ORAL CONTRACEPTIVE PILLS FOR HEAVY MENSTRUAL BLEEDING

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A substantive amendment to this systematic review was last made on 11 February 1997. Cochrane reviews are regularly checked and updated if necessary.

ABSTRACT

Background: Menorrhagia (heavy menstrual bleeding) is a benign yet debilitating social and health condition. The widely accepted clinical definition of menorrhagia is blood loss of 80ml or more per period. This figure is derived from population studies that have shown that the average blood loss is between 30 and 40ml, and 90% of women have blood losses of less than 80ml. Excessive menstrual bleeding is the commonest cause of iron deficiency in the United Kingdom affecting 20-25% of the fertile female population. Menorrhagia is a common problem accounting for 12% of all gynaecological referral in the UK. Ranges 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. 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.

Objective:

To determine whether:

1. the OCP is an effective medical therapy to reduce menorrhagia in both the short term and long term.

2. the effectiveness of combined oral contraceptive pills (OCP) compared with other medical therapies for the treatment of menorrhagia.

3. OCP is a more cost effective method than any other medical treatments of menorrhagia.

4. OCP has fewer side effects than other drugs used for menorrhagia.

Search strategy: We searched the Menstrual Disorders and Subfertility Group trials register (search dates: Oct 1996, May 2002, June 2004) for all publications which describe randomised trials of OCP for the treatment of menorrhagia. This register is based on regular searches of MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, the handsearching 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 the quality of trials and data extraction were performed unblinded by at least two reviewers. Only one trial met the inclusion criteria and none were excluded. The included trial involved a total of 45 women.

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 mefanamic acid groups were combined. There was no significant difference in menstrual blood loss (MBL) between those patients treated with the OCP and danazol, mefenamic acid or naproxen.

Reviewers' conclusions: The one small study identified (Fraser 1991) found no significant difference between groups treated with OCP, mefenamic acid, low dose danazol or naproxen. Overall, the evidence from the one study identified (Fraser 1991) 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.

BACKGROUND

Menorrhagia (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 80ml or more per period. This figure is derived from population studies which have shown that the average blood loss is between 30 and 40ml, and 90% of women have blood losses of less than 80ml (Hallberg 1966; Cole 1971). I n 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 60ml) considered their periods heavy, whilst 40% of those with objectively heavy losses (over 80ml) 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 20-25% 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 50-60ml per month (Rybo 1966; Smith 1982) and indeed 67% of women whose loss is greater than 80ml have actual anaemia (Hallberg 1966). The incidence of anaemia significantly increases when losses exceed 80ml (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 80ml and losses in excess of 80ml 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 30-49 consult their general practitioner each year for menorrhagia (Peto 1993).

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. When taken in a cyclical fashion, it 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.

OBJECTIVES

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

We wish to test the following hypotheses:

1. The oral contraceptive pill (OCP) is an effective medical therapy to reduce menorrhagia in both the short and long term.

2. The OCP is a more cost-effective method than any other medical treatments of menorrhagia.

3. The OCP has fewer side effects than other drugs used for menorrhagia.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled comparisons of OCP versus other medical therapies for the treatment of menorrhagia.

Criteria for exclusion of trials

- irregular menses and intermenstrual bleeding
- pathological causes of menorrhagia
- iatrogenic causes of menorrhagia
- 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 intervention

OCP versus other methods of medical treatment, no treatment or placebo for menorrhagia. All types and dosages of OCP will be considered.

Types of outcome measures

Menstrual bleeding

- objectively assessed blood loss, both short term and long term
- subjectively assessed blood loss, both short term and long term

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 STRATEGY FOR IDENTIFICATION OF STUDIES

See: Cochrane Menstrual Disorders and Subfertility Group search strategy

We searched for all publications which describe (or might describe) randomised trials 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 and June 2004, however no new trials were found.

(1) The Menstrual Disorders and Subfertility Group's trials register was searched for any trials (searched 9 June 2004). This register is based on regular searches of MEDLINE, EMBASE, CINAHL, The Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, the handsearching of 20 relevant journals and conference proceedings, and searches of several key grey literature sources.

(2) For the original search the citation lists of relevant publications, review articles, and included studies were searched.

(3) For the original search the following terms were included in the electronic search strategy of MEDLINE and EMBASE:

(menstru$ adj5 bleedin$).tw.

(heavy adj5 bleed$).tw.

menorrhagia/

menorrhag$.tw.

dysfunctional uterine bleeding.tw.

(iron adj5 anaem$).tw.

(dysfunctional adj5 uter$).tw.

exp contraceptives, oral/

contracept$.tw.

(4) For the original search pharmaceutical companies manufacturing the OCP were also contacted.

METHODS OF THE REVIEW

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.

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.

Quality 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 A (adequate), B (unclear) or C (inadequate). 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.

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.

DESCRIPTION OF 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 patients 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. No trials were excluded.

METHODOLOGICAL QUALITY

The one trial included (Fraser 1991) was a randomised, cross-over trial, but treatment was not blinded and not placebo controlled. Randomisation was by random numbers and allocation was controlled by a laboratory manager (score A). There did not appear to be any clinical differences between groups on history of examination. No intention to treat analysis was used for the seven patients who did not complete the study. The trial treated subjects with each drug for two cycles.

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 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 patients 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 was 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

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).

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.

This review was unable to achieve its stated objectives because of the paucity of the data. A cost effectiveness analysis has not been undertaken because of low numbers. When new information becomes available this will be addressed.

REVIEWERS' 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.

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 menorrhagia.

ACKNOWLEDGEMENTS

The authors would like to thank Prof. Ian Fraser for providing the individual patient data from the trial (Fraser 1991).

POTENTIAL CONFLICT OF INTEREST

None known

NOTES

The updated search in May 2002 and June 2004 was done by the Menstrual Disorders and Subfertility Group.

TABLES

Characteristics of included studies

Study	Fraser 1991
Methods	Randomised, but method not stated. Two post randomisation exclusions occured because patients 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.
Participants	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 peiods.Exclusion criteria: pelvic pathologyWomen 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.
	Group 1 Mefanamic Acid (MFA) or naproxen Group 2 MFA or combined low dose oral contaceptive

Interventions	pillGroup 3 MFA or danazol
Outcomes	Menstrual blood loss (measured by alkaline haematin method)Immediate side effects
Notes	
Allocation concealment	A

REFERENCES

References to studies included in this review

Fraser 1991 *{published data only}*

Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. Australian & New Zealand Journal of Obstetrics & Gynaecology 1991;31:66-70.

** indicates the major publication for the study*

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GRAPHS

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

02 OCP versus naproxen

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Menstrual blood loss (assessed objectively)	1	12	Weighted Mean Difference (Fixed) 95% CI	8.37 [-27.31, 44.05]
02 Menstrual blood loss (assessed subjectively)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Immediate side effects	0	0	Peto Odds Ratio 95% CI	Not estimable

03 OCP versus danazol

Outcome title	No. of studies	No. of participants	Statistical method	Effect size

01 Menstrual blood loss (assessed objectively)	1	12	Weighted Mean Difference (Fixed) 95% CI	19.27 [-24.47, 63.01]
02 Menstrual blood loss (assessed subjectively)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Immediate side effects	0	0	Peto Odds Ratio 95% CI	Not estimable

04 OCP versus mefanamic acid (all)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Menstrual blood loss (assessed objectively)	1	26	Weighted Mean Difference (Fixed) 95% CI	-17.49 [-62.77, 27.79]
02 Menstrual blood loss (assessed subjectively)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Immediate side effects	0	0	Peto Odds Ratio 95% CI	Not estimable

COVER SHEET

Oral contraceptive pills for heavy menstrual bleeding

Reviewer(s)	Iyer V, Farquhar C, Jepson R
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Date new studies sought but none found	09 June 2004
Date new studies found but not yet included/excluded	Information not supplied by reviewer
Date new studies found and included/excluded	Information not supplied by reviewer
Date reviewers' conclusions section amended	Information not supplied by reviewer
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SYNOPSIS

Not enough data on the effects of the oral contraceptive pill on heavy menstrual bleeding

Menorrhagia (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 for the treatment of menorrhagia.

KEYWORDS

Female; Humans; Contraceptives, Oral[*therapeutic use]; Menorrhagia[*drug therapy]