Oral contraceptive pill for heavy menstrual bleeding (Review)

Farquhar C, Brown J

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2009, Issue 4

http://www.thecochranelibrary.com
Oral contraceptive pill for heavy menstrual bleeding

Cindy Farquhar¹, Julie Brown¹

¹Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Contact address: Cindy Farquhar, Obstetrics and Gynaecology, University of Auckland, FMHS Park Road, Grafton, Auckland, 1003, New Zealand. c.farquhar@auckland.ac.nz.

Editorial group: Cochrane Menstrual Disorders and Subfertility Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2009.
Review content assessed as up-to-date: 2 August 2009.


Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background
Menorrhagia (heavy menstrual bleeding) is a benign yet debilitating social and health condition. Treatments prescribed in order to reduce excessive menstrual blood loss include prostaglandin synthetase inhibitors, antifibrinolytics, the oral contraceptive pill and other hormones. The combined oral contraceptive pill (OCP) is claimed to have a variety of beneficial, inducing a regular shedding of a thinner endometrium and inhibiting ovulation thus having the effect of treating menorrhagia and providing contraception.

Objectives
To determine the effectiveness of oral contraceptive pills compared with other medical therapies, placebo or no therapy in the treatment of heavy menstrual bleeding.

Search strategy
We searched the Menstrual Disorders and Subfertility Group trials register (search dates: Oct 1996, May 2002, June 2004, April 2006 and June 2009) for all publications which describe randomised trials of OCP for the treatment of menorrhagia. This register is based on regular searches of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, the hand searching of 20 relevant journals and conference proceedings, and searches of several key grey literature sources.

Selection criteria
All randomised controlled comparisons of OCP versus other medical therapies, placebo or no treatment for the treatment of menorrhagia. Women of reproductive years with regular heavy periods, measured either objectively or subjectively and greater than, or equal to, two months follow up.

Data collection and analysis
All assessments of trial quality and data extraction were performed unblinded by at least two reviewers. Only one trial of 45 women met the inclusion criteria and none were excluded.

Main results
As the trial used a cross-over design, only data from the first treatment period (cycles three and four) were analysed. The results from all the three mefenamic acid groups were combined. There was no significant difference in menstrual blood loss (MBL) between those women treated with the OCP and danazol, mefenamic acid or naproxen.
Authors’ conclusions

One small study found no significant difference between groups treated with OCP, mefenamic acid, low dose danazol or naproxen. Overall, the evidence from the one study is not sufficient to adequately assess the effectiveness of OCP.

This review was unable to achieve its stated objectives because of the paucity of the data.

PLAIN LANGUAGE SUMMARY

Oral contraceptive pills for heavy menstrual bleeding

Heavy menstrual bleeding is a common cause for referral to gynaecologists in countries like the UK. It is a debilitating social and health condition, and it can result in anaemia. The oral contraceptive pill can provide control of the menstrual cycle and a thinner endometrium (the lining of the uterus shed during menstruation). The review showed that the pill reduced menstrual blood loss, but there are not enough data to determine its value in comparison with other drugs.

BACKGROUND

Description of the condition

Heavy menstrual bleeding is a benign yet debilitating social and health condition. This concern with abnormal menstruation is especially a problem of the twentieth century. Previously, late menarche, early menopause, prolonged periods of childbearing and lactational amenorrhoea reduced the number of menses experienced by women in their lifetime. The reduction of family size, by the widespread use of contraception and sterilisation has resulted in an approximate tenfold increase in the number of periods that women experience in their reproductive life (Short 1976). Also, modern contraceptive practices and the widespread use of sterilisation mean that many women will not have experienced a spontaneous menstrual cycle for around ten years prior to and during their childbearing years.

Many methods have been used to measure menstrual blood loss but the presently preferred technique involves the determination of the concentration of haemoglobin in menstrual fluid by its conversion to alkaline haematin (Hallberg 1966; Newton 1977). This method is not normally available except for research purposes, so the clinician has to rely on the patient’s account of the heaviness of her bleeding and clinical examination (Chimbira 1980). Patient’s self-reports have been shown to be inaccurate indicators of menstrual blood loss in a number of studies in which subjective and objective assessments were compared (Hallberg 1966; Chimbira 1980; Haynes 1977). The widely accepted clinical definition of menorrhagia is blood loss of 80 ml or more per period. This figure is derived from population studies which have shown that the average blood loss is between 30 and 40 ml, and 90% of women have blood losses of less than 80 ml (Hallberg 1966; Cole 1971). In a United Kingdom national survey, 31% of women described their blood loss as heavy (MORI 1990). However many women who seek treatment for heavy menstrual bleeding do not actually have greater losses than average (Hallberg 1966; Fraser 1985; Haynes 1977). In one population based study in Scandinavia, 26% of those with losses well within the normal range (below 60 ml) considered their periods heavy, whilst 40% of those with objectively heavy losses (over 80 ml) considered their periods to be moderate or light (Hallberg 1966).

Another way of determining an upper limit of normal for menstrual blood loss is to relate the menstrual blood loss to various haematological indices. Excessive menstrual bleeding is the commonest cause of iron deficiency in the United Kingdom (Cohen 1980), affecting 20 to 25% of the fertile female population (Rybo 1966) and 1.6 million women will have either iron storage deficiency or actual anaemia (Fairhurst 1977). It can be calculated that on a normal western diet a state of negative iron balance will occur if the menstrual blood loss exceeds about 50-60 ml per month (Rybo 1966; Smith 1982) and indeed 67% of women whose loss is greater than 80 ml have actual anaemia (Hallberg 1966). The incidence of anaemia significantly increases when losses exceed 80 ml (Hallberg 1966), though blood may only contribute two to 82% of this fluid (Fraser 1985). On the basis of these findings, the upper limit of normal appears to lie between 60 and 80 ml and losses in excess of 80 ml can be considered pathological.

The size of the problem is expressed by the number of women who seek medical advice for menstrual dysfunction. In one centre in the United Kingdom, 38.3% of referrals to consultant gynaecologists were for menstrual dysfunction (Smith 1992), and 30% of these
referrals were for menorrhagia (Cameron 1990). This accounts for 12% of all gynaecological referrals (Bradlow 1992). In addition, 5% of women aged 30 to 49 consult their general practitioner each year for menorrhagia (Peto 1993).

**Description of the intervention**
A range of medical therapies are prescribed in order to reduce excessive menstrual blood loss, including prostaglandin synthetase inhibitors, antifibrinolytics, the oral contraceptive pill and other hormones. Objective data has shown that, at least in the short term, considerable reduction in the volume of the menses is achievable. The choice of drug depends upon its appropriateness and likely acceptability to an individual (Mishell 1982). The combined oral contraceptive pill (OCP) is claimed to have a variety of beneficial effects other than being a highly reliable method of birth control.

**How the intervention might work**
When taken in a cyclical fashion the combined oral contraceptive pill induces regular shedding of a thinner endometrium and inhibits ovulation. Using this method, good cycle control can be achieved and, together with the provision of contraception, this makes OCP a most acceptable longer term therapy for some women with menorrhagia.

**Why it is important to do this review**
If effective in reducing heavy menstrual bleeding this intervention may be an acceptable long term therapy for some women.

**OBJECTIVES**
To determine the effectiveness of oral contraceptive pills compared with other medical therapies, placebo or no therapy in the treatment of heavy menstrual bleeding.

**METHODS**
Criteria for considering studies for this review

**Types of studies**
All randomised controlled comparisons of OCP versus other medical therapies for the treatment of heavy menstrual bleeding, Criteria for exclusion of trials

- irregular menses and intermenstrual bleeding
- pathological causes of heavy menstrual bleeding
- iatrogenic causes of heavy menstrual bleeding
- post-menopausal bleeding (> 1 year from the last period)

Other points for exclusion will be considered in retrospect so that no potentially relevant trials are missed.

**Types of participants**
- Women of reproductive years
- Regular heavy periods measured either objectively or subjectively greater than, or equal to two months follow up
- Type of settings: primary care, family planning or specialist clinic

**Types of interventions**
OCP versus other methods of medical treatment, no treatment or placebo for heavy menstrual bleeding. All types and dosages of OCP will be considered.

**Types of outcome measures**

**Primary outcomes**
The primary outcome was menstrual bleeding
- objectively assessed blood loss, both short term and long term
- subjectively assessed blood loss, both short term and long term
- patient satisfaction

**Secondary outcomes**
Secondary outcomes were: Immediate side effects

- Unrecognised pathology
  - coagulopathies
  - fibroids
  - pelvic inflammation

- Mortality
- Resource use:

  - To the patient
  - To the general practitioner
  - To the hospital
  - To the health service
Search methods for identification of studies

Electronic searches
We searched for all publications of randomised trials using OCP for the treatment of menorrhagia. The original searches were performed in October 1996. Updated searches of the trials register were completed in May 2002, June 2004 and April 2006 and June 2009 however no new trials were found.

(1) The Menstrual Disorders and Subfertility Group's trials register was searched for any trials (searched June 2009) Appendix 1.

(2) Additional data bases were also searched. MEDLINE refer to Appendix 2, EMBASE refer to Appendix 3, The Cochrane Central Register of Controlled Trials (CENTRAL) refer to Appendix 4 and PsycINFO refer to Appendix 5.

Searching other resources
For the original search the citation lists of relevant publications, review articles, and included studies were searched. Pharmaceutical companies manufacturing the OCP were also contacted.

Data collection and analysis

Selection of studies
Selection of trials for inclusion in the review was performed by one of the reviewers, after employing the search strategy described previously. A second reviewer assessed any trials where there was uncertainty regarding eligibility. Additional information was sought from the principal investigators of the trial which met the eligibility criteria. The investigator did provide further information on the methods of allocation, and inclusion and exclusion criteria.

Data extraction and management
All assessments of the quality of trials and data extraction were performed unblinded by at least two reviewers (CF & VI). One of these reviewers is an expert in the content matter, and the second is a non-content expert.

Assessment of risk of bias in included studies
Risk of bias of the included trial was assessed by both of the reviewers separately. Any discrepancies were assessed by a third reviewer. The quality of allocation concealment was graded as either yes, no or unclear. For the included trial information was collected regarding the method of randomisation, allocation concealment, blinding, whether an intention to treat analysis could possibly be performed and relevant interventions and outcomes. Data was extracted independently by the two reviewers (CF & VI) using forms designed according to the Cochrane guidelines.

Measures of treatment effect
Continuous data was presented using a fixed effect model and mean difference with 95% CI.

Unit of analysis issues
There was no unit of analysis issue, data was based on objective definitions of blood loss.

Dealing with missing data
Not applicable

Assessment of heterogeneity
The heterogeneity between trial results will be tested subjectively if more trials become available in the future, by clinical judgement of differences in patient populations, interventions and outcome assessments, and objectively using appropriate statistical tests. Depending on the results of the heterogeneity assessments, part of the outcomes may be pooled statistically using relevant techniques.

Assessment of reporting biases
The review was unable to assess issues of reporting bias due to only one trial being identified.

Data synthesis
Meta-analysis was not conducted on the data as there was only one trial identified.

Subgroup analysis and investigation of heterogeneity
Not applicable as only one trial identified.

Sensitivity analysis
Not applicable as only one trial identified.

RESULTS

Description of studies
See: Characteristics of included studies.
**Results of the search**
One study was identified that met inclusion criteria.

**Included studies**

Only one trial (Fraser 1991) was identified, and fulfilled the criteria for inclusion in the review. The trial used a cross-over design with subjects being randomised into three groups, and then randomised into two further groups. Treatments given were mefenamic acid, naproxen, low dose danazol and a combined oral monophasic contraceptive pill. The trial was relatively small with only 45 women being randomised and seven dropped out before completion of the study. The duration of treatment was eight cycles, with each treatment period being two cycles.

**Excluded studies**
No studies were excluded.

**Risk of bias in included studies**
Refer to Figure 1 and Figure 2.

---

**Figure 1.** Methodological quality graph: review authors’ judgements about each methodological quality item presented as percentages across all included studies.

Adequate sequence generation?
Allocation concealment?
Blinding?
Incomplete outcome data addressed?
Free of selective reporting?
Free of other bias?

© 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Figure 2. Methodological quality summary: review authors’ judgements about each methodological quality item for each included study.

Allocation
The one trial included (Fraser 1991) was a randomised, cross-over trial. Randomisation was by random numbers and allocation was controlled by a laboratory manager.

Blinding
There was no blinding in the trial.

Incomplete outcome data
No intention to treat analysis was used for the seven women who did not complete the study.

Selective reporting
The main outcomes of relevance appear to have been included.

Other potential sources of bias
None identified.

Effects of interventions
As the trial used a cross-over design, only data from the first treatment period (cycles three and four) were analysed. The results from all three mefenamic acid groups (n=20) were combined to increase the power of the study. The other treatment groups all contained six participants. Individual participant data were obtained for all the treatment and control cycles.

There was no significant difference between reduction in blood loss (measured objectively) at two months in those women treated with the oral contraceptive pill and danazol (WMD 19.27, CI -24.47 to 63.01), OCP and mefenamic acid (WMD 12.53 CI -22.47 to 47.53) or OCP and naproxen (WMD 8.37 CI -27.31 to 44.05). It is worth noting that one third (12 out of 38) of the trial participants did not have the accepted threshold for treatment (MBL less than 60 mls).

Data on side effects were not collected because it included both periods of the study, not just the first treatment period prior to crossover.

The trial did find an overall reduction in menstrual blood loss of 43% in women taking OCP, although the numbers were small (n=6).
DISCUSSION

Summary of main results
In this review one randomised controlled trial of combined oral contraceptive pill for the treatment of menorrhagia versus mefenamic acid, naproxen and danazol was identified (Fraser 1991).

Overall completeness and applicability of evidence
The only outcome of interest measured in the study was objective menstrual blood loss. The objective measurement of blood loss by the Alkaline Haematin method is difficult and is not easily used in routine practice. In future, it may be preferable to develop simpler methods for the objective assessment of menorrhagia, such as pictorial blood loss assessment charts to permit large scale comparative studies of treatment as well as better routine clinical evaluation. Subjective blood loss was measured in the trial, but women were asked to compare the two treatments they received. Therefore, since all data in this review were analysed from a single treatment before the cross-over, these data were unable to be used.

The comparative efficacy of OCP with naproxen, danazol and mefenamic acid was assessed and no significant differences between treatment groups found. There are other known treatments for menorrhagia (such as antifibrinolytic agents) which were not included in the comparison.

The effectiveness of OCP compared to no treatment or placebo was not assessed in this study. However, study investigators did compare the overall effectiveness of the four treatments throughout the entire eight cycles with the baseline measurements. Highly significant reductions in blood loss were found at the end of the study in the oral contraceptive group (43%, P=<0.001), the low dose danazol group (49%, P = 0.006), and in two of the MFA groups (38%, P=0.002 and 39%, p<0.001). The comparative efficacy of all of the treatments should be confirmed by including placebo or no treatment arms in future trials.

Potential biases in the review process
It is believed that all relevant trials have been identified.

Agreements and disagreements with other studies or reviews
The data from one small study makes it difficult to compare results with other studies or review.

AUTHORS’ CONCLUSIONS

Implications for practice
The one small study identified (Fraser 1991) found no significant difference between groups treated with OCP, mefenamic acid, low dose danazol or naproxen. Thus, at this stage, the effectiveness of OCP as compared with the above treatments, cannot be distinguished. Overall, the evidence from the one study identified (Fraser 1991) is not sufficient to adequately assess the effectiveness of OCP for the management of heavy menstrual bleeding.

Implications for research
Placebo controlled randomised controlled trials with adequate patient numbers, duration of at least three to six cycles and adequate follow up are required to establish whether or not the oral contraceptive pill is an effective treatment for heavy menstrual bleeding.

ACKNOWLEDGEMENTS
The authors would like to thank Prof. Ian Fraser for providing the individual patient data from the trial (Fraser 1991). The authors also wish to thank Julie Brown for performing the 2009 update and reformatting the review for the latest Cochrane standards.
REFERENCES

References to studies included in this review

Fraser 1991  [published data only]

Additional references

Bradlow 1992

Cameron 1990

Chimbira 1980

Cohen 1980

Cole 1971

Fairhurst 1977

Fraser 1985

Hallberg 1966

Haynes 1977

Mishell 1982

MORI 1990
MORI. Women's health in 1990. Research conducted on behalf of Parke-Davies Research Laboratories.

Newton 1977

Peto 1993

Rybo 1966

Short 1976

Smith 1982

Smith 1992
Smith SK, Haining REB. The investigation and management of excessive menstrual bleeding. *Recent Advances in Obstetrics & Gynaecology*. Vol. 17, Edinburgh: Churchill Livingstone, 1992.* Indicates the major publication for the study
### Characteristics of included studies

**Fraser 1991**

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, but method not stated. Two post randomisation exclusions occurred because women had contraindications to a therapy. No blinding and no placebo group used. Single centre, cross-over trial. An intention to treat analysis was not used.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial undertaken at University of Sydney, NSW, Australia. 45 ovulatory women. Inclusion criteria: history of menorrhagia and regular periods. Inclusion criteria: Women up to 50 years of age provided they had regular periods. Exclusion criteria: pelvic pathology. Women were not excluded if they had received medical therapy for menorrhagia previously, but it was expected that they had not been on specific treatment for at least 2 months prior to entering the trial.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
</table>
| Group 1 Mefanamic Acid (MFA) or naproxen  
Group 2 MFA or combined low dose oral contraceptive pill  
Group 3 MFA or danazol |

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Menstrual blood loss (measured by alkaline haematin method)  
Immediate side effects |

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Randomisation was by random numbers</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Adequate Allocation was controlled by a laboratory manager.</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>No</td>
<td>No blinding</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td>Study accounts for missing women not analysed</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>All relevant outcomes are detailed</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Yes</td>
<td>yes</td>
</tr>
</tbody>
</table>
## Data and Analyses

### Comparison 1. OCP versus naproxen

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Menstrual blood loss (assessed objectively)</td>
<td>1</td>
<td>12</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>8.37 [-27.31, 44.05]</td>
</tr>
</tbody>
</table>

### Comparison 2. OCP versus danazol

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Menstrual blood loss (assessed objectively)</td>
<td>1</td>
<td>12</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>19.27 [-24.47, 63.01]</td>
</tr>
</tbody>
</table>

### Comparison 3. OCP versus mefenamic acid (all)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Menstrual blood loss (assessed objectively)</td>
<td>1</td>
<td>26</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-17.49 [-62.77, 27.79]</td>
</tr>
</tbody>
</table>

### Analysis 1.1. Comparison 1 OCP versus naproxen, Outcome 1 Menstrual blood loss (assessed objectively).

Review: Oral contraceptive pill for heavy menstrual bleeding

Comparison: 1 OCP versus naproxen

Outcome: 1 Menstrual blood loss (assessed objectively)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OCP N</th>
<th>Mean(SD)</th>
<th>naproxen N</th>
<th>Mean(SD)</th>
<th>Mean Difference IV/Fixed 95% CI</th>
<th>Weight</th>
<th>Mean Difference IV/Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraser 1991</td>
<td>6</td>
<td>66.77 (42.96)</td>
<td>6</td>
<td>58.4 (11.95)</td>
<td></td>
<td>100.0 %</td>
<td>8.37 [-27.31, 44.05]</td>
</tr>
</tbody>
</table>

Total (95% CI) 6 6 100.0 % 8.37 [-27.31, 44.05]

Heterogeneity: not applicable

Test for overall effect: Z = 0.46 (P = 0.65)

Test for subgroup differences: Not applicable
### Analysis 2.1. Comparison 2 OCP versus danazol, Outcome 1 Menstrual blood loss (assessed objectively).

**Review:** Oral contraceptive pill for heavy menstrual bleeding

**Comparison:** 2 OCP versus danazol

**Outcome:** 1 Menstrual blood loss (assessed objectively)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>OCP</th>
<th>Danazol</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraser 1991</td>
<td>N: 6</td>
<td>Mean(SD): 66.77 (42.96)</td>
<td>N: 6</td>
<td>Mean(SD): 47.5 (33.81)</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 6 6 100.0 % 19.27 [-24.47, 63.01]

**Heterogeneity:** not applicable

**Test for overall effect:** Z = 0.86 (P = 0.39)

**Test for subgroup differences:** Not applicable

### Analysis 3.1. Comparison 3 OCP versus mefenamic acid (all), Outcome 1 Menstrual blood loss (assessed objectively).

**Review:** Oral contraceptive pill for heavy menstrual bleeding

**Comparison:** 3 OCP versus mefenamic acid (all)

**Outcome:** 1 Menstrual blood loss (assessed objectively)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraser 1991</td>
<td>N: 6</td>
<td>Mean(SD): 66.77 (42.96)</td>
<td>N: 20</td>
<td>Mean(SD): 84.26 (67.26)</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 6 20 100.0 % -17.49 [-62.77, 27.79]

**Heterogeneity:** not applicable

**Test for overall effect:** Z = 0.76 (P = 0.45)

**Test for subgroup differences:** Not applicable
Appendix 1. MDSG search string

MDSG search string for VI051

Keywords CONTAINS “menorrhagia” or “menorrhagia-outcome” or “Menorrhagia-Symptoms” or “heavy menstrual bleeding” or “heavy menstrual loss” or “heavy bleeding” or Title CONTAINS “menorrhagia” or “menorrhagia-outcome” or “Menorrhagia-Symptoms” or “heavy menstrual bleeding” or “heavy menstrual loss” or “heavy bleeding”

AND

Keywords CONTAINS “oral conjugated estrogen” or “oral contraceptives” or “Oral Contraceptive Agent” or “oral contraceptive pill” or “oral contraceptive” or “oral dydrogesterone” or “oral estradiol” or “Oral Contraception” or “Levonorgestrel” or “Levonorgestrel-Therapeutic-Use” or “Norethisterone” or “Norgestimate” or “Norgestrel” or “ethinyl estradiol + drospirenone” or “ethinyl estradiol-cyproterone acetate” or “ethinyl-estradiol” or “gestodene” or “desogestrel” or “dienogest” or Title CONTAINS “oral conjugated estrogen” or “oral contraceptives” or “Oral Contraceptive Agent” or “oral contraceptive pill” or “oral contraceptive” or “oral dydrogesterone” or “oral estradiol” or “Oral Contraception” or “Levonorgestrel” or “Levonorgestrel-Therapeutic-Use” or “Norethisterone” or “Norgestimate” or “Norgestrel” or “ethinyl estradiol + drospirenone” or “ethinyl estradiol-cyproterone acetate” or “ethinyl-estradiol” or “gestodene” or “desogestrel” or “dienogest”

Appendix 2. MEDLINE search Strategy

Database: Ovid MEDLINE(R) <1950 to April Week 4 2009>

Search Strategy:

--------------------------------------------------------------------------------
1 exp Menorrhagia/ (2902)
2 menorrhagia.tw. (1927)
3 (hypermenorrhea or hypermenorrhoea).tw. (190)
4 (heavy adj2 bleed$).tw. (556)
5 (heavy adj2 period$).tw. (256)
6 (iron adj3 anaemia).tw. (1658)
7 (menstrua$ adj3 bleed$).tw. (1321)
8 or/1-7 (6988)
9 exp contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp chlormadinone acetate/ or exp desogestrel/ or exp levonorgestrel/ or exp norgestrel/ or exp norgestriene/ (37354)
10 contracepti$.tw. (45591)
11 OCP$.tw. (1289)
12 ethinyl estradiol.tw. (2938)
13 levonorgestrel.tw. (2598)
14 (estradiol-norgestrel or norgestrel).tw. (953)
15 (norgestrienone or desogestrel).tw. (910)
16 (chlormadinone acetate or dienogest).tw. (684)
17 (norgestriate or gestodene).tw. (811)
18 or/9-17 (65925)
19 8 and 18 (7953)
20 randomized controlled trial.pt. (269141)
21 controlled clinical trial.pt. (79060)
22 randomized.ab. (179301)
23 placebo.tw. (114729)
24 clinical trials as topic.sh. (142629)
25 randomly.ab. (130168)

Oral contraceptive pill for heavy menstrual bleeding (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Appendix 3. EMBASE search strategy

Database: EMBASE <1980 to 2009 Week 18>
Search Strategy:

1 exp Menorrhagia/ (2793)
2 menorrhagia.tw . (1731)
3 (hypermenorrhea or hypermenorrhoea).tw . (138)
4 (heavy adj2 bleed$).tw . (439)
5 (heavy adj2 period$).tw . (226)
6 (iron adj3 anaemia).tw . (1230)
7 (menstrua$ adj3 bleed$).tw . (984)
8 or/1-7 (5677)
9 contracepti$.tw . (27837)
10 OCP$.tw . (1174)
11 ethinyl estradiol.tw . (1766)
12 levonorgestrel.tw . (2316)
13 (estradiol-norgestrel or norgestrel).tw . (509)
14 (norgestrienone or desogestrel).tw . (818)
15 (chlormadinone acetate or dienogest).tw . (495)
16 (norgestimate or gestodene).tw . (724)
17 exp oral contraceptive agent/ or exp chlormadinone acetate plus ethinylestradiol/ or exp chlormadinone acetate plus mestranol/ or exp desogestrel plus ethinylestradiol/ or exp dienogest plus ethinylestradiol/ or exp drosipirenone plus ethinylestradiol/ or exp estradiol cypionate plus medroxyprogesterone acetate/ or exp ethinylestradiol plus ethisterone/ or exp ethinylestradiol plus gestodene/ or exp ethinylestradiol plus levonorgestrel/ or ethinylestradiol plus megestrol acetate/ or ethinylestradiol plus norethisterone/ or ethinylestradiol plus norethisterone acetate/ or ethinylestradiol plus norgestimate/ or ethinylestradiol plus norgestrel/ or ethynodiol diacetate plus mestranol/ or exp levonorgestrel/ or exp low dose oral contraceptive/ or exp lynestrenol/ or exp lynestrenol plus mestranol/ or exp mestranol plus norethisterone/ or exp mestranol plus norethynodrel/ or exp non ovlon/ or exp norethisterone/ or exp norethynodrel/ or exp sequential contraceptive agent/ or exp triphasic contraceptive agent/ (29643)
18 or/9-17 (45920)
19 8 and 18 (1198)
20 (2008$ or 2009$).em . (791873)
21 19 and 20 (140)
22 Clinical Trial/ (539778)
23 Randomized Controlled Trial/ (168518)
24 exp randomization/ (26765)
25 Single Blind Procedure/ (8141)
26 Double Blind Procedure/ (72299)
27 Crossover Procedure/ (21259)
28 Placebo/ (126291)
29 Randomized controlled trial$.tw . (33222)
30 Rct.tw . (2735)
 Append 4. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2009>

Search Strategy:

1 exp Menorrhagia/ (192)
2 menorrhagia.tw. (261)
3 (hypermenorrhea or hypermenorrhoea).tw. (11)
4 (heavy adj2 bleed$).tw. (55)
5 (heavy adj2 period$).tw. (15)
6 (iron adj3 anaemia).tw. (173)
7 (menstrua$ adj3 bleed$).tw. (144)
8 or/1-7 (659)
9 exp contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp chlormadinone acetat$ or exp desogestrel/ or exp levonorgestrel/ or exp norgestrel$ or exp norgestrienone/ (2574)
10 contracepti$.tw. (2417)
11 OCP$.tw. (39)
12 ethinyl estradiol.tw. (530)
13 levonorgestrel.tw. (617)
14 (estradiol-norgestrel or norgestrel).tw. (121)
15 (norgestrienone or desogestrel).tw. (350)
16 (chlormadinone acetate or dienogest).tw. (115)
17 (norgestimate or gestodene).tw. (255)
18 or/9-17 (4076)
19 8 and 18 (151)
20 limit 19 to yr="2006 -Current" (24)
21 from 20 keep 1-24 (24)
Appendix 5. PsycINFO search strategy

Database: PsycINFO <1806 to April Week 4 2009>

Search Strategy:

1 exp Menorrhagia/ (0)
2 menorrhagia.tw. (53)
3 (hypermenorrhea or hypermenorrhoea).tw. (1)
4 (heavy adj2 bleed$).tw. (18)
5 (heavy adj2 period$).tw. (51)
6 (iron adj3 anaemia).tw. (17)
7 (menstrua$ adj3 bleed$).tw. (56)
8 or/1-7 (177)
9 exp contraceptives, oral/ or exp gestrinone/ or exp contraceptives, oral, combined/ or exp ethinyl estradiol-norgestrel combination/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ or exp chlormadinone acetate/ or exp desogestrel/ or exp levonorgestrel/ or exp norgestrel/ or exp norgestrienone/ (0)
10 contracepti$.tw. (4154)
11 OCP$.tw. (139)
12 ethinyl estradiol.tw. (47)
13 levonorgestrel.tw. (21)
14 (estradiol-norgestrel or norgestrel).tw. (7)
15 (norgestrienone or desogestrel).tw. (4)
16 (chlormadinone acetate or dienogest).tw. (10)
17 (norgestimate or gestodene).tw. (10)
18 or/9-17 (4329)
19 8 and 18 (17)
20 limit 19 to yr="2006 -Current" (3)
21 from 20 keep 1-3 (3)

WHAT'S NEW

Last assessed as up-to-date: 2 August 2009.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 August 2009</td>
<td>New citation required but conclusions have not changed</td>
<td>New authors assigned to update</td>
</tr>
<tr>
<td>10 August 2009</td>
<td>New search has been performed</td>
<td>Search strategy rewritten and a new updated search was performed in June 2009 and no new studies were identified. Patient satisfaction was added to the outcomes</td>
</tr>
</tbody>
</table>
HISTORY


<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 August 2009</td>
<td>Review declared as</td>
<td>No longer to be updated as unlikely to affect conclusions of review</td>
</tr>
<tr>
<td></td>
<td>stable</td>
<td></td>
</tr>
<tr>
<td>7 November 2008</td>
<td>Amended</td>
<td>Comparison: 3 OCP versus danazol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One or more outcomes have no associated study data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.e. outcome deleted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison: 2 OCP versus naproxen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One or more outcomes have no associated study data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.e. outcome deleted</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison: 4 OCP versus mefenamic acid (all)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>One or more outcomes have no associated study data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>i.e. outcome deleted</td>
</tr>
<tr>
<td>7 November 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>11 April 2006</td>
<td>New citation required</td>
<td>Substantive amendment</td>
</tr>
<tr>
<td></td>
<td>and conclusions have</td>
<td></td>
</tr>
<tr>
<td></td>
<td>changed</td>
<td></td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

Cindy Farquhar commented on the draft protocol and review of all versions. Julie Brown was also involved in the update in 2009.
Vadehi Iyer and Ruth Jepson performed searches, selected trials for inclusion, extracted data and wrote the protocol and review, contacted authors, and performed an update of the review in June 2006

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Dept of Obstetrics and Gynaecology, University of Auckland, NZ, Not specified.
External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

NOTES

The updated searches in May 2002, June 2004, April 2006 and June 2009 were done by the Menstrual Disorders and Subfertility Group.

INDEX TERMS

Medical Subject Headings (MeSH)

- Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Contraceptives, Oral [*therapeutic use]; Danazol [therapeutic use]; Drug Therapy, Combination [methods]; Mefenamic Acid [therapeutic use]; Menorrhagia [*drug therapy]; Naproxen [therapeutic use]

MeSH check words

- Female; Humans