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[Intervention Protocol]

Hormonal treatment for uterine adenomyosis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness and safety of hormonal therapies for uterine adenomyosis in premenopausal women.

BACKGROUND

Description of the condition

Epidemiology

Adenomyosis was first described as endometrial glands in the myometrium (middle layer of the uterine wall, consisting mainly of uterine smooth muscle cells) of the uterus. The current definition of adenomyosis is provided in 1972 by Bird: 'the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma (connective or supporting tissue of the endometrial cell) surrounded by the hypertrophic and hyperplastic myometrium' (Bird 1972). This is the classic description of diffuse adenomyosis. When infiltration of the endometrial glands is in the form of grossly visible nodules without a capsule, which are clearly distinct from the myometrium, it is referred to as 'adenomyoma' (Bergeron 2006). This condition is different from endometriosis which is the implantation of endometrial glands outside the uterus. In the 1950s, Sampson's retrograde menstruation theory suggested that menstrual cells arriving in the peritoneal cavity could implant and develop further into endometriotic lesions. This helped to differentiate endometriosis from adenomyosis (Benagiano 2006). The differences between adenomyosis and endometriosis are summarised in Appendix 1.
Adenomyosis is evident in approximately 30% to 60% of women undergoing hysterectomy (Bird 1972; Lee 1984). Around 70% to 80% of adenomyosis cases are reported in women in the fourth and fifth decades of life. Between 5% and 25% of adenomyosis cases are observed in patients younger than 39 years and only 5% to 10% occur in women older than 60 years (Azziz 1989; Benson 1958). Although the diagnosis is usually made in women in their forties and fifties with symptoms, it can be found incidentally in younger women undergoing infertility evaluations or who have signs and symptoms of abnormal uterine bleeding and pain.
Common symptoms include menorrhagia (heavier and increased

amount of flow occurring at regular intervals or loss of more than 80 mL of blood) (40% to 50%), dysmenorrhoea (painful periods) (15% to 30%), metrorrhagia (irregular episodes of bleeding) (10% to 12%) and dyspareunia (difficult or painful sexual intercourse) (7%) (Owolabi 1977). The frequency and severity of the symptoms are related to the extent and depth of the adenomyotic lesions (Levgur 2000). Women with adenomyosis have distinct symptomatology from women with leiomyomas (benign tumours in the uterus) and are more likely to suffer from depression (57.1% versus 24.7%), dysmenorrhoea (65.7% versus 42.3%) and pelvic pain (52.9% versus 21.1%) (Taran 2010).

Clinical presentation

A high percentage of women with adenomyosis are multiparous, with pregnancy facilitating the formation of adenomyosis by allowing adenomyotic foci to be included in the myometrium. Evidence of a significantly increased risk of prior uterine surgery in women with adenomyosis is inconsistent (Taran 2010). Hereditary occurrence has been reported, suggesting a genetic predisposition (Arnold 1995). There is evidence to suggest that iatrogenic induction of the disease can result from endometrial ablation due to trauma from endometrial resection (McLucas 1994).

The pathogenesis of adenomyosis is related to the endometrial stroma being in direct contact with the underlying myometrium, allowing communication and interaction. Physical disruption of the endometrial-myometrial interface may be due to dysfunctional uterine hyperperistalsis, dysfunctional contractility of the sub-endometrial myometrium, or both. The demonstration of oestrogen receptors, progesterone receptors and androgen receptors in the adenomyotic tissue suggests that ectopic endometrium is hormone-dependent (Kitawaki 2006). The other proposed aetiology is a disrupted endometrial and myometrial interface related to angiogenesis and trophoblastic invasion associated with pregnancy (Curtis 2002).

The clinical findings of heavy menstrual bleeding, painful menstruation and an enlarged uterus may suggest adenomyosis, but the diagnosis is established by histological analysis. Diffuse adenomyosis arises more frequently in the posterior wall and less frequently in the anterior wall and cornua or cervix (Emge 1962). One of the histological criteria is the presence of endometrial glands seen 2mm or deeper in the myometrium (Bergeron 2006). There is no uniform consensus on the minimal depth of invasion, but most studies use a cut off of 2.5 mm below the basalis layer (Farquhar 2006).

Current advances in diagnostic methods for adenomyosis mean that histological diagnosis by hysterectomy may not always be required. Preoperative diagnosis can be feasible with less invasive techniques, such as ultrasound and magnetic resonance imaging (MRI), and histologic specimens obtained at hysteroscopic biopsy. The three common radiological methods utilised in the clinical diagnosis of adenomyosis are transabdominal ultrasonography, transvaginal ultrasonography and magnetic resonance imaging (MRI). Diagnostic capacity with a transabdominal scan is limited. Transvaginal ultrasonography is a more feasible option and is more cost-effective than MRI.

The diagnostic criteria for adenomyosis using transvaginal ultrasonography can include the presence of one or more of the following findings: 1) a globular uterine configuration; 2) poor definition of the endometrial-myometrial interface; 3) sub-endometrial echogenic linear striations; 4) myometrial anterior-posterior asymmetry; 5) intramyometrial cysts and 6) a heterogeneous myometrial echo texture (Sun 2010). Transvaginal ultrasonography is highly observer-dependent, but experienced investigators have reported satisfactory accuracy in clinically suspected cases (Dueholm 2006).

T2-weighted MRI images of the uterus have identified a specific area of the inner myometrium, named the 'endo-myometrial junctional zone' that can be clearly distinguished from the endometrium and outer myometrium. An irregular thickening of this zone is now recognised as the hallmark of adenomyosis (Hricak 1983). The MRI diagnostic criteria that are highly predictive of histological adenomyosis include a junctional zone measuring more than 12 mm and haemorrhagic high-signal myometrial spots (Larsen 2011).

With the preoperative diagnostic techniques available, new medical and surgical therapies are being investigated that would eliminate the need for hysterectomy. Although surgery remains the mainstay of management in women who have achieved their desired family size, there is an option for medical therapy in women who wish to preserve their fertility and prefer conservative management. Minimally invasive surgical procedures also enable more conservative treatment options, such as endometrial ablation and resection, laparoscopic excision and magnetic resonance-guided focused ultrasound.

See Appendix 2 for a glossary of terms used.

Description of the intervention

Hormonal therapies for adenomyosis include combined oral contraceptives, gonadotropin-releasing hormone agonists, danazol, intrauterine levonorgestrel- or danazol-releasing devices, and aromatase inhibitors. The target tissue for hormonal therapy is the ectopic endometrium. It has been proposed that hormonal therapy reduces the proliferation of endometrial cells by acting on the ectopic endometrium to decrease uterine volume, with a consequent reduction in menstrual blood loss and dysmenorrhoea (Fedele 2008). Systemic hormonal therapy suppresses the oestrogenic induction of the disease by targeting the hypothalamic pituitary axis and the resultant hypo-oestrogenic status regresses the lesions. Local hormonal therapy targets the ectopic endometrium directly and induces atrophy of the endometrial glands and stromal decidualisation (Fedele 1997; Fedele 2008).

How the intervention might work

The rationale for hormonal therapy is the creation of a local hypo-oestrogenic metabolic state, which induces regression of the adenomyosis and relief of symptoms by reducing abnormal uterine bleeding and pain.

Oral contraceptives

Continuous combined oral contraception and high-dose progestins, such as continuous oral norethindrone acetate or subcutaneous depot medroxyprogesterone, have been found to induce regression of adenomyosis temporarily (Garcia 2011). Nausea, breast discomfort and breakthrough bleeding are common side effects observed with oral contraception and progestins.

Gonadotropin-releasing hormone (GnRH) agonists

GnRH agonists were the first drugs used in the treatment of adenomyosis (Grow 1991). They act by binding to GnRH receptors in the pituitary gland, thereby resulting in down-regulation of GnRH activity. This creates a reversible state of medical menopause. The therapy is administered by intramuscular or subcutaneous injection or as a twice-daily nasal spray. There is a reduction in uterine volume and amenorrhoea, and relief of severe dysmenorrhoea. However, discontinuation of therapy prompts re-growth of the uterus and results in recurrence of symptoms (Grow 1991). In a MRI study after GnRH-agonist treatment a decrease in the junctional zone width was observed in adenomyosis patients (Imaoka 2002). This therapy may therefore be indicated for women with diffuse adenomyosis seeking a pregnancy, as GnRH-a also promotes uterine and endometrial receptivity. It is typically used for limited periods of three to six months because of adverse effects, including hot flashes and decreased bone mineral density. Thus, GnRH agonists may be able to control the symptoms of adenomyosis during therapy. However, due to their side effects and the possible rebound effect after cessation of treatment, their use is limited to cases where immediate conception is desired or as preoperative treatment to facilitate surgery due to reduced uterine volume and vascularisation (Lin 2000).

Hormone-containing intrauterine devices (IUDs)

Insertion of a levonorgestrel-releasing intrauterine device (IUD) leads to endometrial gland atrophy and extensive decidual transformation of the stroma. It has been found to down-regulate the oestrogen receptor in the endometrium. Danazol-loaded intrauterine devices induce remission of dysmenorrhoea, reduced menstrual bleeding and spontaneous conception after removing the IUD (Fedele 1997; Fedele 2008).

Aromatase inhibitors

The rationale for treating adenomyosis with aromatase inhibitors is related to their effect in inhibiting the enzyme aromatase P450, which is expressed in the ectopic endometrium (Fedele 1997; Kitawaki 2006). Joint and muscle pain are common side effects of aromatase inhibitors. In addition, loss of bone density, which leads to higher rates of osteoporosis and bone fractures, and hot flashes are reported (Crew 2007).

Why it is important to do this review

Traditionally hysterectomy has been the most common treatment for symptomatic adenomyosis. However, it can be associated with perioperative and postoperative morbidity, decreased quality of life and high healthcare costs. It is estimated that hysterectomies account for most of these costs, recently estimated to exceed USD 2.1 billion annually in United States (Cardozo 2012). Hysterectomy is also not appropriate for women who wish to preserve their fertility. The availability of noninvasive imaging techniques has enabled preoperative diagnosis of adenomyosis. A noninvasive approach for the treatment of adenomyosis may be preferable for most women and could reduce the burden on healthcare systems by a major reduction in surgical intervention. Clinical studies have reported the effectiveness of hormone therapy in adenomyosis (Taran 2013). A systematic review of available studies will, therefore, contribute to the evidence base and may guide the prescription of hormonal treatment in women who are keen for conservative management.

OBJECTIVES

To evaluate the effectiveness and safety of hormonal therapies for uterine adenomyosis in premenopausal women.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished parallel-group randomised controlled trials (RCTs) will be eligible for inclusion. We will exclude non-randomised studies (for example, studies with evidence of inadequate sequence generation, such as alternate days or patient numbers) as they are associated with a high risk of bias. We will include cross-over trials and will only include data from the first phase in the meta-analyses.

Types of participants

Inclusion criteria

Women of reproductive age (15 to 49 years) diagnosed with adenomyosis by either transvaginal ultrasound or MRI, or a combination of both.

Exclusion criteria

We will exclude women with concomitant gynaecological conditions such as uterine fibroids (> 2 cm) and endometriosis.

Types of interventions

Eligible interventions include the following:

Hormonal therapy

- GnRH analogues
- Hormone-containing intrauterine devices
- Oral contraceptives (combined and progestins)
- Aromatase inhibitors

Eligible comparators

- No treatment
- Placebo
- Active control (hysterectomy)
- Conservative surgery (laparoscopic excision of adenomyotic tissue, endometrial ablation and uterine artery embolisation)
- Other hormones (head to head comparison)

Definition of active control: is an agent used as comparator in a clinical trial presumed to be beneficial in the disease? In adenomyosis surgery hysterectomy is the active control.
The different hormonal therapies and their route of administration include the following: GnRH agonists (intramuscular or subcutaneous injection or twice-daily nasal spray); levonorgestrel intrauterine device (IUD), danazol-loaded IUD, aromatase inhibitors (oral), continuous combined contraception - oestrogen and progesterone (oral); high-dose continuous progestins (oral) or subcutaneous depot preparation.
The minimum duration of therapy is three months.
Surgical therapy includes hysterectomy, laparoscopic excision of adenomyotic tissue, endometrial ablation and uterine artery embolisation.

Types of outcome measures

Primary outcomes

- Change in pain/bleeding
    - Change in menstrual bleeding, as measured by objective assessment methods such as haemoglobin, haematocrit or ferritin levels, or by subjective scales such as the pictorial blood loss assessment chart (PBAC) (Higham 1990). The pictorial blood assessment chart score involves self assessment of the amount of blood loss using a modified pictorial questionnaire, which includes questions on the number and appearance of pads. A score greater than 100 is equivalent to blood loss greater than 80 mL, which defines menorrhagia (Barrington 1997).
    - Change in pain score as assessed subjectively by the patient or by using a validated scale such as a visual analogue scale or numeric rating scale.

- Change in quality of life, as measured using a validated instrument. If studies report more than one scale, we will give preference to the SF-36 over other validated generic scales.

- Adverse effects, measured both subjectively by occurrence and by severity of any symptom or sign (listed below), as reported by participants and objectively both during and at the end of treatment and after a drug-free period.
    - Hypo-oestrogenic (low oestrogen levels) effects: atrophic vaginitis, hot flushes, emotional lability, vaginal dryness and changes in libido.
    - Progestin-related adverse effects such as headache, seborrhoea, acne, breast tenderness and weight gain.
    - Decreased bone mineral density measured using any method of measurement: dual-energy X-ray absorptiometry (DEXA)/single-energy photon absorptiometry (SPA).

The order of priority for assessing outcomes will be objective assessment methods followed by subjective methods, to minimise the risk of bias.
We will report the outcomes at three months as this is the minimum duration of therapy.

Secondary outcomes

- Reduction in uterine volume, as assessed by transvaginal ultrasonography or MRI.
- Recurrence rate, as evidenced by ultrasound or MRI or by symptoms of heavy menstrual bleeding or dysmenorrhoea.
- Fertility outcomes (live birth, clinical pregnancy confirmed by ultrasound).

Search methods for identification of studies

This review will draw on the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group (MDSG) as a whole. We will search for all published and unpublished RCTs of adenomyosis without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

Electronic searches

The search strategies will be developed by the Trials Search Co-ordinator of the MDSG.
We will search the following electronic databases:

- The Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials (Appendix 3);
- Cochrane Central Register of Controlled Trials (CENTRAL) (current issue) (Appendix 4);
- MEDLINE (from 1966 onwards) (Appendix 5);
- EMBASE (from 1988 onwards) (Appendix 6);
- CINAHL (from inception) (Appendix 7);

Other electronic sources of trials will include:

- trial registers for ongoing and registered trials:
    - http://www.clinicaltrials.gov (a service of the US National Institutes of Health);
    - http://www.who.int/trialsearch/Default.aspx (World Health Organization International Trials Registry Platform search portal);

- DARE (Database of Abstracts of Reviews of Effects) in *The Cochrane Library* (for reference lists from relevant non-Cochrane reviews);
- Web of Knowledge (http://wokinfo.com/) (another source of trials and conference abstracts);
- OpenGrey (http://www.opengrey.eu/) (for unpublished literature from Europe);
- LILACS (http://regional.bvsalud.org/php/index.php?lang=en) (for trials from the Portuguese and Spanish-speaking world);
- PubMed and Google Scholar (for recent trials not yet indexed in MEDLINE); and
- Chinese databases available at the time of the search.

Searching other resources

We will handsearch reference lists of articles that are retrieved by the search and contact experts in the field for additional data. We will also handsearch relevant journals and conference abstracts in liaison with the Trial Search Co-ordinator.

Data collection and analysis

Selection of studies

Three review authors (KN, NI, SN) will work independently to screen all the available titles and abstracts initially retrieved by the search and we will retrieve the full texts of all potentially eligible studies. Two review authors (KN, NI) will independently examine these full-text articles for compliance with the inclusion criteria and we will select studies that are eligible for inclusion in the review. If the authors are uncertain about eligibility from the title and abstract, we will retrieve and review the full text. Disagreements will be resolved by discussion among the other review authors. We will document the selection process with a PRISMA flow chart.

Data extraction and management

Two review authors (KN, NI) will independently extract the outcome data from the eligible studies using a data extraction form, which we will pilot test. Any differences will be resolved by discussion among the review authors. We will enter the details of the studies included in the systematic review into the table 'Characteristics of included studies'. We will present studies that are excluded from the review in the table 'Characteristics of excluded studies', with a brief statement of the reason for exclusion. We will contact the authors of the included studies if there is incomplete information reported. We will extract separately the treatment categories of the various hormonal therapies and modes of hormone delivery.

Assessment of risk of bias in included studies

Two review authors (KN, NI) will assess the risk of bias of the included studies under the six domains of the Cochrane 'Risk of bias' tool outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Sequence generation: evidence that an unpredictable random process was used.
2. Allocation concealment: evidence that the allocation list was not available to anyone involved in the recruitment process.
3. Blinding of participants, clinicians and outcome assessors: evidence that knowledge of allocation was not available to those involved in subsequent treatment decisions or follow-up efforts.
4. Completeness of outcome data: evidence that any losses to follow-up were low and comparable between groups.
5. Selective outcome reporting: evidence that major outcomes had been reported in sufficient detail to allow analysis, independently of their apparent statistical significance.
6. Other potential sources of bias. There may be different diagnostic criteria for adenomyosis and this is a potential cause of bias. Evidence of miscellaneous errors or circumstances might influence the internal validity of trial results.

We will seek missing details from the authors. We will present all details in the 'Risk of bias' table for each included study and classify them as 'high', 'low' and 'unclear' risk of bias. We will resolve any differences by discussion or by consulting the third author.

Measures of treatment effect

We will report dichotomous data (bleeding, recurrence, adverse effects) as an odds ratio (OR) with 95% confidence interval (CI). In the case of continuous data (dysmenorrhoea, serum ferritin, quality of life, reduction in uterine volume) on same scale, we will present results as mean differences (MD) with 95% CIs. If similar outcomes are reported using different scales, we will use the standardised mean difference (SMD) with 95% CI. Reduction in heavy menstrual bleeding is one of the primary outcomes and we intend to use change in scores from baseline as the measure of treatment effects. We will combine change and final scores if they use the same units. If final scores are not reported, the preferred measure is change scores.

Unit of analysis issues

The primary analysis will be per woman randomised.

Dealing with missing data

We will contact the authors of the randomised studies to obtain missing data or to resolve any queries that may arise. We will analyse the data on an intention-to-treat basis as far as possible and we will make attempts to obtain missing data from the original trialists. Where these are unobtainable, we will impute individual values for the primary outcomes only. We will subject any imputation undertaken to sensitivity analysis.
If studies report sufficient detail to calculate mean differences but no information on associated standard deviations (SD), we will assume the outcome to have a standard deviation equal to the highest SD from other studies within the same analysis.

Assessment of heterogeneity

We will consider whether the clinical and methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. We will assess heterogeneity using the I^2 statistic. If we find substantial heterogeneity ($I^2 > 50\%$) among the studies we will explore the possible sources by performing sensitivity and subgroup analyses (Higgins 2003; Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aim to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there are 10 or more studies in an analysis, we will use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

If the studies are sufficiently similar in their clinical and methodological aspects and there is no significant heterogeneity, we will use a fixed-effect model to combine the data from the primary studies.
We will perform statistical analysis for the following comparisons with Review Manager (RevMan) 5 (RevMan 2014), in accordance with the guidelines for statistical analysis developed by The Cochrane Collaboration:

- hormonal therapy versus no treatment;
- hormonal therapy versus placebo;
- hormonal therapy versus active control (hysterectomy);
- hormonal therapy versus conservative surgery;
- hormonal therapy A versus hormonal therapy B.

If data are available, we will stratify the primary outcomes in each comparison by type of hormone.
The outcomes 'change in bleeding', 'pain during menstruation' and 'pregnancy' are considered positive outcomes of effectiveness and as a consequence we will consider higher numbers as a benefit. The outcomes 'recurrence rate' and 'adverse effects' are negative effects and we will consider higher numbers harmful. We will display graphically in the meta-analysis forest plots an increase in the odds of a particular outcome, which may be beneficial or detrimental, to the right of the centre line and a decrease in the odds of an outcome to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

If we find significant heterogeneity and data are available, we will conduct subgroup analyses to determine the separate evidence within the following subgroups. However, we will interpret such analyses very cautiously, as subgroups of participants are not randomised comparisons.

- Subgroups by dose of administration of hormones.
- Subgroups by route of administration of hormones.
- Subgroups by duration of administration, less than six months versus more than six months.

If we detect substantial heterogeneity, we will explore the possible explanations in sensitivity analyses. We will take any statistical heterogeneity into account when interpreting the results, especially if there is any variation in the direction of effect.

Sensitivity analysis

To test the robustness of our findings, we will carry out sensitivity analyses of the primary outcomes to explore the effect of

trial quality (risk of bias), after excluding studies with high risk of bias. We will also re-analyse studies using different scales for assessment of symptoms. The analyses will look at whether the review conclusions would have been different if the eligibility was restricted to studies that do not have high risk of bias, a random-effects model had been adopted, alternative imputation strategies had been implemented and the summary effect measure had been risk ratio rather than odds ratio.

'Summary of findings' table

We will prepare a 'Summary of findings' table using GRADEpro or the Guideline Development Tool software for evaluating the overall quality of the body of evidence for the main review outcomes (change in pain, change in bleeding, change in quality of life, adverse effects). We will use the GRADE criteria that assess the risk of bias, consistency of effects, imprecision, indirectness and any publication bias. We will justify, document and incorporate into the reporting of the results for each outcome whether the quality of evidence is high, moderate or low.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Differences between adenomyosis and endometriosis

- Site of endometriotic tissues. In endometriosis, the endometrium abnormally develops outside the uterus. In adenomyosis, instead of lining the uterus, the endometrium grows into the muscular walls of the uterus.
- Aetiology. Endometriosis is thought to be due to retrograde menstruation back into the fallopian tube instead of exiting from the body. Adenomyosis is thought to be due to uterine damage from childbirth or surgery. However, there is no agreed aetiology for either of these conditions.
- Symptoms. Both conditions share symptoms such as heavy menstrual bleeding and painful periods. However, in adenomyosis the pain occurs during menstruation, whereas in endometriosis it may be present before and after menstruation, and also cause painful intercourse. In addition, adenomyosis may be associated with a tender and enlarged uterus.
- Endometriosis occurs during a woman's childbearing years, but it can also occur in women who have never given birth. This can also cause infertility. Adenomyosis can also occur later in a woman's childbearing years.

Appendix 2. Glossary of terms

Adenomyosis: uterine thickening that occurs when endometrial tissue, which normally lines the uterus, moves into the outer muscular walls of the uterus.
Dysmenorrhoea: pain associated with menstruation.
Endometriosis: a condition in which the tissue that lines the inside of the uterus (called the endometrium or endometrial lining) is found growing in other areas outside of the uterus (commonly the ovaries, fallopian tubes and nearby structures of the pelvis).
Hysterectomy: refers to surgical removal of the uterus.
Iatrogenic : refers to illness caused by medical examination or treatment.
Menorrhagia: heavier and increased amount of flow occurring at regular intervals or loss of > 80 mL of blood.
Multiparous : refers to a woman having borne more than one child.
Myometrium : the middle layer of the uterine wall, consisting mainly of smooth muscle cells
Stroma : refers to connective or supporting tissue of the endometrial cell.

Appendix 3. MDSG search string

Menstrual disorders and subfertility database search for KN1930 20.01.14
Title CONTAINS "Adenomas " or "adenomyosis" or Title CONTAINS "Adenomas " or "adenomyosis"

Appendix 4. CENTRAL search strategy

1 Gonadotropin-releasing hormone agonist$.tw.
2 Gonadotrophin-releasing hormone agonist$.tw.
3 GnRH agonist$.tw. (684)
4 buserelin/ or goserelin/ or leuprolide/ or nafarelin/ or triptorelin pamoate/
5 histrelin.tw.
6 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw.
7 (Lupron or Eligard).tw.
8 (Suprefact or Suprecor).tw.
9 (Supprelin or Vantas).tw.
10 Zoladex.tw.
11 (Suprelorin or Ovuplant).tw.
12 Synarel.tw.
13 decapeptyl.tw.
14 or/1-13
15 exp Danazol/

16 Danazol.tw.
17 danoval.tw.
18 danatrol.tw.
19 Danocrine$.tw.
20 17-alpha-ethinyl testosterone.tw.
21 or/15-20
22 exp Levonorgestrel/
23 levonorgestrel.tw.
24 norplant.tw.
25 mirena$.tw.
26 (LNG IUS or LNG IUD).tw.
27 Norgestrel.tw.
28 or/22-27
29 exp aromatase inhibitors/ or aminoglutethimide/ or fadrozole/
30 aromatase inhibitor$.tw.
31 aminoglutethimide.tw.
32 fadrozole.tw.
33 (Testolactone or Teslac).tw.
34 (Anastrozole or arimidex).tw.
35 (Letrozole or Femara).tw.
36 (Exemestane or Aromasin).tw.
37 (Vorozole or Rivizor).tw.
38 (Formestane or Lentaron).tw.
39 (Fadrozole or Afema).tw.
40 or/29-39
41 14 or 21 or 28 or 40
42 adenomyoma$.tw.
43 Adenomyosis.tw.
44 Endometriosis interna.tw.
45 42 or 43 or 44
46 41 and 45

Appendix 5. MEDLINE search strategy

1 exp Adenomyosis/
2 adenomyoma$.tw.
3 Adenomyosis.tw.
4 adenomyoses.tw.
5 Endometriosis interna.tw.
6 Adenomyotic.tw.
7 or/1-6
8 Gonadotropin-releasing hormone agonist$.tw.
9 Gonadotrophin-releasing hormone agonist$.tw.
10 GnRH agonist$.tw.
11 buserelin/ or goserelin/ or leuprolide/ or nafarelin/ or triptorelin pamoate/
12 histrelin.tw.
13 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw.
14 (Lupron or Eligard).tw.
15 (Suprefact or Suprecor).tw.
16 (Supprelin or Vantas).tw.
17 Zoladex.tw.
18 (Suprelorin or Ovuplant).tw.

19 Synarel.tw.
20 decapeptyl.tw.
21 or/8-20
22 exp Danazol/
23 Danazol.tw.
24 danoval.tw.
25 danatrol.tw.
26 Danocrine$.tw.
27 17-alpha-ethinyl testosterone.tw.
28 or/22-27
29 exp Levonorgestrel/
30 levonorgestrel.tw.
31 norplant.tw.
32 mirena$.tw.
33 (LNG IUS or LNG IUD).tw.
34 Norgestrel.tw.
35 or/29-34
36 exp aromatase inhibitors/ or aminoglutethimide/ or fadrozole/
37 aromatase inhibitor$.tw.
38 aminoglutethimide.tw.
39 fadrozole.tw.
40 (Testolactone or Teslac).tw.
41 (Anastrozole or arimidex).tw.
42 (Letrozole or Femara).tw.
43 (Exemestane or Aromasin).tw.
44 (Vorozole or Rivizor).tw.
45 (Formestane or Lentaron).tw.
46 (Fadrozole or Afema).tw.
47 or/36-46
48 21 or 28 or 35 or 47
49 7 and 48
50 randomized controlled trial.pt.
51 controlled clinical trial.pt.
52 randomized.ab.
53 randomised.ab.
54 placebo.tw.
55 clinical trials as topic.sh.
56 randomly.ab.
57 trial.ti.
58 (crossover or cross-over or cross over).tw.
59 or/50-58
60 exp animals/ not humans.sh.
61 59 not 60
62 49 and 61

Appendix 6. EMBASE search strategy

1 exp adenomyosis/
2 endometrial adenoma$.tw.
3 adenomyoma$.tw.
4 Adenomyosis.tw.
5 adenomyoses.tw.
6 Endometri$ interna.tw.
7 Adenomyotic.tw.
8 or/1-7
9 exp gonadorelin agonist/
10 Gonadotropin-releasing hormone agonist$.tw.
11 Gonadotrophin-releasing hormone agonist$.tw.
12 GnRH agonist$.tw.
13 exp buserelin acetate/ or exp buserelin/
14 exp goserelin/
15 exp leuprorelin/
16 exp nafarelin acetate/ or exp nafarelin/
17 exp triptorelin/
18 exp histrelin/
19 histrelin.tw.
20 (buserelin or goserelin or leuprolide or nafarelin or triptorelin).tw.
21 (Lupron or Eligard).tw.
22 (Suprefact or Suprecor).tw.
23 (Supprelin or Vantas).tw.
24 Zoladex.tw.
25 (Suprelorin or Ovuplant).tw.
26 Synarel.tw.
27 decapeptyl.tw.
28 or/9-27
29 exp danazol/
30 Danazol.tw.
31 danoval.tw.
32 danatrol.tw.
33 Danocrine$.tw.
34 17-alpha-ethinyl testosterone.tw.
35 or/29-34
36 exp levonorgestrel/
37 levonorgestrel.tw.
38 norplant.tw.
39 mirena$.tw.
40 (LNG IUS or LNG IUD).tw.
41 (LNGIUS or LNGIUD).tw.
42 Norgestrel.tw.
43 or/36-42
44 exp aromatase inhibitor/
45 exp aminoglutethimide/
46 exp fadrozole/
47 aromatase inhibitor$.tw.
48 aminoglutethimide.tw.
49 fadrozole.tw.
50 (Testolactone or Teslac).tw.
51 (Anastrozole or arimidex).tw.

52 (Letrozole or Femara).tw.
53 (Exemestane or Aromasin).tw.
54 (Vorozole or Rivizor).tw.
55 (Formestane or Lentaron).tw.
56 (Fadrozole or Afema).tw.
57 or/44-56
58 28 or 35 or 43 or 57
59 8 and 58
60 Clinical Trial/
61 Randomized Controlled Trial/
62 exp randomization/
63 Single Blind Procedure/
64 Double Blind Procedure/
65 Crossover Procedure/
66 Placebo/
67 Randomi?ed controlled trial$.tw.
68 Rct.tw.
69 random allocation.tw.
70 randomly allocated.tw.
71 allocated randomly.tw.
72 (allocated adj2 random).tw.
73 Single blind$.tw.
74 Double blind$.tw.
75 ((treble or triple) adj blind$).tw.
76 placebo$.tw.
77 prospective study/
78 or/60-77
79 case study/
80 case report.tw.
81 abstract report/ or letter/
82 or/79-81
83 78 not 82
84 59 and 83

Appendix 7. CINAHL search strategy

CINAHL search strategy for KN1930

#	Query
S69	S54 AND S68
S68	S55 OR S56 or S57 or S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67
S67	TX allocat* random*
S66	(MH "Quantitative Studies")
S65	(MH "Placebos")

(*Continued*)

S64	TX placebo*
S63	TX random* allocat*
S62	(MH "Random Assignment")
S61	TX randomi* control* trial*
S60	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S59	TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S58	TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S57	TX clinic* n1 trial*
S56	PT Clinical trial
S55	(MH "Clinical Trials+")
S54	S6 AND S53
S53	S27 OR S32 OR S40 OR S52
S52	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50
S51	TX Afema
S50	TX (Formestane or Lentaron)
S49	TX (Vorozole or Rivizor)
S48	TX (Exemestane or Aromasin)
S47	TX (Letrozole or Femara)
S46	TX (Anastrozole or arimidex)
S45	TX (Testolactone or Teslac)
S44	TX aromatase inhibitor*
S43	TX fadrozole
S42	TX aminoglutethimide
S41	(MH "Aromatase Inhibitors+")

(*Continued*)

S40	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39
S39	TX Norgestrel
S38	TX (LNGIUS or LNGIUD)
S37	TX (LNG IUS or LNG IUD)
S36	TX mirena*
S35	TX norplant
S34	TX levonorgestrel
S33	(MH "Levonorgestrel")
S32	S28 OR S29 OR S30 OR S31
S31	TX 17-alpha-ethinyl testosterone
S30	TX Danocrine*
S29	TX Danazol
S28	(MM "Danazol")
S27	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26
S26	TX decapeptyl
S25	TX Synarel
S24	TX Zoladex
S23	TX (Supprelin or Vantas)
S22	TX (Suprefact or Suprecor)
S21	TX (Lupron or Eligard)
S20	TX leuprolide
S19	TX histrelin
S18	TX triptorelin
S17	TX nafarelin

(*Continued*)

S16	(MM "Nafarelin")
S15	TX leuprorelin
S14	(MM "Leuprolide")
S13	TX goserelin
S12	(MM "Goserelin")
S11	TX buserelin
S10	TX GnRH agonist*
S9	TX Gonadotrophin-releasing hormone agonist*
S8	TX Gonadotropin-releasing hormone agonist*
S7	(MH "Gonadorelin+")
S6	S1 OR S2 OR S3 OR S4 OR S5
S5	TX Adenomyotic
S4	TX Adenomyosis
S3	TX adenomyoma*
S2	TX endometrial adenom*
S1	(MM "Adenomyosis")

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