Progestogen only versus combined oral contraceptive pills for fibroid related heavy menstrual bleeding (Protocol)

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[Intervention Protocol]

Progestogen only versus combined oral contraceptive pills for fibroid related heavy menstrual bleeding

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ABSTRACT

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

To assess, in women with fibroid related heavy menstrual bleeding, the effectiveness and safety of progestogen-only contraceptives (oral, subdermal, injectable and implanted) compared to combined oral contraceptive pills.

BACKGROUND

Uterine fibroids (or leiomyoma) are a common gynaecologic problem. Uterine fibroids are benign growths of smooth muscle and connective tissue of the uterus (Lethaby 2005; Vollenhoven 1998). They develop from tiny groups of uterine muscle cells and are composed of numerous copies of the same or very few cells, which is termed monoclonal expansion (Cramer 1990; Marshall 1997; Vollenhoven 1998). There are four subtypes of uterine fibroids, depending on their location within the uterus. These include submucous (beneath the endometrial lining or immediately adjacent to the uterine cavity); intramural (entirely within the wall of the uterus); subserous (beneath the outer uterine covering or serosa) and pedunculated (attached to the uterus by a stalk) (Marshall 1997). Of all the four types, the submucous category is most commonly associated with heavy menstrual bleeding.

The prevalence of uterine fibroids varies from place to place (Vollenhoven 1998). Prevalence studies report that 5.4% to 77% of women have uterine fibroids, depending on the population under consideration and the diagnostic method used (Lethaby 2005; Lurie 2005). Women at increased risk of uterine fibroids include women who attained menarche (first menstruation) at a young age (Lumbiganon 1996); women who have neither given birth to a child nor miscarried before (nulliparous women) (Chen 2001; Faerstein 2001; Sato 2000); women who gave birth after one or more previous myomectomies (surgical removal of uterine fibroids) (Fedele 1995); long interval since last birth or miscarriage (Chen 2001); black race, especially African and African-American women (Faerstein 2001; Kjerulff 1996) and high body mass index (Parazzini 1988; Parazzini 1996). Uterine fibroids increase with age until menopause, after which new fibroids are rare (Baird 2003; Marshall 1997).

While uterine fibroids may be asymptomatic (Parker 2007), they

may be associated with heavy menstrual bleeding, dysmenorrhoea (painful menstruation), pelvic pressure and obstructive symptoms such as urinary frequency and constipation. Approximately one-third to one-half of asymptomatic women become symptomatic at some point during their reproductive lives, experiencing irregular uterine bleeding, anaemia, pelvic pain or recurrent pregnancy loss (three or more miscarriages). These symptoms, if not properly and promptly managed, can lead to increased morbidity and mortality, especially in developing countries. The complications of uterine fibroids can have serious impact on the lives of affected women. Hence, uterine fibroids constitute a major gynaecological and public health problem.

Management of uterine fibroids starts from a good history and physical examination. A large fibroid uterus can often be palpated as a firm pelvic mass. The ideal first-line investigation for the diagnosis of uterine fibroids includes pelvic ultrasound (transvaginal and transabdominal). Magnetic resonance imaging (MRI) is useful when planning surgery or as a baseline prior to uterine artery embolization (UAE).

Management of uterine fibroids has been associated with substantial economic burden and healthcare cost. Hartmann et al estimated a healthcare cost in the United States exceeding USD 4600 during the year following a woman's diagnosis of fibroids (Hartmann 2006). In fact, national medical costs associated with fibroids exceed 2 billion dollars annually (Flynn 2006). These estimates of costs were from a societal perspective.

Description of the condition

The etiology of uterine fibroids is not very well understood. However, there is some evidence that estrogens and progestogens contribute to the development of uterine fibroids (Cowan 2004). Progestogens in particular are capable of increasing the mitotic rate of tumours in vitro and thus may have an effect on growth factors or their receptors during the luteal phase (Cowan 2004). Other evidence that points towards the role of hormones includes the discovery of estrogen and progestin receptors on fibroids as well as the observation that fibroids usually shrink after menopause but regrowth may occur with hormonal therapy (Cowan 2004).

Approximately half of all women with uterine fibroids will suffer from clinical symptoms (Sakuhara 2006). The most common clinical presentation is menorrhagia (heavy menstrual bleeding). Menorrhagia is subjectively defined as a complaint of heavy cyclical menstrual bleeding occurring over several consecutive cycles (RCOG 1998). Objectively, it is a total menstrual blood loss equal to or greater than 80 ml per menstruation (Hallberg 1966a). This degree of blood loss can cause disturbances of a woman's occupational, social or sexual life. The presence of such bleeding can also raise concerns about possible underlying endometrial or cervical disease (especially endometrial or cervical cancer) (Hallberg 1966b).

Other presenting symptoms of fibroids include pelvic pain, pelvic pressure, abdominal distension, infertility, lower extremity swelling, constipation and intestinal obstruction (Okogbo 2011). In addition, the presence of uterine fibroids can lead to complications during pregnancy. These include spontaneous miscarriage, intrauterine growth restriction, preterm labor, obstructed labor, postpartum haemorrhage and hydronephrosis (abnormal dilatation of the kidney and ureters) (Okogbo 2011).

Submucous fibroids are described clinically as having the greatest influence on heavy menstrual bleeding and reproductive outcomes. However, subserous fibroids have the greatest pressure effects on surrounding organs. The position of subserous fibroids with respect to position and size relative to other surrounding structures such as the bladder, bowel, vaginal vault and nerve bundles in the pelvis is most often used to explain pressure symptoms (for example increased urinary frequency, constipation or pain with bowel movements, pressure or pain with intercourse, and more generalized pain symptoms).

Uterine fibroids can be managed expectantly, medically or surgically. Medical treatment has been increasingly preferred among women and has been used as a cost effective pharmacological treatment to prevent or decrease the amount of heavy uterine bleeding from uterine fibroids. Levonorgestrel-releasing intrauterine devices were shown to have led to greater reductions in menstrual blood loss and higher rates of complete menorrhagia treatment compared to medroxyprogesterone acetate (Kaunitz 2010). Combined hormonal contraceptives and progestogens are commonly used to regulate heavy uterine bleeding resulting from uterine fibroids (Carr 1993; Friedman 1988). These medications can be useful in women with co-existing dysmenorrhoea (painful menstruation) or oligo-ovulation (defined as infrequent or irregular ovulation, usually with cycles of $\geq$ 36 days or < 8 cycles a year). There is also evidence that these contraceptives may be associated with a decreased risk of uterine fibroids in some women (Grigorieva 2003; Marshall 1998).

Surgical and minimally invasive treatments for uterine fibroids include myomectomy (which can be done via hysteroscopic, laparoscopic, abdominal and robotic methods), hysterectomy (laparoscopic; laparoscopic assisted vaginal, abdominal and robotic), endometrial resection or ablation, uterine artery embolization, magnetic resonance-guided focused ultrasound ablation, laparoscopic uterine artery occlusion with or without utero-ovarian occlusion and bipolar radiofrequency ablation (intrauterine ultrasound-guided or laparoscopic-guided). Treatment needs to be highly individualised for women with symptomatic uterine fibroids.

Description of the intervention

Both oral contraceptives and progestins have been used to treat heavy menstrual bleeding. The combined oral contraceptive pill contains both estrogens and progestogens, whereas the progestogen-only pill lacks estrogen. The combined oral contraceptive pills

are classified according to the type of progestogen they contain and the phase of the menstrual cycle in which they act. Based on the type of progestogen which they contain, they are classified as second generation (norethisterone and levonorgestrel) and third generation (desogestrel, gestodene and norgestimate) oral contraceptive pills. The first generation oral contraceptive pills are no longer in use because they contained high estrogen levels, which caused numerous adverse effects notably thromboembolic disorders. Combined oral contraceptive pills also come with varying doses of estrogen.

It is important to define dosage regimens of oral contraceptive pills. In the United Kingdom, combined oral contraceptive pills are defined as low strength preparations (containing ethinyl estradiol, 20 µg) and standard strength preparations (containing ethinyl estradiol 30 or 35 µg or in 30 to 40 µg phased preparations). In most other parts of the world, 50 µg of estradiol is considered high dose, 30 to 35 µg average dose, and 20 µg or less is considered low dose. Estrogen doses in the oral contraceptive pill should not exceed 50 µg as higher doses increase the risk of complications.

There are some risks associated with combined oral contraceptives that may limit their prescription in certain groups (for example in smokers, obese women, women with a family history of thromboembolism, cardiovascular disease, liver disease or genital bleeding). Some of the absolute contraindications to the use of the combined oral contraceptives include past and present history of cardiovascular disease like family history of being less than 45 years with abnormal lipid profile or haemostatic profile, poorly controlled diabetes or diabetic complications like diabetic retinopathy, blood pressure consistently greater than 160/95 mm Hg, smokers of more than 40 cigarettes per day, smokers over 35 years, women with body mass index (BMI) greater than 35, and focal or crescendo migraine or migraine requiring ergotamine treatment. Other absolute contraindications to the use of the combined oral contraceptive pill include active liver disease like recurrent cholestatic jaundice or cholestatic jaundice occurring in pregnancy, Dubin-Johnson or Rotor's syndrome, liver adenoma or carcinoma, gallstones; pregnancy; undiagnosed genital tract bleeding; estrogen dependent tumours like breast cancer; and medical conditions affected by sex steroids like pemphigoid gestationis. Relative contraindications include hyperprolactinaemia, long-term immobilization, severe depression, family history greater than 45 years with normal lipid and haemostatic profiles, well controlled diabetes mellitus, systolic blood pressure of 135 to 160 mm Hg, diastolic blood pressure of 85 to 95 mm Hg, 5 to 40 cigarettes/day, BMI of 30 to 35 and uncomplicated migraine.

There are four major types of progestogen-only contraceptives. These include the progestogen only pill (POP); injectables; implants and intrauterine systems. The levonorgestrel intrauterine system (LNG-IUS) is a second generation synthetic progestin based contraceptive that is highly efficacious and reversible (Shawki 2009). LNG-IUS (also called Mirena) is a T-shaped device composed of a polyethylene frame 32 mm long with a cylinder around the vertical arm which contains the hormone levonorgestrel (LNG). Of the 52 mg of the total hormone in the cylinder, approximately 20 µg is released per day. It can be inserted into the uterus at any time during the menstrual cycle as long as there is no unprotected sexual intercourse (Endrikat 2009; Hurskainen 2004). Its main actions are on the uterus.

The adverse effects of the progestogen-only contraceptives include irregular vaginal bleeding and changes in the menstrual bleeding pattern; delayed return of fertility after discontinuing depomedroxyprogesterone acetate; weight gain and osteoporosis (bone loss) as a result of hypoestrogenism with long-term treatment.

How the intervention might work

Using immunohistochemistry, aromatase expression has been detected in the endometrium of patients with uterine fibroids presenting with heavy menstrual bleeding (Maia 2008). Combined oral contraceptives have been shown to work by reducing both aromatase expression in the endometrium and heavy menstrual bleeding in patients with symptomatic uterine fibroids (Maia 2007). This suggests that oral contraceptives are effective in reducing the heavy menstrual bleeding associated with uterine fibroids. Also, estrogens in oral contraceptive pills are known to increase angiogenesis (blood vessel formation) and cyclo-oxygenase (COX)-2 expression in the endometrium (Ebert 2005; Ishira 2003; Kelly 2002).

Progestogens exerts an anti-inflammatory effect on the endometrium of patients with uterine fibroids by suppressing nuclear factor (NF)-kappa B induced genes, which in turn leads to reduction of heavy menstrual flow (Critchley 2003; Kelly 2002). The progestin intrauterine device (IUD) has been shown to be effective in decreasing heavy menstrual periods because of the constant release of levonorgestrel into the uterus, which suppresses the endometrium subsequently reducing uterine bleeding (Endrikat 2009). LNG-IUS suppresses endometrial proliferation and endovascular changes to prevent heavy menstrual bleeding. Its main effect is due to an overall reduction in uterine blood flow and endometrial thickness. This endometrial transformation causes atrophy and reduction in the number of steroid receptors, which in turn alters local progestogen regulated mediators (Endrikat 2009). This effect leads to a significant reduction in menstrual blood loss (Endrikat 2009; Rauramo 2004; Reid 2005) and, consequently, an increase in haemoglobin levels (Luukkainen 1995). In addition, the local administration of LNG-IUS produces minor systemic hormonal effects. Local progestins also have both androgenic and antiestrogenic endometrial activities resulting from downregulation of estrogenic receptors (Hurskainen 2004). Overall, strong endometrial suppression explains the progestogenic effect on the uterus, particularly in women with fibroid uteri.

Why it is important to do this review

Heavy menstrual bleeding (menorrhagia) is the commonest and most debilitating symptom of uterine fibroids. About one-third of women with uterine fibroids experience fibroid related heavy menstrual bleeding at some point in their lives. The combined oral contraceptive pills and progestogen-only contraceptives have both been shown to reduce fibroid related heavy menstrual bleeding. However, while some studies have found that progestogen only contraceptives (for example LNG-IUS) reduced menstrual blood loss better than oral contraceptive pills, others have found that combined oral contraceptive pills are better at reducing heavy menstrual blood loss. Again, mixed results have been obtained for patient satisfaction or health related quality of life (HRQOL) in studies comparing progestogen only to combined oral contraceptives. Results regarding the impact of combined oral contraceptives and progestogen only contraceptives on fibroid related heavy menstrual bleeding and patient satisfaction or health related quality of life are inconsistent at the moment. Also, there is no Cochrane review that has examined the efficacy, safety and adverse effects of these methods in controlling fibroid related heavy menstrual bleeding. This prompted the present Cochrane review.

OBJECTIVES

To assess, in women with fibroid related heavy menstrual bleeding, the effectiveness and safety of progestogen-only contraceptives (oral, subdermal, injectable and implanted) compared to combined oral contraceptive pills.

METHODS

Criteria for considering studies for this review

Types of studies

The review will analyse randomised controlled trials (RCTs) comparing progestogen only contraceptives with combined oral contraceptives in women with fibroid related heavy menstrual bleeding. Only trials that are either clearly randomised or claim to be randomised and do not have evidence of inadequate sequence generation, such as date of birth or hospital number, will be included. Crossover trials will be included in the review for completeness but data from the first phase only will be included in meta-analyses as the crossover is not a valid design in the context of this review.

Types of participants

Women who presented with fibroid related heavy menstrual bleeding or pressure symptoms from uterine fibroids will be included in the review. The women must have had an ultrasound or MRI diagnosis of leiomyoma (uterine fibroids).

Types of interventions

Trials comparing progestogen only contraceptives (oral, subdermal, injectable and implanted) versus combined oral contraceptive pills for fibroid related heavy menstrual bleeding.

Types of outcome measures

Primary outcomes

1. Reduction in menstrual blood loss (to be evaluated using pictorial blood assessment charts (PBAC) and alkaline haematin methods of assessing blood loss).
2. Improvement in haemoglobin levels (evaluated using any change in haematocrit or haemoglobin levels before and after treatment of fibroids).

Secondary outcomes

1. Changes in quality of life (measured using Health Related Quality of Life-4 (HRQoL-4) questionnaires that assess the quality of life of the patients in the previous month). The HRQOL-4 questionnaire includes the following four questions: health as assessed by the patient, usually as excellent, very good, good, fair or poor; number of days feeling physically unhealthy; number of days feeling mentally unhealthy (including stress, depression and problems with emotions); and lost days.
2. Adverse effects of the interventions (including irregular menstrual or breakthrough bleeding, headache, dizziness, breast tenderness and enlargement, weight gain, nausea and vomiting, severe abdominal pains, chest pains, visual disturbances, hypertension, development of migraine, development of cerebrovascular accidents, venous thromboembolism, development of breast and cervical cancer, delayed return of fertility and osteoporosis).
3. Improvement in other symptoms associated with uterine fibroids (including improvement in pressure symptoms and development of new fibroids, detected by measuring the fibroids before and after treatment with oral contraceptives or the progestogens).

Search methods for identification of studies

We will search for all published and unpublished RCTs of progestogen only versus combined oral contraceptives for fibroid related heavy menstrual bleeding, without language restriction and

in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator:

Electronic searches

The following electronic databases, trial registers and websites will be searched from inception to the present: Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of controlled trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and CINAHL. The MEDLINE search will be combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the searching chapter of the *Cochrane Handbook for Systematic Reviews of Interventions*. The EMBASE search will be combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials will include the following.

- Trial registers for ongoing and registered trials: 'Current Controlled Trials' (www.controlled-trials.com/), 'ClinicalTrials.gov' a service of the US National Institutes of Health (http://clinicaltrials.gov/ct2/home) and the 'World Health Organization International Trials Registry Platform search portal' (www.who.int/trialsearch/Default.aspx).
- Citation indexes (http://scientific.thomson.com/products/sci/).
- Conference abstracts in the ISI Web of Knowledge (http://isiwebofknowledge.com/).
- LILACS database, as a source of trials from the Portuguese and Spanish speaking world (http://bases.bireme.br/cgibin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F).
- Clinical Study Results for clinical trial results of marketed pharmaceuticals (www.clinicalstudyresults.org/).
- PubMed (www.ncbi.nlm.nih.gov/pubmed/), the random control filter for PubMed will be taken from the searching chapter of the *Cochrane Handbook for Systematic Reviews of Interventions*.
- OpenSIGLE database (http://opensigle.inist.fr/) and Google for grey literature.

Searching other resources

We will handsearch reference lists of articles retrieved by the search and make personal contact with experts in the field and with the manufacturers of combined oral contraceptives and progestogens to obtain any additional relevant data. We will also handsearch any relevant journals and conference abstracts that are not covered in the MDSG register, in liaison with the Trials Search Co-ordinator.

Data collection and analysis

Data collection and analysis will be conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Two review authors will independently scan the titles and abstracts of articles retrieved by the search and obtain the full text of all potentially eligible studies. They will independently examine the full text articles for compliance with the inclusion criteria and select studies eligible for inclusion in the review. We will correspond with study investigators, if required, to clarify study eligibility (for example with respect to participant eligibility criteria and allocation method). Disagreements as to study eligibility will be resolved by consensus or by discussion with a third author.

Data extraction and management

We will extract data from eligible studies using a data extraction form designed and pilot-tested by the authors. Where studies have multiple publications, the main trial report will be used as the reference and additional details supplemented from secondary papers. We will correspond with study investigators in order to resolve any data queries, as required. Two review authors (one a methodologist and one a topic area specialist) will independently extract the data. Any disagreement between these authors will be resolved by a third author.

Assessment of risk of bias in included studies

The included studies will be assessed for risk of bias using the Cochrane risk of bias assessment tool to assess: sequence generation; allocation concealment; blinding of participants, providers and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias such as funding. Two authors will assess these six domains, with any disagreements resolved by consensus or by discussion with a third author. All judgments will be fully described. The conclusions will be presented in the risk of bias table and incorporated into the interpretation of review findings by means of sensitivity analyses.

Measures of treatment effect

For dichotomous data, the numbers of events in the control and intervention groups of each study will be used to calculate Peto odds ratios. For continuous data, mean differences between treatment groups will be calculated if all studies report exactly the same outcomes. If similar outcomes are reported on different scales, the standardised mean difference will be calculated. Ordinal data (for example quality of life scores) will be treated as continuous data. The 95% confidence intervals will be presented for all outcomes.

Unit of analysis issues

All outcomes will be expressed per woman randomised. In the case of crossover trials, only data from the first phase will be included. In the case of cluster randomised data, a sensitivity analysis will be performed excluding those studies.

Dealing with missing data

The data will be analysed on an intention-to-treat basis, as far as possible, and attempts will be made to obtain missing data from the original investigators. Where these are unobtainable, imputation of individual values will be undertaken for the primary outcomes only. If studies report sufficient detail to calculate mean difference but no information on the associated standard deviation (SD), the outcome will be assumed to have a standard deviation equal to the highest SD from other studies within the same analysis. For other outcomes, only the available data will be analysed. Any imputation undertaken will be subjected to sensitivity analysis.

Assessment of heterogeneity

The authors will consider whether the clinical and methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a meaningful summary. Statistical heterogeneity will be assessed by the measure of the I^2 statistic. An I^2 value greater than 50% will be taken to indicate substantial heterogeneity (Higgins 2011). If substantial heterogeneity is detected, possible explanations will be explored in sensitivity analyses.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, the authors will 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, a funnel plot will be used to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies). Within study reporting, bias will be detected by seeking published protocols and comparing the outcomes between the protocol and the final published study.

Data synthesis

The data from primary studies will be combined using fixed-effect models in the following comparisons.

1. Progestogen only versus combined oral contraceptive pills (OCPs) stratified by dose:
(i) low dose (OCPs containing less than 20 µg of ethinyl estradiol);
(ii) standard or average dose (OCPs containing 30 to 35 µg of ethinyl estradiol).

2. Progestogen only versus combined oral contraceptive pills stratified by type:
(i) LNG-IUS (intrauterine progestogen);
(ii) depot-medroxyprogesterone acetate (intramuscular progestogen);
(iii) progestogen only pills (oral progestogen);
(iv) implants (subdermal).

Subgroup analysis and investigation of heterogeneity

Where data are available, subgroup analyses will be conducted to determine the separate evidence within the following subgroups:

1. age (women below 35 years of age versus women above 35 years of age);
2. location of the uterine fibroids (submucosal, intramural or subserosal).

If excessive heterogeneity exists within trials, it will be explored informally using the clinical and design details recorded in the 'Characteristics of included studies' table. Some heterogeneity between trials is anticipated, and possible reasons will be discussed.

Sensitivity analysis

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

1. eligibility was restricted to studies without high risk of bias;
2. alternative imputation strategies had been adopted;
3. a random-effects model had been adopted;
4. the summary effect measure was relative risk rather than odds ratio.

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We would like to acknowledge the Cochrane Menstrual Disorders and Subfertility Group (MDSG) for giving us the opportunity to write a review on this subject. Special thanks to the Co-ordinating Editor of the Cochrane Menstrual Disorders and Subfertility group, Professor Cindy Farquhar. We also thank Jane Clarke, the past Managing Editor of the Cochrane Menstrual Disorders and Subfertility group, and Helen Nagels for their encouragements and advice that led to the registration of the topic for this protocol and completion of the protocol. We are grateful to the Nigerian branch of the South African Cochrane Centre (SACC) for training us in the conduct of systematic reviews. Finally, we want to thank Marian Showell, the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator for helping us with the search strategies.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) - In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1948 to Present)
Search Strategy:
1 exp leiomyoma/ or exp myoma/
2 leiomyoma$.tw.
3 fibroid$.tw.
4 fibromyoma$.tw.
5 fibroma$.tw.
6 hysteromyoma$.tw.
7 myoma$.tw.
8 or/1-7
9 exp progesterone/ or exp medroxyprogesterone/ or exp medroxyprogesterone acetate/
10 progesterone.tw.
11 exp Progestins/
12 progestogen$.tw.
13 Progestin$.tw.
14 exp Levonorgestrel/
15 mirena.tw.
16 Levonorgestrel.tw.
17 LNG-IUS.tw.
18 norplant$.tw.
19 (norgestrel or norgeston).tw.
20 medroxyprogesterone.tw.
21 or/9-20
22 8 and 21
23 randomized controlled trial.pt.
24 controlled clinical trial.pt.
25 randomized.ab.
26 placebo.tw.
27 clinical trials as topic.sh.
28 randomly.ab.
29 trial.ti.
30 (crossover or cross-over or cross over).tw.
31 or/23-30
32 exp animals/ not humans.sh.
33 31 not 32
34 22 and 33

Appendix 2. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials (4th Quarter 2011)
Search Strategy:

1 exp leiomyoma/ or exp myoma/
2 leiomyoma$.tw.
3 fibroid$.tw.
4 fibromyoma$.tw.
5 fibroma$.tw.
6 hysteromyoma$.tw.
7 myoma$.tw.
8 or/1-7
9 exp progesterone/ or exp medroxyprogesterone/ or exp medroxyprogesterone acetate/
10 progesterone.tw.
11 exp Progestins/
12 progestogen$.tw.
13 Progestin$.tw.
14 exp Levonorgestrel/
15 mirena.tw.
16 Levonorgestrel.tw.
17 LNG-IUS.tw.
18 norplant$.tw.
19 (norgestrel or norgeston).tw.
20 medroxyprogesterone.tw.
21 or/9-20
22 8 and 21

Appendix 3. EMBASE search strategy

Database: Embase (1980 to 2011 November 01)
Search Strategy:

1 exp leiomyoma/ or exp uterus tumor/
2 leiomyoma$.tw.
3 myoma$.tw.
4 fibroid$.tw.
5 fibroma$.tw.
6 fibromyoma$.tw.
7 hysteromyoma$.tw.
8 or/1-7
9 exp progesterone/
10 exp medroxyprogesterone acetate/
11 progesterone.tw.
12 exp gestagen/
13 gestagen.tw.
14 progestogen$.tw.
15 Progestin$.tw.
16 exp levonorgestrel/
17 mirena.tw.
18 Levonorgestrel.tw.
19 LNG-IUS.tw.
20 norplant$.tw.

21 (norgestrel or norgeston).tw.
22 medroxyprogesterone.tw.
23 or/9-22
24 8 and 23
25 Clinical Trial/
26 Randomized Controlled Trial/
27 exp randomization/
28 Single Blind Procedure/
29 Double Blind Procedure/
30 Crossover Procedure/
31 Placebo/
32 Randomi?ed controlled trial$.tw.
33 Rct.tw.
34 random allocation.tw.
35 randomly allocated.tw.
36 allocated randomly.tw.
37 (allocated adj2 random).tw.
38 Single blind$.tw.
39 Double blind$.tw.
40 ((treble or triple) adj blind$).tw.
41 placebo$.tw.
42 prospective study/
43 or/25-42
44 case study/
45 case report.tw.
46 abstract report/ or letter/
47 or/44-46
48 43 not 47
49 24 and 48

Appendix 4. PsycINFO search strategy

Database: PsycINFO (1806 to October Week 4 2011)
Search Strategy:

1 leiomyoma$.tw.
2 fibroid$.tw.
3 fibromyoma$.tw.
4 fibroma$.tw.
5 hysteromyoma$.tw.
6 myoma$.tw.
7 or/1-6
8 exp Progesterone/
9 medroxyprogesterone.tw.
10 progesterone.tw.
11 exp Progestational Hormones/
12 progestogen$.tw.
13 Progestin$.tw.
14 Levonorgestrel.tw.
15 mirena.tw.
16 LNG-IUS.tw.
17 norplant$.tw.

18 (norgestrel or norgeston).tw.
19 or/8-18
20 7 and 19

Appendix 5. Menstrual Disorders and Subfertility (MDSG) Specialised register search

Keywords CONTAINS “uterine fibroids” or “uterine leiomyomas” or “uterine myoma” or “uterine myomas ”or “myoma” or “myomas” or “Leiomyoma” or “leiomyomata” or “fibroids” or Title CONTAINS “uterine fibroids” or “uterine leiomyomas” or “uterine myoma” or “uterine myomas” or “myoma” or “myomas” or “Leiomyoma” or “leiomyomata” or “fibroids”
AND
Keywords CONTAINS “Progesterone” or “progestin” or “progestin implant” or “progestins” or “progestogen” or “progestogens” or “Levonorgestrel” or “medroxyprogesterone” or “Medroxyprogesterone Acetate*” or “*Medrogestone” or “*Gestagen” or “LNG-IUS” or “Mirena” or “Norgestimate” or “Norgestrel” or Title CONTAINS “Progesterone”or “progestin”or“progestin implant”or“progestins”or “progestogen”or “progestogens”or“Levonorgestrel”or “medroxyprogesterone”or “Medroxyprogesterone Acetate*” or “*Medrogestone” or “*Gestagen” or “LNG-IUS” or “Mirena” or “Norgestimate” or “Norgestrel”

CONTRIBUTIONS OF AUTHORS

Ahizechukwu Eke conceived, designed and coordinated the protocol. Naima Bridges participated actively in the writing of various sections of this protocol. Manupreet Chawla and Ifeanyichukwu Ezebialu did the literature search and participated in writing the protocol. All the authors agreed on the final version.

DECLARATIONS OF INTEREST

We declare that we have no conflict of interest.

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External sources

- No sources of support was received, Not specified.

NOTES

None