Gonadotrophin-releasing hormone analogues for pain associated with endometriosis (Review)

Brown J, Pan A, Hart RJ

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[Intervention Review]

Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Julie Brown[1], Alice Pan[2], Roger J Hart[3]

[1]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [2]Obstetrics & Gynaecology, University of Auckland, Auckland, New Zealand. [3]School of Women's and Infants Health, The University of Western Australia, King Edward Memorial Hospital and Fertility Specialists of Western Australia, Subiaco, Australia

Contact address: Julie Brown, Obstetrics and Gynaecology, University of Auckland, FMHS, Auckland, New Zealand. j.brown@auckland.ac.nz.

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ABSTRACT

Background

Endometriosis is a common gynaecological condition, characterised by the presence of endometrial tissue in sites other than the uterine cavity (excluding adenomyosis) that frequently presents with pain. The gonadotrophin-releasing hormone analogues (GnRHas) comprise one intervention that has been offered for pain relief in pre-menopausal women. GnRHas can be administered intranasally, by subcutaneous, or intramuscular injection. They are thought to result in down regulation of the pituitary and induce a hypogonadotrophic hypogonadal state.

Objectives

To determine the effectiveness and safety of GnRHas in the treatment of the painful symptoms associated with endometriosis.

Search methods

Electronic searches of the Cochrane Menstrual Disorders and Subfertility Group specialist register, CENTRAL, MEDLINE, EMBASE, PSYCInfo and CINAHL were conducted in April 2010 to identify relevant randomised controlled trials (RCTs).

Selection criteria

RCTs of GnRHas as treatment for pain associated with endometriosis versus no treatment, placebo, danazol, intra-uterine progestagens, or other GnRHas were included. Trials using add-back therapy, oral contraceptives, surgical intervention, GnRH antagonists or complementary therapies were excluded.

Data collection and analysis

Quality assessment and data extraction were performed independently by two reviewers. The primary outcome was pain relief. Relative risk was used as the measure of effect for dichotomous data. For continuous data, mean differences or standardised mean differences were used.

Main results

Forty one trials (n=4935 women) were included. The evidence suggested that GnRHas were more effective at symptom relief than no treatment/placebo. There was no statistically significant difference between GnRHas and danazol for dysmenorrhoea RR 0.98 (95%CI 0.92 to 1.04; P = 0.53). This equates to 3 fewer women per 1000 (95%CI 12 to 6) with symptomatic pain relief in the GnRHa group. More adverse events were reported in the GnRHa group. There was a benefit in overall resolution for GnRHas RR1.10 (95%CI 1.01 to 1.21, P=0.03) compared with danazol. There was no statistically significant difference in overall pain between GnRHas and levonorgestrel SMD -0.25 (95%CI -0.60 to 0.10, P=0.46). Evidence was limited on optimal dosage or duration of treatment for GnRHas. No route of administration appeared superior to another.

Authors' conclusions

GnRHas appear to be more effective at relieving pain associated with endometriosis than no treatment/placebo. There was no evidence of a difference in pain relief between GnRHas and danazol although more adverse events reported in the GnRHa groups. There was no evidence of a difference in pain relief between GnRHas and levonorgestrel and no studies compared GnRHas with analgesics.

PLAIN LANGUAGE SUMMARY

Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Endometriosis is a common condition affecting women of child-bearing age, and is usually due to the presence of endometrial tissue in places other than the uterus. Common symptoms include pain and infertility. GnRHas are a group of drugs often used to treat endometriosis by decreasing hormone levels. This review found evidence to suggest treatment with a GnRHa improved symptom relief compared with no treatment or placebo. There was no evidence of a statistically significant difference when compared with danazol or intra-uterine progestagen. However, there more side effects in the GnRHa group compared with the danazol group. There is not enough evidence to make clear if higher or lower doses of GnRHa are better, or which length of treatment is best.

BACKGROUND

Description of the condition

Endometriosis is characterised by the presence of endometrial tissue in sites other than the uterine cavity. It is a common gynaecological condition affecting woman in their reproductive years as it is generally believed to be an oestrogen dependent disorder. The many observations that support this view include amelioration of pre-existing endometriosis after surgical or natural menopause (Kitawaki 2002), and the growth of endometrial tissue in animals on oestrogen therapy (Bruner-Tran 2002).

Whilst endometriosis is associated with infertility (occasionally as the cause) (Prentice 1996), it frequently presents with the symptom of pain (Barlow 1993). This pain may take the form of dysmenorrhoea (cyclical pain associated with menstruation), dyspareunia (pain on or following sexual intercourse), pelvic or abdominal pain. The patient may also present with cyclical symptoms related to endometriosis at extra-pelvic sites.

The precise pathogenesis (mode of development) of endometriosis remains unclear but it is evident that endometriosis arises by the dissemination of endometrium to ectopic sites and the subsequent establishment of deposits of ectopic endometrium (Haney 1991; McLaren 1996). It has been postulated that the presence of these ectopic deposits gives rise to the symptoms associated with the condition.

Description of the intervention

The gonadotrophin-releasing hormone analogues (GnRHas) are a family of compounds that differ from natural gonadotrophin-releasing hormone (GnRH), a ten amino acid hormone (decapeptide), by modifications in the decapeptide at positions six and ten (Shaw 1991). They may be administered intranasally (IN), by subcutaneous (SC) or intramuscular (IM) injection. Buserelin, goserelin, leuprorelin, leuprolide, nafarelin and triptorelin are some of the most common GnRHas.

Other common treatments for endometriosis include analgesics,

danazol, progestogens (Prentice 2000) including intra-uterine systems, combined oral contraceptive pills (Davis 2007), levonorgestrel and surgical therapies (Jacobson 2009).

How the intervention might work

Non-analgesic medical treatment of endometriosis aims to suppress the ectopic endometrium deposits by inducing atrophy within the hormonally dependent ectopic endometrium (making the endometrial tissue inactive).The observation that endometriosis is rarely seen in the hypo-oestrogenic (low levels of oestrogen) post-menopausal woman led to the concept of medical treatment of endometriosis by induction of a pseudo-menopause. When GnRHas are administered in a non-pulsatile manner (the pituitary is normally stimulated by pulses of natural GnRH and all analogues act on the pituitary at a constant level) their use results in down regulation (switching off) of the pituitary and through the induction of a hypogonadotrophic hypogonadal state (low levels of female hormones due to non stimulation of the ovary).

Why it is important to do this review

The prevalence of endometriosis in the general population is not known but it has been estimated to affect about 7% of women of reproductive age (Haney 1991). The cost of endometriosis is high in both economic and psychosocial terms (Mathias 1996). The annual economic burden of endometriosis in the USA is estimated to be approximately $22 billion which is considerably higher than those of Crohn's disease ($865 million) or migraine ($13-17 billion) (Simoens, 2007). In addition the symptoms associated with endometriosis have a negative impact on physical, mental and social well-being (Kennedy 2005).
Treatment available is dependent upon available resources but also upon the preferences of the individual woman and the gynaecologist. This particularly relates to their decisions concerning the conservation of fertility or requirements for contraception. Other factors include age, degree of symptoms and personal preferences. This review will evaluate the role of GnRHas in the relief of pain in symptomatic women with endometriosis.

OBJECTIVES

To determine the effectiveness and safety of GnRHas in the treatment of the painful symptoms associated with endometriosis.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) comparing the use of GnRHas in the treatment of symptomatic endometriosis were eligible for inclusion. Crossover trials were included in the review providing that pre and post crossover data were available and only the first arm data were used for analysis.

Types of participants

Pre-menopausal women with symptoms ascribed to endometriosis were eligible for inclusion. The clinical diagnosis of endometriosis had to be made by direct visualisation (laparoscopy). Studies were included irrespective of the duration of symptoms. The symptoms considered were: cyclical pain associated with menstruation (dysmenorrhoea) or not associated with menstruation; deep dyspareunia (pain on or following sexual intercourse); lower abdominal or pelvic pain of a non cyclical nature; pain on defecation, and any other painful symptoms ascribed to endometriosis studied in any trial.
Studies were considered in any care setting (primary or secondary).
Exclusions:

- Women with asymptomatic disease or infertility as the only presenting complaint
- Self-reporting of endometriosis
- Trials where GnRHa is administered in post-surgical participants as adjuvant therapy

Types of interventions

Randomised trials reporting the following comparisons were included:

- Trials comparing GnRHas versus no treatment for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing GnRHas versus placebo for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing GnRHas versus analgesics for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing GnRHas versus danazol for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing GnRHas versus intra-uterine progestagen for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing different doses of GnRHas for relieving painful symptoms associated with endometriosis and its related adverse effects

- Trials comparing different treatment length of GnRHas for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing different route of administration of GnRHas for relieving painful symptoms associated with endometriosis and its related adverse effects
- Trials comparing different GnRHas treatment regimes for relieving painful symptoms associated with endometriosis and its related adverse effects

Exclusions:

- Trials comparing GnRHas versus GnRHas in conjunction with add-back therapy as a separate review will be conducted on the subject
- Trials comparing GnRHas with combined oral contraceptive pill (Davis 2007), oral or injectable progestogens (Prentice 2000) or surgical therapies (Jacobson 2009) as they exist under separate reviews.
- Trials comparing GnRHas with GnRH antagonists as that is a registered title of a review to be conducted by the Menstrual Disorders and Subfertility Group of Cochrane Collaboration.
- Trials comparing GnRHas with alternative and complementary medicine

Types of outcome measures

Primary outcomes

- Pain relief defined by using both quantitative measures such as visual analogue scales or categorical outcomes at the end of treatment and when possible at three, six, nine, twelve and twenty-four months follow-up.

Secondary outcomes

- Adverse effects (e.g. hot flushes, insomnia, reduced libido, vaginal dryness and headaches) both short term during therapy and long term extending beyond the treatment period
- Resolution of endometriosis defined by a change in revised American Fertility Society (rAFS) score assessed at second laparoscopy (high score equates to greater severity)
- Quality of life and factors affecting quality of life
- Additional use of analgesics

Cost effectiveness was not an outcome of this review.

Search methods for identification of studies

The search strategy of the Menstrual Disorders and Subfertility Group was utilised to identify all publications that describe or might describe randomised trials of GnRHas in the treatment of symptomatic endometriosis. The search terms used to search the Menstrual Disorders and Subfertility Group specialist register can be referred to in Appendix 1 .

Electronic searches

There were no language restrictions in the searches.
In addition to the Specialist Register, the following electronic databases, trial registers and web sites were searched:

- Ovid The Cochrane Central Register of Controlled Trials (CENTRAL) Appendix 2
- Ovid MEDLINE Appendix 3
- Ovid EMBASE Appendix 4
    - EMBASE will only be searched one year back as the United Kingdom Central Council for Nursing, Midwifery and Health Visiting (UKCC) has hand searched EMBASE to this point and these trials are already in CENTRAL.
- Ovid PSYCInfo Appendix 5
- CINAHL database Appendix 6

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in the Cochrane Handbook of Systematic Reviews of Interventions (Version 5.0.1 chapter 6, 6.4.11) (Higgins 2008)
The EMBASE and CINAHL searches were combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).
Other electronic sources of trials included:

- Trial registers for ongoing and registered trials - 'Current Controlled Trials', "ClinicalTrials.gov' a service of the US national Institutes of Health and 'The World Health Organisation International Trials Registry Platform search portal'
- Citation indexes
- Conference abstracts in the ISI Web of Knowledge
- LILACS database, as a source of trials from the Portugese and Spanish speaking regions of the world
- Clinical Study Results for clinical trial results of marketed pharmaceuticals
- OpenSIGLE database and Google for grey literature

Searching other resources

- All distributors of GnRHas were approached for details of unpublished trials of GnRHas known to or undertaken by them or their parent companies.
- The reference lists of articles retrieved by the search were hand-searched.
- Any relevant journals and conference abstracts that are not covered in the MDSG register were hand-searched in liaison with the Menstrual Disorders and Subfertility Group Trial Search Co-ordinator, Marian Showell.
- Personal communication was made with experts in the field to obtain any additional relevant information.

Data collection and analysis

Selection of studies

One review author scanned the retrieved searches for relevant titles and abstracts of articles retrieved by the search and removed those that were clearly irrelevant. The full text of all potentially eligible studies were retrieved. Two review authors (JB and AP) independently examined the full text articles for compliance with the inclusion criteria. Authors corresponded with study investigators to clarify study eligibility. Where required disagreements as to study eligibility were resolved by consensus or by the assessment of a third author.

Data extraction and management

Data extraction was conducted independently by two review authors (JB and AP) . Data extraction forms were developed and pilot-tested by the authors. Where studies have multiple publications, the main trial report was used as the reference and additional details supplemented from secondary papers. Authors corresponded with study investigators in order to resolve any data queries as required. When disagreements arose between the two review authors, a third review author was contacted to resolve the dispute.

Assessment of risk of bias in included studies

The assessment of the quality of trials identified by the search strategy was undertaken by two of the reviewers. When uncertainty arose regarding suitability for inclusion or when discrepancy arose between the two reviewers (JB and AP), a third reviewer was contacted to make further assessment. The trials were assessed using the Cochrane risk of bias assessment tool to assess:

- sequence generation (low risk: investigators using random number table; computer random number generator; shuffling cards etc. whilst high risk: sequence generated by date of birth; sequence based on hospital or clinic record number etc.)
- allocation concealment (low risk: central allocation; sequentially numbered sealed opaque envelopes etc. whilst high risk: open random allocation schedule; alternation or rotation etc.)
- blinding (low risk: blinding of participants and/or key study personnel; blinding with placebo etc. whilst high risk: incomplete blinding; comparison group with no treatment etc.)
- attrition bias (low risk: no missing outcome data etc. whilst high risk: if attrition is equal or greater than 20% etc.)
- selective outcome reporting and other potential sources of bias (low risk: study protocol is available etc. whilst high risk: not all primary outcomes were reported; outcomes reported were not pre-specified etc.)

If necessary, additional information was sought from the principal investigator of the original trial. All judgments were fully described and the conclusions were presented in the Risk of Bias table.

Measures of treatment effect

Relative risk (RR) was used as the measure of effect for dichotomous data. For continuous data, mean differences (MD) were used whenever outcomes were measured in a standard way across studies. However, as many different methods exist for assessing pain, standardised mean differences(SMD) were calculated when comparing multiple methods. Ordinal data (E.g. quality of life scores) were treated as continuous data. A summary statistic for each outcome was calculated using a fixed effect model and a 95% confidence interval was used.

Unit of analysis issues

Data were presented as per woman randomised. In cross-over trials only the first arm data were used for analysis where data were available, and in case where data were unavailable the primary author was contacted.

Dealing with missing data

The data were analysed on an intention-to-treat basis as far as possible and attempts were made to obtain missing data from the original investigators. If studies reported sufficient detail to calculate mean differences but no information on associated standard deviation (SD), the outcome was assumed to have standard deviation equal to the highest SD from other studies within the same analysis (Note this method was not required in the update). For other outcomes, only the available data were analysed.

Assessment of heterogeneity

The review authors considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. Statistical heterogeneity was assessed by the measure of the I^2 statistic (Higgins 2008). An I^2 measurement greater than 50% indicates substantial heterogeneity and when substantial heterogeneity was detected, possible explanations were explored in subgroup and sensitivity analyses where the quality of study was also taken into account.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, the authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. Care was also taken to search for within study reporting bias such as

trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. A funnel plot was undertaken if there were ten or more studies in an analysis.

Data synthesis

The data from primary studies were combined using fixed effect models in the following comparisons:

1. GnRHas versus no treatment
2. GnRHas versus placebo
3. GnRHas versus analgesics
4. GnRHas versus danazol
5. GnRHas versus levonorgestrel
6. GnRHas stratified by dosage (as defined by study)
   i) high
   ii) low
7. GnRHas stratified by length of treatment
   i) 3 months
   ii) 6 months
8. GnRHas stratified by mode of administration
   i) intranasal
   ii) intramuscular
   iii) subcutaneous
1. GnRHas stratified by different regimes

Subgroup analysis and investigation of heterogeneity

Data were divided into subgroups by dosage (low or high as defined by study), duration of treatment (three, six, nine, twelve and twenty-four months), route of administration (intranasal, intramuscular, subcuticular or depot injection) and drug regimes

Sensitivity analysis

Sensitivity analyses were conducted for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis. These analyses included consideration of whether conclusions would have differed if:

- Eligibility was restricted to studies without high risk of bias (e.g. unclear allocation concealment; attrition rate equal or greater than 20%; incomplete outcome data etc.)
- Studies with outlying results had been excluded;
- Alternative imputation strategies had been adopted;
- A random effect model had been adopted.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.
See: Characteristics of included studies; Characteristics of excluded studies;Characteristics of studies awaiting classification

Results of the search

762 records were identified using the search strategy. After initial screening 124 full-text records were retrieved for more in-depth analysis. 43 randomised controlled trials were included in the meta-analysis, 82 studies were excluded. Two studies (Chan 1993; Chen 2009) are currently awaiting classification. These studies are not included in the meta-analysis.

Included studies

Forty-two randomised controlled trials met our eligibility criteria and were included in this review (Adamson 1994; Agarwal 1997; AN Zoladex 1996; Audebert 1997; Bergqvist 1997; Bergqvist 1998; Burry 1992; Chang 1996; Cheng 2005; Cirkel 1995; Claesson 1989; Dawood 1990; Dlugi 1990; Dmowski 1989a; Fedele 1989; Fedele 1993;Ferreira 2010; Fraser 1991; Gomes 2007; Henzl 1988; Henzl 1990a; Hornstein 1995; Jelley 1986; Lemay 1988; Matta 1988; Miller 1990; Miller 2000; Minaguchi 1986; Moghissi 1987; NEET 1992; Odukoya 1995; Palagiano 1994; Petta 2005; Rock 1993; Rolland 1990; Shaw 1986; Shaw 1990a; Shaw 1992; Skrzypulec 2004; Tummon 1989; Wheeler 1992; Wheeler 1993). See Characteristics of included studies for description.
Five trials were included in two comparisons. Adamson 1994, Henzl 1988 and Moghissi 1987 compared varying dosage of GnRHa in addition to a comparison with danazol, while Dawood 1990 and Dmowski 1989a compared varying route of administration of GnRHa in addition to its comparison with danazol.

Excluded studies

Of the 83 studies that were excluded, 20 were not randomised controlled trials (Anonymous 1993; Anonymous 1999; Bila 1996; Cirkel 1985; Cirkel 1986; Crosignani 1992; Donnez 1990; Franssen 1986; Giorgino 1991; Heinrichs 1998; Henzl 1990;Kiesel 1989; Moodley 2009; Nisolle 1990;Olive 2003; Olive 2004; Ozawa 2006; Ruwe 1998; Shaw 1986a; Vasiljevic 2000), 22 studies did not have relief of pain as an outcome (Acien 1989; Bergquist 1990;Burry 1989; Calvo 2000; de Sa Rosa e Silva 2006; Donnez 1989; el-Roeiy 1988; Fedele 1993a; Franssen 1992; Maouris 1989; Maouris 1991; Matalliotakis 2000; Matalliotakis 2004;Ochs 1993;Rotondi 2002; Roux 1995; Surrey 1993; Tapanainen 1993; Valimaki 1989; Vieira 2007; Wright 1995; Yee 1986), 19 studies did not make comparisons with GnRHas that fitted our 'Types of Interventions' protocol, see Types of interventions for detail. Choktanasiri 2001; Cooke 1989;Crosignani 1996; Dmowski 1989; Donnez 2004; Franke

2000; Kiesel 1989; Kiilholma 1995; Luciano 2004; Magini 1993; Newton 1996; Surrey 1995; Surrey 2002; Tahara 2000; Taskin 1997; Toomey 2003; Vercellini 1994; Warnock 1998; Zupi 2005), five studies looked at the outcome in post-surgical participants (Adiyono 2006; Harada 2000; Ling 1999; Vercellini 2009; Ylikorkala 1995), endometriosis was not the main condition discussed in four studies (Fraser 1996; Shaw 2001; Sorensen 1997; Sowter 1997) and the result of 13 studies were duplicated in other included studies (Allen 1993; Brosens 2001; Burry 1990; Cirkel 1993; Henzl 1989; Hornstein 1992; Jacobs 1991; Jelley 1986a; Kennedy 1990; Lemay 1987; Rock 1991; Shaw 1990; Shaw 1990b). See Characteristics of excluded studies for more details.

Risk of bias in included studies

Details on the quality of each individual study are described in the table 'Characteristics of included studies' where the individual quality criteria was rated for each study.
Authors have been contacted for more information when required.
See Figure 1 for 'risk of bias' table and Figure 2 for 'risk of bias' graph.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

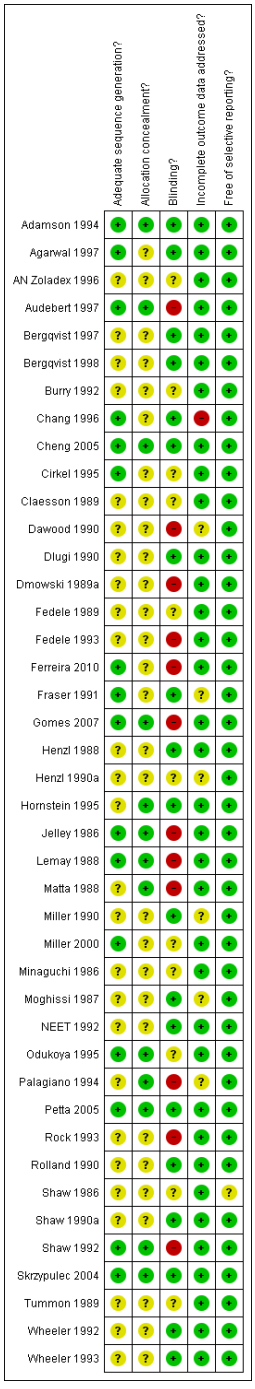
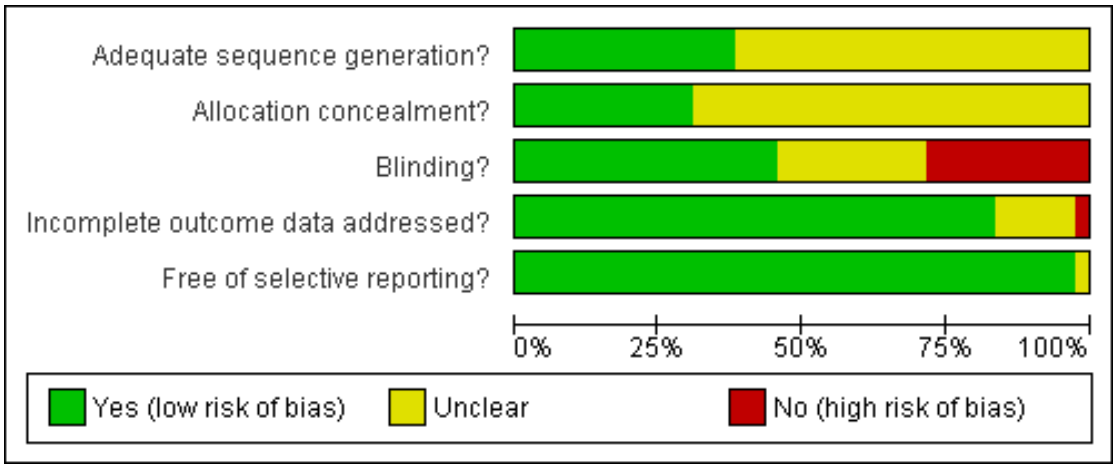


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

In nine trials method of allocation concealment was adequately described (Audebert 1997; Cheng 2005; Gomes 2007; Hornstein 1995; Jelley 1986; Odukoya 1995; Petta 2005; Shaw 1992; Skrzypulec 2004).

Blinding

Twenty trials had adequate blinding where the participants and investigators were blinded by the use of an identical placebo (Adamson 1994; Agarwal 1997; Bergqvist 1997; Bergqvist 1998; Chang 1996; Cheng 2005; Dlugi 1990; Fraser 1991; Henzl 1988; Hornstein 1995;Lemay 1988;Miller 1990; Moghissi 1987; NEET 1992; Petta 2005; Rolland 1990; Shaw 1990a; Skrzypulec 2004; Wheeler 1992; Wheeler 1993). 11 trials were open-trials where there were no blinding (Audebert 1997; Dawood 1990; Dmowski 1989a; Fedele 1993;Ferreira 2010; Gomes 2007; Jelley 1986; Matta 1988; Palagiano 1994; Rock 1993; Shaw 1992). The remaining trials had unclear information or no details on blinding.

Incomplete outcome data

Only one trial did not have adequate reporting of attrition (Chang 1996). No trials lost more than 20% of the original sample during follow up.

Selective reporting

All of the included trials (n=42) reported on their stated primary outcomes and had no additional outcomes that were not stated in their methods section.

Other potential sources of bias

All studies reported baseline equality between groups with respect to age and stage of endometriosis.

Effects of interventions

1. GnRHas versus no treatment

There was only one study which compared GnRHas with no treatment (Fedele 1993) for the outcome of relief of painful symptoms (dysmenorrhoea) . The evidence suggested a statistically significant benefit for GnRHa compared with no treatment for the relief of the pain of dysmenorrhoea associated with endometriosis RR 3.93 (95% CI 1.37 to 11.28, P=0.01). No data were reported on adverse effects.

2. GnRHas versus placebo

Five studies were identified which compared GnRHas with placebo (Bergqvist 1998, Dlugi 1990, Miller 1990, Miller 2000,

Skrzypulec 2004). Only Bergqvist 1998 and Miller 2000 provided usable data.

Bergqvist 1998 demonstrated that there was a statistically significant benefit in favour of GnRHas for the relief of pelvic tenderness RR 4.17 (95% CI 1.62 to 10.68, P=0.003) but no statistically significant differences between groups for dyspareunia (RR 1.16; 95%CI 0.57 to 2.34) or defecation pressure (RR 11.44; 95%CI 0.67 to 196.30). GnRHas appeared to be associated with greater incidence of sleep disturbances (20/24) compared with placebo (9/25), RR 2.31 (95% CI 1.33 to 4.02, P=0.003).

Miller 2000 evaluated pain, using the Endometriosis Symptom Severity Score (ESSS) during the stimulatory phase of GnRHa therapy and found evidence which suggested a significant temporary increase in ESSS with GnRHa therapy compared to placebo with a MD 2.90 (95% CI 2.11 to 3.69, P<0.001).

3. GnRHas versus analgesics

No studies comparing GnRHas and analgesics were identified

4. GnRHas versus danazol

Twenty seven studies compared a GnRHa with danazol (Adamson 1994, AN Zoladex 1996, Audebert 1997, Burry 1992, Chang 1996, Cheng 2005, Cirkel 1995, Claesson 1989, Dawood 1990, Dmowski 1989a, Fedele 1989, Fraser 1991, Henzl 1988, Henzl 1990a, Jelley 1986, Matta 1988, Moghissi 1987, NEET 1992, Odukoya 1995, Palagiano 1994, Rock 1993, Rolland 1990, Shaw 1990a, Shaw 1992, Tummon 1989, Wheeler 1992, Wheeler 1993).

Dichotomous data indicated no evidence of a statistically significant difference between groups for the effectiveness of pain relief in dysmenorrhoea (Adamson 1994;Cirkel 1995; Fedele 1989;Matta 1988;NEET 1992; Palagiano 1994; Wheeler 1992) RR 0.98 (95% CI 0.92 to 1.04, P=0.53); dyspareunia (Adamson 1994; Cirkel 1995; Fedele 1989; Jelley 1986; Matta 1988; NEET 1992; Palagiano 1994) RR 1.02 (95% CI 0.93 to 1.12, P=0.69); pelvic pain (Adamson 1994; Cirkel 1995; Fedele 1989; Matta 1988; NEET 1992; Palagiano 1994; Wheeler 1992) RR 0.96 (95% CI 0.86 to 1.07, P=0.47); induration (Cirkel 1995; NEET 1992) RR 1.10 (95% CI 0.94 to 1.29, P=0.23) and pelvic tenderness (Cheng 2005; NEET 1992; Wheeler 1992) RR 0.98 (95% CI 0.88 to 1.09, P=0.70). Refer to Figure 3. Continuous data from four studies (Cheng 2005; Dmowski 1989a; Tummon 1989; Fraser 1991) also indicated no statistically significant differences between GnRHas and danazol. Refer to Figure 4

Figure 3. Forest plot of comparison: 4 GnRHas versus danazol, outcome: 4.1 Relief of painful symptoms.

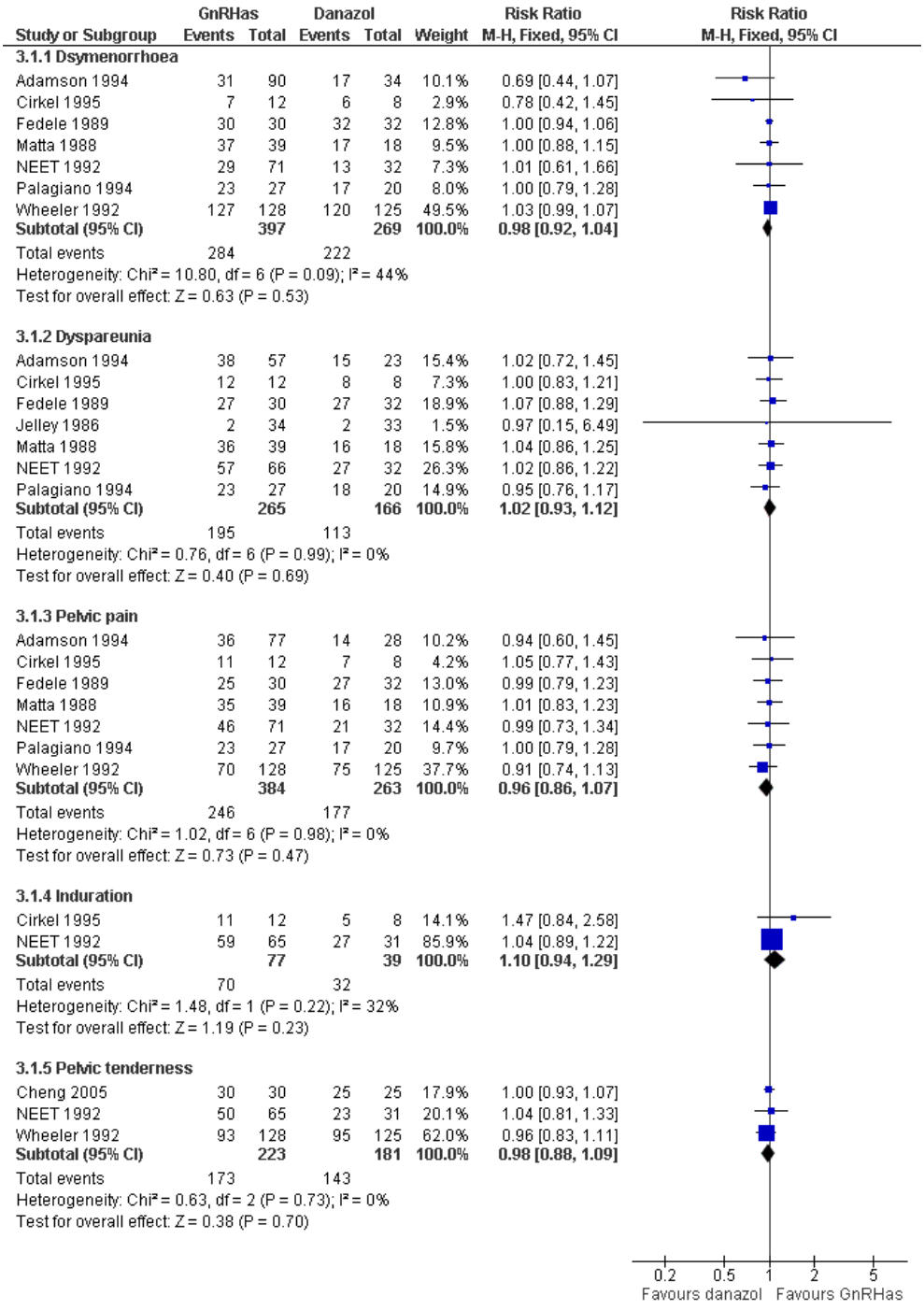
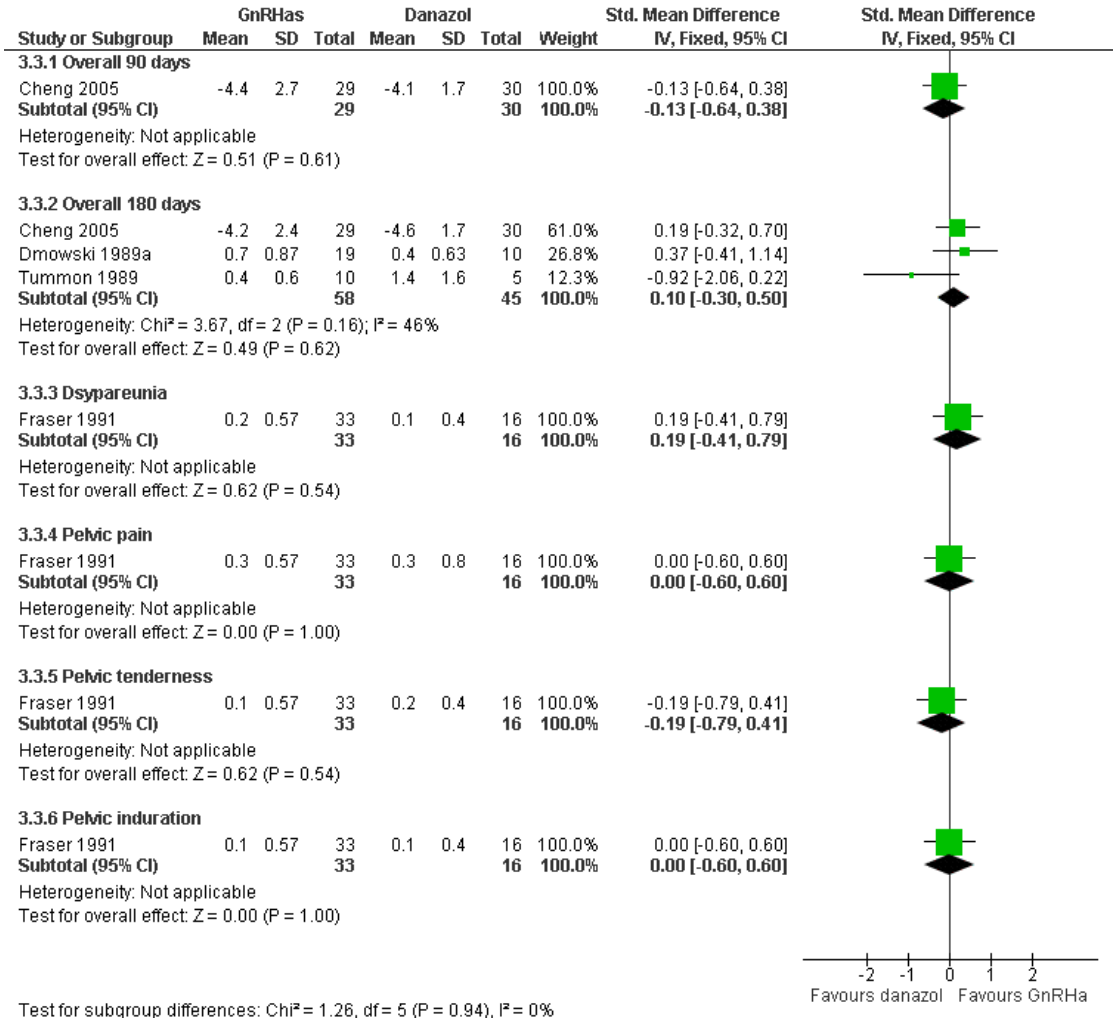
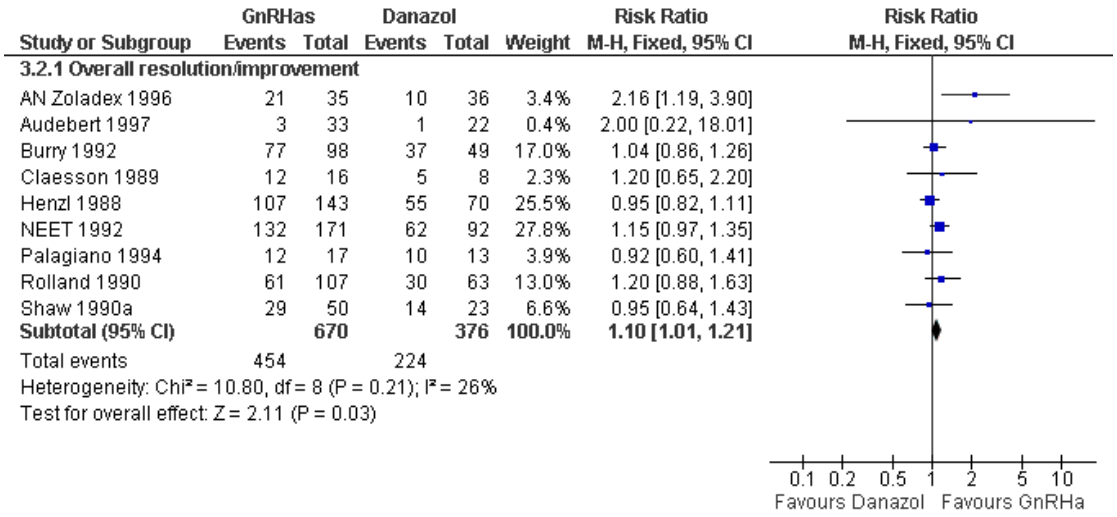


Figure 4. Forest plot of comparison: 4 GnRHas versus danazol, outcome: 4.3 Relief of painful symptoms.



Overall resolution was reported in nine studies (AN Zoladex 1996; Audebert 1997; Burry 1992; Claesson 1989; Henzl 1988; NEET 1992; Palagiano 1994; Rolland 1990; Shaw 1990a) the evidence suggested a benefit in resolution in those groups receiving GnRHas RR1.10 (95% CI 1.01 to 1.21, P=0.03). Refer to Figure 5.

Figure 5. Forest plot of comparison: 4 GnRHas versus danazol, outcome: 4.2 Overall resolution.

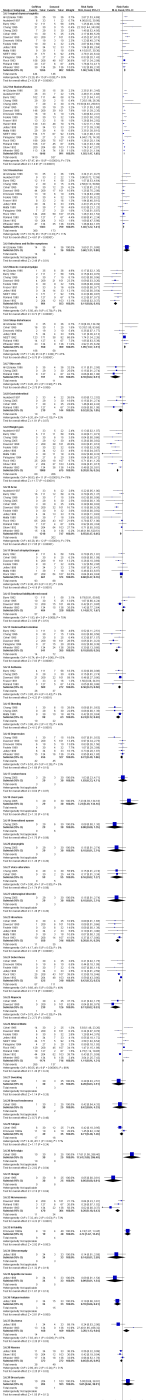


The outcome of improved rAFS score was compared by four studies (Burry 1992, Henzl 1988, Matta 1988, Rock 1993) . There was no evidence to suggest any statistically significant differences between GnRHas (248/488) compared with danazol (109/244), RR 1.14 (95% CI 0.98 to 1.32, P=0.08). The rAFS score at approximately 24 weeks follow up was recorded by ten studies [Cheng 2005, Cirkel 1995, Claesson 1989, Dmowski 1989a, Fedele 1989, Fraser 1991, Henzl 1990a, NEET 1992, Shaw 1992, Tummon 1989]. They found no evidence of a statistically significant difference between groups, SMD -0.01 (95% CI -0.12 to 0.15, P= 0.85).

There were 39 different side effects reported by 19 studies (AN Zoladex 1996, Audebert 1997, Burry 1992, Chang 1996, Cheng 2005, Cirkel 1995, Dawood 1990, Dmowski 1989a, Fedele 1989, Fraser 1991, Henzl 1988, Jelley 1986, Matta 1988, NEET 1992, Palagiano 1994, Rock 1993, Rolland 1990, Shaw 1992, Wheeler 1993).

Five of the most commonly reported side effects were vaginal dryness, hot flushes, headaches, weight gain and acne. Side effects were more frequently reported in groups receiving GnRHas than those receiving danazol. Vaginal dryness was compared in 16 studies, the evidence suggested a significant between GnRHas (444/1266) and danazol (146/802), RR 1.96 (95% CI 1.68 to 2.30, P<0.00001). Nineteen studies looked at hot flushes and found a significant difference between GnRHas (1410/1646) and danazol (537/991), RR 1.55 (95% CI 1.47 to 1.65, P<0.00001), however heterogeneity is high at I^2=73%. Headaches were compared in 16 studies and a statistically significant benefit was found in favour of GnRHas (380/1303) compared to danazol (173/799), RR 1.40 (95% CI 1.22 to 1.61, P<0.00001). Weight gain was reported in 12 studies that found evidence to suggest a statistically significant increase in danazol (206/675) compared to GnRHas (60/1088) RR 0.20 (95% CI 0.16 to 0.26, P<0.00001), heterogeneity was high at I^2= 78%. Acne was reported by 13 studies and evidence suggested a statistically significant increase in danazol (202/747) compared to GnRHas (198/1218) RR 0.55 (95% CI 0.47 to 0.65), heterogeneity high at I^2=75%. Refer to Figure 6.

Figure 6. Forest plot of comparison: 4 GnRHas versus danazol, outcome: 4.6 Side effects.



5. GnRHas versus intra-uterine progestagen

Three studies were included that compared GnRHas with levonorgestrel (Ferreira 2010; Gomes 2007, Petta 2005).

There was no evidence of a statistically significant difference in overall pain score between GnRHas and levonorgestrel SMD -0.25 favouring GnRHas (95% CI -0.60 to 0.10, P=0.46). One study (Gomes 2007) also looked at the rAFS score and appeared to have found no statistically significant difference between GnRHas and levonorgestrel SMD 9.50 favouring levonorgestrel (95% CI -10.77 to 29.7, P=0.36).

6. GnRHa versus GnRHa (varying dosage)

Six studies were identified that compared varying doses of GnRHas:

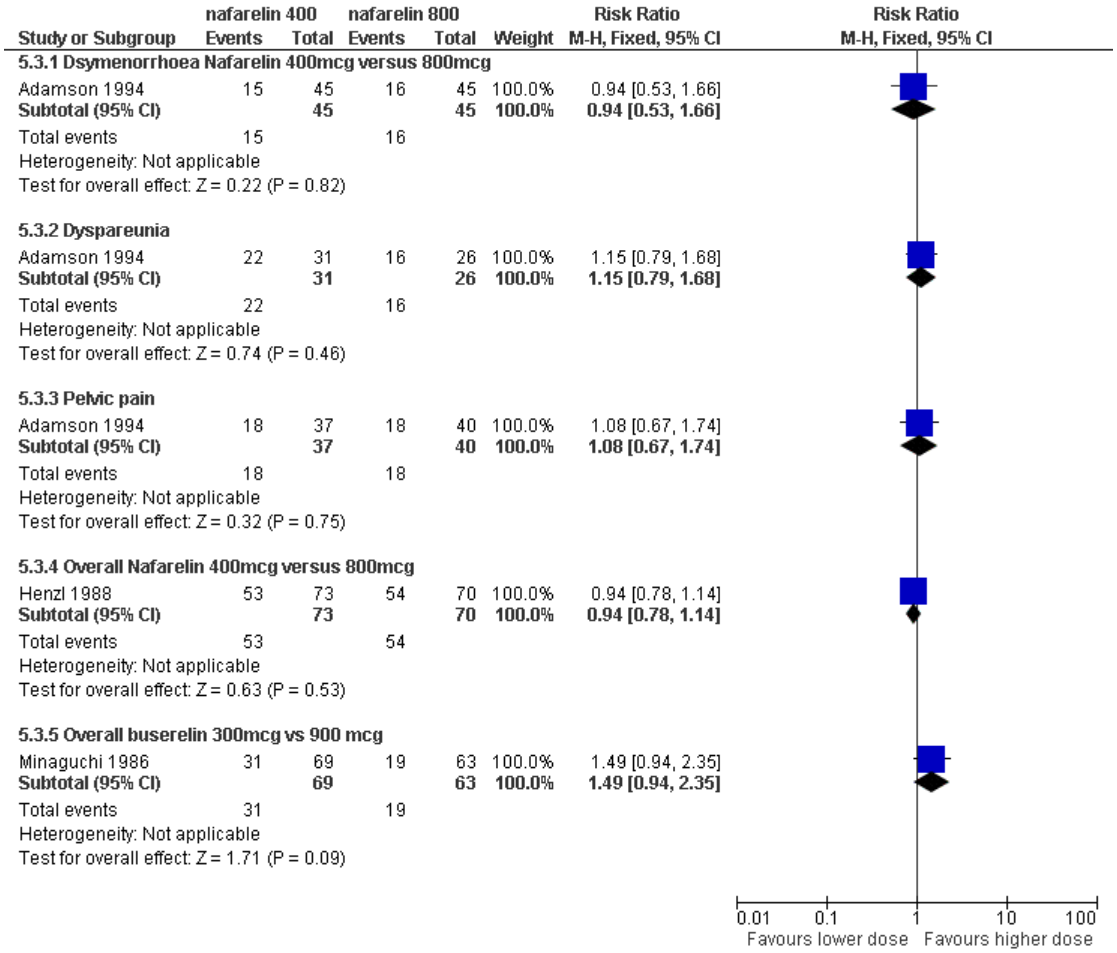
Bergqvist 1997 compared 200mcg vs 400mcg nafarelin daily.

Adamson 1994, Henzl 1988 and Moghissi 1987 compared 400mcg vs 800mcg nafarelin daily.

Minaguchi 1986 compared 300mcg vs 600mcg daily, 300mcg vs 900mcg buserelin daily as well as 600mcg vs 900mcg daily which Shaw 1986 also compared.

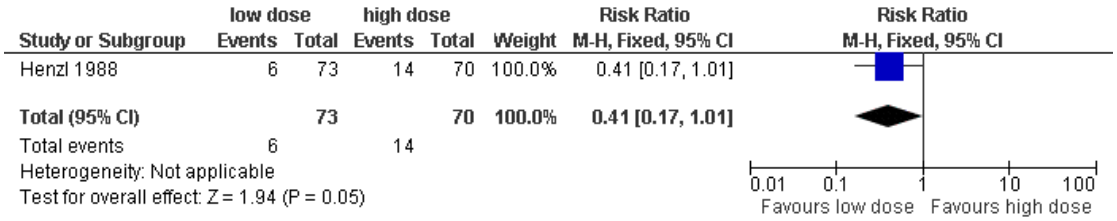
Three studies (Adamson 1994, Henzl 1988, Minaguchi 1986) compared the relief of painful symptoms.The evidence suggested there was no statistically significant differences between the two groups for any outcome (Refer to Figure 7).

Figure 7. Forest plot of comparison: 6 GnRHa versus GnRHa (Varying Dosage), outcome: 6.3 relief of painful symptoms.



One study (Henzl 1988) reported on improvement in rAFS score during a 6 months follow up after treatment and found evidence of a significant difference between low (6/73) and high (14/70) groups, RR 0.41 (95% CI 0.17 to 1.01, P=0.05). Refer to Figure 8

Figure 8. Forest plot of comparison: 6 GnRHa versus GnRHa (Varying Dosage), outcome: 6.2 rAFS score (400mcg vs 800mcg).

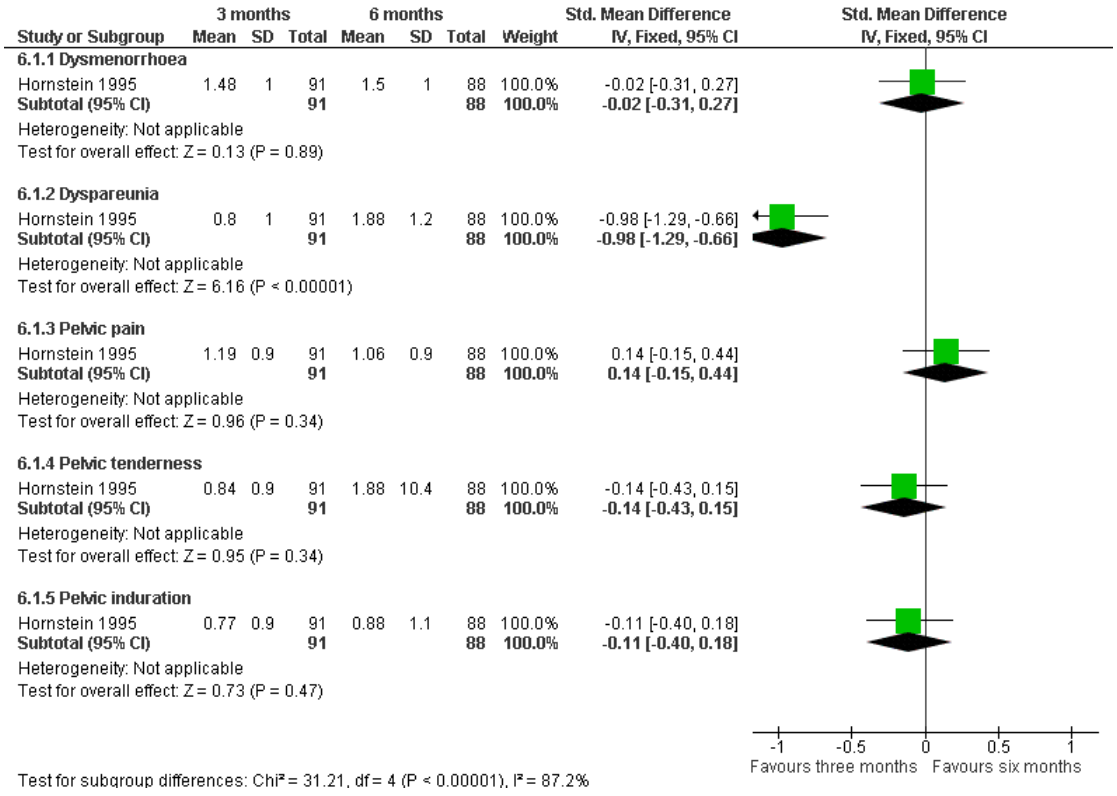


One study Bergqvist 1997) looked at the side effects (hot flushes, sleep disturbances, rhinitis and upper respiratory tract infections) between 200 micrograms daily of GnRHa compared with 400 micrograms daily. The study did not find any evidence to suggest there was any significance in any of the side effects: hot flushes 7/12 for both groups, RR 1.0 (95% CI 0.51 to 1.97); sleep disturbances 9/12 for both groups, RR 1.0 (95% CI 0.63 to 1.59); rhinitis 2/12 200mcg/d versus 5/12 400mcg/d, RR 0.40 (95% CI 0.10 to 1.67) and URTI 1/12 200mcg/d versus 5/12 400mcgd, RR 0.20 (95% CI 0.03 to 1.47).

7. GnRHa versus GnRHa (varying length of treatment)

Hornstein 1995 was the only study to look at relief of painful symptoms for varying length of treatment of GnRHas. The author examined the effect of relief of dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and pelvic induration. Refer to Figure 9. The only outcome to show a statistically significant difference was dyspareunia MD -0.98 (95%CI -1.29 to -0.66; P<0.00001) in favour of a shorter duration.

Figure 9. Forest plot of comparison: 7 GnRHa versus GnRHa (Length of Treatment), outcome: 7.1 Relief of Painful Symptoms (3months vs 6months) at 6 months follow up.



8. GnRHa versus GnRHa (varying routes of administration)

Four studies were included that compared varying routes of administration of GnRHa.

Agarwal 1997 compared intra-nasal (IN) vs intramuscular (IM) depot while Dawood 1990, Dmowski 1989a and Lemay 1988 all compared IN vs subcutaneous (SC) daily.

There was no evidence of a statistically significant difference between IN and IM depot for the relief of painful symptoms associated with endometriosis. The same study had no evidence to suggest there was a statistically significant difference between the episodes of hot flushes experienced in the IN (95/98) or IM depot (93/93) group RR 0.97 (95% CI 0.93 to 1.01, P=0.14).

In the comparison between IN and SC for the relief of painful symptoms associated with endometriosis, there was no evidence to suggest a statistically significant difference for the effectiveness of pain relief between the groups (Lemay 1988) for pelvic pain (RR 1.0; 95%CI 0.53 to 1.87), dyspareunia (RR 1.0; 95%CI 0.57 to 1.75), dysmenorrhoea (RR 1.22; 95%CI 0.75 to 2.06), pelvic tenderness (RR 1.55, 95%CI 0.69 to 3.27), pelvic induration (RR 0.86, 95%CI 0.47 to 1.55). There was also no evidence for a statistically significant difference in the rAFS score between groups MD 9.00 (95% CI -5.93 to 23.93, P=0.24). There was no evidence to suggest any statistically significant differences in adverse effects experienced between the two groups. Hot flushes were encountered in 5/7 IN and 5/6 SC, RR 0.86 (95% CI 0.48 to 1.55, P=0.62); vaginal dryness in 2/7 IN and 2/6 SC, RR 0.86 (95% CI 0.17 to 4.37, P=0.85); headaches in 2/7 IN and 1/6 SC, RR 1.71 (95% CI 0.20 to 14.55, P=0.62) and decreased libido in 1/7 IN and 1/6 SC, RR 0.86 (95% CI 0.07 to 10.96, P=0.91).

DISCUSSION

Summary of main results

GnRHas appear to be more effective at relieving pain associated with endometriosis (pelvic tenderness and ESSS) than either no treatment or placebo. There was no evidence of a difference in pain

relief between GnRHas and Danazol (dysmenorrhoea, dyspareunia, pelvic pain, pelvic induration, pelvic tenderness) although there were more adverse events reported in the GnRHa groups. There was no evidence of a difference in overall pain relief between GnRHas and levonorgestrel and no studies compared GnRHas with analgesics.

It is of note that the cost of danazol is generally less than that of GnRHas but anecdotally the use of danazol has decreased over time due to the irreversible side effect of voice change with this drug (Matabese 2009).

There is limited evidence to draw conclusions regarding the benefit of varying doses, or length of treatment. The route of administration does not appear to be an important factor in attaining benefit.

Overall completeness and applicability of evidence

Although attempts were made to contact authors regarding missing data, there are still some missing data which cannot be included in the analysis. The review authors have attempted to obtain all the relevant published and unpublished material with regards to the objectives of the review. One issue of concern is the methods of reporting pain in the trials. Some trials report overall pain whilst others provide details of specific endometriosis associated pain which includes dysmenorrhoea, dyspareunia, pelvic pain, pelvic induration, pelvic tenderness. There may be some scepticism when generalising overall pain relief and concern when trials do not report on all subcategories of pain.

Quality of the evidence

This was a systematic review of forty one trials including 4742 women. The overall quality of the studies is reasonable. The older studies lack clarity on randomisation and allocation concealment and these authors were often difficult to contact.

Potential biases in the review process

Obtaining additional data from authors has proved difficult due to the age of some of the studies. Raw data were often misplaced or no longer available. One source of bias was an inconsistency in the reporting of adverse events.

Agreements and disagreements with other studies or reviews

The use of add-back therapy to alleviate symptoms is the subject of another registered Cochrane review and the risk of bone demineralisation with GnRHas is discussed in the review by Sagsveen 2003.

AUTHORS' CONCLUSIONS

Implications for practice

This comprehensive review of the literature demonstrates that despite the slight benefit of treatment with a GnRH analogue over the use of danazol, with regard to the overall resolution of endometriosis as assessed by laparoscopy, there is no significant difference in the patients' perception of her symptoms due to her endometriosis. However the side-effect profile of these two drugs were different, with significantly more women experiencing vaginal dryness and hot flushes when treated with GNRH analogues, whereas significantly more women experienced weight gain and acne when treated with danazol. It would appear from the limited data available that GnRH analogue use is more effective at relieving pain symptoms than either no treatment or placebo, although there is no evidence of a benefit of its use over the levonorgestrel intrauterine device. Furthermore there is limited evidence available to determine the optimal dose, route or duration of treatment to alleviate symptoms, although it is generally recommended that treatment should not continue for more than six months, due to the risks associated with bone demineralisation.

Not all aspects of pain relief are discussed in all of the trials and generalisabilty about the relief of specific aspects of pain may be difficult.

Implications for research

More studies of the use of the levonorgestrel intrauterine device versus GnRH analogues would help to determine the place of these treatments in the management of a woman with endometriosis. The impact of the results on the clinical impact is somewhat diluted by the decline in the use of danazol to treat the symptoms of endometriosis. More consistent use of pain outcomes when reporting this measure would be of use in determining which categories are specifically improved by treatment.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adamson 1994

Methods	Prospective randomised double blind controlled study
Participants	213 patients aged 18 to 48 years with laparoscopically confirmed pelvic endometriosis and dysmenorrhoea, dyspareunia or pelvic pain. no surgical procedures were performed during the diagnostic laparoscopy, no patient who had received hormonal treatment during the previous 6 months. 124 patients were randomised who reported the pain symptoms listed above
Interventions	Nafarelin acetate 400mcg bid IN + placebo PO or 6 months (n=45) versus Nafarelin acetate 200mcg bid IN + placebo PO for 6 months (n=45) versus Danazol 400mg bid PO + placebo IN for 6 months (n=34)
Outcomes	Pain: dysmenorrhoea, dyspareunia, pelvic pain.
Notes	Authors responded to methods query

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised randomisation
Allocation concealment?	Yes	Centralised randomisation, sequentially numbered, sealed opaque envelopes
Blinding? All outcomes	Yes	All patients received placebo so patients and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	All women randomised were analysed with intention to treat for main outcome
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Agarwal 1997

Methods	"Multicentre, randomised, double-blind, double-placebo study"
Participants	US study 208 women were randomised, 192 were analysed Age: Nafarelin = 29.8 +/- 0.6 and LA = 31.7 +/- 0.6 (SEM) Inclusion criteria: • Laparoscopically diagnosed endometriosis within 18 months prior to study19-44 years old • Patients demonstrating clinical symptoms and signs • Bone mineral density within normal age range Exclusion criteria: • Conditions or drug therapies that may interfere with the study • Pregnant or lactating women • Danazol use within 6 months prior to study • GnRHa use within 12 months prior to study • OCP within 30 days prior to study treatment • Thyroid disease
Interventions	Nafarelin 200mcg BD IN + placebo every 4 weeks IM for 6 months (n=105) versus LA Depot 3.75mg every 4 weeks IM + placebo BD IN for 6 months (n=103)
Outcomes	Pain: dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness, induration Adverse effects
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	'Randomisation using permuted blocks of random numbers'
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Placebo nasal spray and injection, "Subjects remained blind regarding the study medication and assignment, and the study coordinator and investigator remained blind as to subject treatment status by having injections prepared and administered by a third party"
Incomplete outcome data addressed? All outcomes	Yes	Details for attrition: 24 women withdrew due to:ineffectiveness

Agarwal 1997 (*Continued*)

		3 (Naf) and 3 (LA)adverse effects 4 (Naf) and 8 (LA)lost to follow up 5 (LA)administrative reasons 1 (LA)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

AN Zoladex 1996

Methods	'Multicentre, open, randomised study'
Participants	Australian and NZ Study 71 women were randomised, 48 were analysed Age: Goserelin = 29.5 and Danazol = 29.85 Stage: I to IV Inclusion criteria: • Laparoscopically diagnosed endometriosis within 2 months prior to study • 18-40 years old • rAFS score of equal or greater to 2 • Normal menstrual cycle (21 - 42 days) • Normal cervical smear for previous 12 months Exclusion criteria: • Pregnant or lactating women • Other medical illnesses • Hormone use within 2 months prior to study • Danazol or GnRHa use within 12 months prior to study • Hypersensitivity to trial drugs • Showing signs of virilization • Taking anticoagulant therapy • Surgical treatment
Interventions	Goserelin acetate 3.6mg every 4 weeks SC for 24 weeks (n=35) versus Danazol 200mg TDS PO for 24 weeks (n=36)
Outcomes	Pain: dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness, induration rAFS score Adverse effects
Notes	Authors contacted regarding methods and data, awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**

AN Zoladex 1996 (*Continued*)

Adequate sequence generation?	Unclear	"Patients were randomised in a 1 to 1 ratio"
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	"Analysis was performed on both an 'intention to treat' basis and also on a 'patient treated' basis details given for attrition: 19 in Danazol and 4 in Goserelin group withdrew due to:Adverse effect 9 (Dan)Unwilling to continue 8 (Dan) and 4 (Gos)Withdrawn by investigator 1 (Dan)Other 1 (Dan)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Audebert 1997

Methods	Open, multi-centre, central randomised study
Participants	French study 120 eligible women; 71 were randomised; 55 were analysed Age: 31 +/- 5.9 years Stage: I - IV Inclusion criteria: • Laparoscopically diagnosed endometriosis • Symptomatic • Recurrence of endometriosis after surgery • Over 18 years old • No other hormone therapy except insulin Exclusion criteria: • Amenorrhoea • Patient having had hysterectomy • Pregnant women • Serious illness e.g. liver disease
Interventions	Leuprorelin 3.75mg SC depot every 28 days for 24 weeks (n=33) versus Danazol 600-800mg PO daily for 24 weeks (n=22)
Outcomes	Pain: dysmenorrhoea, dyspareunia, pelvic pain, induration and pelvic tenderness rAFS score

Audebert 1997 (*Continued*)

	Adverse effects
Notes	Cannot use data unless mean and SD specified; author contacted. Author replied that study was sponsored by a pharmaceutical company who hold the raw data. He is attempting to locate a contact for further information

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Central randomisation"
Allocation concealment?	Yes	"Central randomisation"
Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Yes	Sufficient reporting of attrition: • Refuse 2nd laparoscopy n=1 (L) • Lost to follow up n=2 (L) n=9 (D) • Progression of disease n=2 (D) • Not meeting protocol n=1 (D) • Other n=1 (D)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Bergqvist 1997

Methods	"Double-blind randomised study"
Participants	European study 49 eligible women; 49 were randomised and 47 were analysed Age: Median of 30 years (21-46years) Inclusion criteria: • Laparoscopically diagnosed endometriosis • Not to use any hormonal preparations during study • No hormone treatment in previous 3 months • No GnRHas for previous 12 months • No steroid therapy for previous 12 months
Interventions	Nafarelin 200mcg daily IN + placebo PO for 6 months (n=12) versus Nafarelin 400mcg daily IN + placebo PO for 6 months (n=12)

Bergqvist 1997 (*Continued*)

	versus Nafarelin 200mcg daily IN + norethisterone 1.2mg daily PO for 6 months (n=25)
Outcomes	Pain: dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration Adverse effects AFS score
Notes	Need raw data for symptom scores. Authors contacted regarding methods and data. No response to date

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	1:1:2 Naf200:Naf400:Naf200+Norethisterone "randomisation was carried out on a block basis"
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Double blind for patients and investigators
Incomplete outcome data addressed? All outcomes	Yes	Suffient details given for attrition: Mood swings n=1 (Naf+ Norethisterone) Pregnancy n=1 (Naf+ Norethisterone)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Bergqvist 1998

Methods	"Prospective, randomised, placebo-controlled, double-blind, parallel study"
Participants	Swedish study 49 women eligible; 49 were randomised and 46 were analysed Age: mean of 31 years (19-44years) Stage: most mild to moderate (IV n=1) Inclusion criteria: • Menstruating regularly 3 months before study • Clinical symptoms of endometriosis • Not taken oral contraceptive or oral steroid therapy for 3 months • Not taken long acting depot gestagens or GnRHas within past 6 months • Not pregnant in prior 3 months • Not breastfeeding • No history of osteoporosis or coagulation disorders Exclusion criteria:

Bergqvist 1998 (*Continued*)

	• Intraperitoneal adhesions making visual inspection and careful evaluation of the extension of endometriotic lesions difficult or impossible
Interventions	Triptorelin 3.75mg IM depot every 4 weeks for 24 weeks (n=24) versus Placebo IM every 4 weeks for 24 weeks (n=25)
Outcomes	Pain Adverse effects
Notes	Needs raw score for pain. Authors contacted and awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Identical kits for injections: blinding patients and researchers
Incomplete outcome data addressed? All outcomes	Yes	Suffient detail for attrition: • Pregnancy n=1 (P) • Insufficient effect n=1 (P) • Hypoestrogenic side effects + depression n=1 (T)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Burry 1992

Methods	"Multi-centre, double-blind study"
Participants	USA study 169 women eligible; 169 were randomised and 147 analysed for efficacy Inclusion criteria: • Laparoscopically diagnosed endometriosis
Interventions	Nafarelin 400mcg daily IN for 6 months (n=111) versus

Burry 1992 (*Continued*)

	Danazol 600mg daily PO for 6 months (n=58)
Outcomes	Symptoms Change in laparoscopic scores Adverse effects Quality of life score
Notes	Need more info on randomisation and participants and raw data for quality of life. Authors contacted, awaiting response

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	2:1 Nafarelin: Danazol
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	"double-blind"
Incomplete outcome data addressed? All outcomes	Yes	Sufficient details for attrition: • Side effects n=6 (N) n=3 (D) • Elevated liver enzyme n=1 (D) • Administrative reasons n=12
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Chang 1996

Methods	"Randomised comparative study"
Participants	Taiwan study 45 women eligible; 45 were randomised and 33 were analysed Age: Mean of 33 years (LA) Stage: I to IV Inclusion criteria: • Laparoscopic diagnosis of endometriosis • Pain symptoms
Interventions	Leuprorelin acetate 3.75mg SC depot every 28days for 20 weeks (n=30) versus Danazol 200mg QID (800mg/day) PO for 20 weeks (n=15)

Chang 1996 (*Continued*)

Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain Change in AFS score Adverse effects
Notes	Need raw data for pain. Authors contacted, and additional methodological data provided, no raw data

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomisation was in the ratio two LA to one danazol with this study having its randomisation list" "sequentially numbered, identical containers of identical drugs"
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Participants and outcome assessors blinding
Incomplete outcome data addressed? All outcomes	No	No details on attrition
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Cheng 2005

Methods	"Randomised, parallel, comparative study"
Participants	Taiwan study 59 women eligible; 59 were randomised and 41 were analysed for efficacy Age: 34.8 +/- 6.6 (N) and 32.4+/- 7.2 (D) Inclusion criteria: • Laparoscopically diagnosed within 3 months prior to study • Age 18-48 years • Barrier contraception Exclusion criteria: • Pregnancy • Breastfeeding • Menopause or post-menopausal • Use of oestrogen, progesterone or contraceptive steroids in previous 3 months • Impaired hepatic or renal function • Cardiovascular disease • AIDS or other sexually transmitted diseases

Cheng 2005 (*Continued*)

Interventions	Nafarelin acetate 200mcg BD (400mcg/day) IN for 180 days (n=29) versus Danazol 200mg TID (600mg/day) PO for 180 days (n=30)
Outcomes	Total symptom severity score and physician assessed pelvic tenderness Change in laparoscopic score Adverse effects
Notes	Authors provided additional data on methods

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation done by a pharmacy
Allocation concealment?	Yes	Sealed, opaque, sequentially numbered, identical envelopes
Blinding? All outcomes	Yes	Investigators, outcome assessors and clinicians were blinded according to author
Incomplete outcome data addressed? All outcomes	Yes	"All 59 patients were considered as the intent-to-treat population" • 4 withdrawals due to: • Three patients (3/4) underwent Herb drug treatment, withdrawals • All patients (4/4) were anxious with side effects, including significant gain of body weight, acne vagaries, and severe menopausal syndrome. • One patient goes abroad after randomisation
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Cirkel 1995

Methods	”controlled comparative clinical study“
Participants	German study 60 women eligible; 60 were randomised and 55 were analysed Age: 30+/- 0.5 (T) and 30+/- 0.8 (D) Stage: II to IV Inclusion criteria: • Laparoscopically diagnosed endometriosis • No medication affecting pituitary or ovarian function in preceding 6 months Exclusion criteria: • Stage I endometriosis
Interventions	Triptorelin 3.75mg IM depot every 28 days for 24 weeks (n=30) versus Danazol 200mg TDS (600mg/day) PO for 24 weeks (n=25)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration Adverse effects Change in AFS score
Notes	Authors contacted and awaiting response regarding methods.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation list
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	Sufficient detail for attrition: • Refused to fulfil protocol n=3 (D) • Pregnancy n=2 (D)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Claesson 1989

Methods	"Ongoing, Phase III, multi-centre, double-blind, double-dummy study"
Participants	Swedish study 24 women were randomised, 23 were analysed Age: 33.9 (N) and 32.6 (D)
Interventions	Nafarelin 400mcg daily IN for 6 months (n=16) versus Danazol 600mg daily PO for 6 months (n=8)
Outcomes	Pain, dysmenorrhoea, dyspareunia Changes in AFS score
Notes	Authors contacted with regards to methods and raw data. Awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details, "double blind, double dummy"
Incomplete outcome data addressed? All outcomes	Yes	Sufficient data on attrition: • Intercurrent lower back pain n=1 (N)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Dawood 1990

Methods	Multi-centre, open, randomised study
Participants	USA study 355 women eligible and 310 were analysed Inclusion criteria: • Age 20-40 years old • Laparascopically diagnosed endometriosis within 6 weeks of study entry Exclusion criteria: • Danazol treatment in last 6 months

Dawood 1990 (*Continued*)

	• Oral contraceptives in last 2 months • Drugs releasing IUD in last 3 months • Any other investigational drug in 4 weeks • Conditions for which danazol is contraindicated
Interventions	Buserelin 400mcg TDS (1200mcg/day) IN for 6 months (n=149) versus Buserelin 200mcg daily SC for 6 months (n=60) versus Danazol 400-800mg daily PO for 6 months (n=101)
Outcomes	Intermenstrual pelvic pain, dyspareunia, pelvic tenderness and induration Changes in rAFS score Adversse effects
Notes	Authors contacted regarding methods and raw data for pain.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Randomisation schedule" 2:1 Buserelin: Danazol
Allocation concealment?	Unclear	No details
Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Unclear	No details on attrition
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Dlugi 1990

Methods	"Phase III, randomised, double-blind, multi-centre study"
Participants	USA study 63 women eligible; 63 were randomised and 52 were analysed Age: mean of 30 years Stage: I to IV Inclusion criteria:

Dlugi 1990 (*Continued*)

	• Laparoscopically diagnosed endometriosis within 3 months of study entry • Pain secondary to endometriosis • Over 18 years old • No previous treatment with leuprolide acetate or other GnRHas • At least one ovary intact • Non pregnant • Non lactating • No treatment for endometriosis within 3 months of study entry
Interventions	Leuprolide acetate 3.75mg IM depot every 4 weeks for 20 weeks (n=32) versus Placebo (diluent) 2ml IM every 4 weeks for 20 weeks (n=31)
Outcomes	Dysmenorrhoea, pelvic pain, dyspareunia, pelvic tenderness, induration
Notes	Authors contacted for details on allocation concealment and SEMs. Letter returned to sender, author moved with no forwarding address

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Patients were assigned a 3 digit patient number in sequential order from those numbers allocated to each investigator. The patient number encoded the random assignment to a treatment group"
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Patients and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Sufficient details for attrition: 7 withdrawn as subsequently determined they had failed to meet entry requirements, 4 excluded because they had received less than 3 injections of the study drug. There were partial exclusions for efficacy data due to non-compliance with intended study procedures and dosing regimens for 15 patients (7=Leuprolide and 8=placebo) . 27 placebo (24 terminated because of wors-

Dlugi 1990 (*Continued*)

		ened symptoms, 1 because of salpingitis, 1 became pregnant and 1 was non-compliant) and 3 (2 because of intolerable pain and 1 because of an adverse event) leuprolide patients prematurely terminated study
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Dmowski 1989a

Methods	"Open-label, randomised, prospective study"
Participants	USA study 36 women eligible, 36 were randomised and 29 were analysed Age: 30.8 +/- 0.6 (SE) Inclusion Criteria: • Laparoscopically diagnosed endometriosis • No hormonal treatment 8 months prior to study entry
Interventions	Buserelin 400mcg TDS (1200mcg/day) IN for 6 months (n=10) versus Buserelin 200mcg daily SC for 6 months (n=9) versus Danazol 200mg QDS (800mg/day) PO for 6 months (n=10)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain Change in rAFS scores Adverse effects
Notes	Authors contacted regarding allocation concealment

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	2:1 Buserelin: Danazol "Those who were randomised into Buserelin were given an option of SC injections or IN sprays of the drug"
Allocation concealment?	Unclear	No details

Dmowski 1989a (*Continued*)

Blinding? All outcomes	No	"open label"
Incomplete outcome data addressed? All outcomes	Yes	Detail for attrition: 3 in SC Buserelin, 2 in IN Buserelin and 2 in Danazol group. 2 withdrew for family reasons, 3 were non-compliant, 1 had sever emotional side effects on IN Buserelin and 1 was allergic to Danazol
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Fedele 1989

Methods	Randomised study
Participants	Italian study 62 women were randomised and analysed Age: Buserelin = 29.8 +/- 3.3 and Danazol 31.3 +/- 4.3 (SD) Inclusion criteria: • Laparoscopically diagnosed endometriosis within 3 months prior to study • No therapeutic intervention Exclusion criteria: • Bilateral tube occlusion or partner with severe dyspermia • Danazol or other sex hormone use within 6 months prior to study • Systemic or endocrine disease
Interventions	Buserelin 400mcg TDS IN for 6 months (n=30) versus Danazol 200mg TDS PO for 6 months (n=32)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain rAFS score Adverse effects
Notes	Authors contacted for information on raw data for pain scores, and methods. No response to date

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details

Fedele 1989 (*Continued*)

Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	Detail for attrition: • 1 subject from Buserelin group withdrew due to severe pelvic pain
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Fedele 1993

Methods	Multicentre, randomised controlled study
Participants	Italian study 35 women eligible, 35 were randomised, 35 were analysed Stage: I or II Inclusion criteria: • Laparoscopically diagnosed endometriosis • One or more of dysmenorrhoea, pelvic pain and deep dyspareunia
Interventions	Buserelin acetate 1200mcg daily IN for 6 months (n=19) versus Expectant management (n=16) Treatment group followed up for 18 months and expectant management group for 12 months
Outcomes	Dysmenorrhoea, pelvic pain and deep dyspareunia Adverse effects
Notes	Authors contacted regarding methodology and data. Still awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	No	Buserelin acetate versus expectant management (no treatment)

Incomplete outcome data addressed? All outcomes	Yes	All women who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Ferreira 2010

Methods	Randomised, prospective open labelled study
Participants	44 women with endometriosis (confirmed laparoscopically/histologically), aged 18 to 40 years consecutively selected at the pain and endoscopy out-patient clinic at a single centre in Brazil Mean age 28.8 ±4.9 years for LNG-IUS and 41.4±5.8 years for GnRHa All patients had chronic pelvic pain. None had been treated with oral hormone contraceptives for at least 3 months or with depot progestogens or GnRHa for at least 6 months prior to randomisation Exclusion: obese patients (BMI >30kg/m^2).smokers, diabetics, alcohol or drug users, patients wishing to conceive, those with chronic disease, acute and/or chronic inflammatory and/or infectious processes, family history of thromboembolic events, taking medications known to interfere with inflammation markers for a period of less than 15 days before the study
Interventions	LNG-IUS (n=22) versus GnRHa (n=22) 3.75mg leuprolide i.m. monthly treatment for 6 months
Outcomes	BMI, SAP, DAP, HR, pain score (VAS), inflammatory markers
Notes	No ITT analysis

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	'Randomised by computer programme'
Allocation concealment?	Unclear	No details
Blinding? All outcomes	No	Open labelled
Incomplete outcome data addressed? All outcomes	Yes	GnRHa (1 pregnancy before drug administered and 3 moved and lost to follow-up)
Free of selective reporting?	Yes	All a priori outcomes discussed

Fraser 1991

Methods	"Double-blind, double-dummy, randomised, parallel study"
Participants	Australian/New Zealand study 49 women were randomised and 45 were analysed Stage: I to III Inclusion criteria: • Laparoscopically diagnosed endometriosis • Symptomatic • Regular menstrual cycle 24-36 days • Not pregnant • Negative pap smear • Barrier contraception Exclusion criteria: • Concurrent disease which may interfere with drug • Surgical therapy within 6 months prior to study entry • Steroid therapy within 3 months prior to study entry
Interventions	Nafarelin 200mcg BDS (400mcg/d) IN + placebo PO for 6 months (n=33) versus Danazol 200mg TDS (600mg/d) PO + placebo IN for 6 months (n=16)
Outcomes	Dyspareunia, pelvic pain, pelvic tenderness, induration Change in rAFS score Adverse effects
Notes	Authors contacted with regards to allocation concealment. Author replied that the data was difficult to find but would try

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Computer generated list of random numbers"
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Placebo pill + placebo nasal spray so patient and investigators blinded
Incomplete outcome data addressed? All outcomes	Unclear	No details on attrition
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Gomes 2007

Methods	"randomised, controlled clinical study"
Participants	Brazilian study 22 women were randomised, 18 were analysed Age: LNG-IUS = 29.2 +/- 5.5 and Lupron = 32.6 +/- 5.3 Inclusion criteria: • Laparoscopically diagnosed endometriosis made 3 months before enrolment in the study • Chronic pelvic pain that was cyclic • VAS of 3 or more • Regular menstrual cycle (25-35 days) for 3 months or more before study entry • Had not used any hormonal therapy for at least 3 months before study entry • Had not taken long acting progestins or GnRHas within the preceding 9 months • Not pregnant or breastfeeding during the 3 months preceding study • No osteoporosis, coagulation disorders or contraindications to LNG-IUS Exclusion criteria: • Use of medication outside study
Interventions	LNG-IUS IU for 6 months (n=11) versus Lupron Depot 3.75mg IM every 4 weeks for 6 months (n=11)
Outcomes	Pain as defined by VAS Change in laparoscopic outcome as defined by ASRM
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Computer generated system"
Allocation concealment?	Yes	"Sealed envelopes"
Blinding? All outcomes	No	Different route of administration of intervention
Incomplete outcome data addressed? All outcomes	Yes	Detail given for attrition: • 4 withdrawals due to refusal of second laparoscopy
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Henzl 1988

Methods	”parallel, randomised, double-placebo design“
Participants	US, Canadian and Swedish study 236 women were randomised, 213 analysed Age: most 30-40 Stage: 45% had III and IV Inclusion criteria: 18-45 years old. Laparoscopically diagnosed endometriosis within 3 months prior to study enrolment. No hormonal treatment for endometriosis 6 months prior to study
Interventions	Nafarelin IN 200mcg BD + placebo PO for 6 months (n=77) versus Nafarelin IN 400mcg BD + placebo PO for 6 months (n=79) versus Danazol PO 400mg BD + placebo IN for 6 months (n=80)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration AFS score Adverse effects
Notes	Authors contacted regarding randomisation and allocation concealment

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Placebo nasal sprays and tablets to blind patients and researchers, ”both the patients and the investigators were thus blinded regarding the medication“
Incomplete outcome data addressed? All outcomes	Yes	Detail given for attrition: 9 for reasons not related to the study drugs

Henzl 1988 (*Continued*)

		7 in 800mcg Nafarelin and 4 in Danazol due to hot flushes 2 in Danazol due to rapid rise in serum enzymes 1 in Danazol because of a lack of efficacy
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Henzl 1990a

Methods	Randomised study
Participants	European study 194 women were randomised, 167 were analysed Stage: 41% had stage III or IV Inclusion criteria: • Laparoscopically diagnosed endometriosis
Interventions	Nafarelin 200mcg BD IN (n=104) for 6 months versus Danazol 200mgs TDS PO (n=63) for 6 months
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration rAFS score
Notes	Authors contacted with regards to methodology and raw scores for pain. No response to date

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Unclear	No details

Henzl 1990a (*Continued*)

Free of selective reporting?	Yes	A priori outcomes presented

Hornstein 1995

Methods	"double-blind, prospective, multi centre, randomised clinical trial"
Participants	US study 179 women were randomised and analysed Age: 3 months = 31.0 +/- 6.1 and 6 months = 31.3 +/- 5.7 (SEM) Stage: I to IV Inclusion criteria: • 18-46 years old • Laparoscopically diagnosed endometriosis within 24 months prior to study enrolment • 24-36 day menstrual cycle • Symptomatic endometriosis Exclusion criteria: • Hormone treatment 3 months prior to study • Significant illness or lab test abnormality • Prior treatment with Nafarelin • Pregnant or lactating women
Interventions	Nafarelin 200mcg BD IN for 3 months + placebo IN for 3 months after (n=91) versus Nafarelin 200mcg BD IN for 6 months (n=88)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration Adverse effects
Notes	Authors contacted and replied

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Yes	'randomisation was done by a pharmacy'
Blinding? All outcomes	Yes	Placebo nasal spray to blind participants; participants, investigators, outcome assessors and clinicians were blinded

Hornstein 1995 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	All participants who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Jelley 1986

Methods	'Open, prospective, randomised, parallel study', multi centre
Participants	UK study 80 women were randomised, 68 were analysed (so far) Age: Buserelin = 28 and Danazol = 30 (median) Inclusion criteria: • Laparoscopically diagnosed endometriosis • 18 - 40 years old • Symptomatic disease • Active menstrual cycle Exclusion criteria: • Previous use of danazol or hormone treatment without success • Use of danazol within 6 months prior to study • Serious endocrine disease or use of other drugs which may interfere with therapy
Interventions	Buserelin 300mcg TDS IN for 7 months (n=34) versus Danazol 600mg OD PO for 7 months (n=34)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness, induration rAFS score Adverse effects
Notes	Preliminary findings for the first 68 women treated only Attempted to contact author regarding data. Author not contactable

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"The code was derived from random number tables"
Allocation concealment?	Yes	"A sealed envelope was provided for each patient, and opened only after the patient's name had been entered on it"

Jelley 1986 (*Continued*)

Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Yes	Detail for attrition: • 1 randomised patient failed to start treatment as her symptoms improved • So far 4 have withdrawn from study due to adverse effects: 3 (Dan) and 1 (Bus)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Lemay 1988

Methods	Randomised study
Participants	Canadian study 13 women were randomised and analysed Age: 24 - 37 Inclusion criteria: • Laparoscopially diagnosed endometriosis within 6 weeks of study • Not received medical treatment in the previous 6 months Exclusion criteria: • Surgery alone or hormonal treatment and surgery were indicated • Concurrent serious endocrine or systemic disease • History of alcohol or substance abuse • Use of an oral contraceptive within the past 2 months • Drug-releasing intrauterine device within the past 3 month
Interventions	Buserelin 400mcg TDS IN for 6 - 9 months (n=7) versus Buserelin 200mcg OD SC injection for 6 - 9 months (n=6)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration AFS score Adverse effects
Notes	Author contacted regarding methods and replied

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computerised allocation

Lemay 1988 (*Continued*)

Allocation concealment?	Yes	Sealed, opaque, sequentially numbered, identical envelopes
Blinding? All outcomes	No	Only outcome assessors were blinded
Incomplete outcome data addressed? All outcomes	Yes	All participants who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Matta 1988

Methods	Randomised, open label, comparative study
Participants	UK study 61 women were randomised, 56 were analysed Age: 21-40 Stage: "varying degrees" Inclusion criteria: • Laparoscopically diagnosed endometriosis within 6 weeks prior to study Exclusion criteria: • Use of Danazol within past 6 months • Use of other sex steroid within past 3 months • Primary surgery indicated • Serious systemic disease
Interventions	Buserelin 400mcg TDS IN for 6 months (n=41) versus Danazol 400-800mg OD PO for 6 months (n=20)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain AFS score Adverse effects
Notes	Authors contacted regarding methods, and replied

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	2:1 Buserelin: Danazol, "Recruited patients were randomised by an open-label method"

Matta 1988 (*Continued*)

Allocation concealment?	Yes	"centralised randomisation process" "sealed opaque sequentially numbered envelopes
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	Yes	Details given for attrition: • 4 excluded due to failure to attend follow up • 1 declined a second look laparoscopy
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Miller 1990

Methods	"randomised, double-blind" study
Participants	US study - no details of numbers of participants Inclusion criteria: • Laparoscopically diagnosed endometriosis • Experiences significant pain • No treatment of endometriosis within 3 months prior to study
Interventions	Lupron depot 3.75mg IM every 4 weeks for 24 weeks versus Placebo IM every 4 weeks for 24 weeks
Outcomes	Pain Adverse effects
Notes	Study mentioned in paper referring to two studies Authors contacted regarding methods and data, awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	"double-blind", placebo injection so patient is blinded

Miller 1990 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	No details
Free of selective reporting?	Yes	Prespecified outcomes discussed

Miller 2000

Methods	"prospective, randomised, double-blind, parallel, placebo-controlled study"
Participants	US study 120 women were randomised, 120 were analysed Age: 18-40 Inclusion criteria: • Laparoscopically diagnosed endometriosis within 24 months prior to study • Elected to have leuprolide acetate as a treatment option • Sexually active • Not pregnant or breastfeeding • Intact uterus and at least one ovary in good health • Not received treatment for endometriosis within previous 3 months • Not received medroxyprogesterone acetate within previous 6 months • No history of use of a GnRHa Exclusion criteria: • coexisting conditions that might interfere with the conduct or analysis of study • concomitant disease that might cause pain
Interventions	Leuprolide acetate 3.75mg single IM for 4 weeks (n=60) versus Placebo for 4 weeks (n=60)
Outcomes	Pain as defined by VAS and ESSS Quality of Life SF36
Notes	Authors contacted regarding methods and raw data, awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"assigned to groups in the order in which they were enrolled according to a computer generated schedule prepared before the start of the study"
Allocation concealment?	Unclear	No details

Miller 2000 (*Continued*)

Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	All participants who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Minaguchi 1986

Methods	Multicentre study
Participants	Japanese study 191 women were randomised and analysed Stage: II to IV Inclusion criteria: • Laparoscopically diagnosed endometriosis • Over 18 years old • Patients who have received hormonal therapy • Patients with persistent diagnosed endometriosis post-operatively Exclusion criteria: • Patients receiving conservative surgery
Interventions	Buserelin 300mcg OD IN for 6 months (n=69) versus Buserelin 300mcg BD IN for 6 months (n=59) versus Buserelin 300mcg TDS IN for 6 months (n=63)
Outcomes	Intermenstrual abdominal pain, lumbago, dyspareunia, pain on defecation, pelvic tenderness, flexibility of the uterus, nodules in the posterior cul-de-sac, endometrial cyst Adverse effects
Notes	Authors contacted regarding methods and data, awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details

Minaguchi 1986 (*Continued*)

Allocation concealment?	Unclear	”envelope“
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	All women who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Moghissi 1987

Methods	”parallel, double-blind, double-dummy, multi-centre“ study
Participants	US study 141 women were randomised
Interventions	Nafarelin 400mcg OD IN + placebo PO for 6 months (n=52) versus Nafarelin 800mcg OD IN + placebo PO for 6 months (n=48) versus Danazol 800mg OD PO + placebo IN for 6 months (n=42)
Outcomes	Pain rAFS score Adverse effects
Notes	Authors contacted regarding methods and data, awaiting response

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	”randomly assigned“
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	”double-blind, double dummy“, placebo spray and tablet so patient blinded

Moghissi 1987 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	No details
Free of selective reporting?	Yes	All primary outcomes stated were reported on

NEET 1992

Methods	Multicentre, parallel, randomised, double-blind, double-dummy study
Participants	European study 315 women were randomised, 307 were analysed for safety and 263 were analysed for efficacy Inclusion criteria: • Laparoscopically diagnosed endometriosis • 18-45 years old • Not pregnant • Pap smear negative for malignancy • Normal menstrual cycle 21-36 days for previous 4 months • Weight between 45-110 kg Exclusion criteria: • Amenorrhoea • Concurrent disease which may interfere with endometriosis or contraindicate the use of androgenic therapy • Surgical treatment at baseline or within 6 months prior to study • Use of danazol, androgenic hormones, eostrogens, or progestogens within 3 months prior to study
Interventions	Nafarelin 200mcg BD IN + placebo PO for 6 months (n=206) versus Danazol 200mg TDS PO + placebo IN for 6 months (n=101) Note: 8 participants who were randomised never took the study medication
Outcomes	Pain: dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration AFS score Adverse effects
Notes	Authors contacted regarding methods, awaiting response

Risk of bias

Item	Authors' judgement	Description

NEET 1992 (*Continued*)

Adequate sequence generation?	Unclear	"patients were randomised so that 2 were assigned to receive nafarelin for every 1 assigned to receive danazol"
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Placebo tablets and spray so that subjects were blinded
Incomplete outcome data addressed? All outcomes	Yes	Detail for attrition: • "307 were included in the safety analyses, of whom 263 also qualified for the efficacy analyses (171 nafarelin and 92 danazol recipients)" • 25 had been treated < 150 days • 7 were treated > 150 days but refused or otherwise missed the post-treatment laparoscopy • 12 violated the study protocol • 14 discontinued due to adverse events • 4 for intercurrent illness • 4 for personal reasons • 1 due to ineffective treatment • 2 lost to follow up
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Odukoya 1995

Methods	Randomised study
Participants	UK study 21 women were randomised and analysed Age: 33 +/- 5 (SD) Inclusion criteria: • Laparoscopically diagnosed endometriosis • Pelvic pain
Interventions	Leuprolide acetate 3.75 SC monthly for 3 months (n=10) versus Danazol 400mg daily PO for 3 months (n=11)
Outcomes	Pain (Biberoglu + Behrman scale)

Odukoya 1995 (*Continued*)

Notes	Authors contacted regarding methods (blinding) and SD data, awaiting response	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"computer generated"
Allocation concealment?	Yes	"envelope only opened at commencement of treatment"
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	All women who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Palagiano 1994

Methods	Randomised, open study
Participants	Italian study 50 women were randomised, 47 were analysed Age: 20-40 Inclusion criteria: • Laparoscopically diagnosed endometriosis • No treatment for endometriosis within previous 12 months
Interventions	Leuprolide acetate 3.75mg IM monthly for 6 months (n=30) versus Danazol 600mg OD PO for 6 months (n=20)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain Adverse effects
Notes	Authors contacted regarding methods and replied

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"randomly allocated"

Palagiano 1994 (*Continued*)

Allocation concealment?	Yes	Randomisation done by a pharmacy
Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Unclear	Withdrawals after randomisation <10% "drop out patients without M.D. consultation"
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Petta 2005

Methods	Randomised controlled trial
Participants	Brazillian study 83 women were randomised, 71 were analysed Age: LNG-IUS = 29.4 +/- 4.8 and Lupron = 30.5 +/- 6.4 (SD) Stage: I to IV Inclusion criteria: • Laparoscopically and histologically confirmed endometriosis within 3 to 24 months prior to study enrolment • 18-40 years old • Complaints of cyclic chronic pelvic pain with or without dysmenorrhoea • VAS pain score of greater or equal to 3 during the pretreatment cycle • Regular menstrual cycle of 25-35 days for at least 3 months prior to study • Not used hormone treatment for at least 3 months prior to study • Not taken any long acting progestins or GnRHa within 9 months prior to study • Not pregnant or breastfeeding 3 months prior to study • No osteoporosis, coagulation disorders or contra-indications
Interventions	LNG-IUS (Mirena) 20mcg/day 5 years IU for 6 months (n=40) versus Lupron 3.75mg every 28 days IM for 6 months (n=43)
Outcomes	Pain as defined by VAS score Psychological general well being index
Notes	Authors contacted regarding data, awaiting response

Risk of bias

Item	Authors' judgement	Description

Petta 2005 (*Continued*)

Adequate sequence generation?	Yes	”computer generated system“
Allocation concealment?	Yes	”sealed envelopes“
Blinding? All outcomes	Yes	Outcome assessors were the only ones who were blinded according to author
Incomplete outcome data addressed? All outcomes	Yes	”data analysis did not follow intention-to-treat principles“ but details given for attrition: • 6 each from both groups withdrew • 1 pregnant and 5 did not complete pain diary (LNG-IUS) • 6 did not complete pain diary (Lupron)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Rock 1993

Methods	”multi-centre, open, parallel study“
Participants	US study 315 women were randomised and analysed Age: Goserelin = 30.4 and Danazol = 29.7 Stage: I to IV Inclusion criteria: • laparoscopically confirmed endometriosis • AFS score of greater or equal to 2 • Symptomatic (total pelvic score of equal or greater than 3) or asymptomatic disease, with or without infertility Exclusion criteria: • Stage IV disease
Interventions	Goserelin 3.6mg every 28 days SC for 24 weeks (n=208) versus Danazol 400mg BD PO for 24 weeks (n=107)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration rAFS score Adverse effects

Rock 1993 (*Continued*)

Notes	Authors contacted regarding methods and data, awaiting response	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised 2:1 Goserelin: Danazol
Allocation concealment?	Unclear	No details
Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Yes	"All randomised subjects were included in the overall analysis of treatment outcome" details given for attrition: • 15 in Goserelin and 18 in Danazol group withdrew • 6 in Goserelin and 13 in Danazol group withdrew due to adverse events
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Rolland 1990

Methods	Randomised, parallel study
Participants	Dutch study 194 women were randomised, 170 were analysed Inclusion criteria: • Laparoscopically confirmed endometriosis • 18 - 45 years old • Body weight of 45 - 110kg • Menstrual cycle of 24 - 36 days • Symptomatic • Not pregnant • Negative pap smear test Exclusion criteria: • Prescence of amenorrhoea • Interferring concurrent disease • Surgical treatment at baseline laparoscopy or within 6 months prior to study • Gonadal hormone or danazol use within 3 months prior to study • Simultaneous participation in other studies
Interventions	Nafarelin 200mcg BD IN + placebo PO for 6 months (n=127) versus

Rolland 1990 (*Continued*)

	Danazol 200mg BD PO + placebo IN for 6 months (n=67)
Outcomes	Pain defined by symptoms severity score AFS score Adverse effects
Notes	Authors contacted regarding methods and data. Letter returned with author unknown at Department

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	randomised 2:1 Nafarelin: Danazol
Allocation concealment?	Unclear	no details
Blinding? All outcomes	Yes	double placebo, double blind
Incomplete outcome data addressed? All outcomes	Yes	Details for attrition: • 20 in Nafarelin and 4 in Danazol group withdrew due to: • adverse effects 7 (Naf) vs 2 (Dan) • intercurrent illness 1 (Naf) vs 2 (Dan) • personal reasons 3 (Naf) • lost to follow up 3 (Naf) • lack of drug efficacy 1 (Naf) • other 5 (Naf)
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Shaw 1986

Methods	Randomised study
Participants	UK study 20 women were randomised and analysed Age: 30.4 +/- 3.8 (SEM?) Inclusion criteria: • Laparoscopically diagnosed disease • No treatment within 4 months prior to study
Interventions	Buserelin 200mcg TDS IN for 6 months (n=10) versus

Shaw 1986 (*Continued*)

	Buserelin 300mcg TDS IN for 6 months (n=10)
Outcomes	Symptomatic changes rAFS score Adverse effects
Notes	Authors contacted but unable to provide further details as trial was almost 20 years old

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	Detail for attrition: • 1 from Buserelin 300mcg TDS group withdrew after 3 months due to adverse effects
Free of selective reporting?	Unclear	No comparisons between groups for symptomatic changes

Shaw 1990a

Methods	Multi-centre, randomised trial
Participants	UK study 82 women were randomised, 74 were analysed
Interventions	Nafarelin 200mcg BD IN + placebo PO for 6 months (n=55) versus Danazol 200mg TDS PO + placebo IN for 6 months (n=26)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration
Notes	Authors contacted but unable to provide further details as trial was almost 20 years old

Risk of bias

Shaw 1990a (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Patients were blinded and received placebo nasal spray or tablets
Incomplete outcome data addressed? All outcomes	Yes	Details for attrition given: • 8 withdrew: • Nafarelin = 3 due to side effects, 1 left country, 1 poor compliance • Danazol = 2 due to side effects, 1 poor compliance
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Shaw 1992

Methods	"open, randomised comparative study"
Participants	European study, multi centre 307 women were randomised, 286 were analysed Age: 18-40 Stage: I to IV Inclusion criteria: • laparoscopically confirmed endometriosis within 12 weeks prior to study enrolment Exclusion criteria: • No hormonal agents within 8 weeks prior to study • No GnRHas or Danazol within 24 weeks prior to study • No anticoagulants
Interventions	Goserelin acetate 3.6mg every 28 days SC for 24 weeks (n=204) versus Danazol 200mg TDS PO for 24 weeks (n=103)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness, induration rAFS score Adverse effects
Notes	

Shaw 1992 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Randomisation was in the ratio two goserelin: one danazol with each centre having its randomisation list", "The randomised trial of Zoladex and Danazol was a multi centre trial with randomisation envelopes provided by the sponsors ICI to each of the centres as plain sealed envelopes and computerised randomisation lists for each centre" (author's reply)
Allocation concealment?	Yes	"plain, sealed envelopes"
Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Yes	Details given for attrition: • 81 in Goserelin and 54 in Danazol group withdrew due to lack of effect, adverse effects, pregnancy and administrative reasons
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Skrzypulec 2004

Methods	Placebo, randomised, parallel study
Participants	Polish study 34 women were randomised and analysed Age: GnRHa = 31.02 ± 2.5 and Placebo = 32.13 ±1.5 (SD) Inclusion criteria: • Laparoscopically diagnosed endometriosis • Symptomatic • Surgically or pharmacologically treated in 6 months prior • Regular menstrual cycle in prior 3 months • Not pregnant Exclusion criteria: • Cardiovascular burden • Hormone dependent neoplasms • Osteoporosis • Bilateral oophorecystectomy • Abnormal liver and renal tests
Interventions	GnRHa 50mg OD PO for 12 weeks (n=16) versus

Skrzypulec 2004 (*Continued*)

	Placebo PO for 12 weeks (n=18)
Outcomes	Dysmenorrhoea, dyspareunia, pain in pelvic minor
Notes	Author provided additional details on methods

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Centralised randomisation process, computerised allocation according to author
Allocation concealment?	Yes	Sealed, opaque, sequentially numbered, identical envelopes and sequentially numbered, identical containers of identical drugs
Blinding? All outcomes	Yes	Participants, investigators, outcome assessors and clinicians were all blinded according to author
Incomplete outcome data addressed? All outcomes	Yes	All women who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Tummon 1989

Methods	Prospective, randomised study
Participants	US study 15 women were randomised and analysed Age: 32.1 +/- 0.9 (SE) Inclusion criteria: • Laparoscopically diagnosed endometriosis within 3 months prior to study • Infertile women • Regular menstrual cycles
Interventions	Leuprolide 400mcg QDS IN for 26 weeks (n=10) versus Danazol 200mg QDS PO for 26 weeks (n=5)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain rAFS score

Tummon 1989 (*Continued*)

Notes	Authors contacted regarding methods and data, awaiting response	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised 2:1 ratio Leuprolide: Danazol
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Unclear	No details
Incomplete outcome data addressed? All outcomes	Yes	All participants who were randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Wheeler 1992

Methods	"double-blind, multi-centre, randomised trial"
Participants	US study 270 women were randomised and 253 were analysed Age: Leuprolide = 31.0 and Danazol = 29.8 Inclusion criteria: • Laparoscopically diagnosed endometriosis within 4 months prior to study • Over 18 years of age • No surgical treatment at time of laparoscopy • Premenopausal • Not pregnant or lactating • Never previously taken GnRHa • Any other treatment completed at least 3 months prior to study
Interventions	Leuprolide 3.75mg monthly IM + placebo OD PO for 24 weeks (n=134) versus Danazol 800mg OD PO + placebo monthly IM for 24 weeks (n=136)
Outcomes	Dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness rAFS score Analgesic use
Notes	Authors contacted regarding methods and data, awaiting response

Wheeler 1992 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Placebo injection and tablets to blind participants and investigators
Incomplete outcome data addressed? All outcomes	Yes	Details given for attrition: • 17 patients were excluded due to: • failure to meet inclusion criteria 2 (Leu) and 1 (Dan) • non-compliance 3 (Leu) and 10 (Dan) • inadvertent dosing with another patient's designated leuprolide 1
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Wheeler 1993

Methods	Same as Wheeler 1992
Participants	Same as Wheeler 1992 except: **270 woman were randomised and analysed**
Interventions	Same as Wheeler 1992
Outcomes	**Adverse effects**
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details
Allocation concealment?	Unclear	No details
Blinding? All outcomes	Yes	Placebo injection and tablet so participants and investigators are blinded

Incomplete outcome data addressed? All outcomes	Yes	All participants randomised were analysed
Free of selective reporting?	Yes	All primary outcomes stated were reported on

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Acien 1989	Wrong outcomes: pain not an outcome
Adiyono 2006	Wrong participants: post-surgical treatment
Allen 1993	See included study Rock 1993 (abstract)
Anonymous 1993	Not RCT: discussion only
Anonymous 1999	Not RCT
Bergquist 1990	Wrong outcomes: pain not an outcome
Bila 1996	Not RCT
Brosens 2001	See included study Miller 2000 (commentary)
Burry 1989	Wrong outcomes: pain not an outcome
Burry 1990	See included study Burry 1992 (conference proceeding)
Calvo 2000	Wrong outcomes: pain not an outcome
Choktanasiri 2001	Study compares same dose over same time period but one arm is given 3 doses every 8 weeks and the other arm received 2 doses every 12 weeks. It does not therefore fit into any of the comparisons in this review
Cirkel 1985	Not RCT
Cirkel 1986	Not RCT
Cirkel 1993	See included study Cirkel 1995 (conference proceeding)
Cooke 1989	Wrong comparisons: gestrinone vs placebo only
Crosignani 1992	Not RCT

(*Continued*)

Crosignani 1996	Wrong comparisons: comparison not stated in our protocol
de Sa Rosa e Silva 2006	Wrong outcomes: pain not an outcome
Dmowski 1989	Wrong comparisons: focuses on Danazol
Donnez 1989	Wrong outcomes: pain not an outcome
Donnez 1990	Not RCT
Donnez 2004	Wrong comparisons: comparison not stated in our protocol
el-Roeiy 1988	Wrong outcomes: pain not an outcome
Fedele 1993a	Wrong outcomes: pain not an outcome
Franke 2000	Wrong comparisons: add-back therapy
Franssen 1986	Not RCT
Franssen 1992	Wrong outcomes: pain not an outcome
Fraser 1996	Wrong condition: not about endometriosis but rather menorrhagia
Giorgino 1991	Not RCT
Harada 2000	Wrong participants: not laparoscopically diagnosed endometriosis
Heinrichs 1998	Not RCT: Review of other trials
Henzl 1989	See included study Henzl 1988 (review)
Henzl 1990	Not RCT: summarises two original studies
Hornstein 1992	See included study Hornstein 1995 (conference abstract)
Jacobs 1991	See included study Henzl 1988
Jelley 1986a	See included study Jelley 1986
Kennedy 1990	See included study NEET 1992
Kiesel 1989	Wrong comparisons: gestrinone vs danazol only Not RCT
Kiilholma 1995	Wrong comparisons: add-back therapy

(*Continued*)

Lemay 1987	See included study Lemay 1988 (review)
Ling 1999	Wrong participants: not laparoscopically diagnosed endometriosis
Luciano 2004	Wrong comparisons: Leuprolide acetate vs DMPA
Magini 1993	Wrong comparisons
Maouris 1989	Wrong outcomes: pain not an outcome
Maouris 1991	Wrong outcomes: pain not an outcome
Matalliotakis 2000	Wrong outcomes: pain not an outcome
Matalliotakis 2004	Wrong outcomes: pain not an outcome
Moodley 2009	Not RCT: review
Newton 1996	Wrong comparisons: Leuprolide vs Nafarelin
Nisolle 1990	Not RCT
Ochs 1993	Wrong outcomes: pain not an outcome
Olive 2003	Not RCT: review
Olive 2004	Not RCT: review
Ozawa 2006	Not RCT: review
Rock 1991	See included study Rock 1993 (conference proceeding)
Rotondi 2002	Wrong outcomes: pain not an outcome
Roux 1995	Wrong outcomes: pain not an outcome
Ruwe 1998	Not RCT
Shaw 1986a	Not RCT
Shaw 1990	See included study Shaw 1992
Shaw 1990b	See included study Shaw 1992 (Conference proceeding)
Shaw 2001	Wrong condition: not about endometriosis but rather ovarian endometriomas
Sorensen 1997	Wrong condition: not about endometriosis

(*Continued*)

Sowter 1997	Wrong condition: not about endometriosis but rather menorrhagia
Surrey 1993	Wrong outcomes: pain not an outcome
Surrey 1995	Wrong comparisons: add back therapy
Surrey 2002	Wrong comparisons: add-back therapy
Tahara 2000	Wrong comparisons: comparison not stated in our protocol
Tapanainen 1993	Wrong outcomes: pain not an outcome
Taskin 1997	Wrong comparisons: add-back therapy
Toomey 2003	Wrong comparison: complementary medicine
Valimaki 1989	Wrong outcomes: pain not an outcome
Vasiljevic 2000	Not RCT
Vercellini 1994	Wrong comparisons: focuses on Danazol
Vercellini 2009	Wrong participants: post-surgical treatment
Vieira 2007	Wrong outcomes: pain not an outcome
Warnock 1998	Wrong comparisons: focuses on antidepressants in addition to GnRHas
Wright 1995	Wrong outcomes: pain not an outcome
Yee 1986	Wrong outcomes: pain not an outcome
Ylikorkala 1995	Wrong participants: not laparoscopically diagnosed endometriosis
Zupi 2005	Wrong comparisons: add-back therapy

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chan 1993

Methods	"Comparative Study"
Participants	Singapore study 149 woman were randomised

Chan 1993 (*Continued*)

	Inclusion criteria: laparoscopically diagnosed endometriosis
Interventions	Gestrinone for 6 months (n= 44) versus Danazol PO for 6 months (n=57) versus Triptorelin IM for 4 injections (n=48)
Outcomes	Symptoms of endometriosis Side effects of medication Blood for CA125 Vertebral bone scan for bone loss
Notes	Will email author for the full study

Chen 2009

Methods	Randomised, blind parallel trial
Participants	149 women with endometriosis
Interventions	Leuprolide acetate vs Enaltone
Outcomes	Ovarian mass volume, hormone levels, pelvic pain, subjective symptoms
Notes	Awaiting translation from Chinese

DATA AND ANALYSES

Comparison 1. GnRHas versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relief of painful symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Dysmenorrhoea	1	35	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [1.37, 11.28]

Comparison 2. GnRHas versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relief of painful symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 pelvic tenderness	1	49	Risk Ratio (M-H, Fixed, 95% CI)	4.17 [1.62, 10.68]
1.2 Dyspareunia	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.57, 2.34]
1.3 Defecation pain/pressure	1	49	Risk Ratio (M-H, Fixed, 95% CI)	11.44 [0.67, 196.30]
2 Side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Hot flushes/flashes	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.87, 3.02]
2.2 Sleep disturbances	1	49	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [1.33, 4.02]
3 Pain score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Overall at 4 weeks	1	120	Mean Difference (IV, Fixed, 95% CI)	2.90 [2.11, 3.69]

Comparison 3. GnRHas versus danazol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relief of painful symptoms	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Dsymenorrhoea	7	666	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.04]
1.2 Dyspareunia	7	431	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
1.3 Pelvic pain	7	647	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.07]
1.4 Induration	2	116	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.94, 1.29]
1.5 Pelvic tenderness	3	404	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.09]
2 Overall resolution	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Overall resolution/improvement	9	1046	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.21]
3 Relief of painful symptoms	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Overall 90 days	1	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.64, 0.38]
3.2 Overall 180 days	3	103	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.30, 0.50]
3.3 Dsypareunia	1	49	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.41, 0.79]
3.4 Pelvic pain	1	49	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.5 Pelvic tenderness	1	49	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.79, 0.41]

3.6 Pelvic induration	1	49	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 rAFS	10	1012	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.13, 0.12]
4.1 change at 180 days	1	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.81, 0.21]
4.2 24 weeks	9	953	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.12, 0.15]
5 Improved rAFS score	4	732	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.98, 1.32]
6 Side effects	19		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 vaginal dryness/vaginitis	16	2068	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.68, 2.30]
6.2 Hot flushes/flashes	19	2637	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.47, 1.65]
6.3 Headaches	16	2102	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.22, 1.61]
6.4 Infections and flu like symptoms	1	71	Risk Ratio (M-H, Fixed, 95% CI)	3.6 [1.31, 9.88]
6.5 Muscle cramps/myalgia	10	1537	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.06, 0.18]
6.6 Sleep disturbance	7	949	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.57, 2.51]
6.7 Skin rash	3	324	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.02, 0.51]
6.8 Gastrointestinal	4	363	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.05]
6.9 Weight gain	12	1763	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.16, 0.26]
6.10 Acne	13	1965	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.47, 0.65]
6.11 Breast atrophy/changes	7	1035	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.47, 0.76]
6.12 Emotional lability/altered mood	4	804	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.67]
6.13 Oedema/fluid retention	6	896	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.09, 0.26]
6.14 Asthenia	5	781	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.58]
6.15 Bleeding	3	161	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.12, 0.48]
6.16 Depression	6	783	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.49, 1.06]
6.17 Leukorrhoea	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.23, 4.71]
6.18 chest pain	1	59	Risk Ratio (M-H, Fixed, 95% CI)	7.23 [0.39, 134.16]
6.19 Generalised spasm	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.00, 1.35]
6.20 pharyngitis	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.74]
6.21 Voice alteration	2	114	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.27]
6.22 vulvovaginal disorder	1	59	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.74]
6.23 Hirsutism	6	866	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.11, 0.39]
6.24 Seborrhoea	6	835	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.33, 0.53]
6.25 Alopecia	2	365	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.02, 0.53]
6.26 Altered libido	10	1890	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.31]
6.27 Sweating	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.51]
6.28 Breast tenderness	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.04, 4.33]
6.29 Fatigue	2	84	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.40, 1.26]
6.30 Arthralgia	1	55	Risk Ratio (M-H, Fixed, 95% CI)	17.61 [1.08, 286.40]
6.31 Hunger	1	55	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.81]
6.32 Nervousness	3	774	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.10, 0.43]
6.33 Irritability	1	59	Risk Ratio (M-H, Fixed, 95% CI)	4.74 [1.67, 13.45]
6.34 Clitoromegaly	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.59]
6.35 Appetite increase	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 1.54]
6.36 Fatigue/malaise	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.06, 0.61]
6.37 Dizziness	2	337	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [1.13, 9.04]
6.38 Nausea	3	644	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.45, 0.95]
6.39 Breast pain	1	307	Risk Ratio (M-H, Fixed, 95% CI)	5.05 [0.66, 38.91]

Comparison 4. GnRHas versus intra- uterine progestagen device

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relief of painful symptoms	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Overall	3	129	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.60, 0.10]
2 rAFS/ASRM score	1	18	Mean Difference (IV, Fixed, 95% CI)	9.5 [-10.77, 29.77]

Comparison 5. GnRHa versus GnRHa (Varying Dosage)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Side effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Sleep disturbance Nafareline 200mcg versus 400mcg	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.63, 1.59]
1.2 Rhinitis Nafareline 200mcg versus 400 mcg	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.10, 1.67]
1.3 Upper respiratory tract infection Nafareline 200mcg versus 400 mcg	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.47]
1.4 Hot flushes/flashes Nafareline 200mcg versus 400 mcg	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.51, 1.97]
2 rAFS score (400mcg vs 800mcg)	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.17, 1.01]
3 relief of painful symptoms	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Dsymenorrhoea Nafarelin 400mcg versus 800mcg	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.53, 1.66]
3.2 Dyspareunia	1	57	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.79, 1.68]
3.3 Pelvic pain	1	77	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.67, 1.74]
3.4 Overall Nafarelin 400mcg versus 800mcg	1	143	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.14]
3.5 Overall buserelin 300mcg vs 900 mcg	1	132	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.94, 2.35]

Comparison 6. GnRHa versus GnRHa (Length of Treatment)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relief of Painful Symptoms (3months vs 6months) at 6 months follow up	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Dysmenorrhoea	1	179	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.31, 0.27]
1.2 Dyspareunia	1	179	Std. Mean Difference (IV, Fixed, 95% CI)	-0.98 [-1.29, -0.66]
1.3 Pelvic pain	1	179	Std. Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.15, 0.44]
1.4 Pelvic tenderness	1	179	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.43, 0.15]
1.5 Pelvic induration	1	179	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.40, 0.18]

Comparison 7. GnRHa versus GnRHa (Route of Administration)

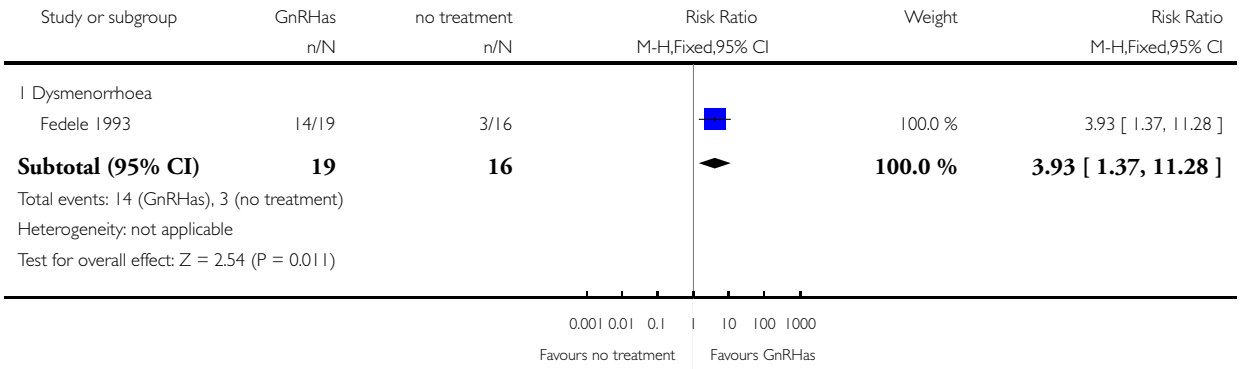
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Side effects (IN vs SC)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Hot flushes/flashes	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.48, 1.55]
1.2 Vaginal dryness	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.17, 4.37]
1.3 Decreased libido	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.07, 10.96]
1.4 Headaches	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.20, 14.55]
2 rAFS score (IN vs SC)	1	19	Mean Difference (IV, Fixed, 95% CI)	9.0 [-5.93, 23.93]
3 Relief of painful symptoms (IN versus IMdepot)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Dysmenorrhea	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.08]
3.2 Dyspareunia	1	166	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.85, 1.43]
3.3 Pelvic pain	1	192	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.78, 1.40]
3.4 Tenderness	1	192	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.09]
3.5 Induration	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.06]
4 Side effects (IN versus IMdepot)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Hot flushes/flashes	1	191	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
5 Improvement in symptoms (IN versus IMdepot)	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [0.58, 3.30]
6 Relief of painful symptoms (IN versus SC)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Pelvic pain	1	5	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.53, 1.87]
6.2 Dyspareunia	1	7	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.57, 1.75]
6.3 Dysmenorrhoea	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.73, 2.06]
6.4 Pelvic tenderness	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.69, 3.27]
6.5 Pelvic induration	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.47, 1.55]

Analysis 1.1. Comparison 1 GnRHas versus no treatment, Outcome 1 Relief of painful symptoms.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 1 GnRHas versus no treatment

Outcome: 1 Relief of painful symptoms

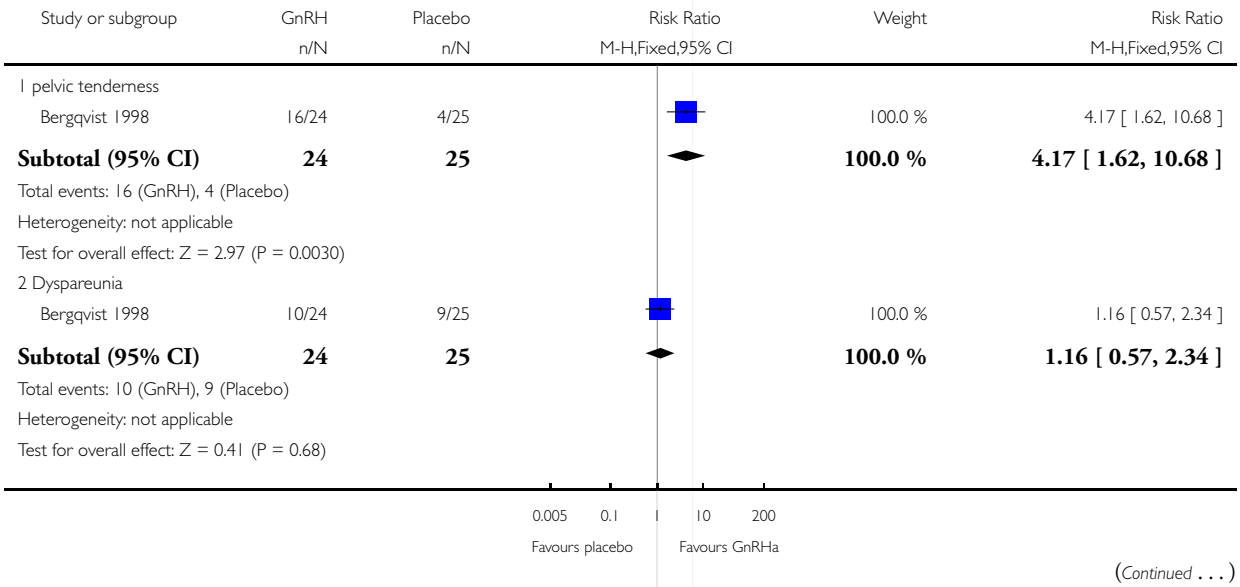


Analysis 2.1. Comparison 2 GnRHas versus placebo, Outcome 1 Relief of painful symptoms.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 2 GnRHas versus placebo

Outcome: 1 Relief of painful symptoms



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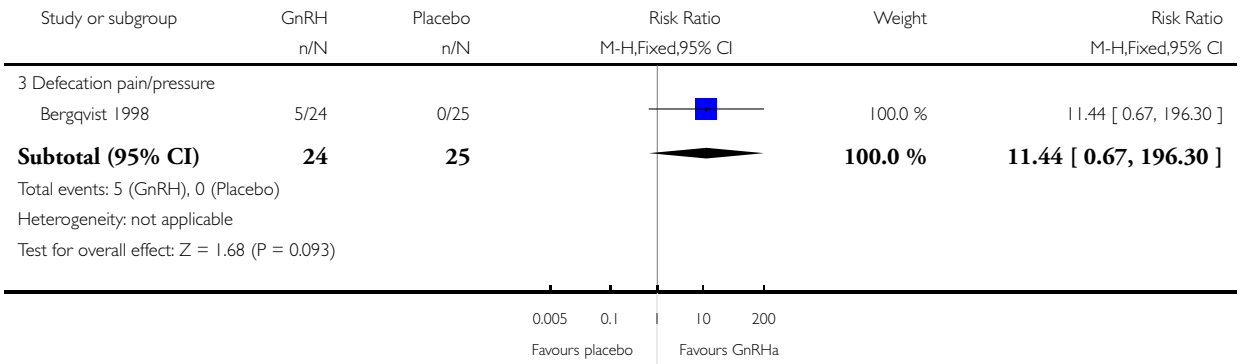
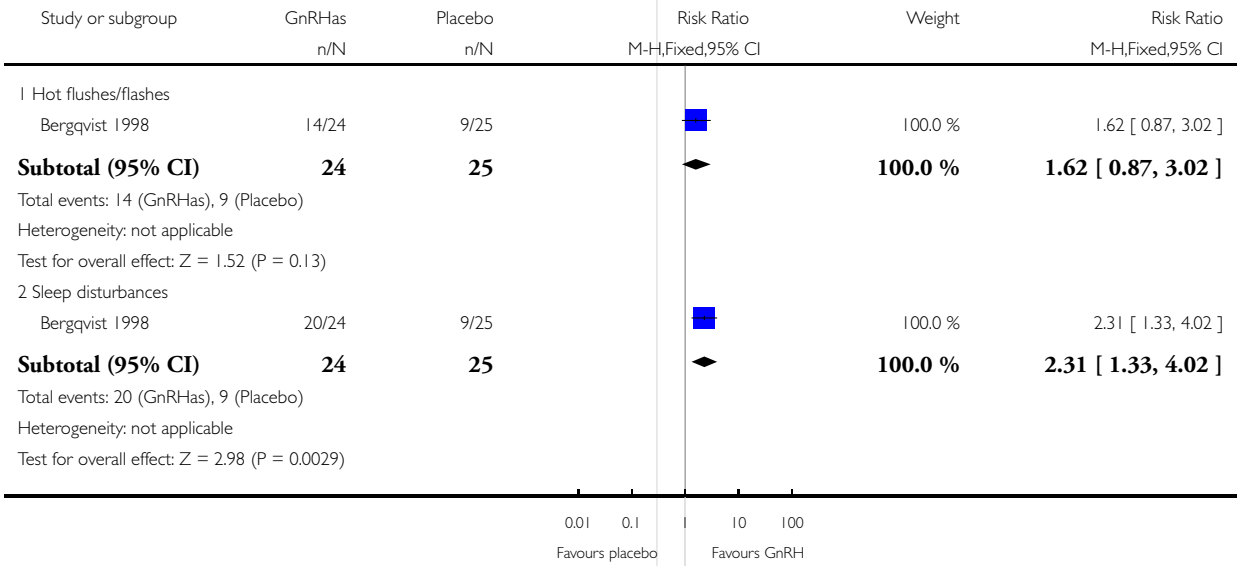


Analysis 2.2. Comparison 2 GnRHas versus placebo, Outcome 2 Side effects.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 2 GnRHas versus placebo

Outcome: 2 Side effects



Analysis 2.3. Comparison 2 GnRHas versus placebo, Outcome 3 Pain score.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 2 GnRHas versus placebo

Outcome: 3 Pain score

Study or subgroup	GnRHa N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Overall at 4 weeks							
Miller 2000	60	7.22 (2.3)	60	4.32 (2.1)		100.0 %	2.90 [2.11, 3.69]
Subtotal (95% CI)	**60**		**60**			**100.0 %**	**2.90 [2.11, 3.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.21 (P < 0.00001)							
Test for subgroup differences: Not applicable							

Analysis 3.1. Comparison 3 GnRHas versus danazol, Outcome 1 Relief of painful symptoms.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 3 GnRHas versus danazol

Outcome: 1 Relief of painful symptoms

Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dsymenorrhoea					
Adamson 1994	31/90	17/34		10.1 %	0.69 [0.44, 1.07]
Cirkel 1995	7/12	6/8		2.9 %	0.78 [0.42, 1.45]
Fedele 1989	30/30	32/32		12.8 %	1.00 [0.94, 1.06]
Matta 1988	37/39	17/18		9.5 %	1.00 [0.88, 1.15]
NEET 1992	29/71	13/32		7.3 %	1.01 [0.61, 1.66]
Palagiano 1994	23/27	17/20		8.0 %	1.00 [0.79, 1.28]
Wheeler 1992	127/128	120/125		49.5 %	1.03 [0.99, 1.07]
Subtotal (95% CI)	**397**	**269**		**100.0 %**	**0.98 [0.92, 1.04]**
Total events: 284 (GnRHas), 222 (Danazol)					

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Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 10.80, df = 6 (P = 0.09); I² =44%					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 Dyspareunia					
Adamson 1994	38/57	15/23		15.4 %	1.02 [0.72, 1.45]
Cirkel 1995	12/12	8/8		7.3 %	1.00 [0.83, 1.21]
Fedele 1989	27/30	27/32		18.9 %	1.07 [0.88, 1.29]
Jelley 1986	2/34	2/33		1.5 %	0.97 [0.15, 6.49]
Matta 1988	36/39	16/18		15.8 %	1.04 [0.86, 1.25]
NEET 1992	57/66	27/32		26.3 %	1.02 [0.86, 1.22]
Palagiano 1994	23/27	18/20		14.9 %	0.95 [0.76, 1.17]
Subtotal (95% CI)	**265**	**166**		**100.0 %**	**1.02 [0.93, 1.12]**
Total events: 195 (GnRHas), 113 (Danazol)					
Heterogeneity: Chi² = 0.76, df = 6 (P = 0.99); I² =0.0%					
Test for overall effect: Z = 0.40 (P = 0.69)					
3 Pelvic pain					
Adamson 1994	36/77	14/28		10.2 %	0.94 [0.60, 1.45]
Cirkel 1995	11/12	7/8		4.2 %	1.05 [0.77, 1.43]
Fedele 1989	25/30	27/32		13.0 %	0.99 [0.79, 1.23]
Matta 1988	35/39	16/18		10.9 %	1.01 [0.83, 1.23]
NEET 1992	46/71	21/32		14.4 %	0.99 [0.73, 1.34]
Palagiano 1994	23/27	17/20		9.7 %	1.00 [0.79, 1.28]
Wheeler 1992	70/128	75/125		37.7 %	0.91 [0.74, 1.13]
Subtotal (95% CI)	**384**	**263**		**100.0 %**	**0.96 [0.86, 1.07]**
Total events: 246 (GnRHas), 177 (Danazol)					
Heterogeneity: Chi² = 1.02, df = 6 (P = 0.98); I² =0.0%					
Test for overall effect: Z = 0.73 (P = 0.47)					
4 Induration					
Cirkel 1995	11/12	5/8		14.1 %	1.47 [0.84, 2.58]
NEET 1992	59/65	27/31		85.9 %	1.04 [0.89, 1.22]
Subtotal (95% CI)	**77**	**39**		**100.0 %**	**1.10 [0.94, 1.29]**
Total events: 70 (GnRHas), 32 (Danazol)					
Heterogeneity: Chi² = 1.48, df = 1 (P = 0.22); I² =32%					
Test for overall effect: Z = 1.19 (P = 0.23)					
5 Pelvic tenderness					
Cheng 2005	30/30	25/25		17.9 %	1.00 [0.93, 1.07]
NEET 1992	50/65	23/31		20.1 %	1.04 [0.81, 1.33]
Wheeler 1992	93/128	95/125		62.0 %	0.96 [0.83, 1.11]

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Favours danazol Favours GnRHas

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Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**223**	**181**		**100.0 %**	**0.98 [0.88, 1.09]**
Total events: 173 (GnRHas), 143 (Danazol)					
Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² =0.0%					
Test for overall effect: Z = 0.38 (P = 0.70)					

Analysis 3.2. Comparison 3 GnRHas versus danazol, Outcome 2 Overall resolution.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 3 GnRHas versus danazol

Outcome: 2 Overall resolution

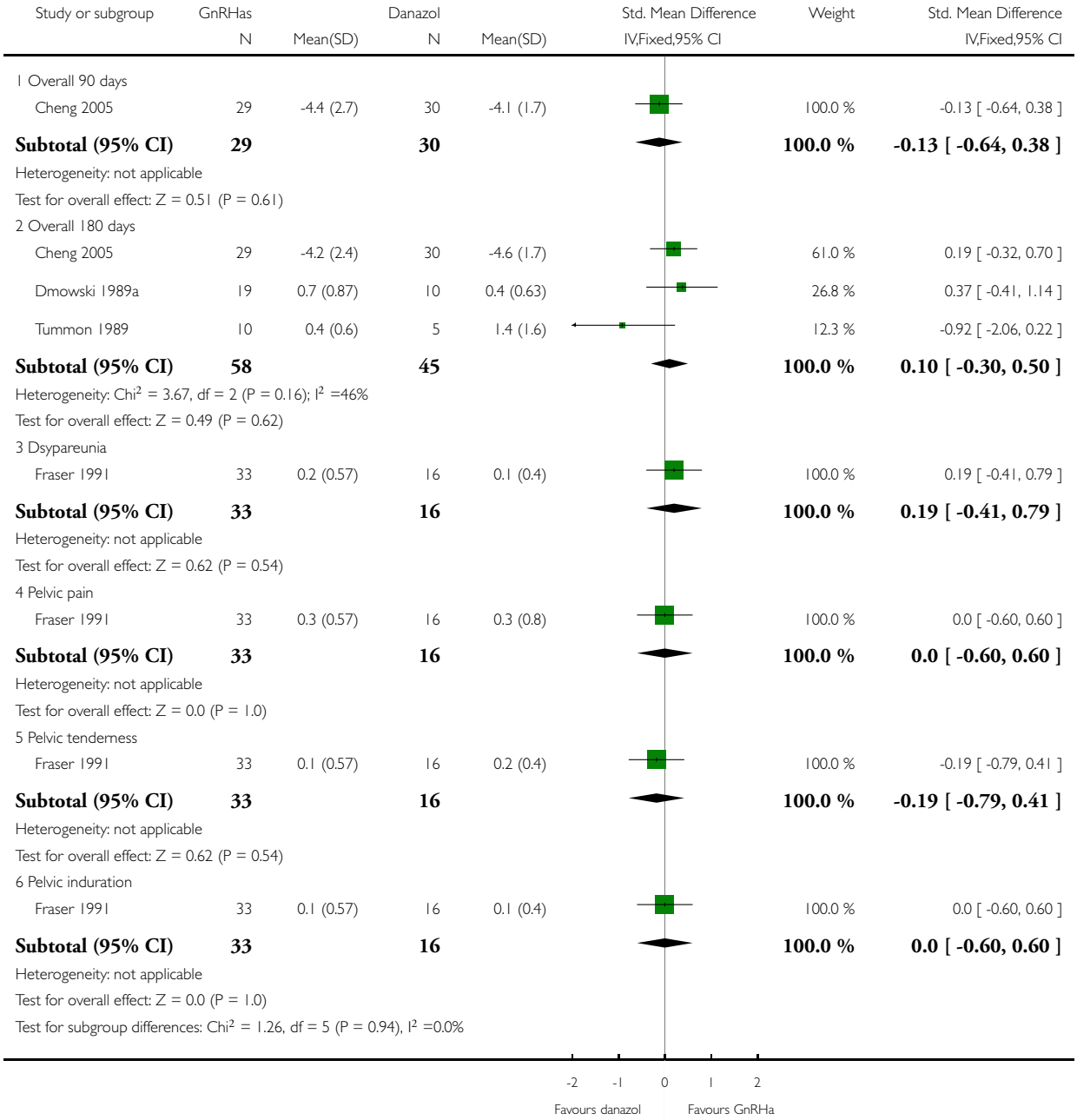
Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Overall resolution/improvement					
AN Zoladex 1996	21/35	10/36		3.4 %	2.16 [1.19, 3.90]
Audebert 1997	3/33	1/22		0.4 %	2.00 [0.22, 18.01]
Burry 1992	77/98	37/49		17.0 %	1.04 [0.86, 1.26]
Claesson 1989	12/16	5/8		2.3 %	1.20 [0.65, 2.20]
Henzl 1988	107/143	55/70		25.5 %	0.95 [0.82, 1.11]
NEET 1992	132/171	62/92		27.8 %	1.15 [0.97, 1.35]
Palagiano 1994	12/17	10/13		3.9 %	0.92 [0.60, 1.41]
Rolland 1990	61/107	30/63		13.0 %	1.20 [0.88, 1.63]
Shaw 1990a	29/50	14/23		6.6 %	0.95 [0.64, 1.43]
Subtotal (95% CI)	**670**	**376**		**100.0 %**	**1.10 [1.01, 1.21]**
Total events: 454 (GnRHas), 224 (Danazol)					
Heterogeneity: Chi² = 10.80, df = 8 (P = 0.21); I² =26%					
Test for overall effect: Z = 2.11 (P = 0.035)					

Analysis 3.3. Comparison 3 GnRHas versus danazol, Outcome 3 Relief of painful symptoms.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 3 GnRHas versus danazol

Outcome: 3 Relief of painful symptoms

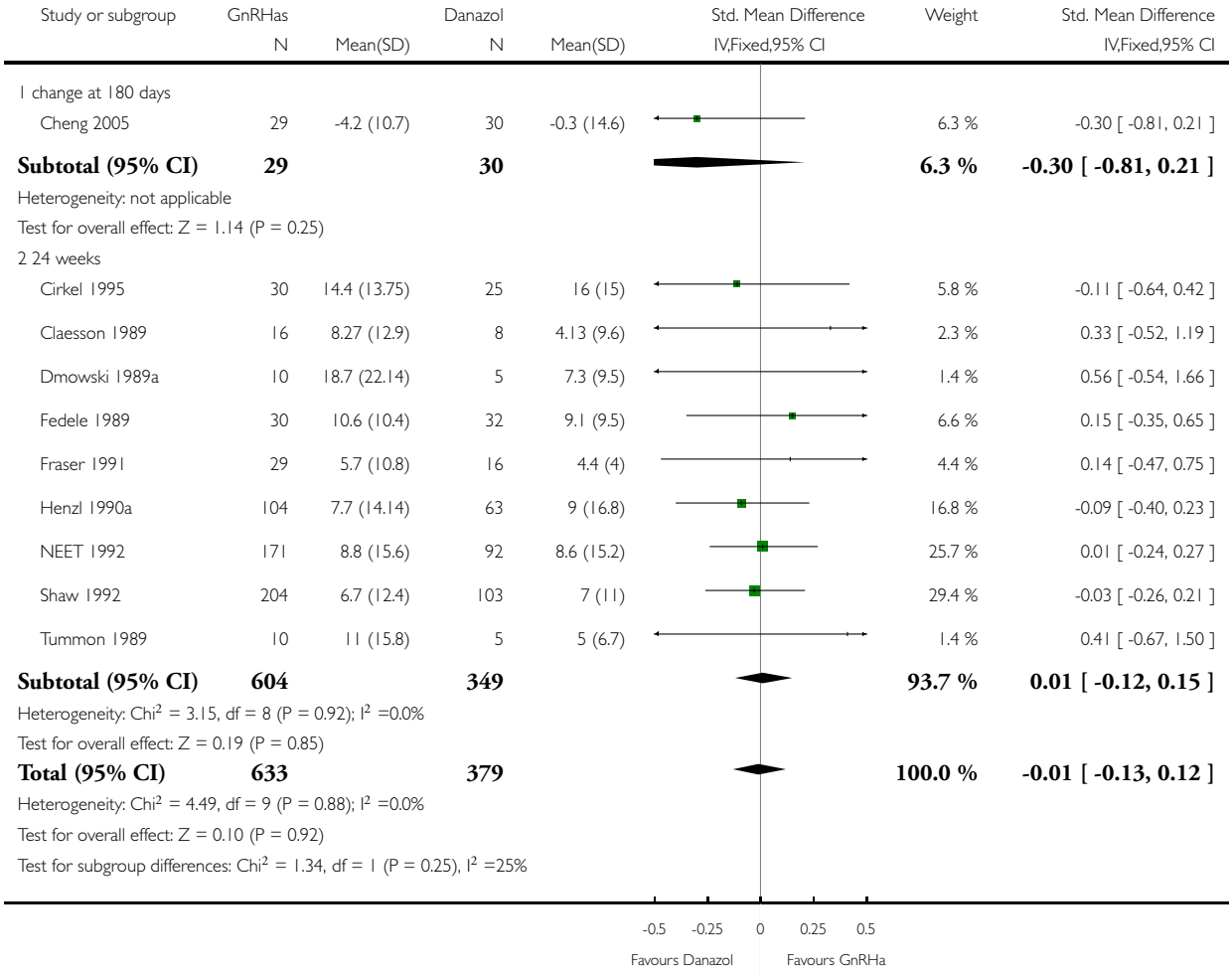


Analysis 3.4. Comparison 3 GnRHas versus danazol, Outcome 4 rAFS.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 3 GnRHas versus danazol

Outcome: 4 rAFS



Analysis 3.5. Comparison 3 GnRHas versus danazol, Outcome 5 Improved rAFS score.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 3 GnRHas versus danazol

Outcome: 5 Improved rAFS score

Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burry 1992	75/98	41/49		37.6 %	0.91 [0.78, 1.08]
Henzl 1988	20/143	11/70		10.2 %	0.89 [0.45, 1.75]
Matta 1988	32/39	13/18		12.2 %	1.14 [0.82, 1.57]
Rock 1993	121/208	44/107		40.0 %	1.41 [1.10, 1.82]
Total (95% CI)	**488**	**244**		**100.0 %**	**1.14 [0.98, 1.32]**

Total events: 248 (GnRHas), 109 (Danazol)

Heterogeneity: Chi^2 = 10.07, df = 3 (P = 0.02); I^2 =70%

Test for overall effect: Z = 1.75 (P = 0.079)

Test for subgroup differences: Not applicable

Analysis 3.6. Comparison 3 GnRHas versus danazol, Outcome 6 Side effects.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 3 GnRHas versus danazol

Outcome: 6 Side effects

Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 vaginal dryness/vaginitis					
AN Zoladex 1996	26/35	10/36		5.7 %	2.67 [1.53, 4.69]
Audebert 1997	6/33	1/22		0.7 %	4.00 [0.52, 30.98]
Burry 1992	12/111	5/58		3.8 %	1.25 [0.46, 3.39]
Chang 1996	21/30	0/15		0.4 %	22.19 [1.44, 343.08]
Cheng 2005	7/29	5/30		2.9 %	1.45 [0.52, 4.05]
Cirkel 1995	13/30	5/25		3.2 %	2.17 [0.89, 5.25]
Dawood 1990	63/209	7/101		5.5 %	4.35 [2.07, 9.15]
Dmowski 1989a	7/19	3/10		2.3 %	1.23 [0.40, 3.74]
Fedele 1989	10/30	4/32		2.2 %	2.67 [0.94, 7.60]
Jelley 1986	19/34	12/33		7.1 %	1.54 [0.89, 2.64]
Matta 1988	9/39	1/18		0.8 %	4.15 [0.57, 30.36]
NEET 1992	31/171	6/92		4.5 %	2.78 [1.20, 6.42]
Palagiano 1994	5/27	7/20		4.7 %	0.53 [0.20, 1.43]
Rock 1993	156/208	48/107		36.8 %	1.67 [1.34, 2.09]
Rolland 1990	20/127	6/67		4.6 %	1.76 [0.74, 4.17]
Wheeler 1993	39/134	26/136		15.0 %	1.52 [0.99, 2.35]
Subtotal (95% CI)	**1266**	**802**		**100.0 %**	**1.96 [1.68, 2.30]**
Total events: 444 (GnRHas), 146 (Danazol)					
Heterogeneity: Chi^2 = 23.29, df = 15 (P = 0.08); I^2 =36%					
Test for overall effect: Z = 8.36 (P < 0.00001)					
2 Hot flushes/flashes					
AN Zoladex 1996	35/35	15/36		2.3 %	2.35 [1.61, 3.45]
Audebert 1997	26/33	7/22		1.3 %	2.48 [1.31, 4.68]
Burry 1992	102/111	44/58		8.7 %	1.21 [1.04, 1.41]
Chang 1996	29/30	2/15		0.4 %	7.25 [1.99, 26.39]
Cheng 2005	7/29	0/30		0.1 %	15.50 [0.93, 259.61]

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Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cirkel 1995	30/30	19/25		3.2 %	1.31 [1.05, 1.65]
Dawood 1990	146/209	39/101		7.9 %	1.81 [1.39, 2.35]
Dmowski 1989a	16/19	6/10		1.2 %	1.40 [0.82, 2.41]
Fedele 1989	28/30	13/32		1.9 %	2.30 [1.50, 3.53]
Fraser 1991	13/33	5/16		1.0 %	1.26 [0.54, 2.92]
Henzl 1988	129/143	48/70		9.7 %	1.32 [1.11, 1.56]
Jelley 1986	29/34	13/33		2.0 %	2.17 [1.39, 3.38]
Matta 1988	29/39	4/18		0.8 %	3.35 [1.38, 8.10]
NEET 1992	154/171	67/92		13.0 %	1.24 [1.08, 1.41]
Palagiano 1994	20/27	3/20		0.5 %	4.94 [1.70, 14.35]
Rock 1993	198/208	75/107		14.8 %	1.36 [1.20, 1.54]
Rolland 1990	106/127	45/67		8.8 %	1.24 [1.03, 1.49]
Shaw 1992	200/204	58/103		11.5 %	1.74 [1.47, 2.07]
Wheeler 1993	113/134	74/136		11.0 %	1.55 [1.31, 1.84]
Subtotal (95% CI)	**1646**	**991**		**100.0 %**	**1.55 [1.47, 1.65]**
Total events: 1410 (GnRHas), 537 (Danazol)					
Heterogeneity: Chi^2 = 67.47, df = 18 (P<0.00001); I^2 =73%					
Test for overall effect: Z = 14.91 (P < 0.00001)					
3 Headaches					
AN Zoladex 1996	13/35	4/36		1.9 %	3.34 [1.21, 9.27]
Audebert 1997	9/33	2/22		1.1 %	3.00 [0.72, 12.59]
Burry 1992	12/111	4/58		2.5 %	1.57 [0.53, 4.64]
Chang 1996	2/30	0/15		0.3 %	2.58 [0.13, 50.60]
Cirkel 1995	19/30	12/25		6.2 %	1.32 [0.81, 2.15]
Dawood 1990	44/209	17/101		10.9 %	1.25 [0.75, 2.08]
Dmowski 1989a	13/19	6/10		3.8 %	1.14 [0.63, 2.06]
Fedele 1989	11/30	4/32		1.8 %	2.93 [1.05, 8.22]
Fraser 1991	8/33	2/16		1.3 %	1.94 [0.46, 8.10]
Jelley 1986	20/34	8/33		3.9 %	2.43 [1.25, 4.72]
Matta 1988	8/39	7/18		4.6 %	0.53 [0.23, 1.23]
Palagiano 1994	7/27	3/20		1.6 %	1.73 [0.51, 5.87]
Rock 1993	144/208	59/107		37.2 %	1.26 [1.03, 1.52]
Rolland 1990	13/127	7/67		4.4 %	0.98 [0.41, 2.34]

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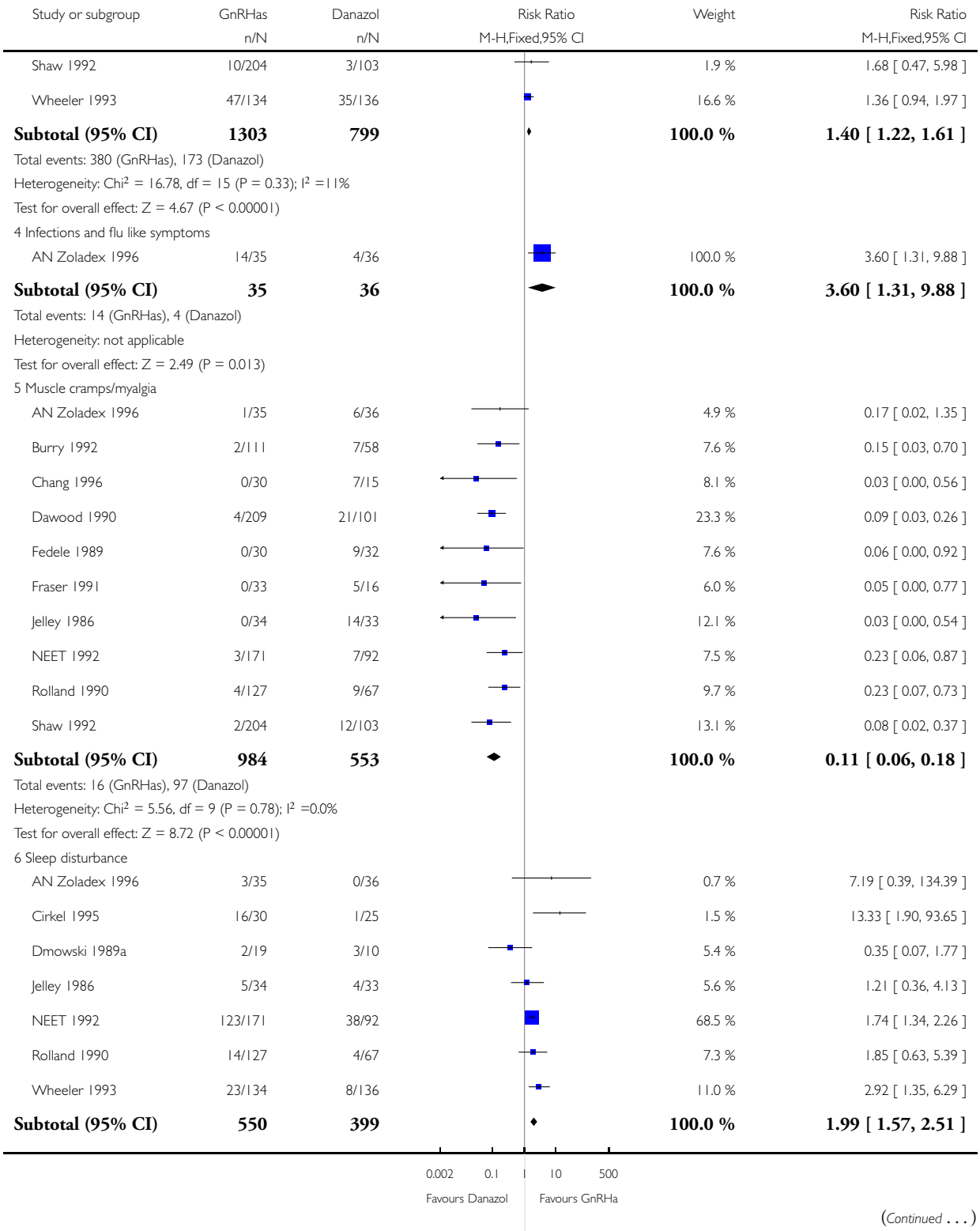

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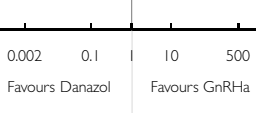
Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 186 (GnRHas), 58 (Danazol)					
Heterogeneity: Chi² = 11.40, df = 6 (P = 0.08); I² =47%					
Test for overall effect: Z = 5.70 (P < 0.00001)					
7 Skin rash					
AN Zoladex 1996	0/35	4/36		32.3 %	0.11 [0.01, 2.05]
Cheng 2005	0/29	3/30		25.0 %	0.15 [0.01, 2.74]
Rolland 1990	0/127	4/67		42.7 %	0.06 [0.00, 1.08]
Subtotal (95% CI)	**191**	**133**		**100.0 %**	**0.10 [0.02, 0.51]**
Total events: 0 (GnRHas), 11 (Danazol)					
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.90); I² =0.0%					
Test for overall effect: Z = 2.75 (P = 0.0059)					
8 Gastrointestinal					
Audebert 1997	3/33	4/22		26.0 %	0.50 [0.12, 2.02]
Cheng 2005	0/29	3/30		18.6 %	0.15 [0.01, 2.74]
Cirkel 1995	7/30	4/25		23.6 %	1.46 [0.48, 4.42]
Rolland 1990	0/127	4/67		31.8 %	0.06 [0.00, 1.08]
Subtotal (95% CI)	**219**	**144**		**100.0 %**	**0.52 [0.26, 1.05]**
Total events: 10 (GnRHas), 15 (Danazol)					
Heterogeneity: Chi² = 6.20, df = 3 (P = 0.10); I² =52%					
Test for overall effect: Z = 1.81 (P = 0.070)					
9 Weight gain					
Audebert 1997	1/33	5/22		2.4 %	0.13 [0.02, 1.07]
Burry 1992	6/111	11/58		5.9 %	0.29 [0.11, 0.73]
Chang 1996	0/30	6/15		3.5 %	0.04 [0.00, 0.66]
Cheng 2005	3/29	12/30		4.8 %	0.26 [0.08, 0.82]
Dawood 1990	2/209	38/101		20.8 %	0.03 [0.01, 0.10]
Fedele 1989	2/30	22/32		8.6 %	0.10 [0.02, 0.38]
Jelley 1986	2/34	12/33		4.9 %	0.16 [0.04, 0.67]
Matta 1988	0/39	11/18		6.3 %	0.02 [0.00, 0.33]
Palagiano 1994	0/27	8/20		3.9 %	0.04 [0.00, 0.72]
Rock 1993	25/208	18/107		9.7 %	0.71 [0.41, 1.25]
Shaw 1992	2/204	27/103		14.6 %	0.04 [0.01, 0.15]
Wheeler 1993	17/134	36/136		14.5 %	0.48 [0.28, 0.81]
Subtotal (95% CI)	**1088**	**675**		**100.0 %**	**0.20 [0.16, 0.26]**
Total events: 60 (GnRHas), 206 (Danazol)					
Heterogeneity: Chi² = 50.83, df = 11 (P<0.00001); I² =78%					
Test for overall effect: Z = 11.77 (P < 0.00001)					



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Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
10 Acne					
Audebert 1997	2/33	6/22		2.8 %	0.22 [0.05, 1.00]
Burry 1992	16/111	12/58		6.1 %	0.70 [0.35, 1.37]
Chang 1996	0/30	7/15		3.8 %	0.03 [0.00, 0.56]
Cheng 2005	0/29	6/30		2.5 %	0.08 [0.00, 1.35]
Cirkel 1995	3/30	9/25		3.8 %	0.28 [0.08, 0.92]
Dawood 1990	10/209	32/101		16.7 %	0.15 [0.08, 0.29]
Fedele 1989	0/30	9/32		3.6 %	0.06 [0.00, 0.92]
Jelley 1986	4/34	13/33		5.1 %	0.30 [0.11, 0.82]
Matta 1988	0/39	7/18		3.9 %	0.03 [0.00, 0.53]
Rock 1993	65/208	43/107		21.9 %	0.78 [0.57, 1.06]
Rolland 1990	7/127	4/67		2.0 %	0.92 [0.28, 3.04]
Shaw 1992	76/204	54/103		27.7 %	0.71 [0.55, 0.92]
Wheeler 1993	15/134	0/136		0.2 %	31.46 [1.90, 520.51]
Subtotal (95% CI)	**1218**	**747**		**100.0 %**	**0.55 [0.47, 0.65]**
Total events: 198 (GnRHas), 202 (Danazol)					
Heterogeneity: Chi^2 = 48.28, df = 12 (P<0.00001); I^2 =75%					
Test for overall effect: Z = 7.05 (P < 0.00001)					
11 Breast atrophy/changes					
Burry 1992	8/111	6/58		7.0 %	0.70 [0.25, 1.91]
Cirkel 1995	0/30	6/25		6.3 %	0.06 [0.00, 1.09]
Dawood 1990	6/209	11/101		13.2 %	0.26 [0.10, 0.69]
Fedele 1989	8/30	7/32		6.0 %	1.22 [0.50, 2.95]
Jelley 1986	3/34	3/33		2.7 %	0.97 [0.21, 4.47]
Matta 1988	1/39	1/18		1.2 %	0.46 [0.03, 6.97]
Rock 1993	67/208	54/107		63.5 %	0.64 [0.49, 0.84]
Subtotal (95% CI)	**661**	**374**		**100.0 %**	**0.60 [0.47, 0.76]**
Total events: 93 (GnRHas), 88 (Danazol)					
Heterogeneity: Chi^2 = 8.36, df = 6 (P = 0.21); I^2 =28%					
Test for overall effect: Z = 4.19 (P = 0.000028)					
12 Emotional lability/altered mood					
Burry 1992	13/111	1/58		3.1 %	6.79 [0.91, 50.65]
Cirkel 1995	10/30	5/25		13.0 %	1.67 [0.66, 4.24]
Dawood 1990	13/209	15/101		48.3 %	0.42 [0.21, 0.85]

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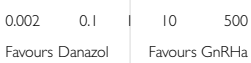
Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wheeler 1993	21/134	15/136		35.5 %	1.42 [0.77, 2.64]
Subtotal (95% CI)	**484**	**320**		**100.0 %**	**1.14 [0.77, 1.67]**
Total events: 57 (GnRHas), 36 (Danazol)					
Heterogeneity: Chi^2 = 11.93, df = 3 (P = 0.01); I^2 =75%					
Test for overall effect: Z = 0.66 (P = 0.51)					
13 Oedema/fluid retention					
Burry 1992	3/111	3/58		4.6 %	0.52 [0.11, 2.51]
Chang 1996	0/30	7/15		11.6 %	0.03 [0.00, 0.56]
Cirkel 1995	2/30	5/25		6.4 %	0.33 [0.07, 1.57]
Dawood 1990	2/209	18/101		28.5 %	0.05 [0.01, 0.23]
Palagiano 1994	0/27	15/20		20.8 %	0.02 [0.00, 0.38]
Wheeler 1993	7/134	24/136		28.0 %	0.30 [0.13, 0.66]
Subtotal (95% CI)	**541**	**355**		**100.0 %**	**0.15 [0.09, 0.26]**
Total events: 14 (GnRHas), 72 (Danazol)					
Heterogeneity: Chi^2 = 10.74, df = 5 (P = 0.06); I^2 =53%					
Test for overall effect: Z = 7.03 (P < 0.00001)					
14 Asthenia					
Burry 1992	4/111	7/58		18.3 %	0.30 [0.09, 0.98]
Cheng 2005	0/29	3/30		6.9 %	0.15 [0.01, 2.74]
Dawood 1990	21/209	22/101		59.1 %	0.46 [0.27, 0.80]
Fraser 1991	1/33	0/16		1.3 %	1.50 [0.06, 34.91]
Rolland 1990	0/127	5/67		14.3 %	0.05 [0.00, 0.86]
Subtotal (95% CI)	**509**	**272**		**100.0 %**	**0.36 [0.23, 0.58]**
Total events: 26 (GnRHas), 37 (Danazol)					
Heterogeneity: Chi^2 = 3.85, df = 4 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 4.23 (P = 0.000023)					
15 Bleeding					
Chang 1996	1/30	6/15		28.5 %	0.08 [0.01, 0.63]
Cheng 2005	0/29	6/30		22.8 %	0.08 [0.00, 1.35]
Matta 1988	9/39	10/18		48.7 %	0.42 [0.20, 0.84]
Subtotal (95% CI)	**98**	**63**		**100.0 %**	**0.24 [0.12, 0.48]**
Total events: 10 (GnRHas), 22 (Danazol)					
Heterogeneity: Chi^2 = 3.86, df = 2 (P = 0.15); I^2 =48%					
Test for overall effect: Z = 4.12 (P = 0.000039)					
16 Depression					
Chang 1996	1/30	7/15		18.5 %	0.07 [0.01, 0.53]



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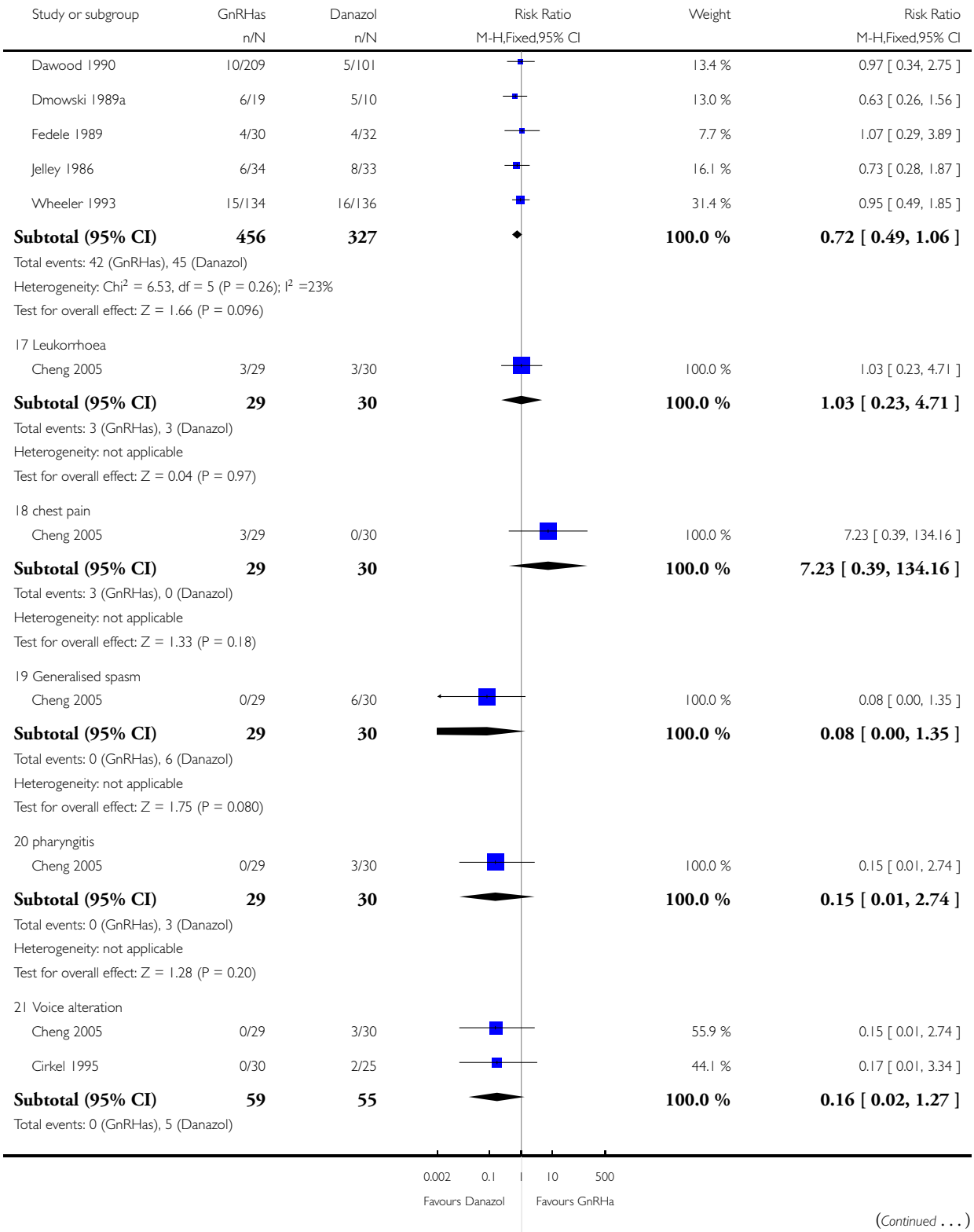

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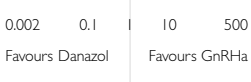
Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² =0.0%					
Test for overall effect: Z = 1.74 (P = 0.082)					
22 vulvovaginal disorder					
Cheng 2005	0/29	3/30		100.0 %	0.15 [0.01, 2.74]
Subtotal (95% CI)	**29**	**30**		**100.0 %**	**0.15 [0.01, 2.74]**
Total events: 0 (GnRHas), 3 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
23 Hirsutism					
Cirkel 1995	0/30	4/25		10.9 %	0.09 [0.01, 1.65]
Dawood 1990	1/209	6/101		18.0 %	0.08 [0.01, 0.66]
Fedele 1989	0/30	6/32		14.0 %	0.08 [0.00, 1.39]
Jelley 1986	0/34	2/33		5.6 %	0.19 [0.01, 3.90]
Matta 1988	0/39	3/18		10.5 %	0.07 [0.00, 1.25]
Rock 1993	10/208	14/107		41.0 %	0.37 [0.17, 0.80]
Subtotal (95% CI)	**550**	**316**		**100.0 %**	**0.20 [0.11, 0.39]**
Total events: 11 (GnRHas), 35 (Danazol)					
Heterogeneity: Chi² = 4.17, df = 5 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 4.89 (P < 0.00001)					
24 Seborrhoea					
Cirkel 1995	1/30	4/25		3.0 %	0.21 [0.02, 1.75]
Dmowski 1989a	5/19	6/10		5.5 %	0.44 [0.18, 1.09]
Fedele 1989	0/30	7/32		5.1 %	0.07 [0.00, 1.19]
Jelley 1986	0/34	3/33		2.5 %	0.14 [0.01, 2.59]
Rock 1993	25/208	43/107		39.5 %	0.30 [0.19, 0.46]
Shaw 1992	56/204	48/103		44.4 %	0.59 [0.43, 0.80]
Subtotal (95% CI)	**525**	**310**		**100.0 %**	**0.42 [0.33, 0.53]**
Total events: 87 (GnRHas), 111 (Danazol)					
Heterogeneity: Chi² = 9.68, df = 5 (P = 0.08); I² =48%					
Test for overall effect: Z = 7.19 (P < 0.00001)					
25 Alopecia					
Cirkel 1995	1/30	4/25		37.1 %	0.21 [0.02, 1.75]
Dawood 1990	0/209	5/101		62.9 %	0.04 [0.00, 0.79]
Subtotal (95% CI)	**239**	**126**		**100.0 %**	**0.11 [0.02, 0.53]**
Total events: 1 (GnRHas), 9 (Danazol)					
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² =0.0%					
Test for overall effect: Z = 2.73 (P = 0.0063)					



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Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
26 Altered libido					
Cirkel 1995	14/30	2/25		1.3 %	5.83 [1.46, 23.26]
Dawood 1990	4/209	8/101		6.2 %	0.24 [0.07, 0.78]
Fedele 1989	6/30	5/32		2.8 %	1.28 [0.44, 3.76]
Jelley 1986	4/34	7/33		4.1 %	0.55 [0.18, 1.72]
NEET 1992	24/171	5/92		3.7 %	2.58 [1.02, 6.54]
Palagiano 1994	4/27	5/20		3.3 %	0.59 [0.18, 1.93]
Rock 1993	129/208	45/107		34.1 %	1.47 [1.15, 1.89]
Rolland 1990	18/127	2/67		1.5 %	4.75 [1.14, 19.85]
Shaw 1992	44/204	52/103		39.7 %	0.43 [0.31, 0.59]
Wheeler 1993	18/134	6/136		3.4 %	3.04 [1.25, 7.43]
Subtotal (95% CI)	**1174**	**716**		**100.0 %**	**1.11 [0.94, 1.31]**
Total events: 265 (GnRHas), 137 (Danazol)					
Heterogeneity: Chi² = 65.05, df = 9 (P<0.00001); I² =86%					
Test for overall effect: Z = 1.20 (P = 0.23)					
27 Sweating					
Cirkel 1995	1/30	3/25		100.0 %	0.28 [0.03, 2.51]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**0.28 [0.03, 2.51]**
Total events: 1 (GnRHas), 3 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.14 (P = 0.25)					
28 Breast tenderness					
Cirkel 1995	1/30	2/25		100.0 %	0.42 [0.04, 4.33]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**0.42 [0.04, 4.33]**
Total events: 1 (GnRHas), 2 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.46)					
29 Fatigue					
Cirkel 1995	6/30	12/25		71.4 %	0.42 [0.18, 0.95]
Dmowski 1989a	11/19	4/10		28.6 %	1.45 [0.62, 3.39]
Subtotal (95% CI)	**49**	**35**		**100.0 %**	**0.71 [0.40, 1.26]**
Total events: 17 (GnRHas), 16 (Danazol)					
Heterogeneity: Chi² = 4.30, df = 1 (P = 0.04); I² =77%					
Test for overall effect: Z = 1.17 (P = 0.24)					
30 Arthralgia					
Cirkel 1995	10/30	0/25		100.0 %	17.61 [1.08, 286.40]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**17.61 [1.08, 286.40]**

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Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 10 (GnRHas), 0 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.02 (P = 0.044)					
31 Hunger					
Cirkel 1995	0/30	8/25		100.0 %	0.05 [0.00, 0.81]
Subtotal (95% CI)	**30**	**25**		**100.0 %**	**0.05 [0.00, 0.81]**
Total events: 0 (GnRHas), 8 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.10 (P = 0.035)					
32 Nervousness					
Dawood 1990	8/209	6/101		21.1 %	0.64 [0.23, 1.81]
Rolland 1990	3/127	6/67		20.5 %	0.26 [0.07, 1.02]
Wheeler 1993	0/134	22/136		58.3 %	0.02 [0.00, 0.37]
Subtotal (95% CI)	**470**	**304**		**100.0 %**	**0.20 [0.10, 0.43]**
Total events: 11 (GnRHas), 34 (Danazol)					
Heterogeneity: Chi^2 = 7.32, df = 2 (P = 0.03); I^2 =73%					
Test for overall effect: Z = 4.23 (P = 0.000024)					
33 Irritability					
Dmowski 1989a	9/19	4/40		100.0 %	4.74 [1.67, 13.45]
Subtotal (95% CI)	**19**	**40**		**100.0 %**	**4.74 [1.67, 13.45]**
Total events: 9 (GnRHas), 4 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.92 (P = 0.0035)					
34 Clitoromegaly					
Jelley 1986	0/34	3/33		100.0 %	0.14 [0.01, 2.59]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**0.14 [0.01, 2.59]**
Total events: 0 (GnRHas), 3 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					
35 Appetite increase					
Jelley 1986	0/34	5/33		100.0 %	0.09 [0.01, 1.54]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**0.09 [0.01, 1.54]**
Total events: 0 (GnRHas), 5 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.096)					
36 Fatigue/malaise					
Jelley 1986	3/34	15/33		100.0 %	0.19 [0.06, 0.61]
Subtotal (95% CI)	**34**	**33**		**100.0 %**	**0.19 [0.06, 0.61]**
Total events: 3 (GnRHas), 15 (Danazol)					

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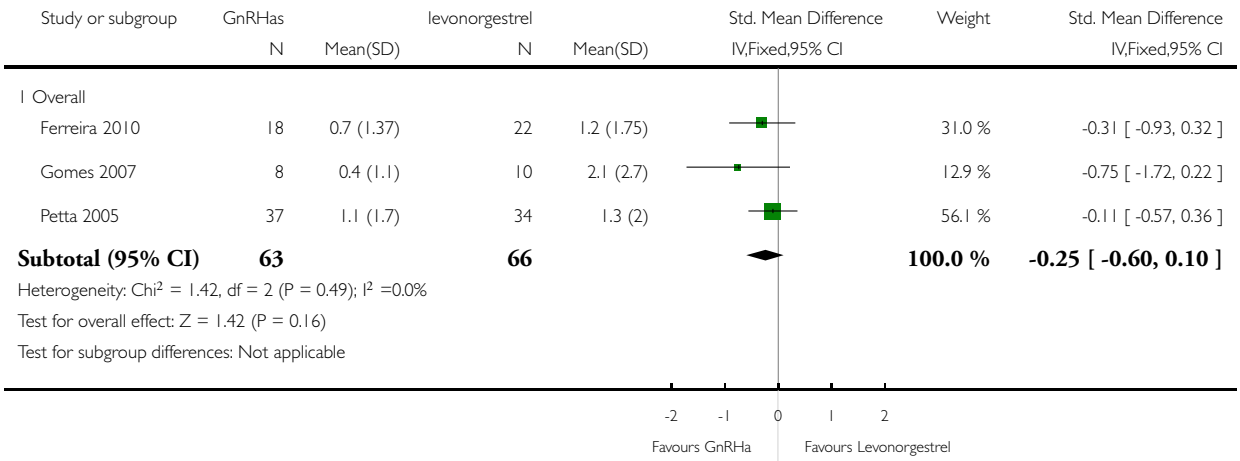
Study or subgroup	GnRHas n/N	Danazol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 2.81 (P = 0.0050)					
37 Dizziness					
Jelley 1986	1/34	4/33		89.1 %	0.24 [0.03, 2.06]
Wheeler 1993	13/134	0/136		10.9 %	27.40 [1.65, 456.32]
Subtotal (95% CI)	**168**	**169**		**100.0 %**	**3.20 [1.13, 9.04]**
Total events: 14 (GnRHas), 4 (Danazol)					
Heterogeneity: Chi² = 7.83, df = 1 (P = 0.01); I² =87%					
Test for overall effect: Z = 2.20 (P = 0.028)					
38 Nausea					
Jelley 1986	11/34	19/33		36.3 %	0.56 [0.32, 0.99]
Shaw 1992	10/204	12/103		30.0 %	0.42 [0.19, 0.94]
Wheeler 1993	17/134	18/136		33.6 %	0.96 [0.52, 1.78]
Subtotal (95% CI)	**372**	**272**		**100.0 %**	**0.65 [0.45, 0.95]**
Total events: 38 (GnRHas), 49 (Danazol)					
Heterogeneity: Chi² = 2.89, df = 2 (P = 0.24); I² =31%					
Test for overall effect: Z = 2.25 (P = 0.024)					
39 Breast pain					
Shaw 1992	10/204	1/103		100.0 %	5.05 [0.66, 38.91]
Subtotal (95% CI)	**204**	**103**		**100.0 %**	**5.05 [0.66, 38.91]**
Total events: 10 (GnRHas), 1 (Danazol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					

Analysis 4.1. Comparison 4 GnRHas versus intra- uterine progestagen device, Outcome 1 Relief of painful symptoms.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 4 GnRHas versus intra- uterine progestagen device

Outcome: 1 Relief of painful symptoms

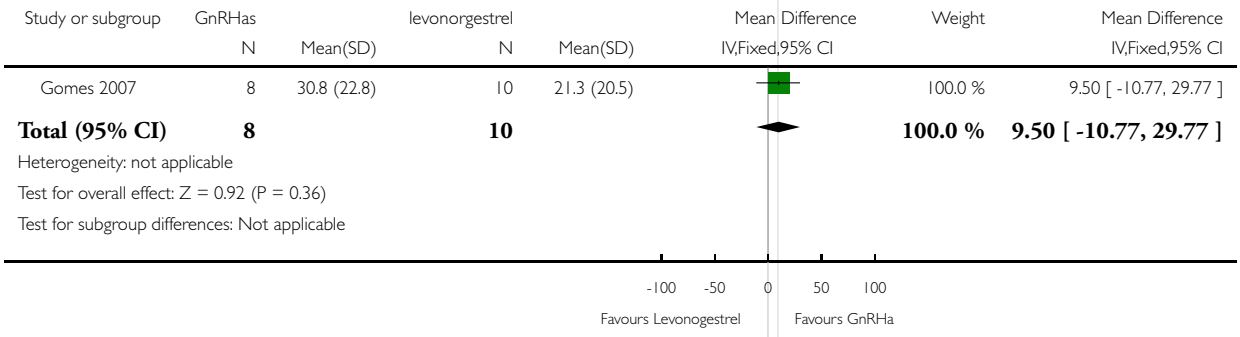


Analysis 4.2. Comparison 4 GnRHas versus intra- uterine progestagen device, Outcome 2 rAFS/ASRM score.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 4 GnRHas versus intra- uterine progestagen device

Outcome: 2 rAFS/ASRM score



Analysis 5.1. Comparison 5 GnRHa versus GnRHa (Varying Dosage), Outcome 1 Side effects.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 5 GnRHa versus GnRHa (Varying Dosage)

Outcome: 1 Side effects

Study or subgroup	Dose A n/N	Dose B n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Sleep disturbance Nafareline 200mcg versus 400mcg					
Bergqvist 1997	9/12	9/12		100.0 %	1.00 [0.63, 1.59]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**1.00 [0.63, 1.59]**
Total events: 9 (Dose A), 9 (Dose B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Rhinitis Nafareline 200mcg versus 400 mcg					
Bergqvist 1997	2/12	5/12		100.0 %	0.40 [0.10, 1.67]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**0.40 [0.10, 1.67]**
Total events: 2 (Dose A), 5 (Dose B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
3 Upper respiratory tract infection Nafareline 200mcg versus 400 mcg					
Bergqvist 1997	1/12	5/12		100.0 %	0.20 [0.03, 1.47]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**0.20 [0.03, 1.47]**
Total events: 1 (Dose A), 5 (Dose B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.58 (P = 0.11)					
4 Hot flushes/flashes Nafareline 200mcg versus 400 mcg					
Bergqvist 1997	7/12	7/12		100.0 %	1.00 [0.51, 1.97]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**1.00 [0.51, 1.97]**
Total events: 7 (Dose A), 7 (Dose B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					

Analysis 5.2. Comparison 5 GnRHa versus GnRHa (Varying Dosage), Outcome 2 rAFS score (400mcg vs 800mcg).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 5 GnRHa versus GnRHa (Varying Dosage)

Outcome: 2 rAFS score (400mcg vs 800mcg)

Study or subgroup	low dose n/N	high dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Henzl 1988	6/73	14/70		100.0 %	0.41 [0.17, 1.01]
Total (95% CI)	**73**	**70**		**100.0 %**	**0.41 [0.17, 1.01]**
Total events: 6 (low dose), 14 (high dose)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.052)					
Test for subgroup differences: Not applicable					

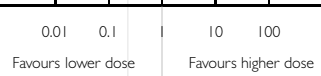
Analysis 5.3. Comparison 5 GnRHa versus GnRHa (Varying Dosage), Outcome 3 relief of painful symptoms.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 5 GnRHa versus GnRHa (Varying Dosage)

Outcome: 3 relief of painful symptoms

Study or subgroup	nafarelin 400 n/N	nafarelin 800 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dsymenorrhoea Nafarelin 400mcg versus 800mcg					
Adamson 1994	15/45	16/45		100.0 %	0.94 [0.53, 1.66]
Subtotal (95% CI)	**45**	**45**		**100.0 %**	**0.94 [0.53, 1.66]**
Total events: 15 (nafarelin 400), 16 (nafarelin 800)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.82)					
2 Dyspareunia					
Adamson 1994	22/31	16/26		100.0 %	1.15 [0.79, 1.68]
Subtotal (95% CI)	**31**	**26**		**100.0 %**	**1.15 [0.79, 1.68]**
Total events: 22 (nafarelin 400), 16 (nafarelin 800)					
Heterogeneity: not applicable					



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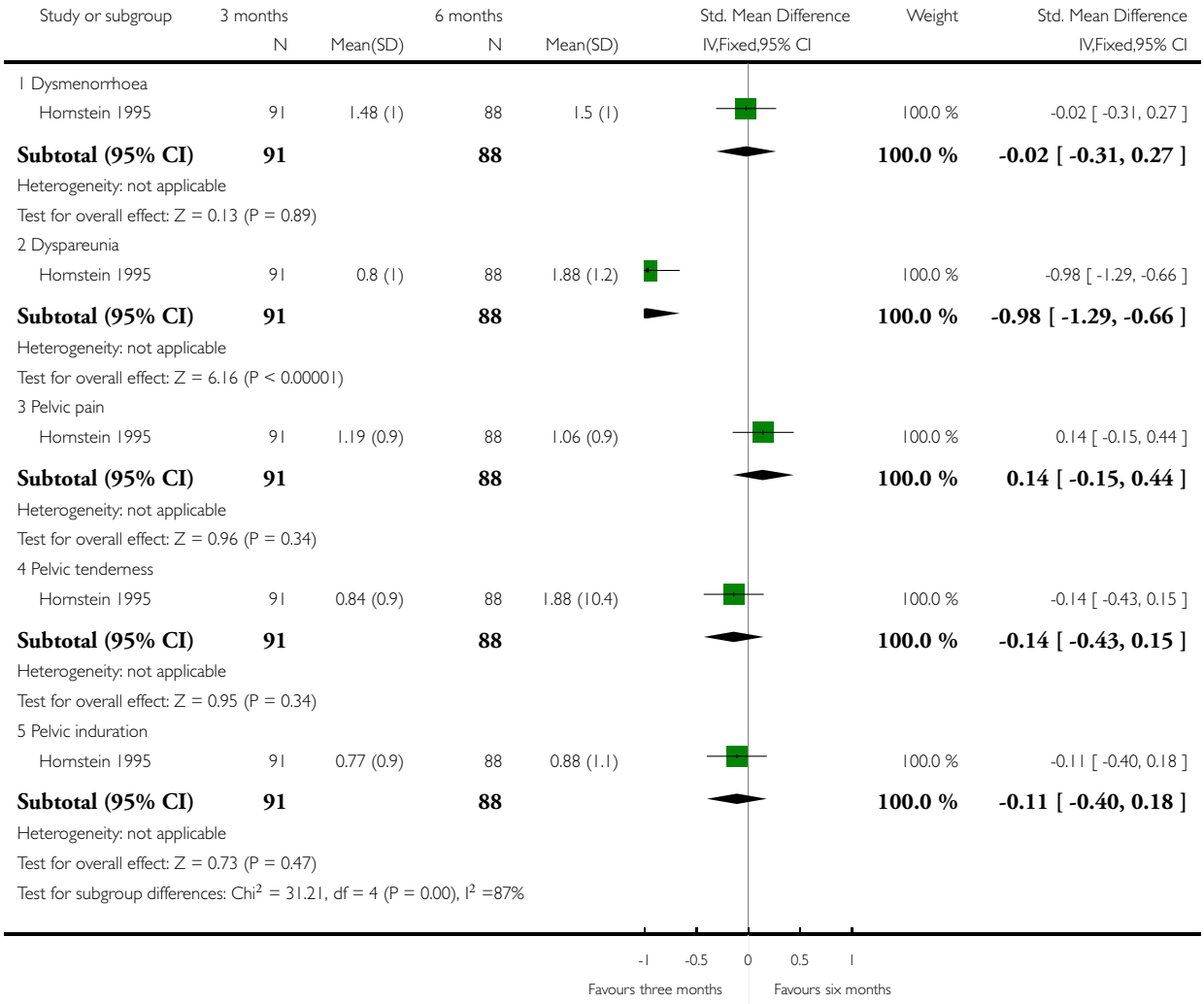
Study or subgroup	nafarelin 400 n/N	nafarelin 800 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.74 (P = 0.46)					
3 Pelvic pain					
Adamson 1994	18/37	18/40		100.0 %	1.08 [0.67, 1.74]
Subtotal (95% CI)	**37**	**40**		**100.0 %**	**1.08 [0.67, 1.74]**
Total events: 18 (nafarelin 400), 18 (nafarelin 800)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					
4 Overall Nafarelin 400mcg versus 800mcg					
Henzl 1988	53/73	54/70		100.0 %	0.94 [0.78, 1.14]
Subtotal (95% CI)	**73**	**70**		**100.0 %**	**0.94 [0.78, 1.14]**
Total events: 53 (nafarelin 400), 54 (nafarelin 800)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
5 Overall buserelin 300mcg vs 900 mcg					
Minaguchi 1986	31/69	19/63		100.0 %	1.49 [0.94, 2.35]
Subtotal (95% CI)	**69**	**63**		**100.0 %**	**1.49 [0.94, 2.35]**
Total events: 31 (nafarelin 400), 19 (nafarelin 800)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.71 (P = 0.088)					

Analysis 6.1. Comparison 6 GnRHa versus GnRHa (Length of Treatment), Outcome 1 Relief of Painful Symptoms (3months vs 6months) at 6 months follow up.

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 6 GnRHa versus GnRHa (Length of Treatment)

Outcome: 1 Relief of Painful Symptoms (3months vs 6months) at 6 months follow up

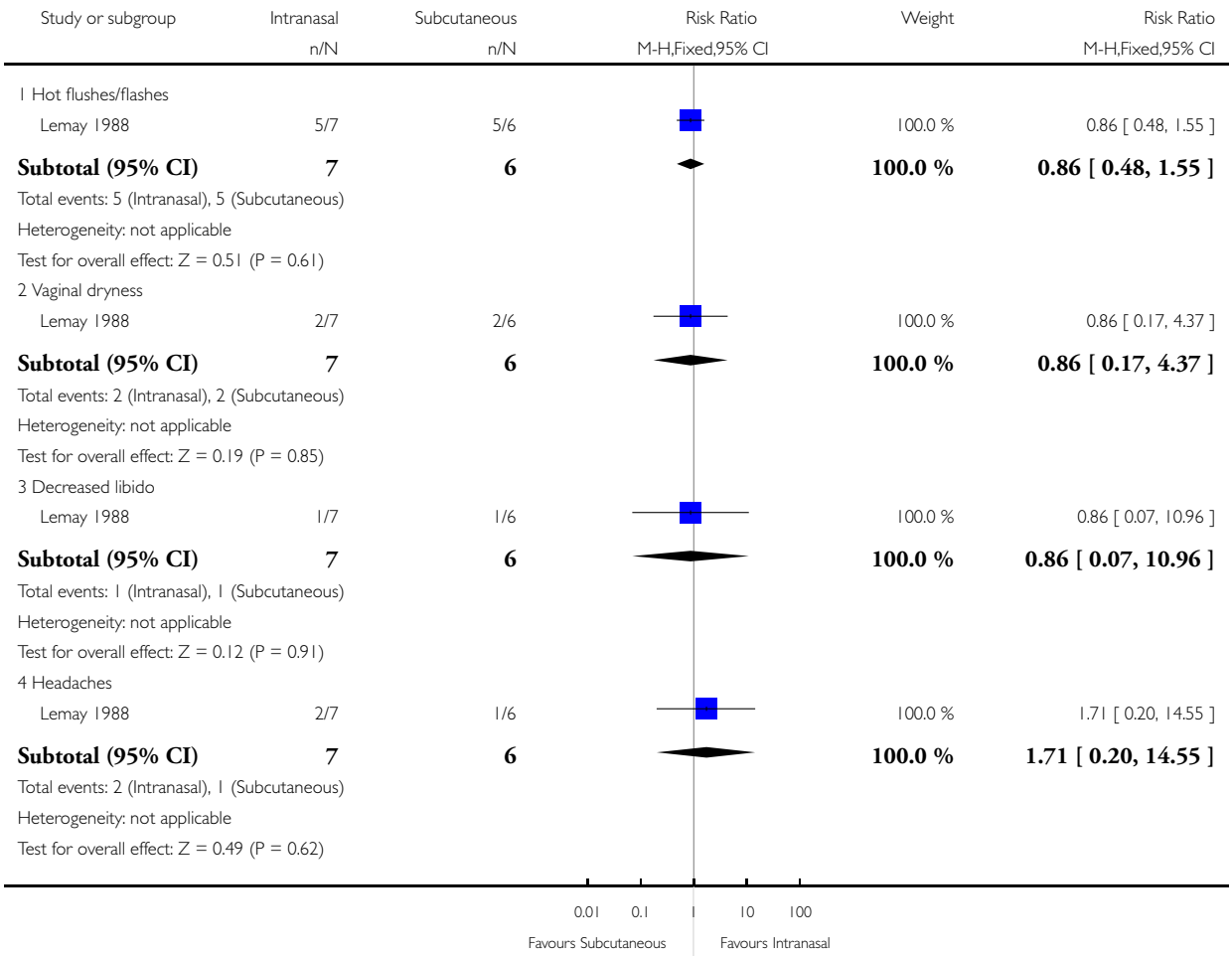


Analysis 7.1. Comparison 7 GnRHa versus GnRHa (Route of Administration), Outcome 1 Side effects (IN vs SC).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 7 GnRHa versus GnRHa (Route of Administration)

Outcome: 1 Side effects (IN vs SC)



Analysis 7.2. Comparison 7 GnRHa versus GnRHa (Route of Administration), Outcome 2 rAFS score (IN vs SC).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 7 GnRHa versus GnRHa (Route of Administration)

Outcome: 2 rAFS score (IN vs SC)

Study or subgroup	Intranasal N	Mean(SD)	Subcutaneous N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Dmowski 1989a	10	18 (22.14)	9	9 (9)		100.0 %	9.00 [-5.93, 23.93]
Total (95% CI)	**10**		**9**			**100.0 %**	**9.00 [-5.93, 23.93]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable

Analysis 7.3. Comparison 7 GnRHa versus GnRHa (Route of Administration), Outcome 3 Relief of painful symptoms (IN versus IMdepot).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 7 GnRHa versus GnRHa (Route of Administration)

Outcome: 3 Relief of painful symptoms (IN versus IMdepot)

Study or subgroup	intranasal n/N	IMdepot n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Dysmenorrhea					
Agarwal 1997	77/99	77/93		100.0 %	0.94 [0.82, 1.08]
Subtotal (95% CI)	**99**	**93**		**100.0 %**	**0.94 [0.82, 1.08]**
Total events: 77 (intranasal), 77 (IMdepot)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					
2 Dyspareunia					
Agarwal 1997	52/86	44/80		100.0 %	1.10 [0.85, 1.43]
Subtotal (95% CI)	**86**	**80**		**100.0 %**	**1.10 [0.85, 1.43]**
Total events: 52 (intranasal), 44 (IMdepot)					
Heterogeneity: not applicable					

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Study or subgroup	intranasal n/N	IMdepot n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.71 (P = 0.48)					
3 Pelvic pain					
Agarwal 1997	49/99	44/93		100.0 %	1.05 [0.78, 1.40]
Subtotal (95% CI)	**99**	**93**		**100.0 %**	**1.05 [0.78, 1.40]**
Total events: 49 (intranasal), 44 (IMdepot)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
4 Tenderness					
Agarwal 1997	53/99	58/93		100.0 %	0.86 [0.67, 1.09]
Subtotal (95% CI)	**99**	**93**		**100.0 %**	**0.86 [0.67, 1.09]**
Total events: 53 (intranasal), 58 (IMdepot)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.22)					
5 Induration					
Agarwal 1997	73/99	74/91		100.0 %	0.91 [0.78, 1.06]
Subtotal (95% CI)	**99**	**91**		**100.0 %**	**0.91 [0.78, 1.06]**
Total events: 73 (intranasal), 74 (IMdepot)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					

Analysis 7.4. Comparison 7 GnRHa versus GnRHa (Route of Administration), Outcome 4 Side effects (IN versus IMdepot).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 7 GnRHa versus GnRHa (Route of Administration)

Outcome: 4 Side effects (IN versus IMdepot)

Study or subgroup	Intranasal n/N	IMdepot n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Hot flushes/flashes					
Agarwal 1997	95/98	93/93		100.0 %	0.97 [0.93, 1.01]
Subtotal (95% CI)	**98**	**93**		**100.0 %**	**0.97 [0.93, 1.01]**
Total events: 95 (Intranasal), 93 (IMdepot)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.48 (P = 0.14)					

Analysis 7.5. Comparison 7 GnRHa versus GnRHa (Route of Administration), Outcome 5 Improvement in symptoms (IN versus IMdepot).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 7 GnRHa versus GnRHa (Route of Administration)

Outcome: 5 Improvement in symptoms (IN versus IMdepot)

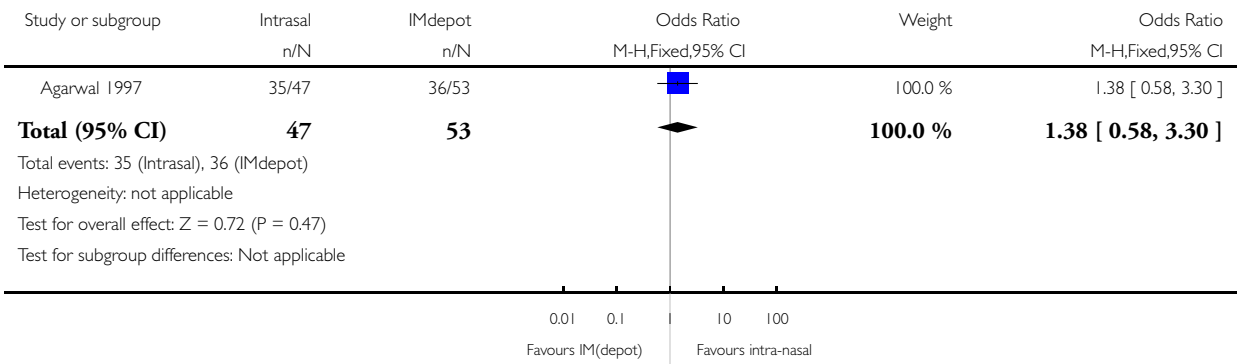
Study or subgroup	Intrasal n/N	IMdepot n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Agarwal 1997	35/47	36/53		100.0 %	1.38 [0.58, 3.30]
Total (95% CI)	**47**	**53**		**100.0 %**	**1.38 [0.58, 3.30]**

Total events: 35 (Intrasal), 36 (IMdepot)

Heterogeneity: not applicable

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7 GnRHa versus GnRHa (Route of Administration), Outcome 6 Relief of painful symptoms (IN versus SC).

Review: Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

Comparison: 7 GnRHa versus GnRHa (Route of Administration)

Outcome: 6 Relief of painful symptoms (IN versus SC)

Study or subgroup	IN n/N	SC n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pelvic pain					
Lemay 1988	3/3	2/2		100.0 %	1.00 [0.53, 1.87]
Subtotal (95% CI)	**3**	**2**		**100.0 %**	**1.00 [0.53, 1.87]**
Total events: 3 (IN), 2 (SC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Dyspareunia					
Lemay 1988	5/5	2/2		100.0 %	1.00 [0.57, 1.75]
Subtotal (95% CI)	**5**	**2**		**100.0 %**	**1.00 [0.57, 1.75]**
Total events: 5 (IN), 2 (SC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
3 Dysmenorrhoea					
Lemay 1988	5/5	4/5		100.0 %	1.22 [0.73, 2.06]
Subtotal (95% CI)	**5**	**5**		**100.0 %**	**1.22 [0.73, 2.06]**
Total events: 5 (IN), 4 (SC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.45)					
4 Pelvic tenderness					
Lemay 1988	7/7	2/3		100.0 %	1.50 [0.69, 3.27]
Subtotal (95% CI)	**7**	**3**		**100.0 %**	**1.50 [0.69, 3.27]**
Total events: 7 (IN), 2 (SC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
5 Pelvic induration					
Lemay 1988	4/5	3/3		100.0 %	0.86 [0.47, 1.55]
Subtotal (95% CI)	**5**	**3**		**100.0 %**	**0.86 [0.47, 1.55]**
Total events: 4 (IN), 3 (SC)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.51 (P = 0.61)					

APPENDICES

Appendix 1. Specialist register search terms

Keywords CONTAINS "*Endometriosis" or "dysmenorrhea" or "dysmenorrhoea" or "dyspareunia" or "pelvic pain" or "pain-dysmenorrhea" or "pain-dyspareunia" or "pain-endometriosis" or "pain-pelvic" or "menstrual pain" or "dyschezia" or "abdominal pain" or Title CONTAINS" *Endometriosis" or "dysmenorrhea" or "dysmenorrhoea" or "dyspareunia" or "pelvic pain" or "pain-dysmenorrhea" or "pain-dyspareunia" or "pain-endometriosis" or "pain-pelvic" or "menstrual pain" or "dyschezia" or "abdominal pain"
AND
Keywords CONTAINS "Gonadorelin" or "GnRh" or "GnRHa" or "GnRHa-gonadotropin" or "Gonadotrophin releasing agonist" or "Gonadotrophin releasing hormones" or "gonadotrophins" or "gonadotropin" or "gonadotropin releasing hormone agonist" or "goserelin acetate" or "Gosereline " or "Luteinising hormone releasing hormone" or "Lutenising hormone releasing hormone" or "LHRH" or "LHRH agonists" or "LHRH antagonists" or "leuprorelin" or "leuprorelin acetate" or "leuprolin" or "leuprolide depot" or "Leuprolide" or "leuprolide acetate" or "buserelin" or "Buserelin Acetate" or "buserelin naferelin" or "busereline" or "Nafarelin" or "Nafarelin Study Group" or "triptoielin" or "triptorelin" or "triptoreline" or "triptorelyn" or "triptrolein" or "Zoladex" or "Lupron" or "luprorelix" or "decapeptyl" or "decapeptyl" or "decapeptyl-daily" or "decapeptyl-depot"

Appendix 2. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2009>
Search Strategy:
---
1 exp Endometriosis/ (375)
2 exp Dysmenorrhea/ (273)
3 dysmenorrh$.tw. (536)
4 (pain$ adj5 menstrua$).tw. (150)
5 dyspareunia.tw. (157)
6 (pelvi$ adj2 pain$).tw. (362)
7 (pain$ adj3 defecat$).tw. (73)
8 (Dyschesia or Dyschezia).tw. (7)
9 Endometrios$.tw. (629)
10 or/1-9 (1639)
11 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (1612)
12 (gonadotropin-releasing hormone$ or gonadotrophin-releasing hormone$).tw. (907)
13 GnRH$.tw. (1431)
14 luteinizing hormone-releasing hormone$.tw. (231)
15 lhrh$.tw. (327)
16 fsh-releasing hormone$.tw. (1)
17 gonadorelin$.tw. (5)
18 lh fsh releasing hormone$.tw. (1)
19 lh rh$.tw. (136)
20 (buserelin or goserelin or leuprolide).tw. (908)
21 (nafarelin or triptorelin).tw. (245)
22 (leuprorelin or naferelin).tw. (82)
23 (suprecur or suprefact).tw. (8)
24 (Zoladex or lupron).tw. (239)
25 (prostap or enantone).tw. (7)
26 (lucrin or trenantone$).tw. (2)
27 (synarel or synarella).tw. (3)
28 (decapeptyl or gonapeptyl).tw. (50)
29 Elagolix.tw. (1)
30 or/11-29 (2968)

31 10 and 30 (310)
32 from 31 keep 1-310 (310)

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1950 to November Week 2 2009>
Search Strategy:
---
1 exp Endometriosis/ (13905)
2 exp Dysmenorrhea/ (2665)
3 dysmenorrh$.tw. (3130)
4 (pain$ adj5 menstrua$).tw. (844)
5 dyspareunia.tw. (1820)
6 (pelvi$ adj2 pain$).tw. (4582)
7 (pain$ adj3 defecat$).tw. (269)
8 (Dyschesia or Dyschezia).tw. (140)
9 Endometrios$.tw. (12214)
10 or/1-9 (24507)
11 exp gonadotropin-releasing hormone/ or exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp nafarelin/ or exp triptorelin/ (25929)
12 (gonadotropin-releasing hormone$ or gonadotrophin-releasing hormone$).tw. (11259)
13 GnRH$.tw. (14772)
14 luteinizing hormone-releasing hormone$.tw. (4863)
15 lhrh$.tw. (5789)
16 fsh-releasing hormone$.tw. (54)
17 gonadorelin$.tw. (121)
18 lh fsh releasing hormone$.tw. (27)
19 lh rh$.tw. (3241)
20 (buserelin or goserelin or leuprolide).tw. (3022)
21 (nafarelin or triptorelin).tw. (657)
22 (leuprorelin or naferelin).tw. (274)
23 (suprecur or suprefact).tw. (26)
24 (Zoladex or lupron).tw. (494)
25 (prostap or enantone).tw. (23)
26 (lucrin or trenantone$).tw. (4)
27 (synarel or synarella).tw. (11)
28 (decapeptyl or gonapeptyl).tw. (199)
29 Elagolix.tw. (2)
30 or/11-29 (34249)
31 randomized controlled trial.pt. (290742)
32 controlled clinical trial.pt. (82944)
33 randomized.ab. (195989)
34 placebo.tw. (123192)
35 clinical trials as topic.sh. (150116)
36 randomly.ab. (141239)
37 trial.ti. (85409)
38 (crossover or cross-over or cross over).tw. (45884)
39 or/31-38 (685431)
40 (animals not (humans and animals)).sh. (3413380)
41 39 not 40 (634444)
42 10 and 30 and 41 (296)
43 from 42 keep 1-296 (296)

Appendix 4. EMBASE search strategy

Database: EMBASE <1980 to 2009 Week 47>
Search Strategy:
---

1 exp Endometriosis/ (11479)
2 exp Dysmenorrhea/ (3835)
3 dysmenorrh$.tw. (2292)
4 (pain$ adj5 menstrua$).tw. (629)
5 dyspareunia.tw. (1609)
6 (pelvi$ adj2 pain$).tw. (4145)
7 (pain$ adj3 defecat$).tw. (259)
8 (Dyschesia or Dyschezia).tw. (119)
9 (abdom$ adj2 pain$).tw. (24575)
10 Endometriosis.tw. (9889)
11 or/1-10 (44344)
12 (gonadotropin-releasing hormone$ or gonadotrophin-releasing hormone$).tw. (10038)
13 GnRHa$.tw. (853)
14 luteinizing hormone-releasing hormone$.tw. (3788)
15 lhrh$.tw. (5181)
16 fsh-releasing hormone$.tw. (9)
17 gonadorelin$.tw. (166)
18 lh fsh releasing hormone$.tw. (2)
19 lh rh$.tw. (2009)
20 (buserelin or goserelin or leuprolide).tw. (3021)
21 (nafarelin or triptorelin).tw. (723)
22 (leuprorelin or naferelin).tw. (331)
23 (suprecur or suprefact).tw. (1067)
24 (Zoladex or lupron).tw. (2633)
25 (prostap or enantone).tw. (296)
26 (lucrin or trenantone$).tw. (204)
27 (synarel or synarella).tw. (263)
28 (decapeptyl or gonapeptyl).tw. (1329)
29 Elagolix.tw. (2)
30 exp gonadorelin/ or exp gonadorelin agonist/ or exp goserelin/ or exp histrelin/ or exp leuprorelin/ or exp lutrelin/ or exp nafarelin/ or exp nafarelin acetate/ or exp ovurelin/ or exp triptorelin/ (33058)
31 or/12-30 (37986)
32 Clinical Trial/ (564805)
33 Randomized Controlled Trial/ (176320)
34 exp randomization/ (27165)
35 Single Blind Procedure/ (8721)
36 Double Blind Procedure/ (74829)
37 Crossover Procedure/ (21985)
38 Placebo/ (134235)
39 Randomi?ed controlled trial$.tw. (36010)
40 Rct.tw. (3032)
41 random allocation.tw. (652)
42 randomly allocated.tw. (10615)
43 allocated randomly.tw. (1377)
44 (allocated adj2 random).tw. (567)
45 Single blind$.tw. (7772)
46 Double blind$.tw. (87493)
47 ((treble or triple) adj blind$).tw. (143)

48 placebo$.tw. (114270)
49 prospective study/ (87391)
50 or/32-49 (741138)
51 case study/ (6547)
52 case report.tw. (124576)
53 abstract report/ or letter/ (517281)
54 or/51-53 (645921)
55 50 not 54 (715332)
56 (2008$ or 2009$).em. (1146469)
57 11 and 31 and 55 (650)
58 57 and 56 (102)
59 from 58 keep 1-102 (102)

Appendix 5. PSYCInfo search strategy

Database: PsycINFO <1806 to November Week 3 2009>
Search Strategy:
---
1 exp Dysmenorrhea/ (142)
2 dysmenorrh$.tw. (266)
3 (pain$ adj5 menstrua$).tw. (179)
4 dyspareunia.tw. (308)
5 (pelvi$ adj2 pain$).tw. (304)
6 (pain$ adj3 defecat$).tw. (13)
7 (Dyschesia or Dyschezia).tw. (3)
8 Endometrios$.tw. (113)
9 or/1-8 (1065)
10 (gonadotropin-releasing hormone$ or gonadotrophin-releasing hormone$).tw. (393)
11 GnRH$.tw. (354)
12 luteinizing hormone-releasing hormone$.tw. (178)
13 lhrh$.tw. (149)
14 fsh-releasing hormone$.tw. (1)
15 gonadorelin$.tw. (3)
16 lh fsh releasing hormone$.tw. (1)
17 lh rh$.tw. (32)
18 (buserelin or goserelin or leuprolide).tw. (55)
19 (nafarelin or triptorelin).tw. (14)
20 (leuprorelin or naferelin).tw. (1)
21 (suprecur or suprefact).tw. (0)
22 (Zoladex or lupron).tw. (9)
23 (prostap or enantone).tw. (0)
24 (lucrin or trenantone$).tw. (0)
25 (synarel or synarella).tw. (0)
26 (decapeptyl or gonapeptyl).tw. (2)
27 Elagolix.tw. (0)
28 exp gonadotropic hormones/ or exp hormones/ or exp follicle stimulating hormone/ or exp luteinizing hormone/ (38084)
29 or/10-28 (38233)
30 9 and 29 (54)
31 from 30 keep 1-54 (54)

Appendix 6. CINAHL search strategy

Database: CINAHL <1982 to December 2009>
Search Strategy:
---
1 (”endometriosis“) or (MH ”Endometriosis“)
2 (”gonadotropin“) or (MH ”Gonadorelin“)
3 1 and 2

WHAT'S NEW

Last assessed as up-to-date: 26 September 2010.

Date	Event	Description
27 September 2010	New search has been performed	Two additional studies added to review

HISTORY

Protocol first published: Issue 4, 2010

Review first published: Issue 12, 2010

Date	Event	Description
8 April 2010	Amended	Authorship amendment made
17 March 2010	New citation required and major changes	Substantive amendment. Type of intervention has been limited to GnRHas versus placebo or no treatment; GnRHas versus danazol; analgesics; and levonorgestrel
17 March 2010	Amended	This protocol is a new version of a previously published review which required a major methodological restructure Prentice 1999

CONTRIBUTIONS OF AUTHORS

In the update of this review Julie Brown and Alice Pan were responsible for identification of studies and data extraction and entry and the writing of the review drafts. Roger Hart was responsible for providing comments and clinical input.

The original authors of the review were:

Andrew Prentice, Department of Obstetrics and Gynaecology, Rosie Maternity Hospital, Cambridge, UK

Alison Deary, Clinical Pharmacology, Addenbrooke's Hospital, Cambridge, UK

Sandra Goldbeck-Wood, Obstetrics and Gynaecology/Psychosexual Medicine, Ipswich Hospital, Cambridge, UK

Cindy Farquhar, Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Stephen Smith, Faculty of Medicine, Imperial College, London, UK

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Uiniversity of Auckland, New Zealand.

Lead author AP (who is an undergraduate medical student) has been funded to complete the review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences made since the publication of the protocol in April 2010.

Significant changes have been made since this review was first published in 1999 by Andrew Prentice. However the main objective has remained the same: to determine the effectiveness and safety of GnRHas in the treatment of the painful symptoms associated with endometriosis.

The review published in 1999 stated under 'Type of Participants' that "the diagnosis of endometriosis was made by direct visualisation (laparoscopy). Trials where the diagnosis had been made by history alone or by some other imaging technique would have been considered...". This was modified so that "the clinical diagnosis of endometriosis had to be made by direct visualisation (laparoscopy)" only. Trials where the diagnosis was made by techniques other than direct visualisation were excluded. Trials where GnRHa is administered in post-surgical participants as adjuvant therapy was also specifically stated to be excluded in this current review.

Numerous modifications have been made under 'Type of Interventions'. The review published in 1999 compared GnRHa, any dosage or route of administration, with no treatment, placebo, danazol, gestrinone, progestogens, combined oral contraceptive pill, surgical ablation of endometriotic deposits, surgical treatments that purport to interrupt neural pathways (e.g. LUNA), combination of GnRHas and hormone replacement therapy, and another GnRHa. Treatments designed only to achieve relief of symptoms such as treatment with non-steroidal anti-inflammatory drugs or other analgesics were not considered. The current review has removed GnRHas comparisons with gestrinone, progestogens (Prentice 2000), combined oral contraceptive pill (Davis 2007), and combination of GnRHas and hormone replacement therapy as they are described under separate reviews. The current review limited comparisons of GnRHas with other medical therapies only and excluded comparisons with any surgical intervention (Jacobson 2009). Since the main objective of the review was to look at the effectiveness and safety of GnRHas in treatment of endometriosis-associated painful symptoms, trials that compared GnRHas with other analgesics would have been considered but no trials were identified. The current review also considered trials which compared GnRHas with the relatively new levonorgestrel but excluded trials that compared GnRHas with GnRH antagonists as that is a registered title of a review to be conducted by the Menstrual Disorders and Subfertility Group of Cochrane Collaboration.Trials that compared one type of GnRHa with another were excluded as that would not have contributed towards the objective, instead trials which compared different dosages, length of treatment, routes of administration, and treatment regimes of GnRHas were considered.

Outcomes of pain relief, adverse effects and resolution of endometriotic implants were considered in both reviews. Quality of life and the additional use of analgesics were additional outcomes that were considered in the current review. Cost-effectiveness was specifically stated as an outcome not considered in the current review.

Risk of bias. Funnel plot to be conducted if eight or more studies included has been altered to 10 or more studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [therapeutic use]; Drug Administration Routes; Dysmenorrhea [drug therapy]; Dyspareunia [drug therapy]; Endometriosis [*drug therapy]; Estrogen Antagonists [therapeutic use]; Gonadotropin-Releasing Hormone [*analogs & derivatives]; Levonorgestrel [therapeutic use]; Pain [*drug therapy]; Pelvic Pain [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans