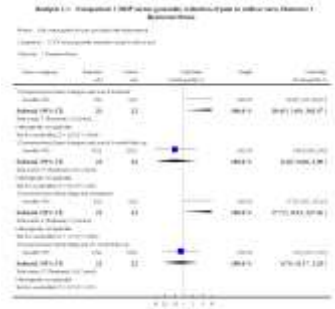
Combined oral contraceptives - cyclical administration
Supporting documentation, 2007

- May provide prophylaxis against development or recurrence of endometriosis
- Regular, reduced menstrual bleeding may be beneficial
- Further research required
- Cochrane review: one trial showed reduction in non-menstrual symptoms

Oral contraceptives for pain associated with endometriosis
Davis et al 2009

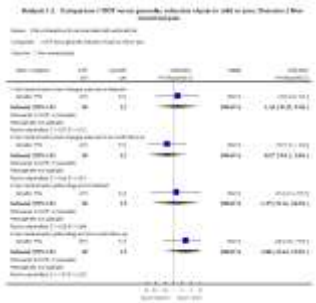
- One study, 57 patients (Vercellini et al 1993)
- Cyclical COC (20 mcg EE + 150 mcg Desogestrel) vs GnRHa (Goserelin 3.6 mg) for 6 months

Oral contraceptives for pain associated with endometriosis
Davis et al 2009



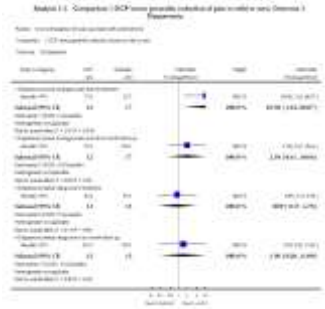
Dysmenorrhoea

Oral contraceptives for pain associated with endometriosis
Davis et al 2009



Non-menstrual pain

Oral contraceptives for pain associated with endometriosis
Davis et al 2009



Dyspareunia

Oral contraceptives for pain associated with endometriosis
Davis et al 2009

- Conclusions
  - No significant differences in non-menstrual pain
  - Symptoms recurred in all patients six months after treatment
  - No difference in dyspareunia rates during or after treatment
  - Hot flushes, insomnia and vaginal dryness more common with GnRHa

Progestagens

Supporting documentation, 2007

- Progestins exert an antiproliferative effect by causing initial decidualisation of endometrial tissue followed by atrophy
- They can be considered as a first choice for the treatment of endometriosis because they are as effective in reducing AFS scores and pain as danazol or GnRH analogues and have a lower cost and a lower incidence of side effects than danazol or GnRH analogues (Vercellini et al., 1997)
- No evidence that any single agent or any particular dose is preferable to another

Progestagens

Supporting documentation, 2007

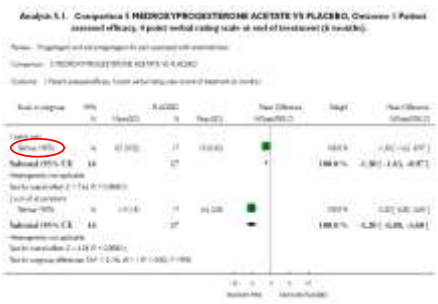
- Side effects
  - Nausea
  - Weight gain
  - Fluid retention
  - Breakthrough bleeding due to hypo-oestrogenemia
  - Depression
  - Other mood disorders

Progestagens and anti-progestagens for pain associated with endometriosis

Prentice et al 2009

- Overton et al 1994
  - Dydrogesterone 40 or 60 mg od or bd vs placebo, luteal phase only, for 6 months
  - Outcome parameters: pain score, AFS score, pregnancy rates
  - 62 patients, only 39 completed second look L'copy, AFS I-II
- Vercellini et al 1996
  - DMPA 150 mg vs COC (20 mcg)+Danazol
  - Outome measure: patient satisfaction at 1 year
- Telimaa et al 1987
  - MPA 100 mg daily vs Danazol 200 mg tds vs placebo, 180 days
  - 16-18 patients in each group, AFS Stage I-III
  - 27% patients had some surgical intervention

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

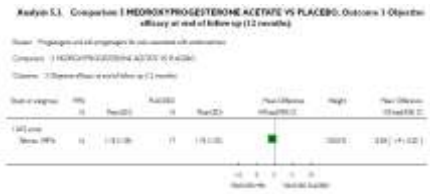


Pain at 6 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

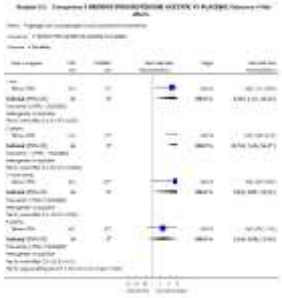
Pain at 12 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



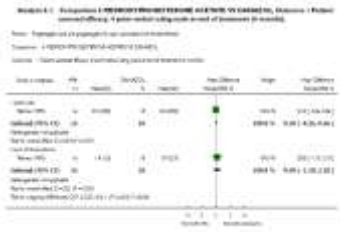
AFS Score at 12 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



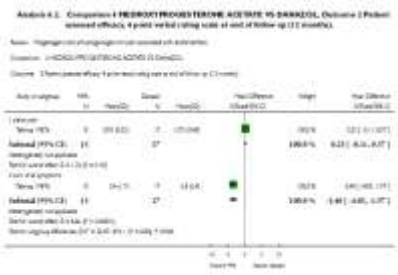
Side effects

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



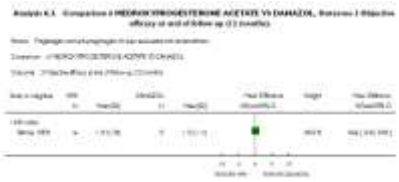
Pain at 6 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



Pain at 12 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



AFS score at 12 months

Progestagens and anti-progestagens for pain associated with endometriosis
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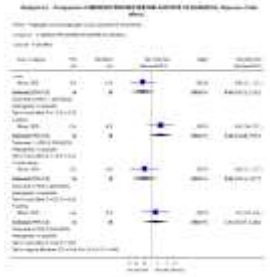
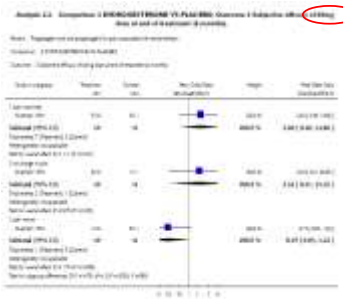


Side effects

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

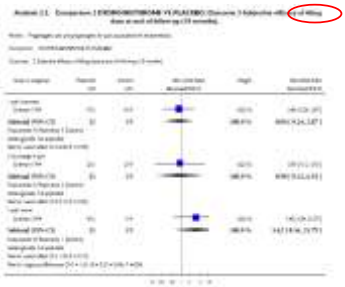
Pain at 6 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



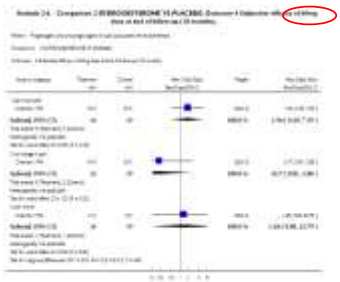
Pain at 6 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



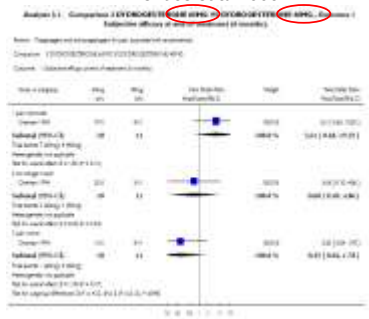
Pain at 18 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



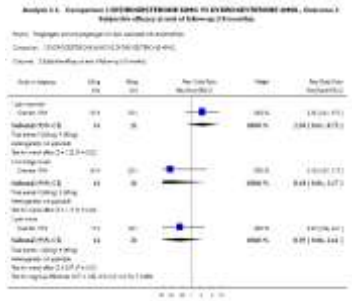
Pain at 18 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



Pain at 6 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



Pain at 18 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

- Vercellini et al 1996
  - DMPA more effective in reducing dysmenorrhoea at 12 months than COC+Danazol
  - No difference in reduction rates of non-menstrual pain and dyspareunia
  - Higher incidence of bloating and spotting with DMPA

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

- Conclusions – Progestagens
  - There is a paucity of data
  - Progestagens are effective for pain symptom associated with endometriosis
  - Progestagens are no more or less effective than other medical treatment options
  - Results should be interpreted with caution

ESHRE Guidelines 2005

Local and depot preparations

The levonorgestrel intrauterine system (LNG-IUS) may be effective at reducing endometriosis-associated pain (Vercellini *et al.*, 1999a), but there is insufficient evidence to make recommendations.

Revised guidelines, 2007

A	The levonorgestrel intra-uterine system (LNG IUS) reduces endometriosis associated pain.	Evidence Level 1a

A systematic review identified two RCTs and three prospective observational studies, all involving small numbers and a heterogeneous group of patients (Varma et al., 2005). Nevertheless, the evidence suggests that the LNG IUS reduces endometriosis associated pain (Petta et al., 2005; Vercellini et al., 1999a) with symptom control maintained over 3 years (Lockhat et al., 2004; Lockhat et al., 2005).

Progestagens
Supporting documentation, 2007

- Local and depot preparations
  - LNG-IUS
    - Vercellini 1999, 2005, Petta 2005, Varma 2005, Fedele 2001, Lockhat 2005
  - DMPA-SC
    - Crosignani et al
  - Implanon (Etonogestrel)
    - Yisa et al 2004, 2005

LNG-IUS

- A prospective non comparative pilot study
- 20 women with recurrent moderate or severe dysmenorrhoea
- Results
  - 1 lost to FU – amenorrhoea and satisfied
  - 1 requested removal due to side effects
  - 1 IUS expelled
  - In remaining 17 visual analogue and verbal rating scores fell
  - 4 women very satisfied and 11 satisfied with treatment

Vercellini et al 1999 Fertil Steril

LNG-IUS

- Prospective therapeutic non randomised trial for rectovaginal endometriosis
- 11 symptomatic patients with proven rectovaginal endometriosis
- Dysmenorrhoea, pelvic pain and deep dyspareunia were greatly improved
- The size of lesions was significantly reduced

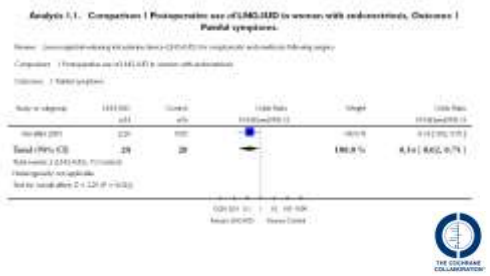
Fedele et al 2001 Fertil Steril

LNG-IUS

Vercellini et al 2003

- Open label parallel group randomized controlled study
- Randomized to Mirena or expectant management following laparoscopic surgery
- At 1 yr moderate or severe dysmenorrhoea experienced by 2/20 v 9/20
- Satisfaction with treatment reported by 15/20 v 10/20

LNG-IUS for symptomatic endometriosis following surgery
Abou-Setta et al 2009



Danazol

Supporting documentation, 2007

- Suppresses GnRH and gonadotrophin secretion
- Inhibits steroidogenesis
- Increases metabolic clearance of oestrogen and progesterone
- Interacts with endometrial androgen and progesterone receptors
- High androgen, low oestrogen environment and subsequent amenorrhoea
- Dose 400-800 mg daily

Danazol – side effects

Supporting documentation, 2007

- Due to hyperandrogenism and hypo-oestrogenemia
- Weight gain
- Fluid retention
- Fatigue
- Nausea
- Acne
- Hirsutism
- Oily skin
- Muscle cramps
- Reduced libido
- Reduced breast size
- Emotional disturbances
- Atrophic vaginitis
- Hot flushes
- Hepatocellular damage
- Irreversible deepening of voice

Danazol – contraindications

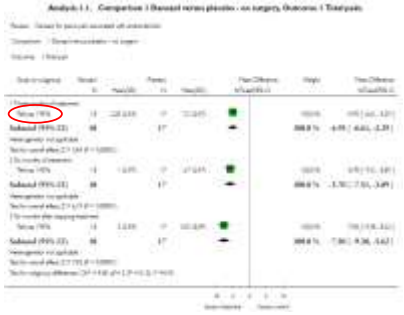
Supporting documentation, 2007

- Hypertension
- Pregnancy
- Impaired renal function
- Congestive heart failure

Danazol for pain associated with endometriosis Selak et al 2010

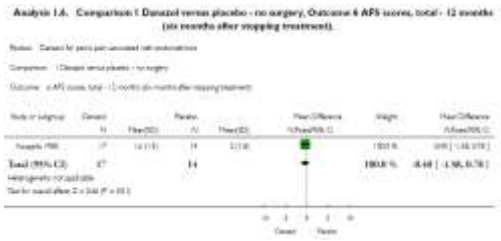
- Bianchi et al 1999
  - 77 postsurgery women, Danazol 600 mg vs placebo, 3 months, AFS III-IV
- Kauppila et al 1988
  - 87 postsurgery women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months, AFS I-II
- Telimaa et al 1987a
  - 59 women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months, AFS I-II
- Telimaa et al 1987b
  - 60 women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months
- Telimaa et al 1990
  - 87 women, Danazol 600 mg vs MPA 100 mg vs placebo, 6 months, AFS I-II

Danazol for pain associated with endometriosis Selak et al 2010



Total pain

Danazol for pain associated with endometriosis Selak et al 2010



AFS score

Danazol for pain associated with endometriosis Selak et al 2010

- Conclusions
  - Danazol is effective for symptoms and signs of endometriosis
  - Significant unpleasant side effects

Gestrinone

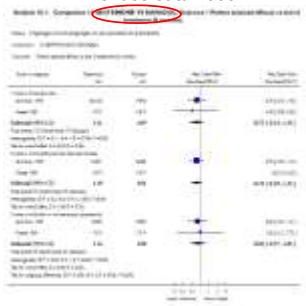
Supporting documention, 2007

- 19 nortestosterone derivative
- Androgenic, antiprogestagenic, anti-gonadotrophic, anti-oestrogenic
- Cellular inactivation and degeneration of endometriosis
- Amenorrhoea rates of 50-100%
- Dose 1.25-2.5 mg twice weekly
- Side effect profile similar but less prominent to Danazol

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

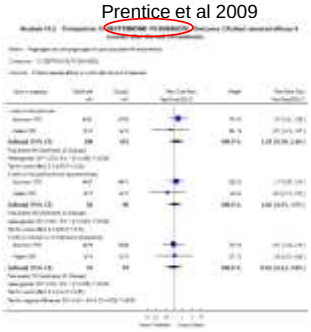
- Fedele et al 1989
  - Gestrinone 2.5 mg twice-thrice weekly vs Danazol 600-800 mg daily, 39 patients
- Bromham et al 1995
  - Gestrinone vs Danazol, 269 patients
- GISG 1996
  - Gestrinone vs GnRH, 55 patients
- Hornstein et al 1990
  - Gestrinone 1.25 mg vs 2.5 mg twice weekly, 12 patients

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



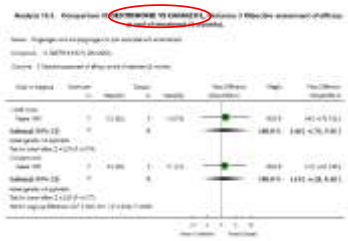
Pain at 6 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



Pain at 12 months

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009



AFS score

Progestagens and anti-progestagens for pain associated with endometriosis
Prentice et al 2009

- Conclusions
  - No difference in subjective or objective efficacy between Gestrinone and Danazol
  - More greasy skin and hirsutism with Gestrinone, but more decreased breast size, muscle cramps and hunger with Danazol
  - GnRHa slightly better for dysmenorrhoea at the end of treatment, but Gestrinone better 6 months after treatment
  - No significant difference between side effect profile of Gestrinone and GnRHa
  - No difference of efficacy between Gestrinone 1.25 and 2.5 mg

GnRHa

ESHRE Guidelines 2005

Duration of GnRH agonist treatment

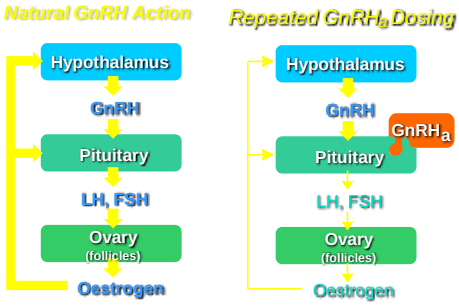
A	Treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief (Hornstein *et al.*, 1995). Treatment for up to 2 years with continued estrogen–progestogen 'add-back' appears to be effective and safe in terms of pain relief and bone density protection (Surrey and Hammond, 2002). However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.	Evidence level IB

GnRHa

Supporting documentation, 2007

- GnRHa bind to pituitary receptors and cause downregulation of gonadotrophic activity
- Suppressed ovarian steroid production
- Pseudomenopause and hypo-oestrogenism

GnRH Agonists: Mode of Action



GnRHa
Supporting documentation, 2007

- Side effects
  - Caused by hypo-oestrogenism
  - Hot flushes
  - Vaginal dryness
  - Reduced libido
  - Reduced bone density
  - Reversibility of bone loss is equivocal, but may resolve within 12 months if treatment is restricted to 6 months

GnRHa for pain associated with endometriosis
Prentice et al 2005 -withdrawn

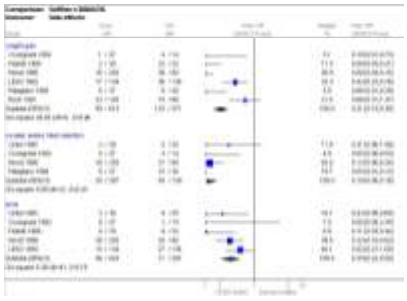
- 26 trials considered in Cochrane Review
- 17/26 comparisons with other trials
  - Predominantly danazol
  - ~1300 women included
- Only one trial compared GnRHa with placebo
- GnRHas and Danazol appear equally effective
- Differences exist in risk rather than benefit

Trials Included in Cochrane Review

Nature of Comparison	n
With Danazol	15
With GnRHa with addback	5
With alternate GnRHa formulation	3
With Gestrinone	1
With Combined Oral Contraceptive	1
With Placebo	1

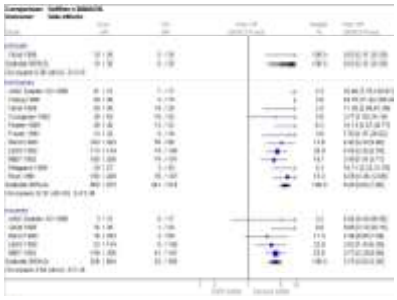
GnRHa v Danazol

Side Effects Favouring GnRHa



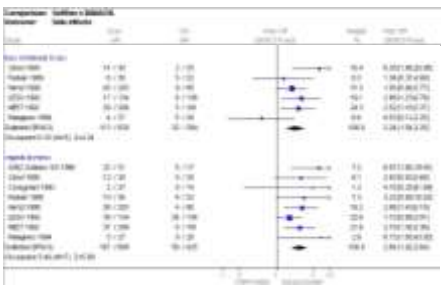
GnRHas v Danazol

Side Effects Favouring Danazol I



GnRHa v Danazol

Side Effects Favouring Danazol II



GnRHa - Add-back therapy

Supporting documentation, 2007

- Aim is to treat endometriosis and pain effectively, while preventing vasomotor symptoms and bone loss
- Progestagens
  - NET 1.2 mg
  - Norethindrone acetate 5 mg
  - Medrogestone 10 mg not effective
- HRT
  - Tibolone 2.5 mg
  - E+P combination

GnRHa: bone mineral density Sagsveen et al 2009

- 30 trials, 2391 women included
- 15 trials, 910 women analysed

Nature of Comparison	n
With Danazol or Gestrinone	9
With GnRHa and progesterone only addback	4
With GnRHa and E+P addback	11
With GnRHa and high dose E+P addback	3
With GnRHa and calcium regulating agents	3
Three monthly with one monthly	1
With Placebo	1

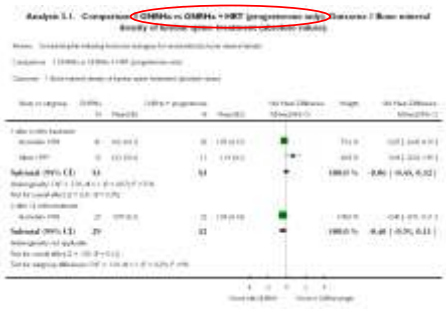
GnRHa: bone mineral density Sagsveen et al 2009

BMD during treatment

GnRHa: bone mineral density
Sagsveen et al 2009

BMD at follow up

GnRHa: bone mineral density
Sagsveen et al 2009



GnRHa: bone mineral density
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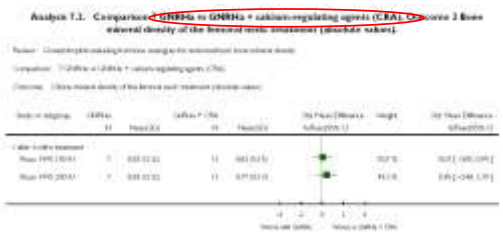

GnRHa: bone mineral density
Sagsveen et al 2009

- Conclusions
  - Danazol/Gestrinone and E+P are effective against bone loss with GnRHa
  - Progesterone only addback is not protective against bone loss
  - Results do not allow conclusion on the effect of Calcium regulators

GnRHa - Draw-back therapy
Supporting documentation, 2007

- Nafarelin 400 mcg/day for 1 month followed b 200 mcg/day for 5 months vs Nafarelin 400 mcg/day for 6 months (Tahara et al 2000)
- Similar oestradiol levels (30 pg/mL)
- Less bone loss

Other medical treatment options

Supporting documentation 2007

- Aromatase inhibitors
- Anti-angiogenic agents
- Progesterone antagonists
- Selective progesterone receptor modulators

Conclusions

- NSAIDs – Insufficient evidence
- Ovarian supression with hormones is effective
- No significant differences in efficacy, but side effect profiles differ