Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density

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Title

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Reviewers

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Internal sources of support

University of Cambridge, UK
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None

Contribution of reviewers

Andrew Breeze: Developed the protocol, extracted and entered data in the first phase of work on the review

Jessica Farmer: Screened titles and abstracts to assess whether the studies met the inclusion criteria, extracted data from the included trials, entered data from the included studies and wrote the majority of the results and discussion sections

Andrew Prentice: Developed the protocol and revised final drafts of the review

Mette Sagsveen: Screened titles and abstracts to assess whether the studies met the inclusion criteria, extracted data from the included trials, entered data from the included studies, contacted study authors for additional information and wrote parts of the results and discussion sections

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Potential conflict of interest

None known

Abstract

Background

Gonadotrophin-releasing hormone analogues (GnRHas) are generally well tolerated, and are effective in relieving the symptoms of endometriosis (Prentice 2003). Unfortunately the low oestrogen state that they induce is associated with adverse effects including an acceleration in bone mineral density (BMD) loss.

Objectives

To determine the effect of treatment with gonadotrophin-releasing hormone analogues (GnRHas) on the bone mineral density of women with endometriosis, compared to placebo, no treatment, or other treatments for endometriosis, including GnRHas with add-back therapy.

Search strategy

We searched the Cochrane Menstrual Disorders and Subfertility Group's specialised register of controlled trials (23rd October 2002) and the Cochrane Central Register of Controlled Trials (Cochrane Library, issue 4, 2002). We also carried out electronic searches of MEDLINE (1966 - March Week 2 2003) and EMBASE (1980 - March Week 2 2003). We also searched the reference lists of articles and contacted researchers in the field.

Selection criteria

Prospective, randomised controlled studies of the use of GnRHas for the treatment of women with endometriosis were considered, where bone density measurements were an end point. The control arm of the studies was either placebo, no treatment, another medical therapy for endometriosis, or GnRHas with add-back therapy.

Data collection & analysis

Two reviewers (JF and MS) independently assessed trial quality and extracted data. Study authors were contacted for additional information.

Main results

Thirty studies involving 2,391 women were included, however only 15, involving 910 women, could be included in the meta-analysis. The meta-analysis showed that danazol and progesterone + oestrogen add-back are protective of BMD at the lumbar spine both during treatment and for up to six and twelve months after treatment, respectively. Between the groups receiving GnRHa and the groups receiving danazol/gestrinone, there was a significant difference in percentage change of BMD after six months of treatment, the GnRH analogue producing a reduction in BMD from baseline and danazol producing an increase in BMD (SMD -3.43; 95 % CI -3.91 to -2.95). Progesterone only add-back is not protective; after six months of treatment absolute value BMD measurements of the lumbar spine did not differ significantly from the group receiving GnRH analogues (SMD 0.15; 95 % CI -0.21 to 0.52). In the comparison of GnRHa versus GnRHa + HRT add-back, that is oestrogen + progesterone or oestrogen only, there was a significantly

bigger BMD loss in the GnRHa only group (SMD -0.49 95 % CI -0.77 to -0.21). These numbers reflect the absolute value measurements at the lumbar spine after six months of treatment. Due to the small number of studies in the comparison we are unable to conclude whether calcium-regulating agents are protective. No difference was found between low and high dose add-back regimes but again only one study was identified for this comparison. Only one study comparing GnRH analogues with placebo was identified, but the study gave no data. No studies comparing GnRH with the oral contraceptive pill (OCP) or progestagens were identified.

Reviewers' conclusions

Both danazol and progesterone + oestrogen add-back have been shown to be protective of BMD, while on treatment and up to six and 12 months later, respectively. However, by 24 months of follow-up there was no difference in BMD in those women who had HRT add-back. Studies of danazol versus GnRHa did not report long-term follow-up. The significant side effects associated with danazol limit its use.

Background

Endometriosis is a common gynaecological condition, affecting an unknown proportion of pre-menopausal women. Endometriosis occurs when endometrial tissue, which is normally only found in the lining of the womb, appears in other parts of the body, such as the ovaries, Fallopian tubes, pelvis and bowel. The condition is oestrogen-dependent, and while the removal of both ovaries has long been known to provide permanent relief of symptoms (Graves 1925), in women of child-bearing potential, this is often not an acceptable option. Medical therapies, therefore, aim to have the same effect as removing the ovaries, but in a reversible fashion, with the aim of reducing circulating levels of oestrogens, allowing the endometriotic deposits to become inactive, and alleviating symptoms.

One of the treatments for endometriosis is gonadotrophin-releasing hormone analogues (GnRHas), which work by inducing a temporary menopause-like state, with very low levels of circulating oestrogens. GnRH analogues are generally well tolerated by women and are effective agents for relieving the symptoms of endometriosis (Prentice 2003). Although generally well tolerated, some women experience adverse effects such as hot flushes, vaginal dryness and loss of libido due to the oestrogen deficiency. Unfortunately, one of the other side-effects of low oestrogen levels is an acceleration of bone mass loss, as seen following the menopause (Nilas 1987; Christiansen 1993). This is significant as it could put these women at increased risk of fractures or developing osteoporosis. Oestrogen in pre-menopausal women prevents resorption of calcium from the bones, maintaining bone mineral density. Once oestrogen levels are lowered at the time of menopause, either natural or induced, this protective effect is lost, and the loss of bone density accelerates. Other treatments for endometriosis also reduce oestrogen levels, and there is some evidence that some of them have a similar effect on bone density, for example medroxyprogesterone acetate (Depo Provera) (Cundy 1991). Danazol has some androgenic properties, which help to conserve bone density, as do other therapies, such as norethisterone and gestrinone. However, the significant androgenic side effects (for example hirsutism and acne) and adverse effects on lipid profile associated with danazol limit its usefulness as a first line treatment for endometriosis (Selak 2003). Common side effects of danazol use are weight gain, acne, hirsutism, oily skin and hair, myalgia (muscle pain) and headache (Henzl 1990; Miller 1990; Rock 1993).

There has been some debate that the bone density of women with endometriosis who are not being treated is less than that of their healthy counterparts. However, with the exception of one study (Comite 1989), this has not been shown to be the case (Dodin 1991; Lane 1991). Lane compared 85 women with laparoscopically proven endometriosis with 52 women who were of a similar age, had regular menstrual cycles, and no major medical problems. No differences were found between the bone mineral density of the two groups. Dodin compared 26 women with endometriosis with 26 similar, healthy women, and again found no difference in their bone mineral densities. It would seem reasonable to suppose, therefore, that if the bone density of women with endometriosis is found to have decreased after a course of treatment for endometriosis, it is a side-effect of the treatment that is the cause, rather than the disease itself.

In recent years, so-called "add-back" therapy has been used to alleviate the side effects of GnRH analogues, which are both temporary, for example hot flushes, loss of libido (sex drive), and possibly permanent -i.e. the loss of bone density. Add-back therapy means adding hormones or non-hormonal substances to the GnRHa treatment in order to avoid some of these side effects caused by the GnRHa-induced suppression of oestrogen. Hormones used as add-back are

progesterone alone, oestrogen alone or a combination of oestrogen and progesterone. Examples of non-hormonal add-back regimes are vitamin D, calcitonin and parathyroid hormone (PTH). The dosage, duration and type of add-back therapy varies. It is often in the form of hormone replacement therapy, but there have also been studies of GnRH analogues in combination with various agents influencing calcium metabolism in bones. This review seeks to examine the effects on bone density of GnRH analogues treatment.

Objectives

To determine the effects of GnRH analogues on the bone mass density of women with endometriosis, we have tested the following hypotheses

1. That treatment with GnRH analogues causes a greater loss of bone mineral density than placebo or no treatment.

2. That treatment with GnRH analogues causes a greater loss of bone mineral density than treatment with danazol

3. That treatment with GnRH analogues causes a greater loss of bone mineral density than treatment with progestagens.

4. That treatment with GnRH analogues causes a greater loss of bone mineral density than treatment with the oral contraceptive pill.

5. That treatment with GnRH analogues alone causes a greater loss of bone mineral density than treatment with GnRH analogues plus hormone replacement therapy.

6. That treatment with GnRH analogues causes a greater loss of bone mineral density than treatment with GnRH analogues plus calcium-regulating agents.

7a. That administration of GnRH analogues intramuscularly causes a greater loss of bone mineral density than if they were administered sub-cutaneously.

7b. That administration of GnRH analogues sub-cutaneously causes a greater loss of bone mineral density than if they were administered intra-nasally.

7c. That administration of GnRH analogues intramuscularly causes a greater loss of bone mineral density than if they were administered intra-nasally.

8. That the bone density loss in women treated with GnRH analogues is reversible once treatment has finished.

Criteria for considering studies for this review

Types of studies

All prospective, randomised controlled studies comparing GnRH analogues with placebo, no treatment or other medical therapies for the treatment of women with endometriosis were considered for inclusion. Open studies as well as double-blind studies were considered, since it is

difficult to blind either investigators or participants when GnRHa treatment causes menstrual periods to stop, while placebo, or another treatment may not. Studies including participants being treated for a mixed group of benign gynaecological conditions were included providing that the group of women contained some with endometriosis and that the treatment regimen was consistent across groups and was treatment aimed at the management of endometriosis.

Types of participants

Premenopausal women suffering from endometriosis diagnosed visually by laparoscopy or laparotomy, or presumptively, from symptom history.

Types of interventions

Gonadotrophin-releasing hormone analogues versus placebo, no treatment, danazol, progestagens, the oral contraceptive pill (OCP), GnRH analogues plus hormonal or non-hormonal add-back, and GnRH analogues plus calcium-regulating agents were considered. Trials comparing GnRH analogues given by different administration routes were also considered. Only trials where the treatment period exceeded six months were considered for inclusion. The reason for this decision is that shorter treatment periods do not seem to treat the disease effectively (Audebert 1998).

Types of outcome measures

The objective measurement of bone density was considered. Any method of measurement was considered - methods used to measure bone mineral density are dual-energy photon absorptiometry (DPA), dual-energy x-ray absorptiometry (DXA) single-energy photon absorptiometry (SPA), single-energy x-ray absorptiometry (SXA) and quantitative computed tomography (QCT). Measurements taken at the lumbar spine and femoral head were considered, whilst those at the distal forearm were excluded because here measurements are of cortical bone which is less affected by GnRHa therapy (Whitehouse 1990; Ylikorkala 1990). Bone density measurements at the end of treatment and in the follow-up period were included. Measurements were grouped according to the anatomical location of measurements and the timing of measurements.

Search strategy for identification of studies

The review drew on the search strategy developed for the Menstrual Disorders and Subfertility group. We searched the Cochrane Menstrual Disorders and Subfertility Group's specialised register of controlled trials (23rd October 2002) and the Cochrane Central Register of Controlled Trials (Cochrane Library, issue 4, 2002). We also carried out electronic searches of MEDLINE (1966 - March week 2, 2003) and EMBASE (1980 - March week 2, 2003).

The following Medical Subject headings (MeSH terms) and all combinations of these words were used: terms included endometriosis, bone mineral density, gonadotrophin-releasing hormone analogue, buserelin, goserelin, leuprorelin, leuprolide, triptorelin, nafarelin and add-back therapy.

We also searched the reference lists of articles and contacted researchers in the field.

Methods of the review

SELECTION OF STUDIES

The review was undertaken by two reviewers (JF and MS). The search strategy described previously was employed to obtain titles, and, where possible, abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened by JF and MS, who discarded studies that were clearly ineligible but aimed to be overly inclusive rather than risk losing relevant studies. Copies of the full articles were obtained. Both reviewers independently assessed whether the studies met the inclusion criteria. Disagreements were resolved by referring to an expert in the field (Professor C. Farquhar) for discussion. Further information was sought from the authors where papers contained insufficient information to make a decision about eligibility.

QUALITY ASSESSMENT

The quality of all studies that were deemed eligible for the review was then assessed independently by the two reviewers, with discrepancies being resolved as above. The quality of allocation concealment was graded as either adequate (A), unclear (B) or inadequate (C), following the detailed descriptions of these categories provided by the Cochrane Menstrual Disorders and Subfertility Group. Other aspects of study quality, including the extent of blinding, whether the groups were comparable at baseline, the extent of losses to follow-up, non-compliance and whether the outcome assessments were standardised, were assessed using a standard checklist developed by the Menstrual Disorders and Subfertility Review Group. This information was presented in a table describing the included studies, and provides a context for discussing the reliability of the results.

DATA EXTRACTION

Having decided on studies to include, JF and MS independently extracted information from them using the proformas designed by the review group. Discrepancies were resolved by discussion. For each included trial, information was collected regarding the location of the study, methods of the study (as per the quality assessment checklist), the participants (age range, eligibility criteria), the nature of the interventions, and data relating to the outcomes specified above. Where possible, missing data was sought by the authors. Additional information was received from Miss Karen Bancroft (Whitehouse 1990), Dr Patrycja Fiegler (Kaminski 2001), Dr Henk Franke (Franke 2000), Dr Christian Gnoth (Gnoth 1999), Dr Milan Henzl (Henzl 1990), Professor Kamran Moghissi (Moghissi 1996) , Dr Christian Roux (Roux 1995), Dr Markus Seibel (Sillem 1999), Dr Eric Surrey (Surrey 1992) and Professor Olavi Ylikorkala (Ylikorkala 1990). Responses were received from Dr Joel Finkelstein (Finkelstein 1994) and Dr John Rock (Rock 1993).

ANALYSIS

Statistical analyses were performed according to the statistical guidelines for reviewers in the Menstrual Disorders and Subfertility Review Group. All outcomes were continuous. Standard mean differences were used for comparisons because many different methods were used to measure bone mineral density. Although the different methods gave different absolute values, they conceptually measured the same parameter. Different methods of measuring bone density were thus considered together and not subjected to separate sub-group analysis. When there were

multiple treatment arms in a study with a common control the control numbers were divided equally between the arms. If the control group contained an uneven number of participants (as was the case with Hornstein 1998) so that numbers could not be equally divided then the analysis was done in both ways to detect possible differences in the results caused by an unequal division of the numerator and denominator. Heterogeneity in the data was noted and cautiously explored using previously identified characteristics of the studies, particularly assessments of quality. Sensitivity analyses were undertaken to examine the viability of the results in relation to a number of factors including study quality and the source of the data (published or unpublished). See Review Group module details for more information.

CHANGES TO THE ORIGINAL PROTOCOL

Prior to data extraction the reviewers agreed to leave out studies measuring bone mineral density at the forearm/radius and calcaneus. The reason for this decision is that turnover of cortical bone is approximately one eighth of trabecular bone and therefore the effects of GnRH agonists are more profound in trabecular than cortical bone in time periods studied (Dawood 1989; Ylikorkala 1990). At this point we also decided to include only trials where the treatment period exceeded six months. The reason for this decision is that shorter treatment periods do not seem to treat the disease effectively (Audebert 1998).

TIMELINE

It is the intention of the reviewers that a new search for trials will be carried out every two years and the review updated accordingly.

Description of studies

Seventy-seven documents were found with the adopted search strategy. Twenty-four were directly excluded as their title and abstract did not meet the basic inclusion criteria. Fifty-three were identified which could potentially provide data about the effect of gonadotrophin-releasing hormone analogues on bone mineral density. Further evaluation based on the inclusion criteria showed 30 trials eligible for inclusion in this review. Altogether 23 studies were excluded. Full agreement between the two researchers was obtained concerning inclusion or exclusion of trials.

EXCLUDED STUDIES

Twenty-three studies failed to meet the inclusion criteria for reasons outlined in the table of excluded studies.

INCLUDED STUDIES

Thirty studies have been included and reviewed in detail. See the table of included studies for details.

PARTICIPANTS

The included studies comprised 2,391 women having BMD measurements. Results from 910 women are reported in the meta-analysis. All women included were premenopausal with an age range of 20 - 44 years. All women with endometriosis had been diagnosed or confirmed laparoscopically. One trial also included women with unexplained menorrhagia (heavy menstrual bleeding) (Eldred 1992), and two trials included women with fibroids (Lindsay 1996; Mukherjee

1996). Trials used varying inclusion and exclusion criteria: Three trials (Kiesel 1996; Lindsay 1996; Franke 2000) included women depending upon their American Fertility Society (AFS) score although the score cut-off varied from >2 to >5. Surrey 1992 and Gregoriou 1997 excluded women who had fewer than four visible endometriotic lesions. Several trials excluded women who were taking drugs known to affect bone metabolism (Eldred 1992; Fukushima 1993; Howell 1995; Roux 1995; Lindsay 1996; Mukherjee 1996; Gregoriou 1997) or women with diseases that would affect bone metabolism (Dodin 1991; Fukushima 1993; Howell 1995; Mukherjee 1996; Gregoriou 1997). Other trials excluded women who were taking particular medications that could effect bone mineral density. See the table of included studies for further details.

For other inclusion and exclusion criteria see the table of included studies.

INTERVENTIONS

The following interventions were tested in the included trials: GnRH analogue vs placebo (one trial; Miller 1990), GnRH analogue vs danazol or gestrinone (nine trials; Henzl 1990; Miller 1990; Whitehouse 1990; Dodin 1991; Chan 1993; Fukushima 1993; Rock 1993; Dawood 1995; Vercillini 1996), GnRH analogue vs GnRH analogue + progesterone-only hormonal add-back (four trials; Surrey 1992; Kiesel 1996; Hornstein 1998; Sillem 1999), GnRH analogue vs GnRH analogue + oestrogen and progesterone or oestrogen-only add-back (11 trials; (Edmonds 1994; Howell 1995; Vella 1995; Lindsay 1996; Moghissi 1996; Gregoriou 1997; Hornstein 1998; Gnoth 1999; Aisaka 2000; Franke 2000; Irahara 2000), GnRH analogue vs GnRH analogue + calcium-regulating agents (three trials; Roux 1995; Mukherjee 1996; Somekawa 1999) GnRH analogue + add-back vs GnRH analogue + add-back (high dose) (three trials; Eldred 1992; Moghissi 1996; Hornstein 1998), GnRH analogue (3-monthly administration) versus GnRH analogue (1-monthly preparation) (one trial; Crosignani 1996). Tibolone, a synthetic steroid, is here grouped together with the oestrogen only/oestrogen + progesterone add-back as it exhibits oestrogenic, progestagenic and androgenic activity (Lindsay 1996). No trials comparing depot GnRH analogues vs intranasal GnRH analogues were obtained. Neither were any trials comparing GnRH analogues vs the oral contraceptive pill or progestagens obtained. See table of included studies for further details.

OUTCOMES

All trials measured bone mineral density (BMD). Methods for measuring BMD were Dual energy x-ray absorptiometry (DEXA) (16 trials), Dual energy photon absorptiometry (DPA) (three trials), Single energy photon absorptiometry (SPA) (three trials), Quantitative Computerised Tomography (QCT) (three trials). Five trials used more than one method of BMD measurements. Three trials failed to mention the method of bone mineral density measurement (Chan 1993; Vella 1995; Kiesel 1996). These authors have been contacted and we are awaiting responses. The sites for measuring bone mineral density used in the trials were lumbar spine and hip (femoral neck, Ward's triangle, trochanteric area and intertrochanteric area). See the table of included studies for further details.

Methodological quality of included studies

See Table 01 "Quality of Included Studies" for a summary of the methodological quality of included trials.

RANDOMISATION AND ALLOCATION CONCEALMENT

Ten studies had adequate randomisation. Four of these studies randomised by code (Eldred 1992; Dawood 1995; Lindsay 1996; Vercillini 1996), one randomised according to a computer-generated sequence (Crosignani 1996), three randomised by a centralised scheme (Roux 1995; Gnoth 1999; Sillem 1999), one randomised with sealed, opaque, sequentially numbered, identical envelopes (Franke 2000) and one stated that cases were sequentially numbered (Whitehouse 1990).

In twenty studies the adequacy of the method of randomisation was unclear. Sixteen of these studies stated that the trial was randomised but gave no further details, whereas one study randomised by sequential numerical allocation to a randomisation list before commencing the trial (Gregoriou 1997), one study randomised by permuted blocks of four at each of the 26 study sites (Hornstein 1998), one study randomised by lottery (Mukherjee 1996) and one study randomised to therapeutic groups based on order of entry, and not severity of disease (Surrey 1992). None of the studies used clearly inadequate methods of randomisation.

In twenty-five studies it was unclear whether the allocation concealment was adequate or not. Five studies had clearly adequate allocation concealment. One study (Franke 2000) used sealed, opaque, sequentially numbered, identical envelopes, another study used computerised allocation (Surrey 1992), whilst the last three studies (Roux 1995; Gnoth 1999; Sillem 1999) stated that they used a centralised randomisation process.

STUDY DESIGN

There were 15 single centre studies and 15 multi centre studies. All trials that did not state that they were multi centre were counted as single centre.

BLINDING

There were five open label studies, two single blinded studies (in both it was the assessor of bone mineral density that was blinded), 17 double-blind studies and one triple blind study. Five studies did not state any information on blinding. We have contacted the authors of these studies and are currently awaiting replies.

POWER CALCULATION

Twenty-six trials did not mention power calculations. Four trials had performed power calculations. Hornstein 1998 stated that "the initial sample size was chosen to ensure an 80 % power to detect a difference between any two dosing regimens with regard to mean percentage bone loss. Calculation was not performed to take into account dropout during follow-up." Moghissi 1996 stated that the sample size had adequate power to detect a 2 % difference in the percentage change in bone mineral density. Mukherjee 1996 stated that the trial had an 80 % power to detect a 10 % change with an alfa level of 0.05. Vercillini 1996 stated that "a post hoc analysis of our data indicated that, assuming an alpha level of 0.05, our study had a power of 89 % for the difference in bone mineral density variations at the end of treatment."

SOURCES OF FUNDING
Crosignani 1996 - Takeda Italia Farmaceutici, Italy
Dawood 1995 - TAP Pharmaceuticals
Dodin 1991 - ICI Pharma, Canada
Eldred 1992 - Syntex Research Europe
Franke 2000 - Astra Zeneca and Novo Nordisk
Henzl 1990 - Syntex Research, Palo Alto, California, USA
Hornstein 1998 - TAP Pharmaceuticals
Howell 1995 - Zeneca Pharmaceuticals
Lindsay 1996 - Organon International, the Netherlands
Miller 1990 - TAP Abbott Research and Development
Moghissi 1996 - Zeneca Pharmaceuticals, Delaware, USA
Mukherjee 1996 - Depot Lupron supplied by TAP Pharmaceuticals
Rock 1993 - ICI Pharmaceuticals Group, a business unit of Zeneca Inc, Delaware, USA
Surrey 1992 - TAP Pharmaceuticals , Illinois, USA
Vercillini 1996 - Poli Industria Chimica, Italy

Results

1) GNRH ANALOGUES VS PLACEBO
Only one study (Miller 1990 study 1) was identified for this comparison, but the study gave no data.

2) GNRH ANALOGUES VS DANAZOL/GESTRINONE
Nine studies were identified for this comparison. Three studies (Henzl 1990; Chan 1993; Rock 1993) did not provide sufficient data for the meta-analysis. We are awaiting responses from these authors. The results from the six studies with sufficient data are presented below, together with some comments on the findings in the trials not included in the meta-analysis. Chan 1993 is not mentioned as the trial did not report any clear results.

a) Lumbar spine - after six months treatment - absolute values
Three studies (Whitehouse 1990; Dodin 1991; Fukushima 1993) reported absolute values of bone mineral density at the lumbar spine after six months of treatment. The summary statistic showed a significant difference between the two treatments with GnRHa groups having a significantly lower absolute BMD than danazol groups (SMD -1.17 95% CI -1.73 to -0.62).

b) Lumbar spine - after six months treatment - percentage change
Four studies (Miller 1990; Whitehouse 1990; Dawood 1995; Vercillini 1996) reported percentage change of bone mineral density at the lumbar spine after six months treatment. The summary statistic showed a significant difference between the two treatments with the danazol/gestrinone groups having a percentage increase from baseline whilst the GnRHa showed a percentage decrease from baseline (SMD -1.12 95% CI -1.38 to -0.86). When a sensitivity analysis was performed, removing Vercillini 1996, the only study in this comparison that used gestrinone rather than danazol, there was still a significant difference between treatments (SMD -1.14 95% CI -1.42 to -0.85). Also, removing the trials that measured BMD using QCT (Miller 90 Study2

QCT; Whitehouse 1990; Dawood 1995) there was still a significant difference between the groups (SMD -0.96 95% CI -1.23 to -0.69).

These findings are supported by Rock 1993 who states that mean bone mineral density of the lumbar spine decreased from baseline in the GnRHa group and increased in the danazol group at the end of six months of treatment. The findings are not supported by Henzl 1990 as his results suggest no significant bone mineral density loss between danazol and GnRHa treatment groups.

c) Femoral neck - after six months treatment - absolute values
One study (Dodin 1991) reported absolute values of bone mineral density at the femoral neck after six months of treatment. This study showed a statistically significant difference between the two treatments, with the GnRH analogue group having a significantly lower bone mineral density than the danazol group (SMD -1.05 95% CI -1.95 to -0.14).

d) Femoral neck - after six months treatment - percentage change
One study (Miller 90 study2 DPA) reported percentage change of bone mineral density at the femoral neck after six months of treatment. This study showed no statistically significant difference between treatments (SMD -0.31 95% CI -0.78 to 0.16).

e) Lumbar spine - follow -up after six months treatment and six months follow-up - absolute values
Two studies (Dodin 1991; Fukushima 1993) reported absolute values of bone mineral density at the lumbar spine after six months of treatment and six months of follow-up. The summary statistic showed a significant difference between the two treatments - GnRH analogue group bone mineral density being significantly lower than the danazol group bone mineral density (SMD -1.42 95% CI -2.20 to - 0.63).

f) Lumbar spine - follow-up after six months treatment and six months follow-up - percentage change
Two studies (Dawood 1995; Vercillini 1996) reported percentage change of bone mineral density at the lumbar spine after six months of treatment and six months of follow-up. The summary statistic showed a significant difference between the two treatments with the danazol/gestrinone groups having a percentage increase in BMD from baseline and the GnRHa groups having a percentage decrease from baseline (SMD -1.27 95% CI -1.89 to -0.65). When a sensitivity analysis was performed, removing Vercillini 1996 (which used gestrinone rather than danazol) the result remained significant (SMD -3.13 95% CI -5.04 to -1.23).

g) Femoral neck - follow-up after six months treatment and six months follow-up - absolute values
One study (Dodin 1991) reported absolute values of bone mineral density at the femoral neck after six months of treatment and six months of follow-up. This study showed no statistically significant difference between treatments (SMD -0.52 95% CI -1.69 to 0.64).

3) GNRH ANALOGUES VS GNRH ANALOGUES + ADD-BACK (PROGESTERONE ONLY)

Four studies were identified for this comparison. One (Kiesel 1996) of these did not provide sufficient data. The authors have been contacted and we are still awaiting the reply. The results from the meta-analysis of the other three studies are presented below. These results are supported by Kiesel 1996. See the additional table "descriptive data for trials not included in the meta-analysis" for more information.

a) Lumbar spine - after six months of treatment - absolute values
Two studies (Hornstein 1998; Sillem 1999) reported absolute values of bone mineral density at the lumbar spine after six months of treatment. The summary statistic showed no difference between the two treatments (SMD -0.06 95% CI -0.45 to 0.32).

b) Lumbar spine -after twelve months of treatment - absolute values
One study (Hornstein 1998) reported absolute values of bone mineral density at the lumbar spine after twelve months of treatment. This study showed no statistical difference between the two treatments (SMD -0.40 95% CI -0.91 to 0.11).

c) Femoral neck - after six months of treatment - absolute values
One study (Sillem 1999) reported absolute values of bone mineral density at the femoral neck after six months of treatment. This study showed no statistical difference between the two treatments (SMD 0.11 95% CI -0.71 to 0.93).

d) Lumbar spine - after six months of treatment - percentage change
One study (Surrey 1992) reported percentage change of BMD at the lumbar spine after six months of treatment. This study showed there was a statistical difference between the two treatments (SMD -1.07 95% CI -2.03 to -0.12) favouring GnRHa + progesterone.

e) Lumbar spine -follow-up after twelve months treatment and twelve months follow-up - percentage change
One study (Hornstein 1998) reported percentage change from baseline of bone mineral density at the lumbar spine after twelve months of treatment and twelve months of follow-up. This study showed no statistical difference between the two treatments (SMD -0.66 95% CI -1.44 to 0.13).

f) Lumbar spine - follow-up after twelve months treatment and twenty-four months follow-up - percentage change
One study (Hornstein 1998) reported percentage change from baseline of bone mineral density at the lumbar spine after twelve months of treatment and twenty-four months of follow-up. This study showed no statistical difference between the two treatments (SMD -0.89 95% CI -2.25 to 0.47).

4) GNRH ANALOGUES VS GNRH ANALOGUES + ADD-BACK (OESTROGEN AND PROGESTERONE/ OESTROGEN ONLY
Eleven studies were identified for this comparison. However, seven (Edmonds 1994; Howell 1995; Vella 1995; Moghissi 1996; Gregoriou 1997; Aisaka 2000; Irahara 2000) did not provide data of sufficient quality to be entered into the meta-analysis. These authors have been contacted for further data and we are awaiting replies. The results from the four studies with sufficient data

are presented below. Tibolone, a synthetic steroid, is grouped together with the oestrogen and progesterone/ oestrogen only add-back as it exhibits estrogenic, progestagenic and androgenic activity.

a) Lumbar spine - after six months of treatment - absolute values
Four studies (Lindsay 1996; Hornstein 1998; Gnoth 1999; Franke 2000) reported absolute values of bone mineral density at the lumbar spine after six months of treatment. The summary statistic showed a significant difference between GnRH analogue and GnRH analogue + oestrogen and progesterone groups with the bone mineral density of the GnRHa + add-back group being significantly higher than the BMD of the GnRHa only group (SMD -0.49 95% CI -0.77 to -0.21). We performed sensitivity analyses, taking out Lindsay 1996 which used tibolone as add-back, and Hornstein p + ld o since all the other studies used high dose add-back. When these studies were taken out separately and together the summary statistic remained significant (with Lindsay 1996 removed SMD -0.40 95% CI -0.70 to -0.10, with Hornstein p + ld o removed SMD -0.58 95% CI -0.90 to -0.25 and with both studies removed SMD -0.46 95% CI -0.82 to -0.09).

b) Lumbar spine - after twelve months of treatment - absolute values
One study (Hornstein 1998) reported absolute values of bone mineral density at the lumbar spine after twelve months of treatment. The summary statistic showed a significant difference between the two treatments with the bone mineral density of the GnRHa + add-back group being significantly higher than that of the GnRHa only group (SMD -0.56 95% CI -1.02 to -0.10).

c) Femoral neck - after six months treatment - absolute value
Two studies (Lindsay 1996; Gnoth 1999) reported absolute values of bone mineral density at the femoral neck after six months of treatment. The summary statistic showed no difference between the two treatments (SMD -0.09 95% CI -0.61 to 0.42).

d) Lumbar spine - after twelve months treatment and twelve months follow-up - percentage change
One study (Hornstein 1998) reported percentage change of bone mineral density at the lumbar spine after twelve months of treatment and twelve months of follow-up. This study had two treatment arms with oestrogen + progesterone add-back (as described above). In order to include both treatment arms in the meta-analysis we assigned half the GnRHa only group to each treatment arm. The summary statistic showed a significant difference between the two treatments with GnRHa only producing a significantly greater percentage reduction in bone mineral density from baseline than the GnRHa + oestrogen and progesterone add-back groups (SMD -1.19 95% CI -1.88 to -0.51).

e) Lumbar spine - after twelve months treatment and twenty-four months follow-up - percentage change
One study (Hornstein 1998) reported the percentage change of bone mineral density at the lumbar spine after twelve months of treatment and twenty-four months of follow-up. The summary statistic showed no significant difference between the two treatments (SMD -0.66 95% CI -1.90 to 0.59).

The results suggesting that there is a significant difference between the treatment groups, favouring GnRHa + add-back, are supported by the studies not included in the meta-analysis. See table "descriptive data for trials not included in the meta-analysis" for more details.

5) GNRH ANALOGUES VS PROGESTAGENS
No studies were identified for this comparison.

6) GNRH ANALOGUES VS ORAL CONTRACEPTIVE PILL
No studies were identified for this comparison.

7) GNRH ANALOGUES VS CALCIUM REGULATING AGENTS
Three studies were identified for this group. One study (Mukherjee 1996) did not provide sufficient data to be entered into the meta-analysis.

a) Lumbar spine - after six months treatment - absolute values
One study (Roux 1995) reported absolute values of bone mineral density at the lumbar spine after six months of treatment. The summary statistic showed no difference between the two treatments (SMD 0.22 95% CI -0.43 to 0.88).

b) Femoral neck -after six months of treatment - absolute values

One study (Roux 1995) reported absolute values of bone mineral density at the femoral neck after six months of treatment. The summary statistic showed no difference between the two treatments (SMD 0.26 95% CI -0.40 to 0.91).

c) Lumbar spine - after six months of treatment - percentage change

One study (Somekawa 1999) reported the percentage change from baseline of bone mineral density at the lumbar spine after six months of treatment. This study had three treatment arms of GnRHa + calcium-regulating agent - one group received oral metatetrenone (vitamin K) 45 mg per day, one group received oral 1, 25 $(OH)^2$ - D^3 0.5 mg per day and the last group received oral metatetrenone 45 mg per day + oral 1, 25 $(OH)^2$ - D^3 0.5 mg per day. The summary statistic showed a significantly greater percentage reduction in bone mineral density from baseline with the GnRHa only groups when compared to the GnRHa + calcium-regulating agent groups (SMD -2.47 95% CI -3.05 to -1.89).

The study not included in the meta-analysis, Mukherjee 1996, reported that GnRHa treatment produced a significant decrease in bone density at the anteroposterior and lateral spine, whilst no significant change was demonstrated in etidronate-treated patients.

8) GNRH ANALOGUES (MONTHLY PREPARATION) VS GnRH ANALOGUES (3-MONTHLY PREPARATION)
One study (Crosignani 1996) was identified for this comparison. The trial stated a statistically significant variation of lumbar spine bone mineral density observed at the end of GnRHa

treatment in both study groups (P<0.01), the percentage decrease over basal being 5.2 % and 4.9 % respectively. But the study did not provide sufficient data for comparison of the groups, so we contacted the authors and are still awaiting a reply.

9) GNRH ANALOGUE DEPOT VS GNRH ANALOGUE INTRANASALLY (IN)
No studies were identified for this comparison.

10) GNRH ANALOGUES + LOW DOSE HRT VS GNRH ANALOGUES + HIGH DOSE HRT
Three studies were identified for inclusion into this group. However, two (Eldred 1992; Moghissi 1996) did not provide sufficient data to be entered into the meta-analysis. The authors of these studies have been contacted and we are awaiting further data. The results of the one study that did provide sufficient data for the meta-analysis are presented below.

a) Lumbar spine - after six months treatment - absolute values
One study (Hornstein 1998) reported absolute values of bone mineral density at the lumbar spine after six months of treatment. This study showed no significant difference between the two treatments (SMD -0.08 95% CI -0.52 to 0.36).

b) Lumbar Spine - after twelve months of treatment - absolute values
One study (Hornstein 1998) reported absolute values of bone mineral density at the lumbar spine after twelve months of treatment. This study showed no significant difference between the two treatments (SMD -0.08 95% CI -0.61 to 0.44).

c) Lumbar Spine - after twelve months of treatment and twelve months of follow-up - percentage change
One study (Hornstein 1998) reported absolute values of bone mineral density at the lumbar spine after twelve months of treatment and twelve months of follow-up. This study showed no significant difference between the two treatments (SMD 0.12 95% CI -0.62 to 0.87).

d) Lumbar Spine - after twelve months of treatment and twenty-four months of follow-up - percentage change
One study (Hornstein 1998) reported absolute values of bone mineral density at the lumbar spine after twelve months of treatment and twenty-four months of follow-up. This study showed no significant difference between the two treatments (SMD 0.11 95% CI -1.21 to 1.43).

Both Eldred 1992 and Moghissi 1996 support the finding that there is no significant difference in bone mineral density after GnRHa treatment and either high dose or low dose HRT. See table "descriptive data for trials not included in the meta-analysis" for further details.

Discussion

This review set out to determine the effect of treatment with gonadotrophin-releasing hormone

analogues (GnRHas) on the bone mineral density (BMD) of women with endometriosis, compared to placebo, no treatment or other treatments used for endometriosis. We have only been able to complete part of these objectives because no studies were found comparing GnRHas with no treatment, OCP or progestagens. Unfortunately a large number of our included studies (15 out of a total of 30) did not provide enough data to be entered into the meta-analysis. We have contacted the authors of these studies and are currently awaiting responses. Meanwhile the main findings from these studies have been reported in Table 02 "Descriptive data for trials not included in the meta-analysis."

GNRHA VS DANAZOL/GESTRINONE

Our findings broadly show that treatment with danazol or gestrinone has a protective effect on BMD when compared to treatment with GnRH analogues. After six months of treatment women treated with danazol had a significantly higher absolute value of BMD than GnRHa group women at the lumbar spine. Analysis of BMD percentage change from baseline at the lumbar spine after six months showed that whilst GnRHa groups had a reduction in BMD from baseline, the danazol groups actually had an increase in percentage BMD from baseline. This result was not unexpected, since danazol is known to have a directly suppressive effect on bone resorption presumably because of testosterone (Whitehouse 1990; Dawood 1995; Morgante 1999). At the femoral neck after six months treatment there was found to be no difference in percentage change from baseline between groups. However, this comparison included only one study. Follow-up results, after six months of treatment and six months follow-up, also showed danazol groups to have significantly higher absolute values of BMD and significantly smaller percentage changes from baseline at the lumbar spine when compared to GnRHa groups. At the femoral neck no difference was found between treatments but this comparison included only one study. In conclusion danazol has been shown to be protective of bone mineral density when compared to GnRH analogues. However, the significant androgenic side effects and adverse effects on lipid profile associated with danazol limit its usefulness as a first line treatment for endometriosis (Selak 2003). Common side effects of danazol use are weight gain, acne, hirsutism, oily skin and hair, myalgia and headache (Henzl 1990; Miller 1990; Rock 1993).

GNRHA VS GNRHA + PROGESTERONE ONLY ADD-BACK

The addition of only progesterone to GnRHa therapy is not protective of BMD. All, but one result (Surrey 1992), showed no statistical difference between the two treatment groups, either on treatment or during follow-up off treatment. The reason for the one exception is not clear. The trial states the two treatment groups were similar in terms of mean age and prior therapeutic experience, but more patients with severe endometriosis were randomised to receive GnRHa only. There is evidence that women with endometriosis does not have any different bone mineral density than their healthy counterparts (Dodin 1991; Lane 1991), although we do not know whether BMD changes could be greater the more severe the endometriosis is. In conclusion, progesterone add-back does not have a protective effect on bone mineral density when prescribed with GnRH analogues.

GNRHA VS GNRHA + PROGESTERONE AND OESTROGEN/OESTROGEN ONLY ADD-BACK

This comparison had the highest number of trials that could not be entered into the meta-analysis because of insufficient data (six out of eleven trials in the comparison). The results from studies that did provide adequate data for the meta-analysis show that during treatment the use of progesterone + oestrogen add-back is protective of bone mineral density at the lumbar spine. They also show that twelve months after treatment bone mineral density remains higher in groups that received add-back. The results showed no difference between groups after twenty-four months of follow-up but the number of participants analysed was small (n = 13) and the comparison included only one study so we are unable to draw any firm conclusions based on this result. The results showed no difference in bone mineral density between groups at the femoral neck after treatment, but this comparison included only one study and therefore we are unable to draw any conclusions based on this result.

In conclusion we have found progesterone + oestrogen add-back to be protective of bone mineral density at the lumbar spine both during and after treatment and would therefore recommend the use of this add-back during treatment with GnRH analogues. Also hypoestrogenic side effects of hot flushes and loss of libido were significantly less in the group that received add-back (Edmonds 1994; Howell 1995; Moghissi 1996). This difference between the groups was not seen for vaginal dryness and headaches, though. However it must be noted that the studies included used differing add-back regimes and it is not possible with the evidence available to state which add-back regime is most effective.

GNRHA VS GNRHA + CALCIUM-REGULATING AGENTS (CRA'S)

This comparison was limited by the small number of studies that were found for inclusion (only three studies were found and only two provided enough data for the meta-analysis). All calcium-regulating agents (CRA's) were allocated to the same comparison. However, our results suggest that using different calcium regulating agents as add-back might have differing effects on BMD. Roux 1995 used calcitonin as add-back and the results from this study showed no significant BMD difference between GnRHa only and add-back groups at either the femoral neck or lumbar spine after six months of treatment. However, the results from Somekawa 1999 which used vitamin D and vitamin K add-back did show a significant difference between the percentage change of BMD from baseline in GnRHa only groups and all GnRHa + add-back groups. However, these results do not allow us to draw any solid conclusions about the type of CRA's that should be used in conjunction with GnRHas. They can only be used to suggest that this might be an area for further research.

GNRHA + LOW DOSE HRT VS GNRHA + HIGH DOSE HRT

Our findings show no differences in BMD between GnRHa + low dose HRT and GnRHa + high dose HRT both during treatment and during follow-up. However, this comparison is limited by the inclusion of only one study and we are therefore unable to conclude whether or not use of high-dose HRT is protective of bone mineral density. The adverse effects of HRT make the use of high dose HRT for this purpose unlikely.

METHOD OF BONE MINERAL DENSITY MEASUREMENT

The method of bone mineral density measurement is an important methodological consideration. In this review we have entered data from all methods of BMD measurement. However, there is some suggestion that certain methods of measurement are more accurate than others. It is generally agreed that Single Photon Absorptiometry and Dual Photon Absorptiometry are less accurate methods than Quantitative Computed Tomography (QCT) and the newer method of Dual Energy X-ray Absorptiometry (DEXA) (Whitehouse 1990; Eldred 1992; Uemura 1993). Whilst DEXA and QCT are of about equal clinical value (Wahner 1989), DEXA allows measurement of the femoral head, has a lower radiation dose and is a more precise method, particularly for measurements of the anterior/posterior spine. Because QCT provides a measure of volumetric density, measurements may give an overestimate of actual changes (Wells 2002). In half of the studies included in the meta-analysis measurements were done by DEXA, whilst QCT was used in three, DPA used in two, and two studies used more than one method (QCT and DPA or DEXA and DPA). The method of measurement does not seem to have influenced the results, although it is evident that QCT measurements gave higher percentage changes of BMD. QCT was used in four studies, all in the GnRHa versus danazol/gestrinone group. In a sensitivity analysis removing the studies using QCT, the overall result was not changed; there was still evidence of a significant difference in BMD between GnRHa and danazol/gestrinone groups.

LENGTH OF TREATMENT

As stated in the "changes to the original protocol" section, we only included studies where treatment was given for a minimum of six months. This was because medical treatment less than six months is less likely to cure the women of the disease (Audebert 1998). Only one study (Chang 1996) was excluded due to this change. It is a strength to the review that most of the included studies gave treatment for six months, as this makes the trials easily comparable.

LENGTH OF FOLLOW-UP

Sixteen of the studies did not do any follow-up measurements, ten studies followed up their women for half a year and three studies did one-year follow-up measurements. The longest follow-up was two years, but only one study had this length of follow-up (Hornstein 1998). In the GnRHa versus danazol/gestrinone comparison there was a significant difference during treatment and in the six months follow-up, except from at the femoral neck after six months of treatment and six months of follow-up. What about the longer-term follow-up? If one perhaps could prove that there was no significant difference in bone mineral density on a longer term, women would be spared the androgenic side effects and adverse effects on lipid profile from danazol treatment. In the GnRHa versus GnRHa and progesterone only group the two-year follow-up results are consistent with the results during treatment, as is also the case when comparing low dose HRT to high dose HRT. Comparing GnRHa to GnRHa plus oestrogen and progesterone/oestrogen only add-back, the result changed from significant difference during treatment and at the one year follow-up to non-significant at the two-year follow-up measurement. The fact that not all comparison groups had follow-up measurements, and the ones that did only had a few trials doing follow-up measurements, weakens our results.

Reviewers' conclusions

Implications for practice

Primarily clinicians and women with endometriosis will make decisions about the choice of drug based on their ability to control the symptoms of a disease. In endometriosis the main symptom is pain and women tend to make treatment decisions based on a treatments effectiveness for this condition. A previous review has shown no difference in efficacy between medical treatments for pain associated with endometriosis (Prentice 2003). However if a treatment causes a reduction in bone mineral density then this is a very important side effect since a reduction of one standard deviation (SD) in bone mass is associated with an increase of fifty to one hundred percent in the incidence of fractures (Dawood 1995). Therefore it should be an important consideration when making treatment decisions.

This review has shown that both danazol/gestrinone and progesterone + oestrogen add-back are protective against the reduction of bone mineral density caused by GnRH analogues. However, as danazol is associated with a number of adverse side effects we would recommend the use of progesterone + oestrogen add-back in the treatment of endometriosis. However, two years after treatment is stopped, no difference was seen between the group receiving GnRHa only and the group receiving GnRHa + HRT add-back.

Implications for research

Future research should consider the dose regimens of oestrogen and progesterone add-back therapy, the length of treatment and duration of response. Alternatives to hormone replacement therapy should also be investigated further; particularly calcium-regulating agents.

Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Aisaka 2000	Randomisation: randomised trial Blinding: not stated Design: not stated	Number of women: 53 Diagnosis: not stated Inclusion criteria: not stated Exclusion criteria: not stated Age: not stated Location: Japan	group 1: leuprolin + mestranol 0.05mg and norethisterone 1mg/tab 1 tab/day. group 2: leuprolin alone Duration of treatment: 3 years of leuproline +add-back, then 6 months of leuproline alone Duration of follow-up: none	Outcome: bone mineral density Measured at: Lumbar spine (L1-L4) Method: Dual Energy X-ray Absorptiometry (DEXA) Timing: not stated		B
Chan 1993	Randomisation: randomised trial Blinding: not stated Design: not stated	Number of women: 149 Diagnosis: laparoscopic Inclusion criteria: not stated Exclusion criteria: not stated Age of participants: not stated Location: not stated	group 1: 6 months of gestrinone. group 2: 6 months of danazol and group 3: 4 im injections of tryptorelin. Duration of treatment: 6 months Duration of follow-up: 2 years	Outcome: bone mineral density Measured at: Vertebral spine. Method: not stated Timing: baseline, end of treatment, 6 months post-treatment and 2 years after diagnosis		B
Crosignani 1996	Randomisation: according to a computer-generated sequence Blinding: none - open label trial Design: multicentre trial	Number of women: 30 Diagnosis: laparoscopic Inclusion criteria: premenopausal women aged 18-38, written consent, symptomatic endometriosis stages I-IV of the rAFS Exclusion criteria: major disease Age of participants: 18-38 years Location: Italy	group 1: 3 -monthly depot leuprolide IM 11.25 mg, n=15 group 2: Monthly depot leuprolide IM 3.75 mg, n=15 Duration of treatment: 6 months Duration of follow-up: none	Outcome: bone mineral density Measured at: lumbar spine; L2-L4 Method: DEXA Timing: baseline and end of treatment	1participant from group 1 excluded because she didn't want to undergo venipunctures and follow-up laparoscopy. 1 patient from group 2 stopped therapy at the 3rd month because of desire to conceive. Study sponsored by Takeda Italia Farmaceutici, Italy.	B

Dawood 1995	Randomisation: by code Blinding: double Design: Multicentre, double - dummy trial	Number of women: 12 Diagnosis: laparoscopic Inclusion criteria: no use of specific hormone treatment or oral-contraceptive use in the 6 months before enrolment in the study. No previous use of GnRH analogue. Exclusion criteria: use of contraception other than the barrier method Age: 23 - 39 years Location: USA	group 1: 3.7mg leuprolide acetate monthly injection + oral placebo every day group 2: 800mg danazol orally + monthly placebo injection. Duration of treatment: 24 weeks Duration of follow-up: 12 months	Outcome: bone mineral density Measured at: Lumbar spine (T12 - L4) and lower forearm Method: Quantitative Computerised Tomography (QCT) Timing: base;ome, 6 months, 12 months and 18 months	Trial sponsored by TAP pharmaceuticals	B
Dodin 1991	Randomisation: randomised control trial. Blinding: none - open label trial Design: not stated	Number of women: 26 Diagnosis: laparoscopic Inclusion criteria: Exclusion criteria: oral contraceptive use during the treatment period or for the 6 months after the treatment period, diseases known to affect bone metabolism, pregnancy. Age: 22-37 years Location: Canada	group 1: goserelin implant injected s.c into the anterior abdominal wall every 29 days for 6 months. group 2: Danazol 400mg twice daily administered orally. Duration of treatment: 6 months Duration of follow-up: 6 months	Outcome: bone mineral density Measured at: Femoral neck and lumbar spine (L2-L4) Method: Dual Photon Absorptiometry (DPA) Timing: baseline, after 3 months of treatment, end of treatment, 3 months post-treatment and 6 months post-treatment	3 participants excluded due to oral contraceptive use. Post treatment 8 participants (5 in GnRh group and 3 in danazol group) became pregnant and were therefore excluded. Study sponsored by ICI Pharma Canada	B
Edmonds 1994	Randomisation: randomised control trial Blinding: not stated Design: not stated	Number of women: 50 Diagnosis: laparoscopic Inclusion criteria: significant pelvic pain. Exclusion criteria: no pelvic pain. Age: not stated Location: UK	group 1: goserelin 3.6mg/month as s.c depot. group 2: goserelin 3.6mg per month + 17-oestrodiol 25ug through the skin twice weekly and medroxyprogesterone acetate 5mg/day po. Duration of treatment: 6 months	Outcome: bone mineral density Measured at the lumbar spine, femoral neck and ward's triangle Method: dual energy x ray absorptiometry (DEXA) Timing: baseline, end of treatment, 12 weeks		B

			Duration of Follow-up: 6 months	post-treatment and 24 weeks post-treatment		
Eldred 1992	Randomisation: by code Blinding: double blind Design: multi centre trial	Number of women: 94 Diagnosis: laparoscopic (endometriosis) or unexplained menorrhagia. Inclusion criteria: women with laparoscopically proven endometriosis or unexplained menorrhagia aged 18-46, definite regular menstrual cycle of 22-35 days, plasma FSH concentration < 20 IU/l and plasma LH/FSH ratio less than three in the early follicular phase Exclusion criteria: pregnancy, hormonal treatment or any drug that might effect bone metabolism during the 3 months pre-study, unwillingness to use barrier contraception throughout the study, concurrent disease or abnormality on heamatological and biochemical screening on renal, liver and thyroid function tests or in calcium, phosphorus and alkaline phosphatase test. Age: 23 - 46 years Location: UK	Group 1: Nafarelin 400 ug IN + 0.7mg norethisterone PO daily. Group 2: Nafarelin 400 ug IN+ 1.4 mg norethisterone PO daily. Group 3: Nafarelin 400 ug IN+2.45mg norethisterone PO daily. Group 4: Nafarelin 400 ug IN+placebo. Duration of treatment: 6 months Duration of follow-up: 6 months	Outcome:bone mineral density Measured at: L2-L4 and the distal forearm Method: Single Photon Absorptiometry (SPA) and DPA Timing: baseline, cessation of treatment and 6 months post-treatment	31 women left the study early; 20 because of adverse effects, 4 were lost to follow-up, 4 had unsatisfactory therapeutic response and 3 were non-compliant with protocol. Sponsored by Syntex Research Europe	B
Franke 2000	Randomisation: sealed,	Number of women: 41	group 1: goserelin acetate s.c	Outcome: bone mineral	1 participang in group 1	A

	opaque, sequentially numbered, identical envelopes Blinding: double - blind Design: multicentre trial	Diagnosis: laparoscopic Inclusion criteria: Women included if AFS score > 2 Exclusion criteria: not stated Age: Mean age of group 1 29.9 years and mean age of group 2 31.2 years. Location: The Netherlands	3.6mg every 4 weeks +oral placebo. group 2: goserelin acetate s.c 3.6mg every 4 weeks + 2mg 17ß-E^2 and 1mg norethisterone acetate daily for 24 weeks. Duration of treatment: 24 weeks Duration of follow-up: none	density Measured at: lumbar spine (L2-L4) Method: DEXA Timing: baseline and end of treatment	discontinued treatment due to severe climateric symptoms. Trial sponsored by AstraZeneca and Novo Nordisk, who also supplied the active drugs and placebo.	
Fukushima 1993	Randomisation: Blinding: single blind (to assesor of bone mineral density) Design: single centre	Number of women: 28 Diagnosis: laparoscopic Inclusion criteria: regular menstrual cycles, negative cervical cytology and body weight within 25% of the normal range. Exclusion criteria: conditions that might affect calcium metabolism, administration of drugs known to affect sex hormone levels or bone metabolism during the study. Age: 21 - 46 years Location: Japan	Group I: danazol 400mg/day orally Group 2: buserelin 900ug/day intranasally. Duration of treatment: 24 weeks Duration of follow-up: 6 months	Outcome: Bone mineral density Measured at: lumbar spine (L3) Method: QCT Timing: baseline, cessation of treatment and 6 months post-treatment	9 participants did not complete the study for reasons unrelated to treatment.	B
Gnoth 1999	Randomisation: by centralised randomisation process Blinding: double blind Design: not stated	Number of women: 27 Diagnosis: laparoscopic Inclusion criteria: laparoscopically confirmed endometriosis (rAFS I-IV), no hormomal pretreatment at least 8 weeks prior to study entry, age 18-45, normal bone mineral density prior to study	group 1: leuprolin acetate 3.75mg IM + oral placebo each day. group 2: leuprolin acetate 3.75mg IM + 20µg ethinyl oestrodiol and 0.15mg desogestrel per day. Duration of treatment: 6 months	Outcome: bone mineral density Measured at: Lumbar spine (L2-L4), femoral neck, and Ward's triangle Method: DEXA Timing: baseline and end of treatment	Pre-treatment measurements of one women was not done. 1 early pregnancy post -treatment. The reply from the authors state that there were no exclusions post-randomisation or losses to follow-up, but remarks that one woman withdrew directly	A

		entry, signed informed consent and willingness to participate in the study including second look laparoscopy Exclusion criteria: reduced bone mineral density prior to study entry, absolute or relative contraindication against ethinyl estradiol or desogestrel, pregnancy, medical history or any event of thrombosis, any form of hemoglobin disorders, hypertension, liver function disorders, any history of malignant diseases, any estrogen related disorders like otosclerosis, herpes gestationis, history of severe pruritus in pregnancy or additional medication with: antiepileptics, antibiotics, Rifampicin, Isoniazid, Phenylbutazon, Griseofulvin, Chlorpromazin, Nitrofurantoin or Dihydroergotamin. Age: group 1; 34.8 +/- 5 yrs, group 2; 35 +/- 5 yrs Location: Germany	Duration of follow-up: none		after the first medical investigation and randomisation. She did not tell the reasons for her decision. There were taken no measurements from her. This participant was completely excluded from the evaluation and replaced.
Gregoriou 1997	Randomisation: by sequential numerical allocation to a randomisation list before	Number of women: 40 Diagnosis: laparoscopic Inclusion criteria: minimum	group 1: leuprolide acetate depot 3.75mg IM every 4 weeks.	Outcome: bone mineral density Measured at: lumbar spine	B

	commencing trial. Blinding: none -open label Design: not stated	of 4 endometriotic lesions, endometriotic symptoms and pelvic pain graded at least 3 (severe), negative cervical smear. Exclusion criteria: smoking, medications that might affect bone metabolism, medical conditions that could affect bone metabolism. Age: Mean age of group 1 28.3 years and mean age of group 2 29.1 years. Location: Greece	group 2: leuprolide acetate depot 3.75mg every 4 weeks + 1.25mg daily oral conjugated equine oestrogens on days 1 to 25 and 5mg oral medroxyprogesterone acetate on days 16-25. Duration of treatment: 24 weeks Duration of follow-up: 6 months	(L2 - L4) and femoral neck Method: DEXA Timing: Baseline, end of treatment and 6 months post-treatment		
Henzl 1990	This trial reports two different studies. The characteristics of these two studies are reported as Henzl 1990 study 1 and Henzl 1990 study 2.				Study sponsored by Syntex Research, Palo Alto, California	D
Henzl 1990 study 1	Randomisation: randomised trial Blinding: double Design: multi centre	Number of women: 236, but only 213 did BMD measurements Diagnosis: laparoscopic Inclusion criteria: completion of more than 150 days of treatment, pre-and post-treatment laparoscopic examinations and evaluation of clinical symptoms of endometriosis Exclusion criteria: premature withdrawal from treatment either for medical reasons (adverse effects, laboratory	group 1: nafarelin 400 ug/day IN (NAF 400), n= 73 group 2: nafarelin 800 ug/day IN (NAF 800), n= 70 group 3: danazol 800 mg/day PO (DAN 800), n=70 Duration of treatment: 6 months Duration of follow-up: not stated	Outcome: bone mineral density Measured at: lumbar spine Method: QCT and DPA Timing: not stated	Only 213 of the 236 women randomised did bone mineral density analysis. This loss of 23 women is not sufficiently explained in the text. The trial only states that one person was excluded because of non-compliance, two women receiving DAN 800 were withdrawn prematurely because of a rapid rise in liver enzyme levels. Study sponsored by Syntex Research, Palo Alto, California	B

		abnormalities, intercurrent illness or unsatisfactory therapeutic response) or due to problems in study administration. Age: 11 % less than 25 yrs, 29 % between 25 and 30 yrs, 40 % between 30 and 35 yrs and 20 % more than 35 yrs. Location: Sweden, Canada and USA				
Henzl 1990 study 2	Randomisation: randomised trial Blinding: double Design: multi centre	Number of women: 194 Diagnosis: laparoscopic Inclusion criteria: completion of more than 150 days of treatment, pre-and post-treatment laparoscopic examinations and evaluation of clinical symptoms of endometriosis Exclusion criteria: premature withdrawal from treatment either for medical reasons (adverse effects, laboratory abnormalities, intercurrent illness or unsatisfactory therapeutic response) or due to problems in study administration. Age: 11 % less than 25 yrs, 29 % between 25 and 30 yrs, 40 % between 30 and 35 yrs and 20 % more than 35 yrs. Location: Sweden, Canada	group 1: nafarelin 400 ug/day IN (NAF 400), n= 104 group 2: danazol 600 mg/day PO (DAN 600), n= 63 Duration of treatment: 6 months Duration of follow-up: not stated	Outcome: bone mineral density Measured at: lumbar spine Method: QCT and DPA Timing: not stated	Study sponsored by Syntex Research, Palo Alto, California	B

		and USA				
Hornstein 1998	Randomisation: by permuted blocks of four at each of the 26 study sites Blinding: double Design: multicentre trial - placebo controlled	Number of women: 201 Diagnosis: surgical (laparoscopy or laparotomy) Inclusion criteria: regular cycles, diagnosis within 12 months of the start of trial, persistent/recurrent pain, if previous surgical treatment then pain must have returned to baseline. Exclusion criteria: Age: 18 - 43 years Location: USA	group 1: lupron depot 3.75 mg every 4 weeks + daily oral placebo. group 2: lupron depot 3.75 mg every 4 weeks + daily oral norethidrone 5mg + oestrogen placebo. group 3: lupron depot 3.75 mg every 4 weeks + daily oral norethidrone 5 mg + conjugated equine oestrogens 0.625mg daily. group 4: lupron depot 3.75 mg every 4 weeks + daily oral norethidrone 5 mg + conjugated equine oestrogens 1.25mg. All participants received 1000mg of calcium per day during treatment and follow-up. Duration of treatment: 52 weeks Duration of follow-up: 2 years	Outcome: bone mineral density Measured at: lumbar spine Method: DEXA Timing: 0 months, 6 months, 12 months, 18 months, 24 months, 28 months, 32 months, 36 months.	Only 123 of the original participants completed the trial and entered year 1 of follow-up. Only 60 patients entered year 2 of follow-up. Trial sponsored by TAP Pharmaceuticals	B
Hornstein p + hd o						D
Hornstein p + ld o						D
Hornstein prog only						D
Howell 1995	Randomisation: randomised trial Blinding: none - open label Design: not stated	Number of women: 50 Diagnosis: laparoscopic Inclusion criteria: Exclusion criteria: drugs known to affect bone	group 1: 3.6 mg s.c depot injection of goserelin every 4 weeks. group 2: 3.6mg s.c injection every four weeks and	Outcome: bone mineral density Measured at: lumbar spine (L2-L4), Ward's triangle and femoral neck	20 participants did not complete all the bone mineral density assessments - 2 did not complete treatment and the other 18 did not complete	B

		metabolism in the 6 months preceding the trial, medical conditions known to affect bone mineral density or bone mineral metabolism. Age: Mean age of group 1: 29 years and mean age of group 2: 30 years Location: UK	transdermal estrogen 25ug daily and 5mg medroxyprogesterone acetate daily for 20 weeks commencing with the second goserelin depot. Duration of treatment: 24 weeks Duration of follow-up: 6 months	Method: DEXA Timing: baseline, end of treatment, 3 months post-treatment and 6 months post-treatment	follow up. Study sponsored by Zeneca Pharmaceuticals	
Irahara 2000	Randomisation: randomised trial Blinding: not stated Design: not stated	Number of women: 21 Diagnosis: Laparoscopy or laparotomy Inclusion criteria: Negative smear and negative mammogram in 6 months prior to the start of the study, no previous hormonal treatment received for endometriosis Age: 30 - 49 years Location: Japan	group 1: monthly injection of 3.75mg leuprolide acetate depot. group 2: monthly injection of 3.75mg leuprolide acetate + 0.625mg conjugated equine estrogen + 2.5mg Medroxyprogesterone acetate every other day from 2nd month of GnRHa treatment. Duration of treatment: 6 months Duration of follow-up: none	Outcome: bone mineral density Measured at: lumbar spine (L2 - L4) Method: DEXA Timing: baseline and end of treatment		B
Kiesel 1996	Randomisation: randomised trial Blinding: double blind Design: multi centre	Number of women: 123 Diagnosis: laparoscopic Inclusion criteria: AFS score > 5. Exclusion criteria: pregnancy, breast feeding, recent use of sex hormones, danazol or GnRH agonists, clinically significant renal, hepatic,haemopoetic or endocrine disorders, cervical	group 1: goserelin 3.6mg every 4 weeks + oral placebo every day group 2 : goserelin 3.6mg every 4 weeks for 6 months + placebo every day for 3 months and then medrogestone (10mg/day) for 3 months. group 3: goserelin 3.6mg every 4 weeks + 6 months	Outcome: bone mineral density Measured at: Lumbar spine, femoral neck and Ward's triangle Method: not stated Timing: baseline and end of treatment	1 participant excluded from trial prior to treatment and 9 participants did not complete treatment.	B

		abnormalities, sensitivity to GnRH analogues or hypothalamic hormones. Age: not stated Location: Germany	medrogestone (10mg per day) Duration of treatment: 6 months Duration of follow-up:			
Lindsay 1996	Randomisation: by code Blinding: double blind Design: multicentre	Number of women: 31 - 29 with endometriosis and 2 with fibroids. Diagnosis: surgical diagnosis of endometriosis Inclusion criteria: AFS score of II or higher or fibroids that required surgery. Exclusion criteria: smoking, asian origin, medications that might affect bone mineral density measurements or any type of menstrual cycle suppression in the last 3 months. Age: Mean age of group 1 31.9 years and mean age of group 2 33.1years. Location: UK	group 1: triptorelin 3.75mg IM every 4 weeks + oral placebo daily. group 2: triptorelin 3.75mg IM every 4 weeks + 2.5mg tibolone daily po. Duration of treatment: 24 weeks Duration of follow-up: none	Outcome: bone mineral density Measured at: lumbar spine (L2-L4) and the femoral neck Method: DEXA Timing: baseline and end of treatment	2 participants excluded from the trial due to resumption of smoking. Trial sponsored by Organon International	B
Miller 1990	This trial reports two different studies; one comparing leuprolide and placebo, the other comparing leuprolide and danazol. The data is entered as Miller 1990 study				Study sponsored by TAP-Abbott Research and Development	D

	1 and Miller 1990 study 2, respectively.					
Miller 1990 study 1	Randomisation: randomised trial Blinding:double blind Design: multi centre	Number of women: not stated Diagnosis: laparoscopic Inclusion criteria: significant pain secondary to the endometriosis Exclusion criteria: treatment of endometriosis within the 3 months prior to initiating the study Age: not stated Location: USA	group 1: Lupron depot 3.75 mg IM monthly group 2: Placebo IM monthly Duration of treatment: 24 weeks Duration of follow-up: not stated	Outcome: bone mineral density Measured at: Method: DPA + more Timing: not stated	1 Lupron participant and 1 placebo participant withdrew from the study due to adverse events. After 3 months of dosing, those participants who had achieved little or no pain relief were allowed to discontinue the study.	B
Miller 90 study2 DPA	Randomisation: randomised trial Blinding:double blind Design: multi centre, 22 centres	Number of women: 270 Diagnosis: laparoscopic Inclusion criteria: premenopausal women aged 18 or more, laparoscopic diagnosis of endometriosis within a 4-month period before study entry, use of barrier contraception throughout the study and 6 weeks after the last injection, if previously on OCP the patient must have resumed normal spontaneous menses for at least 2 cycles, any other treatment for endometriosis must have been completed > 3 months before study entry and diagnostic laparoscopy performed after discontinuation of previous	group 1: Lupron depot 3.75 mg monthly + placebo capsules daily, n= 128 group 2: Danazol 800 mg daily + monthly placebo injections, n= 125 Duration of treatment: 24 weeks Duration of follow-up: none	Outcome: bone mineral density Measured at: the spine and the femoral neck Method: the spine - by DPA in 17 centres and QCT in 5 centres, the femoral neck - by DPA in 9 centres Timing: baseline and end of treatment (week 24)	17 women were excluded: 3 did not meet inclusion criteria (leuprolide group; 2, danazol group; 1), 13 were non-compliant with dosing regimen (leuprolide group; 3, danazol group; 10) and 1 because of inadvertent dosing with another participant's designated leuprolie. Each investigator determined bone density by his or her usual method. The study was sponsored by TAP Pharmaceuticals Inc.	B

		therapy Exclusion criteria: pregnancy, lactating women, previous GnRH agonist treatment, surgical treatment of endometriosis or adhesions at time of laparoscopy Age: 18-44 years Location: USA				
Miller 90 Study2 QCT	The characteristics of this study are the same as for Miller 1990 Study 2 DPA and are entered under this heading. The reason for separation was to make sure that all data from the trial could be identified separately in the analysis					D
Moghissi 1996	Randomisation: randomised trial Blinding: double blind Design: multicentre	Number of women: 345 Diagnosis: laparoscopic Inclusion criteria: premenopausal women, 18-45 years of age, with confirmed diagnosis of endometriosis and pelvic symptoms, diagnosis of stage I-IV endometriosis confirmed during the initial laparoscopy. If a laparoscopy included therapeutic intervention, patients had to have an initial clinical response, recurrence of pelvic symptoms, and stability in severity of pelvic	group 1: goserelin 3.6mg every 28 days +oral placebo. group 2: goserelin 3.6mg every 28 days + conjugated oestrogen 0.3mg daily + medroxyprogesterone acetate 5mg daily. group 3: goserelin 3.6mg every 28 days +conjugated oestrogen 0.625mg daily +medroxyprogesterone 5mg daily HRT therapy was started on day 15 of the treatment period and continued daily for the next 22 weeks.	Outcome: bone mineral density Measured at: lumbar spine, L2-L4 Measured using: DEXA or DPA Timing: baseline, week 12, end of treatment, week 48 and week 72, or at the time of withdrawal, provided that withdrawal occured 3 months or more after the last bone mineral density assessment	Sponsored by Zeneca Pharmaceuticals, Wilmington, Delaware.	B

	symptoms for at least three months before pretreatment assessments Exclusion criteria: Positive urine pregnancy test, pregnancy or lactation, if a nursing mother, use of nontrial hormonal agents such as oestrogen, progesterone, or clomiphene within 60 days before pretreatment assessments until the end of the study, use of any drug at doses suppressing the hypothalamic-pituitary-adrena l axis, serious concomitant condition, long-term exposure (over three months) to GnRH agonists within 12 months before pretreatment assessments, baseline bone mineral density measurements over 2 SDs below that of age-matched controls, hypersensitivity to previous hormone therapy or oestrogen or progestin replacement therapies, and any condition that would preclude a patient from receiving study therapy. Age: 29.6 +/- 6.6 in placebo group, 30.7+/- 6.0 in lowdose HRT group and 29.4 +/- 5.7 in highdose HRT group. Location: USA	Duration of treatment: 24 weeks Duration of follow-up: 48 weeks

Mukherjee 1996	Randomisation: by lottery Blinding: double blind Design: multicentre	Number of women: 31 Diagnosis: laparoscopic diagnosis of endometriosis (n=10) or a diagnosis of leiomyoma (n=21). Inclusion criteria: Exclusion criteria: medical illness or were taking medication that could affect bone metabolism. Age: 24 - 46 years Location: USA	group 1: lupron depot (3.75mg) + oral placebo. group 2: lupron depot and two weeks of oral etidronate 400mg, per two month cycle. Duration of treatment: 6 months Duration of follow-up: none	Outcome: bone mineral density Measured at: lumbar spine (L2 -L4) and femoral neck Method: DEXA Timing: baseline and end of treatment	2 participants in the placebo group lost to follow-up. 1 of the participants in the etidronate group excluded from trial as very small. Depot Lupron supplied by TAP pharmaceuticals.	B
Rock 1993	Randomisation: randomised trial Blinding: none - open label Design: multicentre	Number of women: 315, but only 58 did BMD measurements Diagnosis: laparoscopy or laparotomy Inclusion criteria: symptomatic or asymptomatic endometriosis with or without infertility, written informed consent, rAFS score of 2 or above for active peritoneal and ovarian implants Exclusion criteria: stage IV endometriosis Age: 20-42 years Location: USA	group 1: 3.6 mg Zoladex SC as an implant every 28 days group 2: 400 mg Danazol PO twice daily (ie. 800 mg/day). This could be adjusted to 200 mg thrice daily, 200 mg twice daily, or followed by any one of these three regimens if clinically indicated Duration of treatment: 24 weeks Duration of follow-up: 48 weeks	Outcome: bone mineral density Measured at: lumbar spine; L2-L4 Method: DPA Timing: baseline and after treatment according to the text of the article. At weeks 0, 12, 24, 48 and 72 according to figure 6 in the article.	14 participants, with stage IV endometriosis were included because their investigators believed that significant components of stage IV endometriosis could benefit from hormonal treatment. Study sponsored by a grant from ICI Pharmaceuticals Group, a business unit of Zeneca Inc, Wilmington, Delaware.	B
Roux 1995	Randomisation: centralised Blinding: double blind. Design: single centre	Number of women: 42 Diagnosis: signs or symptoms or laparoscopy. Inclusion criteria: diagnosed endometriosis Exclusion criteria:	All participants received triptorelin 3.75mg IM every four weeks + nomegestrol acetate 5mg/day during the first 3 weeks following injection and then 1g calcium	Outcome: bone mineral density Measured at: lumbar spine (L2 - L4), femoral neck, Ward's triangle, trochanteric area, intertrochanteric area,	2 participants failed to complete the study - one was lost to follow up and one was excluded due to orthapaedic material in the lumbar spine.	A

		amenorrhoea, taking drugs known to affect bone metabolism, evidence of an associated disease, interuption of more than 15 days in the administration of the drug. Age: 20 - 44 years Location: France	carbonate daily for 27 weeks. In addition group 1 received placebo intranasal spray, group 2 received salmon calcitonin 100 IU IN daily, and group 3 received salmon calcitonin 200 IU IN daily. Duration of treatment: 27 weeks Duration of follow-up: 6 months	distal radius and proximal radius. Method: DEXA Timing: baseline, cessation of treatment and 6 months post-treatment		
Roux 1995 100 IU	See Roux 1995					D
Roux 1995 200 IU	See Roux 1995					D
Sillem 1999	Randomisation: centralised randomisation process Blinding: double Design: double-dummy trial	Number of women: 23 Diagnosis: laparoscopic Inclusion criteria: laparoscopically proven endometriosis, symptomatic endometriosis and regular menstruation Exclusion criteria: osteopaenia, osteoporosis or other skeletal disease, significant non-skeletal disease, pregnancy, lactation, use of medications known to interfere with bone metabolism in the three months prior to enrolment, psychiatric disorders. Age: 22 - 37 years Location: Germany	group 1: goserelin 3.6mg every 4 weeks s.c + oral placebo group 2: goserelin 3.6mg every 4 weeks s.c +5mg medrogestone orally twice daily Duration of treatment: 6 months Duration of follow-up: none	Outcome: bone mineral density Measured at: lumbar spine, ward's triangle and femoral neck. Method: DEXA Timing: baseline and end of treatment	The reply from the author states that there were losses to follow-up, but does not give any further information.	A

Somekawa +vitK +vitD						D
Somekawa 1999	Randomisation: randomised trial Blinding: triple blind Design: not stated	Number of women: 110 Diagnosis: not stated Inclusion criteria: presence of endometriosis or uterine leiomyoma Exclusion criteria: Heavy exercise, smoking, alcoholism, liver disease, ischaemic heart disease, diabetes, renal disease, metabolic or other endocrine diseases which could influence bone turnover, history of carcinoma. Age: 25 - 52 years Location: Japan	group 1: 1.88mg leuprolide acetate/month administered s.c group 2: 1.88mg s.c leuprolide acetate/month + oral menatetrenone 45mg/day group 3: 1.88mg s.c leuprolide acetate/month + oral 1,25 $(OH)^2$-D^3 0.5mg/day group 4: 1.88mg s.c leuprolide acetate/month + oral menatetrenone 45mg/day + 1,25 $(OH)^2$ -D^3 0.5mg/day. Duration of treatment: 6 months Duration of follow-up: none	Outcome: bone mineral density Measured at: lumbar spine (L2 -L4) Method: DEXA Timing: baseline and end of treatment	6 women withdrew from the trial (3 because of side-effects, 3 for personal reasons)	B
Somekawa 1999 + vitD						D
Somekawa 1999 + vitK						D
Surrey 1992	Randomisation: randomised to therapeutic groups based on order of entry (and not severity of disease) Blinding: single blind Design: not stated	Number of women: 20 Diagnosis: laparoscopic Inclusion criteria: symptomatic endometriosis diagnosed by laparoscopy Exclusion criteria: calcium supplements during the treatment, less than four endometriotic implants, endometrioma greater than 5cm in diameter. Age: Mean age of group 1 32.9 years and mean age of group 2 28.9 years.	group 1: leuprolide acetate 3.75mg im every 28 days. group 2: leuprolide acetate 3.75mg im every 28 days and norethindrone po 5mg for the first four weeks and then 10 mg daily for the remaining 20 weeks. Duration of treatment: 24 weeks Duration of follow-up: 24 weeks	Outcome: bone mineral density Measured at: lumbar spine (L2-L4) Method: DEXA Timing: baseline, end of treatment and 24 weeks post-treatment	3 participants lost to follow-up. Sponsored by TAP pharmaceuticals	A

		Location: USA				
Vella 1995	Randomisation: randomised trial Blinding: not stated Design: not stated	Number of women: 30 Diagnosis: not stated Inclusion criteria: not stated Exclusion criteria: not stated Age: not stated Location: not stated	group 1: goserelin group 2: goserelin + premarin (conjugated oestrogens) 1.25mg Duration of treatment: 6 months Duration of follow-up: not stated	Outcome: bone mineral density Measured at: the lumbar spine (L2-L4), femoral neck and ward's triangle. Method: not stated Timing: not stated		B
Vercillini 1996	Randomisation: by code Blinding: double-blind Design: multicentre	Number of women: 55 Diagnosis: laparoscopic Inclusion criteria: not stated Exclusion criteria: used any drugs other than NSAIDs in the last 6 months, if they had concomitant disorders that might cause gynaecological pain, if there were contraindications to the use of gestrinone or GnRh analogues, abnormal baseline BMDs or refusal to use barrier contraception. Age: 18 - 40 years Location: Italy	group 1:oral gestrinone 2.5mg twice a week. group 2: leuprolide acetate 3.75mg IM depot every 4 weeks. Duration of treatment: 6 months Duration of follow-up: 6 months	Outcome: bone mineral density Measured at: the lumbar spine (L2-L4) Method: DEXA Timing: baseline, end of treatment and 6 months post-treatment	Only 41 participants underwent complete follow-up. Study funded by Poli Industria Chimica, Italy	B
Whitehouse 1990	Randomisation: cases were sequentially numbered Blinding: double blind Design: not stated	Number of women: 24 Diagnosis: laparoscopic Inclusion criteria: endometriosis diagnosed at laparoscopy, consent to participate in study of Nafarelin and Danazol in the treatment of endometriosis, consent to bone mineral	group 1: nafarelin 200mg twice daily administered intranasally group 2: danazol 200mg. Duration of treatment: 6 months Duration of follow-up: 6 months	Outcome: bone mineral density Measured at: T12-L3 Method: single and dual QCT Timing: Baseline, end of treatment and 6 months post-treatment	2 participants did not complete trial - one became pregnant and one failed to return for final assessment. The results from these participants were excluded from analysis.	B

density measurements by
QCT
Exclusion criteria: medically
unsuitable to undergo
quantitative computerized
tomography
Age: 24 -44 years
Location: UK

Characteristics of excluded studies

Study ID	Reason for exclusion
Agarwal 1997	Trial compared two different kinds of GNRH analogue.
Agarwal 1999	Looked at age-related effect of GNRH analogue therapy on bone mineral density.
Chang 1996	Treatment time less than six months and bone mineral density data was only measured in patients receiving leuprolin acetate.
Cirkel 1995	No measurements of bone mineral density were taken.
Claesson 1989	Bone mineral density measurements made at distal forearm only.
Dawood 1989	Bone mineral density measured at distal radius and ulna. Measured at lumbar spine only for the danazol groups.
Dawood 1997	Compared two different doses of GnRH analogue only.
Finkelstein 1994	Three studies. Excluded because of uncertainty over the number of patients randomised and analysed. Authors were contacted but were unable to provide any further information regarding the trials.
Fogelman 1994	Two studies reported - first used healthy controls and second study looked at premenstrual tension.
Giorgino 1991	Not randomised.
Kaminski 2001	Measured bone mineral density only of the calcaneus.
Morgante 1999	Participants treated for six months with GnRH therapy, then switched either to danazol or placebo.
Orwoll 1994	Comparison of nafarelin for three months and nafarelin for six months.
Pierce 2000	Trial only partially randomised - some subjects were not randomised but were put into a treatment group according to their preference.
Segura 1994	Not randomised.
Surrey 1995	Compared two different add-back regimes - one a calcium regulating agent with progesterone and the other progesterone only - this not in our objectives.
Surrey 1998	This was only a literature review, not a randomised trial.
Tahara 2000	Participants randomised to receive either GnRH analogue full dose for 24 weeks or GnRH analogue full dose for four weeks and then half dose for 20 weeks.

Taskin 1997	Trial compared GnRH analogue + tibolone versus GnRH analogue + iron pill.
Uemura 1993	Not randomised. Trial compared women with endometriosis with healthy controls.
Uemura 1994	Not randomised.
Ylikorkala 1990	Bone mineral density measured at the distal radius only.
Zamberlan 1997	Trial studied hirsute hyperandrogenic women and not those with endometriosis.

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Additional tables

01 Quality of Included Studies

Study ID	Allocation Concealed	Randomisation method	Blinding	Follow-up	BMD at >1 site	Other bias
Aisaka 2000	Unclear	Not stated	Not stated	None	No - lumbar spine only	
Chan 1993	Unclear	Not stated	Not stated	None	No - spine only	
Crosgnani 1996	Unclear	According to a computer-generated sequence	Open label	None	No - lumbar spine only	
Dawood 1995	Unclear	By code	Double	12 months	Yes - lumbar spine and lower forearm	
Dodin 1991	Unclear	Not stated	Open label	6 months	Yes - lumbar spine and femoral neck	
Edmonds 1994	Unclear	Not stated	Not stated	6 months	Yes - lumbar spine, femoral neck and Ward's triangle	
Eldred 1992	Unclear	By code	Double	6 months	Yes - lumbar spine and distal forearm	31 women left the study early; 20 because of adverse effects, four were lost to follow-up, four had unsatisfactory therapeutic response and three were non-compliant with the protocol
Franke 2000	Adequate	Sealed, opaque, sequentially	Double	None	No - lumbar spine only	

		numbered, identical envelopes				
Fukushima 1993	Unclear	Not stated	Single (to assessor of bone mineral density)	6 months	No - lumbar spine only	9 patients did not complete the study for reasons unrelated to treatment
Gnoth 1998	Adequate	By centralised randomisation process	Double	None	Yes - lumbar spine, femoral neck and Ward's triangle	
Gregoriou 1997	Unclear	By sequential numerical allocation to a randomisation list before commencing trial	Open label	6 months	Yes - lumbar spine and femoral neck	
Henzl 1990 study 1	Unclear	Not stated	Double	None	No - lumbar spine only	Only 213 of 236 women randomised did bone mineral density analysis. This loss of 23 women is not sufficiently explained in the text.
Henzl 1990 study 2	Unclear	Not stated	Double	None	No - lumbar spine only	
Hornstein 1998	Unclear	By permuted blocks of four at each of the 26 study sites	Double	2 years	No - lumbar spine only	Only 123 of the original women completed the trial and entered year one of follow-up. Only 60 women entered year two of follow-up.
Howell 1995	Unclear	Not stated	Open label	6 months	Yes - lumbar spine, femoral neck and Ward's triangle	20 women did not complete all the bone mineral density measurements - 2 did not complete treatment and the other 18 did not complete follow-up

Irahara 2000	Unclear	Not stated	Not stated	None	No - only lumbar spine	
Kiesel 1996	Unclear	Not stated	Double	None	Yes - lumbar spine, femoral neck and Ward's triangle	One women excluded from trial and nine patients did not complete treatment
Lindsay 1996	Unclear	By code	Double	None	Yes - lumbar spine and femoral neck	
Miller 1990 study 1	Unclear	Not stated	Double	None	Not stated	After three months of dosing, those women who had achieved little or no pain relief were allowed to discontinue the study
Miller 1990 study 2	Unclear	Not stated	Double	None	Yes - the spine and femoral neck	
Moghissi 1996	Unclear	Not stated	Double	48 weeks	Not stated	
Mukherjee 1996	Unclear	By lottery	Double	None	Yes - lumbar spine and femoral neck	
Rock 1993	Unclear	Not stated	Open label	48 weeks	No - lumbar spine only	There were 315 study participants, but only 58 of these did bone mineral density measurements.
Roux 1995	Adequate	Centralised randomisation process	Double	6 months	Yes - lumbar spine, femoral neck, Ward's triangle, trochanteric area, distal radius and proximal radius	

Sillem 1999	Adequate	Centralised randomisation process	Double	None	Yes - lumbar spine, femoral neck and Ward's triangle	
Somekawa 1999	Unclear	Not stated	Triple	None	No - lumbar spine only	
Surrey 1992	Unclear	Randomised to therapeutic groups based on order of entry and not severity of disease according to the article. Computerised allocation according to reply from author	Single	24 weeks	No - lumbar spine only	
Vella 1995	Unclear	Not stated	Not stated	None	Yes - lumbar spine, femoral neck and Ward's triangle	
Vercillini 1996	Unclear	By code	Double	6 months	No - lumbar spine only	Only 41 women underwent complete follow-up
Whitehouse 1990	Unclear	Cases were sequentially numbered	Double	6 months	No - lumbar spine only	

Additional tables

02 Descriptive data for trials not included in the meta-analysis

Study ID	Treatment studied	Site of measurement	Way of measurement	Number of women	Study conclusion
Aisaka 2000	GnRHa vs GnRHa + oestrogen/progestero ne	Lumbar spine	DEXA	53	The BMD values showed a significant decrease during GnRHa administration without the add-back.
Chan 1993	GnRHa vs danazol/gestrinone	Lumbar spine		149	No clear results reported
Crosignani 1996	Monthly GnRHa vs 3-monthly GnRHa	Lumbar spine	DEXA	30	A statistically significant variation of lumbar spine bone mineral density was observed at the end of leuprolide (GnRHa) treatment in both study groups (P<0.01), the percentage decrease over basal being 5.2 and 4.9% in the 3-monthly and monthly depot arms respectively.
Edmonds 1994	GnRHa vs GnRHa + oestrogen/progestero ne	Lumbar spine, femoral neck and Ward's triangle	DEXA	50	The mineral loss is reduced by 50 % to 2.5 % overall by the addition of HRT and there is a significant difference in the rate of return to normal of bone mineral density during post-treatment follow-up. In neither group was there a complete return to the pretreatment levels during the six months of follow-up.
Eldred 1992	GnRHa + lowdose HRT vs GnRHa + highdose HRT	Lumbar spine	SPA and DPA	94	Densitometry of the spine showed decreases at six months in all groups, that is nafarelin and placebo, nafarelin + norethisterone 0.7, 1.4 and 2.45 mg respectively. Six months after stopping nafarelin, with or without norethisterone, bone mass was not significantly different from baseline. The differences between the group receiving placebo and the groups receiving doses of norethisterone were all non-significant.
Gregoriou 1997	GnRHa vs GnRHa + oestrogen/progestero ne	Lumbar spine and femoral neck	DEXA	40	The mean loss of 4.2% from the lumbar spine in the GnRHa group at the end of treatment was significant (P<0.001) compared to the baseline value. On the contrary, the 0.9% loss in the lumbar spine in the GnRH + HRT group was not significantly different from baseline. Similarly, bone loss in the femoral neck was 1.2 % in the GnRH + HRT group, but 4.5% in the GnRH group, which is

					significantly greater (P<0.001). Six months after treatment, bone mineral density at the lumbar spine in the GnRHa + HRT group had recovered toward the baseline level (-0.3%), but that in the GnRHa group remained significantly lower than pretreatment (-1.8%) (P<0.001). At the femoral neck in the GnRHa group there was no recovery of bone density, while bone density in the GnRHa + HRT group had partially recovered (-3.6% and -0.7%, respectively).
Henzl 1990 study 1	GnRHa vs danazol/gestrinone	Lumbar spine	QCT and DPA	236, but only 213 did BMD measurements	Results suggest no significant difference in bone mineral density loss between danazol and GnRHa treatment groups.
Henzl 1990 study 2	GnRHa vs danazol/gestrinone	Lumbar spine	QCT and DPA	194	Results suggest no significant difference in bone mineral density loss between danazol and GnRHa treatment groups.
Howell 1995	GnRHa vs GnRHa + oestrogen/progesterone	Lumbar spine, femoral neck and Ward's triangle	DEXA	50	The amount of bone mineral density loss was significantly less in the HRT group at the lumbar spine, although it was not prevented completely.
Irahara 2000	GnRHa vs GnRHa + oestrogen/progesterone	Lumbar spine	DEXA	21	The control group significantly (P<0.01) decreased BMD of the lumbar spine (mean percentage change: -6.3%) after six months of treatment; however, add-back therapy prevented this BMD reduction (mean percentage change: -0.8%).
Kiesel 1996	GnRHa vs GnRHa + progesterone	Lumbar spine, femoral neck and Ward's triangle		123	Statistically significant reductions from baseline (P<0.01) were seen in each region and for each treatment, with the exception of the effect of immediate add-back on Ward's triangle. Generally, the losses at the end of the 24-week treatment period were less in the HRT groups than in the goserelin (GnHRa) monotherapy group, although the only statistically significant difference was in the lumbar spine region when comparing goserelin monotherapy (-5.5%) with goserelin plus deferred HRT (-3.8%; P<0.05).
Moghissi 1996	GnRHa + lowdose oestrogen/progesterone vs GnRHa + highdose oestrogen/progesterone	Lumbar spine	DEXA	345	Some degree of BMD loss was seen in all groups; however, rates of loss in the highdose and lowdose HRT groups were significantly less than that in the GnRHa + placebo group. At week 24, the mean percentage decreases from baseline in BMD for the placebo, lowdose HRT and highdose HRT were 4.1 %, 2.0 % and 1.5 %, respectively. There were no statistically significant differences between the

					lowdose HRT and the highdose HRT groups. During the follow-up period, the three groups had a rapid recovery of BMD that approached baseline values.
Mukherjee 1996	GnRHa vs GnRHa + calcium-regulating agents	Lumbar spine and femoral neck	DEXA	31	GnRHa treatment produced a significant decrease (4% to 10%) in bone density at the anteroposterior and lateral spine in placebo-treated patients. No significant change was demonstrated in etidronate-treated patients. Etidronate blocks bone mineral density changes associated with GnRHa therapy.
Rock 1993	GnRHa vs danazol/gestrinone	Lumbar spine	DPA	315, but only 58 did BMD measurements	Mean bone mineral density decreased from baseline by 5.4% in the Zoladex (GnRHa) group and increased by 1.0% in the danazol group at the end of treatment.
Vella 1995	GnRHa vs GnRH + oestrogen/progestero ne	Lumbar spine, femoral neck and Ward's triangle		30	The Zoladex (GnRHa) only group had a significant loss in both vertebral and femoral neck bone densities at the end of the six month periods whilst the Zoladex and Premarin (conjugated oestrogens) group had as such loss.

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Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 01 Bone mineral density of lumbar spine: treatment (absolute values)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Whitehouse 1990	15	149.60(22.60)	9	157.00(20.00)		44.33	-0.33 [-1.16, 0.50]
Dodin 1991	17	0.98(0.12)	9	1.17(0.12)		35.84	-1.63 [-2.46, -0.81]
Fukushima 1993	10	144.10(11.40)	9	170.80(9.60)		19.82	-2.41 [-3.65, -1.16]
Subtotal (95% CI)	42		27			100.00	-1.17 [-1.73, -0.62]
Test for heterogeneity: Chi² = 8.30, df = 2 (P = 0.02), I² = 75.9%							
Test for overall effect: Z = 4.15 (P < 0.0001)							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-100 -50 0 50 100
Worse with GNRHA Worse w danazol/ges

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 02 Bone mineral density of lumbar spine: follow-up (absolute values)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 months treatment and 6 months follow-up							
Dodin 1991	11	1.00(0.10)	5	1.13(0.08)		44.28	-1.30 [-2.47, -0.12]
Fukushima 1993	10	148.30(12.80)	9	164.70(6.70)		55.72	-1.51 [-2.56, -0.46]
Subtotal (95% CI)	21		14			100.00	-1.42 [-2.30, -0.53]
Test for heterogeneity: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%							
Test for overall effect: Z = 3.54 (P = 0.0004)							
02 after 6 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
05 after 12 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 after 12 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-10 -5 0 5 10
Worse with GNRHA Worse w danazol/gest

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 03 Bone mineral density of the femoral neck: treatment (absolute values)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Dodin 1991	16	0.80(0.12)	8	0.93(0.12)		100.00	-1.05 [-1.95, -0.14]
Subtotal (95% CI)	16		8			100.00	-1.05 [-1.95, -0.14]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 2.26 (P = 0.02)							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-10 -5 0 5 10
Worse with GnRHa Worse w danazol/gest

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 04 Bone mineral density of the femoral neck: follow-up (absolute values)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 months treatment and 6 months follow-up							
Dodin 1991	11	0.83(0.14)	4	0.88(0.06)		100.00	-0.52 [-1.69, 0.64]
Subtotal (95% CI)	11		4			100.00	-0.52 [-1.69, 0.64]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.88 (P = 0.38)							
02 after 6 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
05 after 12 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 after 12 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-10 -5 0 5 10
Worse with GnRHa Worse w danazol/gest

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 07 Bone mineral density of lumbar spine: treatment (percentage change)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Miller 90 Study2 QCT	8	-15.10(4.80)	9	6.20(5.10)		2.02	-4.07 [-5.90, -2.24]
Miller 90 study2 DPA	102	-4.30(4.04)	91	-0.10(4.77)		76.00	-0.95 [-1.25, -0.65]
Whitehouse 1990	15	-6.60(6.51)	9	2.20(1.90)		6.03	-2.14 [-3.20, -1.08]
Dawood 1995	6	-14.00(0.50)	6	5.40(2.20)		0.22	-11.23 [-16.82, -5.63]
Vercillini 1996	22	-3.04(4.77)	19	0.88(2.12)		15.73	-1.02 [-1.67, -0.36]
Subtotal (95% CI)	153		134			100.00	-1.12 [-1.38, -0.86]
Test for heterogeneity: Chi² = 27.45, df = 4 (P < 0.0001), I² = 85.4%							
Test for overall effect: Z = 8.43 (P < 0.00001)							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-100 -50 0 50 100
Worse with GNRHA Worse with danazol/g

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 08 Bone mineral density of lumbar spine: follow-up (percentage change)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 months treatment and 6 months follow-up							
Dawood 1995	6	-4.20(3.80)	6	8.20(3.50)		10.70	-3.13 [-5.04, -1.23]
Vercillini 1996	22	-1.08(3.26)	19	2.06(2.51)		89.30	-1.05 [-1.71, -0.39]
Subtotal (95% CI)	28		25			100.00	-1.27 [-1.89, -0.65]
Test for heterogeneity: Chi² = 4.12, df = 1 (P = 0.04), I² = 75.7%							
Test for overall effect: Z = 4.00 (P < 0.0001)							
02 after 6 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
05 after 12 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 after 12 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-10 -5 0 5 10
Worse with GNRHA Worse with danazol/g

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 02 GNRHa vs danazol/gestrinone
Outcome: 09 Bone mineral density of the femoral neck, treatment (percentage change)

Study or sub-category	N	GNRHa Mean (SD)	N	danazol/gestrinone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Miller 90 study2 DPA	38	-2.70(7.40)	32	-0.40(7.35)		100.00	-0.31 [-0.78, 0.16]
Subtotal (95% CI)	38		32			100.00	-0.31 [-0.78, 0.16]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.28 (P = 0.20)							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

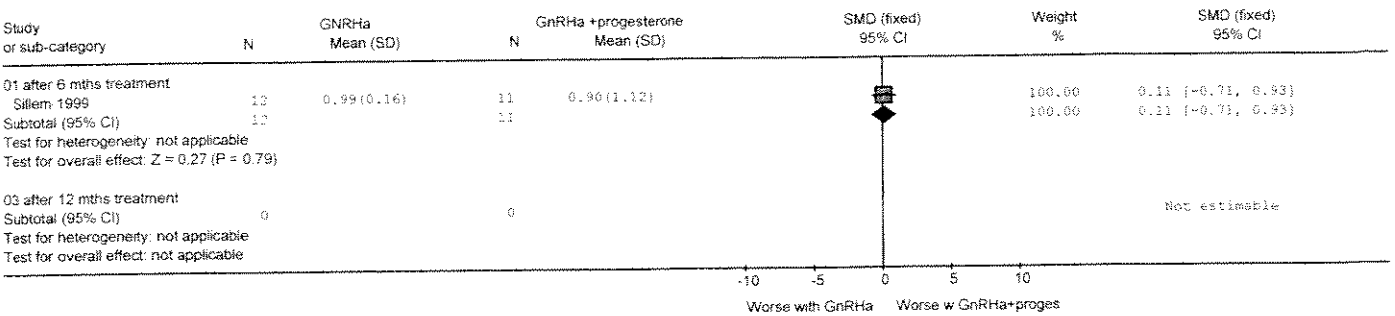
-10 -5 0 5 10
Worse with GnRHa Worse with danazol/g

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 03 GNRHa vs GNRHa + *HRT* (progesterone only)
Outcome: 01 Bone mineral density of lumbar spine: treatment (absolute values)

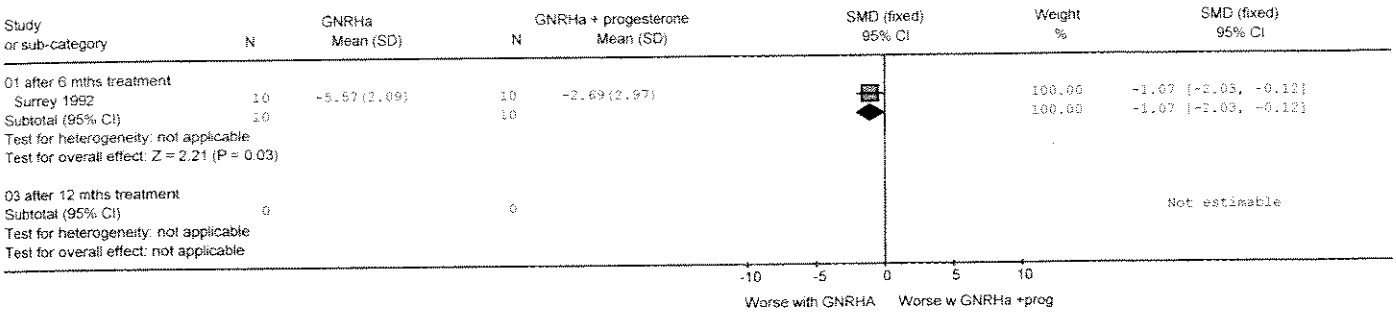
Study or sub-category	N	GNRHa Mean (SD)	N	GnRHa + progesterone Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Hornstein 1998	41	1.02(0.11)	42	1.05(0.13)		79.21	-0.25 [-0.68, 0.19]
Sillem 1999	12	1.23(0.16)	11	1.14(0.10)		20.79	0.64 [-0.20, 1.49]
Subtotal (95% CI)	53		53			100.00	-0.06 [-0.45, 0.32]
Test for heterogeneity: Chi² = 3.39, df = 1 (P = 0.07), I² = 70.5%							
Test for overall effect: Z = 0.31 (P = 0.75)							
03 after 12 mths treatment							
Hornstein 1998	29	0.99(0.10)	32	1.04(0.14)		100.00	-0.40 [-0.91, 0.11]
Subtotal (95% CI)	29		32			100.00	-0.40 [-0.91, 0.11]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.55 (P = 0.12)							

-4 -2 0 2 4
Worse with GNRHA Worse w GnRHa+proges

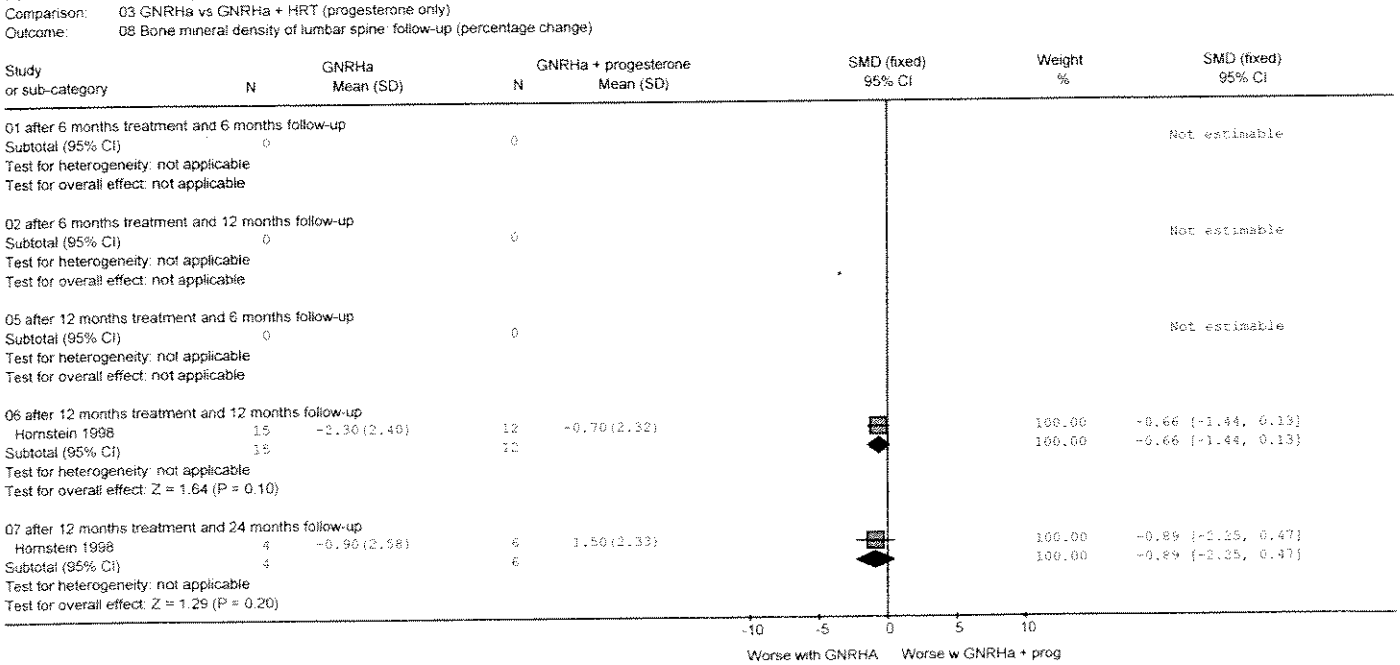
Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 03 GNRHa vs GNRHa + HRT (progesterone only)
Outcome: 03 Bone mineral density of the femoral neck: treatment (absolute values)



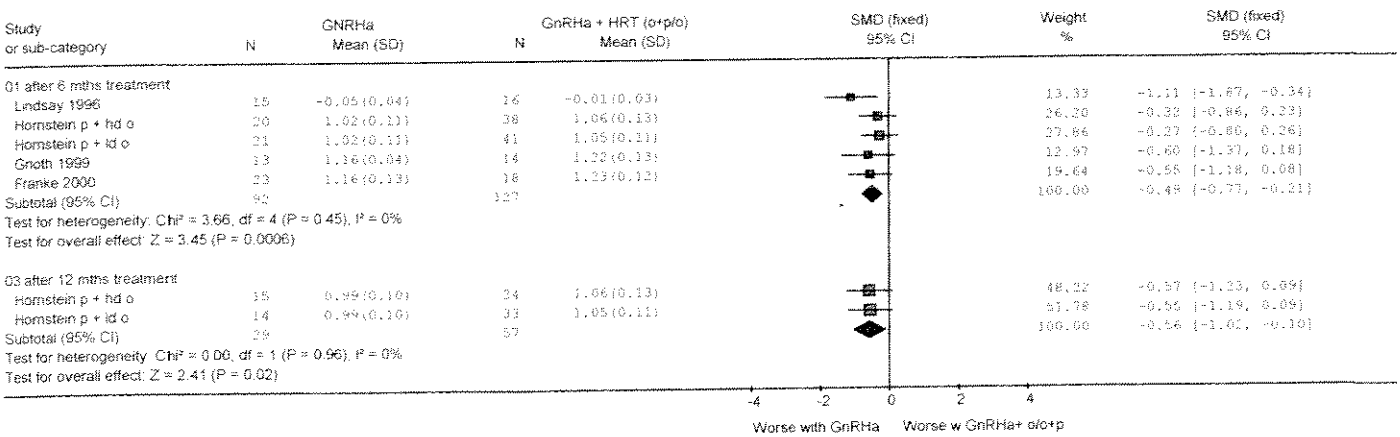
Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 03 GNRHa vs GNRHa + HRT (progesterone only)
Outcome: 07 Bone mineral density of lumbar spine: treatment (percentage change)



Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 03 GNRHa vs GNRHa + HRT (progesterone only)
Outcome: 08 Bone mineral density of lumbar spine: follow-up (percentage change)



Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 04 GNRHa vs GNRHa + HRT (oestrogen and progesterone/oestrogen only)
Outcome: 01 Bone mineral density of lumbar spine: treatment (absolute values)



Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 04 GNRHa vs GNRHa + HRT (oestrogen and progesterone/oestrogen only)
Outcome: 03 Bone mineral density of the femoral neck: treatment (absolute values)

Study or sub-category	GNRHa N	GNRHa Mean (SD)	GnHRa + HRT (o+p/o) N	GnHRa + HRT (o+p/o) Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Lindsay 1996	15	-0.02(0.04)	16	-0.01(0.02)		53.20	-0.31 [-1.02, 0.40]
Gnoth 1999	13	0.99(0.13)	14	0.97(0.12)		46.80	0.16 [-0.60, 0.91]
Subtotal (95% CI)	28		30			100.00	-0.09 [-0.61, 0.42]
Test for heterogeneity: Chi² = 0.78, df = 1 (P = 0.38), I² = 0%							
Test for overall effect: Z = 0.35 (P = 0.72)							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-4 -2 0 2 4
Worse with GnRHa Worse w GnRHa+ o/o+p

Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 04 GNRHa vs GNRHa + HRT (oestrogen and progesterone/oestrogen only)
Outcome: 08 Bone mineral density of lumbar spine: follow-up (percentage change)

Study or sub-category	GNRHa N	GNRHa Mean (SD)	GNRHa + o/o+p N	GNRHa + o/o+p Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
02 after 6 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
05 after 12 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 after 12 months treatment and 12 months follow-up							
Hornstein p + hd o	8	-2.30(2.40)	14	0.50(2.32)		52.72	-1.15 [-2.09, -0.20]
Hornstein p + ld o	7	-2.30(2.40)	14	0.80(2.39)		47.28	-1.24 [-2.24, -0.24]
Subtotal (95% CI)	15		28			100.00	-1.19 [-1.88, -0.51]
Test for heterogeneity: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%							
Test for overall effect: Z = 3.40 (P = 0.0007)							
07 after 12 months treatment and 24 months follow-up							
Hornstein p + hd o	2	-0.90(2.58)	4	0.90(2.36)		48.35	-0.60 [-2.39, 1.20]
Hornstein p + ld o	2	-0.90(2.58)	5	1.20(2.46)		51.65	-0.71 [-2.45, 1.02]
Subtotal (95% CI)	4		9			100.00	-0.66 [-1.90, 0.59]
Test for heterogeneity: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%							
Test for overall effect: Z = 1.03 (P = 0.30)							

-4 -2 0 2 4
Worse with GNRHA Worse w GNRHa +o/o+p

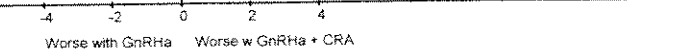
Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 07 GNRHa vs GNRHa + calcium-regulating agents (CRA)
Outcome: 01 Bone mineral density of lumbar spine: treatment (absolute values)

Study or sub-category	GNRHa N	GNRHa Mean (SD)	GnRHa + CRA N	GnRHa + CRA Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Roux 1995 100 IU	7	1.03(0.09)	13	1.01(0.15)		50.25	0.14 [-0.78, 1.06]
Roux 1995 200 IU	7	1.03(0.09)	13	0.99(0.14)		49.75	0.31 [-0.62, 1.23]
Subtotal (95% CI)	14		26			100.00	0.22 [-0.43, 0.88]
Test for heterogeneity: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%							
Test for overall effect: Z = 0.67 (P = 0.50)							
02 after 9 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-4 -2 0 2 4
Worse with GNRHA Worse w GnRHa + CRA

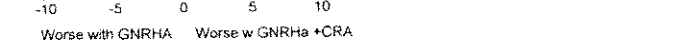
Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 07 GNRHa vs GNRHa + calcium-regulating agents (CRA)
Outcome: 03 Bone mineral density of the femoral neck: treatment (absolute values)

Study or sub-category	N	GNRHa Mean (SD)	N	GnRHa + CRA Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Roux 1995 100 IU	7	0.83(0.12)	13	0.82(0.15)		50.70	0.07 [-0.85, 0.99]
Roux 1995 200 IU	7	0.83(0.12)	13	0.77(0.13)		49.30	0.45 [-0.48, 1.39]
Subtotal (95% CI)	14		26			100.00	0.26 [-0.40, 0.91]
Test for heterogeneity: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%							
Test for overall effect: Z = 0.77 (P = 0.44)							
02 after 9 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



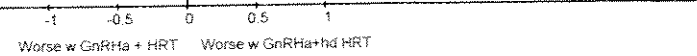
Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 07 GNRHa vs GNRHa + calcium-regulating agents (CRA)
Outcome: 07 Bone mineral density of lumbar spine: treatment (percentage change)

Study or sub-category	N	GNRHa Mean (SD)	N	GNRHa + CRA Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Somekawa +vitK +vitD	9	-5.25(0.52)	36	-3.59(0.35)		20.98	-4.08 [-5.34, -2.81]
Somekawa 1999 + vitD	9	-5.25(0.52)	25	-4.13(0.70)		44.45	-1.66 [-2.53, -0.79]
Somekawa 1999 + vitK	9	-5.25(0.52)	26	-3.72(0.61)		34.57	-2.54 [-3.52, -1.55]
Subtotal (95% CI)	27		77			100.00	-2.47 [-3.05, -1.89]
Test for heterogeneity: Chi² = 9.55, df = 2 (P = 0.008), I² = 79.1%							
Test for overall effect: Z = 8.35 (P < 0.00001)							
02 after 9 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 after 12 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 10 GNRHa + HRT vs GNRHa + high dose HRT
Outcome: 01 Bone mineral density of lumbar spine. treatment (absolute values)

Study or sub-category	N	GNRHa + HRT Mean (SD)	N	GnRHa +high dose HRT Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 mths treatment							
Hornstein 1998	41	1.05(0.11)	38	1.06(0.13)		100.00	-0.08 [-0.52, 0.36]
Subtotal (95% CI)	41		38			100.00	-0.08 [-0.52, 0.36]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							
02 after 9 mths treatment							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 after 12 mths treatment							
Hornstein 1998	33	1.05(0.11)	24	1.06(0.13)		100.00	-0.08 [-0.61, 0.44]
Subtotal (95% CI)	33		24			100.00	-0.08 [-0.61, 0.44]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							



Review: Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density (Without Surrey)
Comparison: 10 GNRHa + HRT vs GNRHa + high dose HRT
Outcome: 08 Bone mineral density of lumbar spine: follow-up (percentage change)

Study or sub-category	N	GNRHa + HRT Mean (SD)	N	GNRHa +high dose HRT Mean (SD)	SMD (fixed) 95% CI	Weight %	SMD (fixed) 95% CI
01 after 6 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
02 after 6 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 after 9 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
04 after 9 months treatment and 12 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
05 after 12 months treatment and 6 months follow-up							
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 after 12 months treatment and 12 months follow-up							
Hornstein 1998	14	0.80 (2.39)	14	0.50 (2.32)		100.00	0.12 [-0.62, 0.87]
Subtotal (95% CI)	14		14			100.00	0.12 [-0.62, 0.87]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.33 (P = 0.74)							
07 after 12 months treatment and 24 months follow-up							
Hornstein 1998	5	1.20 (2.46)	4	0.90 (2.36)		100.00	0.11 [-1.21, 1.43]
Subtotal (95% CI)	5		4			100.00	0.11 [-1.21, 1.43]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.16 (P = 0.87)