Oral contraceptive pill for primary dysmenorrhoea (Review)

Wong CL, Farquhar C, Roberts H, Proctor M

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[Intervention Review]

Oral contraceptive pill for primary dysmenorrhoea

Chooi L Wong[1], Cindy Farquhar[2], Helen Roberts[3], Michelle Proctor[4]

[1]O & G, FMHS, Auckland, New Zealand. [2]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [3]Obstetrics & Gynaecology, Faculty of Medicine and Health Sciences University of Auckland, Auckland, New Zealand. [4]Psychological Service, Department of Corrections, Auckland, New Zealand

Contact address: Chooi L Wong, O & G, FMHS, Auckland, New Zealand. cwon164@ec.auckland.ac.nz.

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ABSTRACT

Background

Dysmenorrhoea (painful menstrual cramps) is common. Combined OCPs are recommended in the management of primary dysmenorrhoea.

Objectives

To determine the effectiveness and safety of combined oral contraceptive pills for the management of primary dysmenorrhoea.

Search strategy

We conducted electronic searches for randomised controlled trials (RCTs) in the Cochrane Menstrual Disorders and Subfertility Group Register of controlled trials CENTRAL, CCTR, MEDLINE, EMBASE, and CINAHL (first conducted in 2001, updated on 5 November 2008).

Selection criteria

RCTs comparing all combined OCPs with other combined OCPs, placebo, no management, or management with nonsteroidal anti-inflammatories (NSAIDs) were considered.

Data collection and analysis

Twenty three studies were identified and ten were included. Six compared the combined OCP with placebo and four compared different dosages of combined OCP.

Main results

One study of low dose oestrogen and four studies of medium dose oestrogen combined OCPs compared with placebo, for a combined total of 497 women, reported pain improvement. For the outcome of pain relief across the different OCPs the pooled OR suggested benefit with OCPs compared to placebo (7 RCTs: Peto OR 2.01 [95% CI 1.32, 3.08]).The Chi-squared test for heterogeneity showed there is significant heterogeneity with an I^2 statistic of 64% and a significant chi-square test (14.06, df=5, p=0.02). A sensitivity analysis removing the studies with inadequate allocation concealment suggested significant benefit of treatment with the pooled OR of 2.99 (95% CI 1.76, 5.07) and heterogeneity no longer statistically significant and I^2 statistic of 0%.

Three studies reported adverse effects (Davis 2005; Hendrix 2002; GPRG 1968) The adverse effects were nausea, headaches and weight gain. Two studies reported if women experienced any side effect and no evidence of an effect was found (3 RCTs: OR = 1.45 (95% 0.71, 2.94). There was no evidence of statistical heterogeneity.

There were no studies identified that compared combined OCP versus non steroidal anti-inflammatory drugs

There was no evidence of a difference for the pooled studies for 3rd generation pro gestagens (OR = 1.11 (95% CI 0.79 - 1.57)). For the 2nd generation versus 3rd generation the OR was 0.44 (95% CI 0.23-0.84) suggesting benefit of the 3rd generation OCP but this was for a single study (Winkler 2003).

Authors' conclusions

There is limited evidence for pain improvement with the use of the OCP (both low and medium dose oestrogen) in women with dysmenorrhoea. There is no evidence of a difference between different OCP preparations.

PLAIN LANGUAGE SUMMARY

Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhoea

Dysmenorrhoea is painful menstruation (woman's monthly bleeding) with the symptoms including cramping, headaches, nausea and vomiting. An excess of the hormone prostaglandin is a known cause. The synthetic hormones in combined oral contraceptive pills suppress ovulation, which could result in a reduction in dysmenorrhoea. The OCP reduces the amount of prostaglandin produced by glands in the lining of the uterus; which then reduces both uterine blood flow and cramps. The preparations of OCP with doses less than 35 mcg were effective and should be the preparation of choice.

BACKGROUND

Description of the condition

Dysmenorrhoea is the term for describing painful menstrual cramps. It is a common gynaecological problem that can affect as many as 50% of women, and 15% of these women suffer severely enough to temporarily render them incapacitated which, results in absences from work or school (Dawood 2006). The impacts are significant both in terms of quality of life and global economy. In the US alone it was estimated that there is an annual loss of 600 million work hours costing over 2 billion dollars (Dawood 1984).

Dysmenorrhoea is commonly subcategorised into primary and secondary dysmenorrhoea. Menstrual pain without organic pathology is considered to be primary dysmenorrhoea (Coco 1999). When the pelvic pain is associated with an identifiable pathological condition, such as endometriosis or ovarian cysts, it is considered to be secondary dysmenorrhoea.

The initial onset of primary dysmenorrhoea is usually at or shortly after (6 to 12 months) menarche, when ovulatory cycles are established. The pain duration commonly ranges from 8 to 72 hours and is associated with menstrual flow. In contrast secondary dysmenorrhoea is more likely to develop years after the onset of menarche and occur premenstrually as well as during menstruation.

Aetiology of the condition

The aetiology (cause) of primary dysmenorrhoea has been the subject of considerable debate. Experimental and clinical research has identified the over-production or imbalanced amount of uterine prostaglandins as a substantial contributing factor to the painful cramps that are the major symptom of dysmenorrhoea (Dawood 2006). Prostaglandin production is controlled by progesterone; immediately prior to menstruation progesterone levels drop causing prostaglandin production to increase. If these prostaglandins are overproduced cramping can occur. The process of ovulation is also implicated; dysmenorrhoea mostly only occurs in ovulatory cycles, which helps explain why the initial onset of primary dysmenorrhoea occurs shortly after menarche, when ovulatory cycles become established (Dawood 1990).

Description of the intervention

Research as early as 1937 has shown that dysmenorrhoea responds favourably to ovulation inhibition (Karnaky 1975), and that the

synthetic hormones in the combined oral contraceptive pill can be used to manage dysmenorrhoea. These hormones act by suppressing ovulation and lessening of the endometrial lining of the uterus. Therefore menstrual fluid volume decreases along with the amount of prostaglandins produced, which then reduces dysmenorrhoea by decreasing uterine motility, and uterine cramping.

The use of combined oral contraceptive pills (OCP) has been advocated as a treatment for primary dysmenorrhoea since their introduction for general use in 1960. However this type of long term hormonal/endocrine therapy is viewed by some as only potentially useful if long term contraception is also desired (Chan 1981). OCP use for secondary dysmenorrhoea is also questioned, as although this type of treatment may have some favourable effect on dysmenorrhoea ultimately the organic cause of the pain must be addressed (Smith 1993).

Adverse effects of intervention

One potential drawback of the use of OCPs is the possible adverse effects that can accompany the two hormones used. Oestrogen related side effects may include nausea, vomiting, headaches, breast tenderness, and changes in body weight; progesteronic side effects may include acne, weight gain, increased hair growth, and depression. Citing a cause-and-effect relationship between OCPs and these adverse effects may be misleading as they are also observed in women with dysmenorrhoea. Placebo-controlled double-blind studies suggesting that many of these adverse effects can also occur with similar frequency in placebo-using control groups, and even in the general population (Goldzieher 1971; Goldzieher 1995). More potentially serious complications of oestrogens are deep venous thrombosis (blood clotting in the veins), and arterial disease such as heart attacks and stroke, although these are rare. In order to lessen any potential side effects lower dose OCPs have been developed. In contrast to older OCPs, which contain 50-150 micrograms of oestrogen, modern pills are low dose (<35 micrograms). The level of progestogen has also decreased along with a move from first or second generation progestogens (such as norgestrel, levonorgestrel, norethisterone) to third generation progestogens (such as desogestrel, gestodene) which are more selective and have different effects on metabolic parameters. Therefore combined OCPs can be categorised according to the level of oestrogen and the type of progestogen they contain.

How the intervention might work

Clinical trials show that OCPs effectively treat dysmenorrhoea by inhibiting ovulation and reducing prostaglandin levels. In an open trial of 661 women from the general population, 63% experienced dysmenorrhoea pre-treatment but after 12 months of OCP treatment only 12% still experienced dysmenorrhoea (Gauthier 1992). In an open clinical trial of a low dose OCP involving 100,000 women, of those who had dysmenorrhoea as a pre-existing condition, 65% (23,500 women) of the dysmenorrhoeic sample who were first time users of oral contraceptives felt relief from dysmenorrhoea as a result of treatment (Brill 1991). Therefore there is some evidence in general populations that combined OCPs can effectively treat dysmenorrhoea.

Why it is important to do this review

Although combined oral contraceptives have long been promoted as the management for primary dysmenorrhoea, very few trials have been conducted to study efficacy and associated adverse events of their use. In addition, most of these trials are of poor methodological quality which exposes them to various biases. It is important to recognize that in this review.

Dysmenorrhoea is a debilitating gynaecological condition that impacts significantly on women around the world. Not only does it cause great loss in personal health, but having to take time off work or school has also resulted in loss of productivity, eventually leading to economic loss. Proper management of dysmenorrhoea will therefore be beneficial to individuals and society.

There has also been a lot of debate around the issue of the risks of adverse events, if they were worth the benefits of OCPs in managing dysmenorrhoea. This review therefore aimed to establish the usefulness of OCPs in managing dysmenorrhoea in general population by comparing all relevant randomised controlled trials.

OBJECTIVES

To determine the effectiveness and safety of combined oral contraceptive pills for the management of primary dysmenorrhoea.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials that compare all types of combined oral contraceptives (oestrogen/progestogen) with other combined oral contraceptives, placebo, no treatment, or treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of primary dysmenorrhoea. Cross-over trials will only be included if pre and post crossover data available and there was a washout period of two cycles.

Types of participants

Inclusion criteria:

Women in the trials had to meet these inclusion criteria for the trial to be included in the review.
- Women of reproductive age
- Women with primary dysmenorrhoea (moderate/severe pain for at least one day of menses). Trials where the severity of dysmenorrhoea is not formally assessed will be included if the potential participant's have sought medical advice for perceived pain.
- Women with a lack of obvious pelvic pathology, diagnosed with a physical examination
- Women with dysmenorrhoea in the majority of menstrual cycles
- Women with regular ovulatory menstrual cycles (21 to 35 day cycle)
Exclusion criteria:
If more than 20% of women in the trial meet any of the exclusion criteria the trial was not included in the review.
- Women with identifiable pelvic pathology or dysmenorrhoea from IUD use
- Women with infrequent dysmenorrhoea

Types of interventions

Combined oral contraceptives versus placebo, versus no treatment, versus NSAIDs, versus other combined OCPs.
The types of interventions were analysed according to the level and type of hormones used in the oral contraceptive:
1. Combined OCP compared with placebo or no treatment.
2. OCP compared with NSAIDs
3. OCP compared with OCP
For comparison 1-3, then stratification will be according to the type of OC:
i. low oestrogen (< or equal to 35 micrograms of oestrogen) and 1st/2nd generation progestogen
ii. low oestrogen (< or equal to 35 micrograms of oestrogen) and 3rd generation
iii. moderate oestrogen (>35 mcg and < 100 mcg) and 1st/2nd generation
Oral contraceptives containing 100mcg or more of oestrogen have been discontinued due to the increased risk of adverse effects associated with high levels of oestrogen and will be excluded from this review.

Norgestrel, levonorgestrel, and norethisterone are classed as first or second generation progestogens. Desogestrel and gestodene are classed as third generation progestogens.

Types of outcome measures

Primary outcomes:
1. Pain improvement- measured with the visual analogue scale (VAS), Moos Menstrual Disorder Questionnaires (MMDQ) or as dichotomous data (pain improvement). Pain measured with the VAS is preferable as it is a more objective and sensitive measure than dichotomous data (Melzack 1994).
2. Adverse side effects from treatment (incidence of side effects and type of side effects)
Secondary outcomes:
1. Requirements for additional medication (measured as a number of women requiring analgesics additional to their assigned treatment)
2. Absence from work or school (measured as a ratio of women reporting absences from work or school, and also as hours/days of absence as a more selective measure)

Search methods for identification of studies

All reports which described (or might have described) randomised controlled trials of combined oral contraceptives in the treatment of primary dysmenorrhoea were obtained using the following search strategy. The original search was performed in 2001. Updated searches were completed in 5th November 2008. The search was not restricted by language. Search strategies were revised and redeveloped in the update of the review. Please refer to previous version of review for details on old search strategies.
Electronic Searches (details of specific search strategies for each database/register)
1) The Menstrual Disorders and Subfertility Group's Specialised Register of controlled trials was searched with the following words in the title, abstract or keyword sections. See Review Group for more details on the makeup of the Specialised Register.
Keywords CONTAINS "dysmenorrh" or "pelvic pain" or "menstrual cramps" or "menstrual pain" or"pain-pelvic" or (Title CONTAINS "dysmenorrh" or "pelvic pain" or "menstrual cramps" or "menstrual pain" or"pain-pelvic")
AND
Keywords CONTAINS "combined oral contraceptive" or "oral contraceptive" or "progestagen" or "Progesterone" or "progestin" or "progestogen" or "Norgestrel" or "norethisterone" or "desogestrel" or "gestodene" or "estrogen" or "oestrogen" or "oestrodiol" or "Estradiol" or "non steroidal" or "NSAID" or "mefenamic acid" or "naproxen" or "ibuprofen" or "Flurbiprofen" or "Meclofenamic Acid" or "Meclofenamate" or "diclofenac" or "acetly salicylic acid" or "aspirin" or Title CONTAINS "combined oral contraceptive" or "oral contraceptive" or "progestagen" or "Progesterone" or "progestin" or "progestogen" or "Norgestrel" or "norethisterone" or "desogestrel" or "gestodene" or "estrogen" or "oestrogen" or "oestrodiol" or "Estradiol" or "non steroidal" or "NSAID" or "mefenamic acid" or "naproxen" or "ibuprofen" or "Flurbiprofen" or "Meclofenamic Acid" or "Meclofenamate" or "diclofenac" or "acetly salicylic acid" or "aspirin"
2) EMBASE (1980 to 2008 Week 06):
3) MEDLINE (1950 to January Week 5 2008):
4) CINAHL - Cumulative Index to Nursing & Allied Health Literature (1982 to December Week 1 2007):
5) The Cochrane Central Register of Controlled Trials (1st Quarter 2008)

Searching other resources
1) The National Research Register (NRR), a register of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service (NHS), as well as entries from the Medical Research Council's Clinical Trials Register, and details on reviews in progress collected by the NHS Centre for Reviews and Dissemination, was searched for any trials with dysmenorrhoea or dysmenorrhea as a keyword. The Clinical Trials Register, a registry of both federally and privately funded US clinical trials was also searched for the same keywords.
2) The citation lists of relevant publications, review articles, abstracts of scientific meetings and included studies were also searched.

Data collection and analysis

Selection of studies

The selection of trials for inclusion in the update of review was performed by the two reviewers (CW and CF) after employing the search strategy described previously. This was done previously by the two original reviewers (MW and CF).

Data extraction and management

Included trials were analysed for the following quality criteria and methodological details. This information is presented in the table of included studies and provides a context for discussing the reliability of results:
Trial characteristics
1. Method of randomisation
2. Presence or absence of blinding to treatment allocation
3. Quality of allocation concealment
4. Number of women randomised, excluded or lost to follow up
5. Whether an intention to treat analysis was done
6. Whether a power calculation was done
7. Duration, timing and location of the study
Characteristics of the study women
1. Age and any other recorded characteristics of women in the study
2. Other inclusion criteria
3. Exclusion criteria
Interventions used
1. Type of combined OCP used
2. Levels of oestrogen and progestogen
Outcomes
1. Methods used to measure pain relief achieved by treatment
2. Methods used to measure adverse effects

Assessment of risk of bias in included studies

The Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) recommends the explicit reporting of:

- Sequence generation

Was sequence generation adequate (e.g. use of a random number table, a computer random number generator or coin tossing), inadequate (e.g. use of date of birth or clinical record number) or unclear (insufficient information about the process of sequence generation)?

- Allocation concealment

Was allocation concealment adequate (e.g. use of central allocation or opaque sealed envelopes), inadequate (e.g. use of an open random allocation schedule, date of birth or case record number) or unclear (insufficient information about the process of allocation concealment)?

- Blinding of participants, providers and outcome assessors

Was blinding adequate (e.g. participants and researchers were all blinded and it was unlikely that blinding could have been broken, either participants or some researchers are not blinded but outcome assessment was blinded or no blinding was used but this is not likely to influence outcomes), inadequate (e.g. no blinding or incomplete blinding and outcomes are likely to be influenced by this) or unclear (insufficient information about the process of blinding)?

- Incomplete outcome data

Was outcome data addressed adequately (e.g. there was no missing outcome data, reasons for missing outcome data were unlikely to be related to true outcome or missing outcome data was balanced in numbers across intervention groups), inadequate (e.g. reasons for missing outcome data were likely to be related to true outcome) or unclear (insufficient information about the process of addressing outcome data)?

- Selective outcome reporting

Was the study free of selective reporting? Adequate (e.g. the study protocol is available and all pre-specified outcomes have been reported or the study protocol is not available but it is clear that all pre-specified outcomes have been reported), inadequate (e.g. not all pre-specified primary outcomes have been reported) or unclear (insufficient information about the process of outcome reporting).

- Other sources of bias for RCTs

Was the study free of other bias? Adequate (the study seems to be free of other bias), inadequate (e.g. extreme baseline imbalance, a potential source of bias related to the specific study design used or early stopping) or unclear (insufficient information about other sources of bias).
Each of these domains as assessed as 'Yes' (indicating a low risk of bias), 'Unclear' (indicating an uncertain risk of bias) or 'No' (indicating a high risk of bias). No study was automatically excluded as a result of a rating of 'Unclear' or 'No'. Where it was unclear, authors of studies were contacted about the methods used and also any missing data was sought.The risk of bias assessment in the 'Characteristics of included studies' tables in the review have been completed, including commentary about each of the domains where possible. This will lead to an overall assessment of

the risk of bias of included. A summary of the risk of bias table has been added to the figure section.

Measures of treatment effect

When extracting data from the trials for the outcome of pain relief it was decided a priori to only count substantial changes in pain as pain relief, if the trial reported sufficient data. For example the number of women changing from severe pain to mild or no pain would be included as experiencing pain relief, but not women changing from severe to moderate pain. The OR has been used for dichotomous outcomes and weighted mean difference for continuous outcomes. In the case of missing variance such as standard deviations the measure was imputed from the other similar studies. (The use of the imputation method was added in the update of 2008).

Unit of analysis issues

No unit of analysis issues were identified in this review.

Dealing with missing data

Where missing data was reported, the analysis was performed using the initial number of patients who were randomised.

Assessment of heterogeneity

The overlap of the confidence intervals for the results of individual studies will be visually inspected as a general indication the presence of statistical heterogeneity. More formally, a statistical test for heterogeneity, the chi-squared test will be included in the graphical output of the review. The chi-squared test assesses whether observed differences in results are compatible with chance alone. A low p-value (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity of treatment effects (variation in effect estimates beyond chance). An I^2 statistic describing the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) will be calculated. A value greater than 50% may be considered substantial heterogeneity.

A priori, it was planned to look at the possible contribution of differences in trial design to any heterogeneity identified in this manner. Where possible, the outcomes were pooled statistically.

Data synthesis

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Cochrane Collaboration and published in the handbook.

For dichotomous data (for example, proportion of women with a specific adverse effect), results for each study were expressed as an odds ratio with 95% confidence intervals and combined for meta-analysis with RevMan software using the Peto Mantel-Haenszel method.

Continuous differences between groups in the meta-analysis were shown as a weighted mean difference (WMD). where the same scales are applied, and 95% confidence interval. A fixed approach was used for primary analysis. Where statistical heterogeneity was observed, sensitivity to the choice of model was assessed by comparison with a random effects analysis.

If other scales or labels were used these were collapsed into dichotomous data if possible, based on the authors descriptions of the scale. If outcomes were presented in terms of pain intensity rather than pain relief these were considered and where possible converted into dichotomous categories.

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were planned.

Sensitivity analysis

Sensitivity analyses were planned on the basis of allocation of concealment only.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Twenty three studies were considered for inclusion and ten met the inclusion criteria. One of the studies had three reports, the first related to pain outcomes and the second publication reported treatment discontinuation rates and losses to follow up of the original study and third providing further outcome data on pain and adverse events. (Davis 2005). Two of the studies reported some pain outcomes for a subgroup of women who had dysmenorrhoea but pain improvement and pain scores were not reported and therefore no data could be usefully extracted (Bassol 2000, Hendrix 2002).

TRIALS EXCLUDED FROM THE REVIEW

Thirteen studies were excluded. One excluded trial (Iannotti 1991) compared three treatments. Piroxicam (a non-steroidal, anti-inflammatory), a triphasic estroprostogenic compound and a Vitamin D complex were given to all women for 5 months each in an uncontrolled, non-randomised trial; therefore the trial does not meet the prescribed inclusion criteria. Another excluded trial compared two monophasic and one triphasic combined oral contraceptives however allocation to each group was retrospective not random. Two excluded trials used combined oral contraceptives with 100mcg estrogen (Karasawa 1968; Kremser 1971). It was recommended by the British Scowen committee in 1970 that combined

OCPs with levels of estrogen this high be withdrawn from the market. By 1988 very high dose pills were discontinued by the major pharmaceutical companies. One of the excluded trials was a case control study (Kristjansdottir 2000). Five studies included only small proportion of women with dysmenorrhea (Foidart 2000; Kaunitz 2000;Kwiecien 2003 Moore 1999; Reisman 1999) and one of the studies was excluded a none of the patients had dysmenorrhoea (Creatsas 1998). One of the original studies was identified as not a truly randomised trial and was therefore excluded (Matthews 1968). A further study was not an RCT and was excluded (Tallian 1994) (. La Guardia 2003 was an RCT comparing 5 different OCP preparations for efficacy, cycle control and safety and only described dysmenorrhoea as an adverse event. See table of excluded studies for more details.

TRIALS INCLUDED IN THE REVIEW

All assessments of the quality of trials and data extraction were performed independently by the two reviewers (CW and CF) using forms designed according to Cochrane guidelines. This was done previously by the two original reviewers (MW and CF). Additional information on trial methodology or original trial data was to be sought from the principal author of trials. However, for the trials that were more than 20 years old this was not deemed to be feasible, therefore four of the authors were not written to as their trials (GPRG 1968; Nakano 1971; Buttram 1969a; Cullberg 1972) were published more than 20 years ago. Out of the remaining six authors who were being contacted, three of them responded. (Hendrix 2002; Davis 2005; Winkler 2003)

Types of intervention

Of the ten included studies, six compared combined oral contraceptives with placebo as treatment for primary dysmenorrhoea (GPRG 1968; Nakano 1971; Buttram 1969a; Cullberg 1972; Hendrix 2002; Davis 2005), two compared combined oral contraceptives with different types of progestogens (Serfaty 1998; Endrikat 1999) and two compared combined oral contraceptives with different doses of estrogen.(Bassol 2000; Winkler 2003) One study also had a sequential arm combined OCP (Buttram 1969a). See table of included studies for more detail

No studies were identified comparing OCP and NSAIDs.

Study design

One study was of crossover design randomised women every month to a treatment, and women were followed for between 3 to 6 months in total (Nakano 1971). The other studies were of parallel design.

Treatment length and follow up

Treatment length varied among the included trials; GPRG 1968 had an intervention period of two months; Cullberg 1972 also had a treatment length of two months but then included a month of post-treatment follow up; Buttram 1969a had a three month treatment period; Nakano 1971 had intervention periods of between 3 to 6 months; Hendrix 2002 had a four month treatment length; Davis 2005 treated the women for three months; Winkler 2003 and Serfaty 1998 had a treatment length of 6 months; Bassol 2000 and Endrikat 1999 had an intervention periods of 12 months.one had two months of treatment followed by a month of follow up (Cullberg 1972), Follow up for the remaining studies: three were of a three month duration (Buttram 1969a; GPRG 1968; Davis 2005), one was of four month duration (Hendrix 2002), one had six months of treatment with no follow up (Serfaty 1998) and one was followed by five months of follow up (Winkler 2003), and two had a treatment length of twelve cycles (Bassol 2000; Serfaty 1998). Three other trials did not report any follow up period (Davis 2005; Endrikat 1999; Serfaty 1998).

Study location and sources of women

The included studies originated from a wide variety of countries; USA, UK, Sweden, Japan, Germany, Argentina, Brazil, Chile, Mexico, France, Austria, Switzerland, Italy, and the Netherlands. The women in the studies were also recruited from a variety of sources; student nurses, private practice patients and the local hospital (Buttram 1969a); local telephone company, student nurses, university students and two hospitals (Cullberg 1972); general practitioner's patients (GPRG 1968); hospital outpatients (Nakano 1971); college students (Davis 2005). The remaining five studies did not state from where the women were recruited.

Selection of women

Five studies included a number of women without dysmenorrhoea however it was possible to separate the information and data on these two groups and women without dysmenorrhoea were not included in this review (Bassol 2000Cullberg 1972; Winkler 2003; Serfaty 1998; Endrikat 1999).

Six of the studies made explicit attempts in the form of clinical or pelvic exams to rule out pelvic pathology as a cause for dysmenorrhoea (Buttram 1969a; Nakano 1971; Hendrix 2002; Bassol 2000; Endrikat 1999; Serfaty 1998). One other study included very little information on the selection of women other than they had dysmenorrhoea (GPRG 1968), while Cullberg 1972 stated that women had to be absent of disease but included no information on how this was assessed.

One study stated that pelvic examinations were not done to exclude secondary causes of dysmenorrhoea to avoid discouraging enrolments by younger adolescents (Davis 2005). The other study did not include any information on if any pelvic exams were done (Winkler 2003). Other exclusion criteria included planned or suspected pregnancy, contraindications to OCPs use, use of drugs that would interfere with pharmacokinetics of OCPs, recent miscarriage or abortion, abnormal genital bleeding, injectable hormonal contraceptives users, drugs use and abnormal genital bleeding.

Severity of dysmenorrhoea

Two trials included women with any severity level of dysmenorrhoea (Cullberg 1972; Endrikat 1999). Five trials (Buttram 1969a;

GPRG 1968; Nakano 1971; Hendrix 2002; Davis 2005) clearly stated the severity levels of dysmenorrhoea that would be included and how this would be defined. Buttram 1969a stated they would only include women with severe dysmenorrhoea defined as incapacitating pain for two or more days. GPRG 1968 stated they would include anything but mild dysmenorrhoea, which they defined as dysmenorrhoea that is relieved by analgesics and where no additional medication is normally required. Nakano 1971 stated they would include women with dysmenorrhoea that necessitated absence from duty. Hendrix 2002 stated that only women with history of Grade 2 or Grade 3 dysmenorrhoea would be included and Andersch and Milsom dysmenorrhoea assessment tool was used to establish the grading system. Davis 2005 also used the Robinson modification of Andersch scale to classify the severity of dysmenorrhoea and would include women with moderate dysmenorrhoea, which is defined as sometimes or always experiencing very painful menstrual cramps, or severe dysmenorrhoea, which indicates sometimes or always cutting back on activities in addition to experiencing painful menstrual cramps. The remaining three trials questioned the women and categorised them into different severity levels (slight/mild, moderate, severe) based on the women own judgement without using formal definitions (Bassol 2000; Serfaty 1998; Winkler 2003).

Outcome measures

All ten studies assessed the primary outcome of pain relief. GPRG 1968 assessed pain relief with a three point scale (complete, partial or none) at monthly intervals and reported these as total pain relief scores. Buttram 1969a assessed pain relief by changes in dysmenorrhoea on a four point scale (from severe to mild, moderate or absent or no improvement), this assessment was based on pain relief after the final cycle of treatment. Nakano 1971 assessed pain relief on a three point scale (complete, some, none) and reported scores for each month of treatment. Cullberg 1972 assessed dysmenorrhoea as improved, unchanged or worse based on pain scores at the end of the two months treatment. Both Hendrix 2002 and Davis 2005 assessed pain relief with MMDQ on a five point Likert scale (0 = no experience of symptom, 1 = mild, 2 = moderate, 3 = strong, 4= severe) and reported the outcome as the mean change of scores from baseline to last observed menses. Endrikat 1999 and Bassol 2000 questioned the women if they did or did not experience pain relief at 3 monthly intervals and reported the proportion of women who had experienced pain relief after the final cycle of treatment. Serfaty 1998 assessed dysmenorrhoea as complete relief, improved, no change or worsened and reported the monthly proportion of women with dysmenorrhoea in a graph form for six cycles of treatment. Winkler 2003 reported the outcome for pain relief as improved or not improved.

Two trials reported mean change in pain scores as its primary outcome for pain relief (Davis 2005;Hendrix 2002). For two of the trials included in the meta-analysis for the comparison of 1st /2nd generation progestogens versus placebo, only women experiencing complete relief were included as those experiencing pain relief (GPRG 1968; Nakano 1971); one trial was included that reported the number of women changing from severe pain to no pain/mild pain (Buttram 1969a); the other trial in the meta-analysis categorised women as those whose pain improved or did not improve (Cullberg 1972). This trial may be a source of heterogeneity as its categorisation of dysmenorrhoea was not as sophisticated as the other trials. For trials with different comparisons, one trial also grouped women as those whose pain improved or did not improve (Winkler 2003); one trial included those who experienced complete relief or improvement in pain as those experiencing pain relief (Serfaty 1998); the other trial reported the number of women who experienced relief or no relief (Endrikat 1999).

Three studies reported adverse effects by group (Davis 2005, GPRG 1968; Hendrix 2002), additional use of analgesics (Davis 2005; GPRG 1968) and absence from work or school (Hendrix 2002; GPRG 1968) although three additional studies reported withdrawing from the study as a result of adverse events (GPRG 1968; Hendrix 2002). Davis 2005; Endrikat 1999; Serfaty 1998; Winkler 2003)

Withdrawals: For the GPRG 1968 trial a number of women dropped out of the trial before completing three months of treatment, therefore the meta-analysis only included those who completed three full months of treatment. Adverse events were not a reason for withdrawal. One study reported 4/22 women (18%) withdrawing from the final analysis, however two of these women were excluded due to breakthrough bleeding (Nakano 1971). Cullberg 1972 had 23 drop outs out of the 322 women initially randomised, however only 213 of the 322 women had dysmenorrhoea and results were reported for only 203 of those women. Therefore dropouts from the dysmenorrhoea group were less than 10%, while dropouts from the overall trial were only 7%. Reasons given for withdrawals varied (from the overall group there were five pregnancies, six women who disappeared, four with somatic complaints such as bleeding, skin troubles or nausea, three with "interfering illness", and four who changed their minds). This data was not suitable for inclusion in the analysis. Hendrix 2002 reported 25/77 women (32%) not being included in the final analysis; four were excluded due to protocol violations, and the rest discontinued the treatment due to various reasons (non-compliance, personal reasons, pre-existing pregnancy and unknown reasons). The text specifically states that there were no withdrawals for adverse events. Only 7/76 women discontinued in Davis 2005 and only 2 of them were not included in the final analysis due to lost to follow up and pregnancy and three were for adverse events. Three studies (Bassol 2000; Endrikat 1999; Winkler 2003) included women with no dysmenorrhoea in the trials, therefore although withdrawals of the women were mentioned, but no number was reported specifically for the dysmenorrhoea group. The percentage of withdrawals was therefore applied to the subgroup of women with dysmenorrhoea. For example, in Endrikat 1999 13% of women withdrew and this percentage was assumed to ap-

ply to the women with dysmenorrhoea. Serfaty 1998 stated that only 213 out of 1016 women initially randomised had dysmenorrhoea and 40 of them dropped out of the study prior to completion. Most common reasons for withdrawals were unacceptable bleeding problems and adverse events. The one remaining study did not report withdrawals (Buttram 1969a).

For the Cullberg 1972 trial, data on pain relief was reported as a percentage of the women in the group and these percentages had to be recalculated into numbers of women to be included in the meta-analysis. In the meta-analysis for the comparison of 1st/2nd generation progestogens versus placebo, the placebo group for the Cullberg 1972 trial was evenly split between the three different types of progestogens evaluated in the trial. This was done to allow comparisons to be made and to ensure that the women in the placebo group were not over represented in the summary statistic.

Baseline comparability

One study failed to provide any data on the baseline comparability of the two intervention groups (Nakano 1971). The other studies compared the groups on a number of factors including; age, ethnicity, drugs history, alcoholic consumption, smoking habits, gynaecologic history, marital status, education, parity, pain, other symptoms, days off work or in bed, duration of pain and menses. Two studies reported a difference between the intervention groups; GPRG 1968 stated that the placebo group contained a slightly higher proportion of more severe cases but presented no data to confirm this statement and Hendrix 2002 stated that the placebo group had a lower percentage of women who required time off work or school due to dysmenorrhoea.

Types of compounds used

A number of different types of oestrogen/progestogen compounds were used and four of the trials (Buttram 1969a; GPRG 1968; Cullberg 1972; Nakano 1971) used medium doses of oestrogen and 1st or 2nd generation progestogens. Of these trials, mestranol 0.08mg and chlormadinone acetate 2mg taken sequentially was used in one arm of a trial and combined mestranol 0.1mcg and norethindrone was used in another arm and compared with a third placebo arm (Buttram 1969a). Mestranol 0.05mg and norethisterone 1mg was used in one trial (GPRG 1968). 0.05 mg of mestranol is equivalent to 35mcg of ethinyl estradiol. Two other trials included 0.05mg ethinyl oestradiol with different levels of the progestogen norgestrel; 1mg, 0.5mg and 0.06mg (Cullberg 1972); 0.5mg (Nakano 1971).

The remaining trials all used low doses of ethinyl oestradiol and 1st or 2nd or 3rd generation progestogens. Hendrix 2002 used two doses of ethinyl estradiol, 0.02mg and 0.01mg, and 0.15mg desogestrel. Ethinyl estradiol 0.02mg and desogestrel 0.15mg was used in three trials (Endrikat 1999; Serfaty 1998; Bassol 2000) and they were compared against 0.075mg gestodene with same doses of ethinyl estradiol in two of them (Endrikat 1999; Serfaty 1998) while Bassol 2000 used 0.03mg ethinyl estradiol combined with 0.075mg gestodene. The remaining two trials included 0.02mg ethinyl estradiol with 0.01mg levonorgestrel (Davis 2005; Winkler 2003), and 0.15mg gestodene was used as a comparison in Winkler 2003.

Compliance

Compliance with the treatment protocol was only assessed by five of the included trials (Hendrix 2002; Davis 2005; Winkler 2003; Endrikat 1999; Serfaty 1998). Assessment of compliance was done in different ways across different studies; by counting the pills or checking the pill packs (Hendrix 2002; Davis 2005), by general questioning (Davis 2005; Endrikat 1999), and referring to the diary cards or menstrual charts (Davis 2005; Endrikat 1999: Winkler 2003). Although Serfaty 1998 stated that compliance was assessed, but no information was provided on how it was done. Cullberg 1972 told women that urinary specimens may be taken at follow up visits to analyse hormone content in an attempt to ensure compliance but samples were not actually taken.

Risk of bias in included studies

Allocation concealment and randomisation method Figure 1; Figure 2

Three of the included studies were given an allocation score of A; Cullberg 1972 stated that randomisation was performed statistically by the pharmaceutical company via a secure code; Hendrix 2002 stated that locked files were utilised at onsite computer system to secure the randomisation list; Davis 2005 stated that the randomisation list was prepared by an assistant who was not involved in the conduct of the study and they made sure that all the package was identical in appearance and had a unique ID number. Six of the included studies were assigned an allocation score of B, due to unclear methods (Buttram 1969a; Nakano 1971; Bassol 2000; Endrikat 1999; Serfaty 1998, Winkler 2003), one trial stated that allocation to each treatment group was random but gave no details (Buttram 1969a). The other trial stated that allocation was via the "envelop method" but gave no further details, this could refer to the use of opaque sealed envelopes but it is not enough detailed information to adequately assess allocation concealment (Nakano 1971). The other included study was assigned allocation scores of B as due to a clerical error all the placebo pills had a different mark to the treatment pills meaning that identification of the groups (although not the actual assignment) was possible (GPRG 1968). Winkler 2003 stated that the randomisation lists were managed centrally and were sent to the centres together with the trial medication and therefore was assessed as unclear.

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

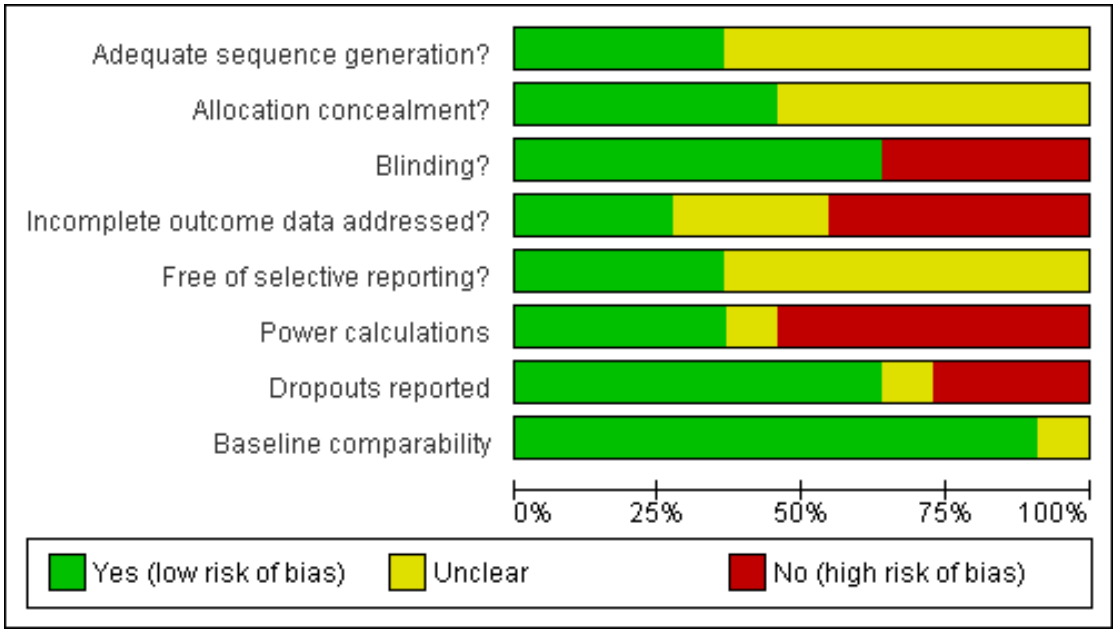
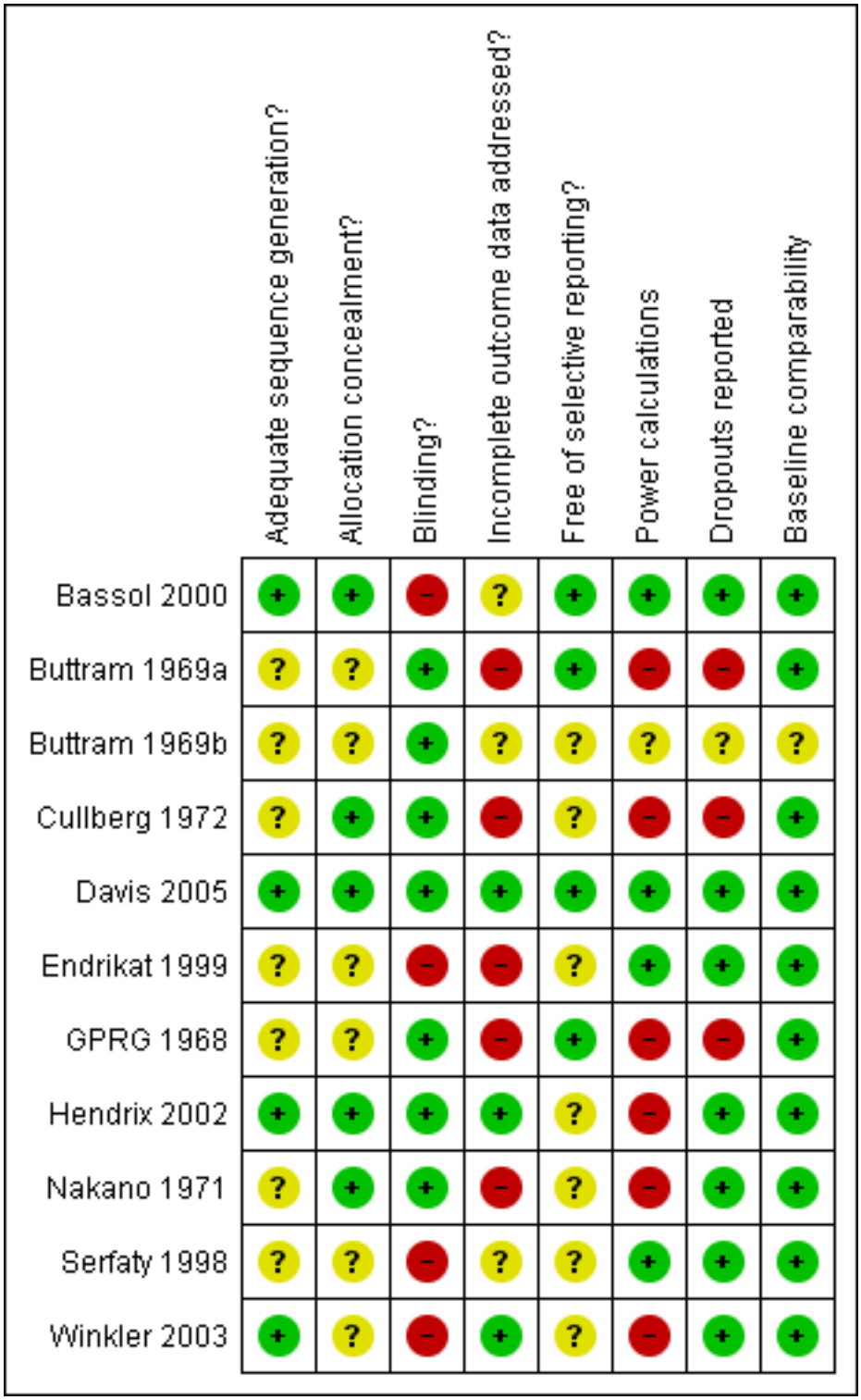


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Blinding

Double-blinding was used in six studies, and the remaining four trials were all open-label trials (Bassol 2000; Winkler 2003; Endrikat 1999; Serfaty 1998). Blinding was unclear in the GPRG 1968 study due to the fact that there were different markings on the two sets of pills which made it possible to identify pills used for treatment and placebo groups, although those allocating and receiving the pills were unaware of the meaning of the markings or that each set had different markings.

Intention-to-treat analysis

Three studies stated that intention-to-treat analysis was performed. (Hendrix 2002; Davis 2005; Winkler 2003) In Davis 2005, there were two dropouts and the analysis was based only on the patients who provided data. Hendrix 2002 reported protocol violations and only analysed the cases after exclusion and therefore does not report an ITT analysis. One study was not clear on how many women were randomized to each treatment modality. (Bassol 2000) The remaining studies did not provide additional on if intention-to-treat analysis was performed. (Nakano 1971; Cullberg 1972; Buttram 1969a; GPRG 1968; Endrikat 1999; Serfaty 1998)

Power Calculation

Power calculation was performed by three of the studies (Davis 2005; Bassol 2000; Serfaty 1998), and Davis 2005 and Serfaty 1998 stated that the number of women recruited would allow for a power of 80% although as Davis 2005 only enrolled 76 participants and Serfaty 1998 enrolled 1016 participants. The reason for the difference is that the smaller study by Davis was only in women with dysmenorrhoea and was a placebo controlled trial whereas the trial by Serfaty was a drug comparison study with a subgroup of women who had dysmenorrhoea. The remaining trials did not state in the study if any power calculation was performed prior to the study

Conflict of interest

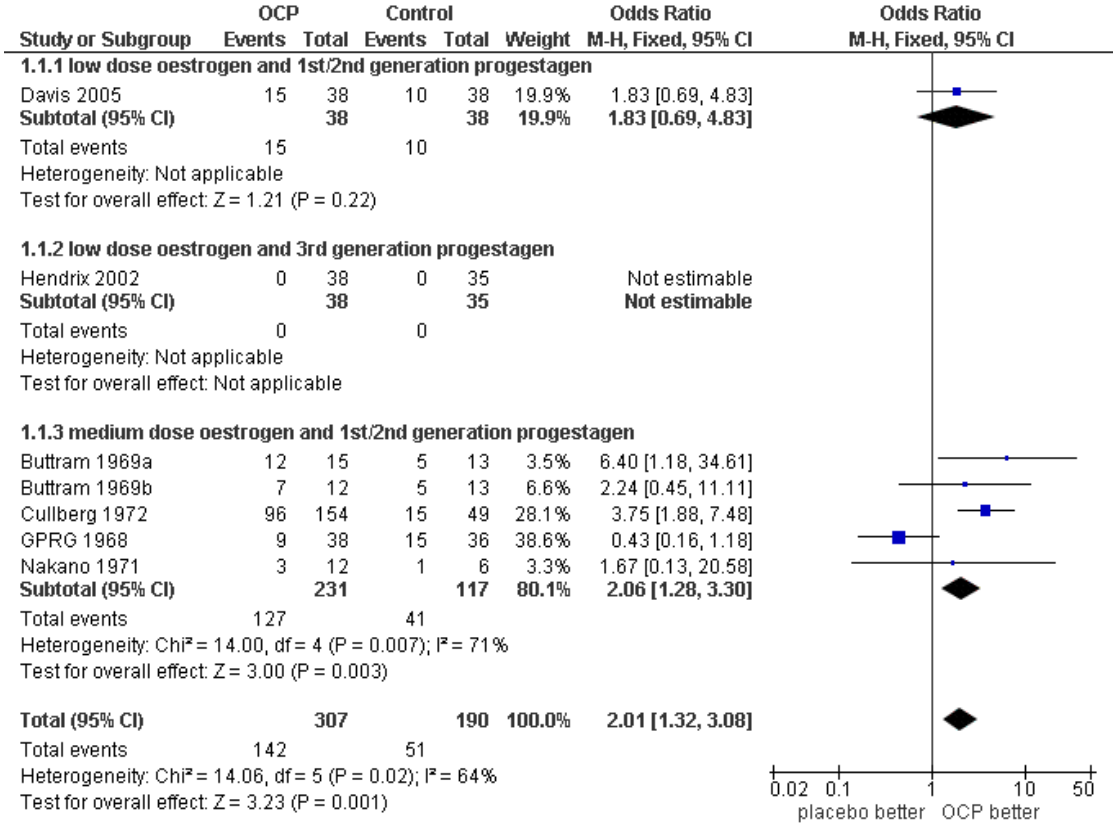
Four trials stated they received partial support from pharmaceutical companies (Buttram 1969a; Hendrix 2002; Winkler 2003; Serfaty 1998). One trial was supported by the Swedish Medical Council (Cullberg 1972), one trial was supported by the National Institute of Child Health and Human Development (Davis 2005), one trial was supported by Schering Laboratory in Mexico (Bassol 2000), and three trials failed to mention sources of funding or support (GPRG 1968; Nakano 1971; Endrikat 1999).

Effects of interventions

1. Combined oral contraceptive pill versus placebo or no treatment

Pain improvement Figure 3

Figure 3. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.1 Pain improvement.

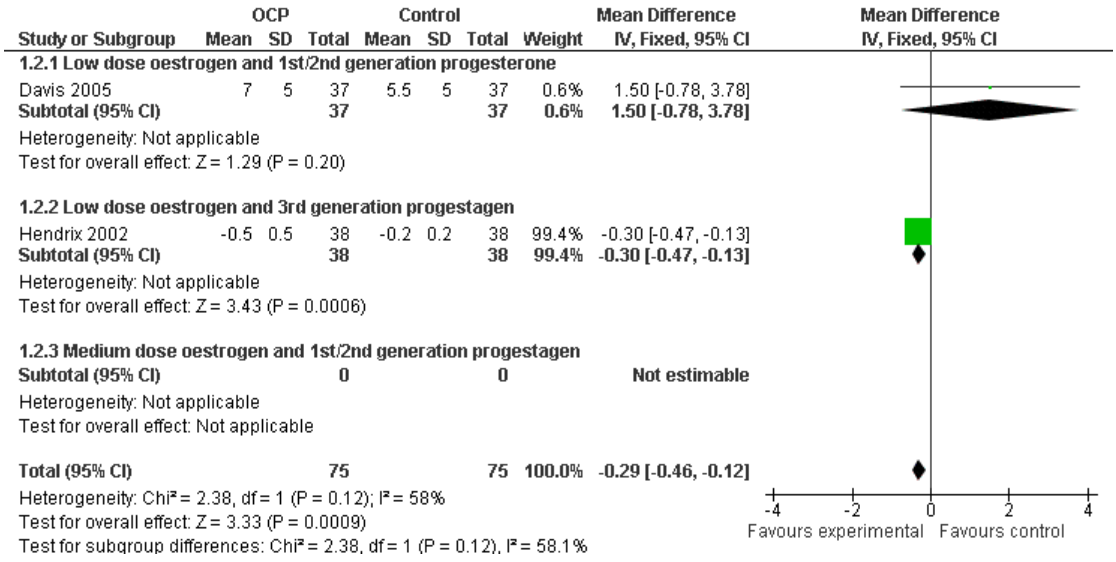


Two studies of low dose oestrogen and five studies of medium dose oestrogen combined OCPs compared with placebo, for a combined total of 497 women, reported pain improvement. For the outcome of pain relief across the different OCPs the pooled OR suggested benefit with OCPs compared to placebo (Peto OR 2.01 [95% CI 1.32, 3.08]]).

The Chi-squared test for heterogeneity showed there is significant heterogeneity with an I^2 statistic of 64% and a significant chi-square test (14.06, df=5, p=0.02). One explanation for this is the disparate results of Cullberg 1972 and GPRG 1968. GPRG 1968 had a mistake with the blinding procedure although unbinding as a result seems unlikely to have occurred. A sensitivity analysis removing the studies without adequate allocation concealment resulted in Davis 2005; Cullberg 1972; Hendrix 2002; Nakano 1971 remaining and suggesting significant benefit of treatment with the pooled OR of 2.99 (95% CI 1.76, 5.07) and heterogeneity no longer statistically significant and I^2 statistic of 0%.

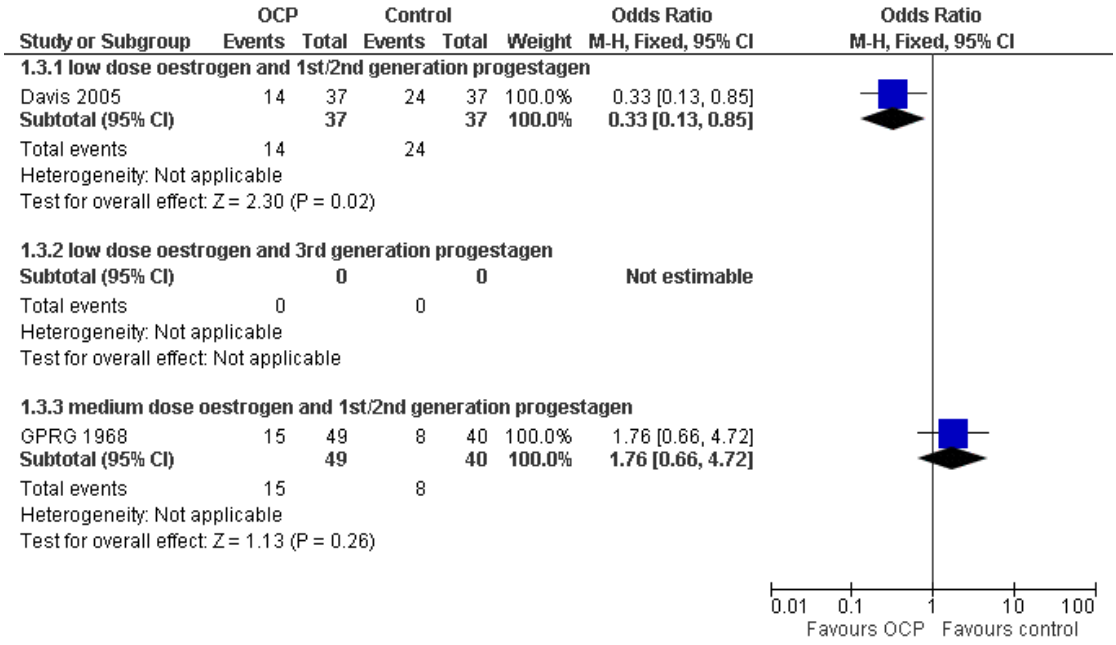
Pain scores Figure 4

Figure 4. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.2 Pain score (mean change).



The pooled pain scores of low dose oestrogen and 2nd and 3rd generation progestagen's reported pain scores with a weighted mean difference of -0.29 (95%CI -0.46, -0.12). Heterogeneity: Chi² = 2.38, df = 1 (P = 0.12); I² = 58%.Figure 5

Figure 5. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.3 Additional analgesia required.

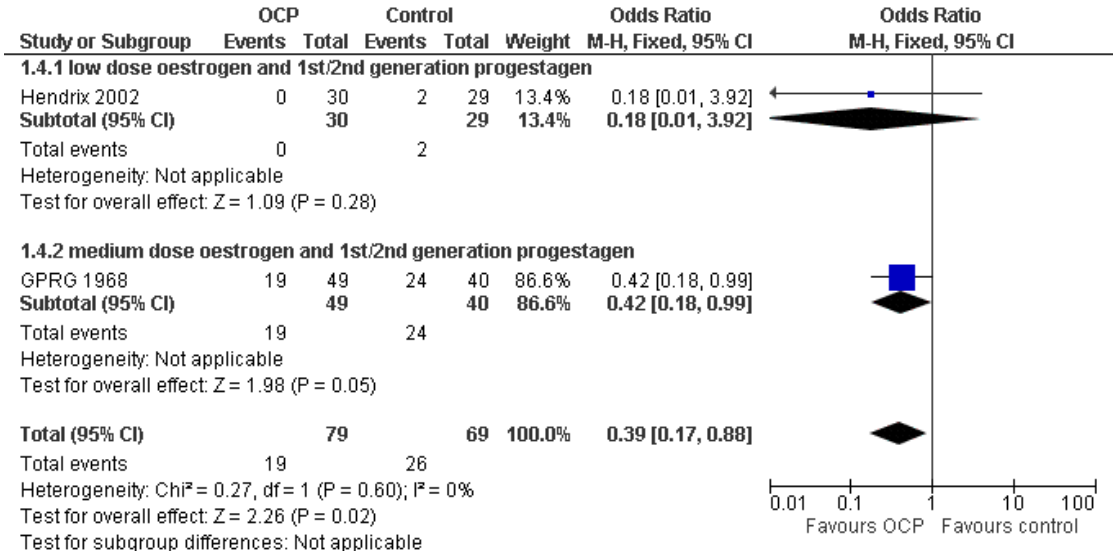


Additional pain relief

Three studies reported this outcome. In the study of low dose oestrogen and 1st/2nd generation progestogens there was reduced need for additional pain relief with an OR of 0.33 (95%CI 0.13,0.85) Davis 2005 but in the medium dose oestrogen pills there was no evidence of a benefit and the pooled OR was 0.75 (95% CI 0.39, 1.43) . There was significant statistical heterogeneity with a Chi-square test=5.79, df=1 and I^2 =83%. Once GPRG 1968 was removed from the analysis because of inadequate allocation concealment then only one study Davis 2005 remains (OR = 0.33 (95% CI 0.13-0.85).

Absence from school Figure 6

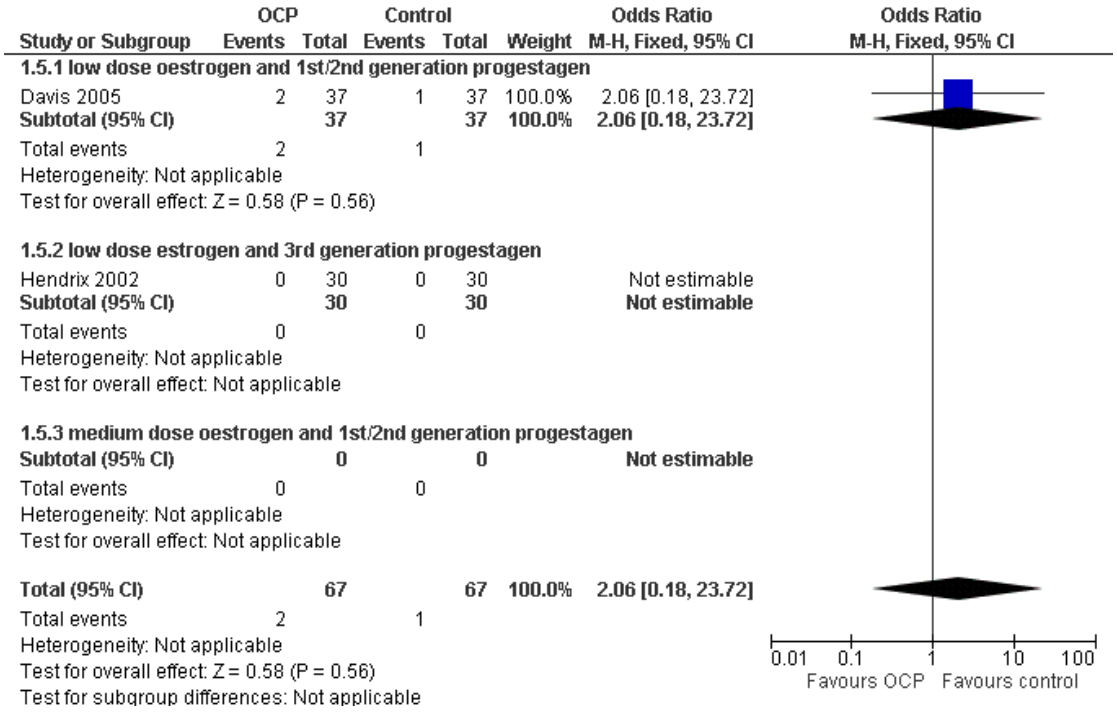
Figure 6. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.4 Absence from school or work.



Only two studies reported this outcome. (Hendrix 2002; GPRG 1968) The pooled OR for the two studies was 0.39 (95% 0.17,0.88) suggesting benefit with the OC pill. No evidence of statistical heterogeneity.

Withdrawals from treatment Figure 7

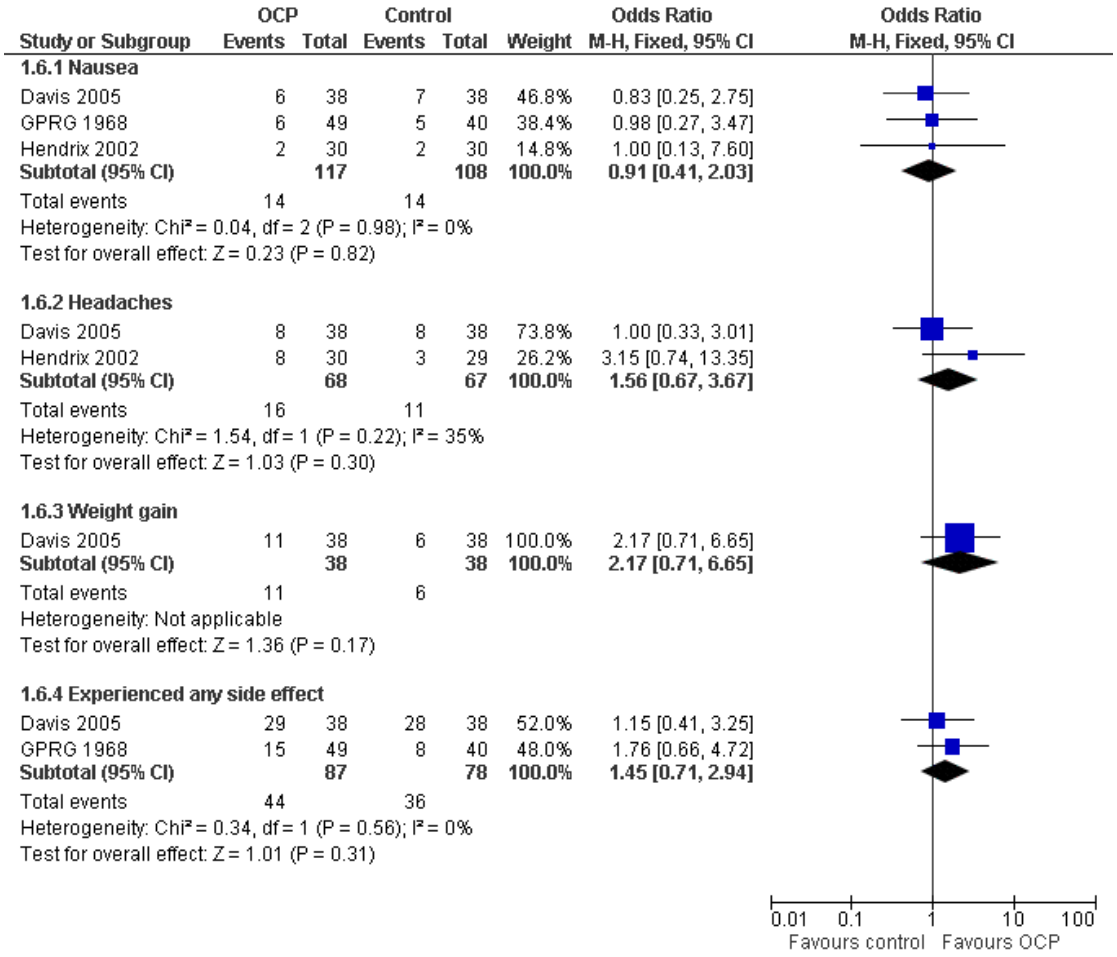
Figure 7. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.5 Withdrawals from treatment.



Only two studies reported this outcome. (Davis 2005; Hendrix 2002) The pooled OR for the two studies was 2.06 (95% 0.18-0.23.72) suggesting no evidence of increased withdrawals with the OC pill and no evidence of statistical heterogeneity.

Adverse events Figure 8

Figure 8. Forest plot of comparison: 1 Combined OCP versus placebo or no treatment, outcome: 1.6 Adverse events.



Three studies reported adverse effects (Davis 2005; Hendrix 2002; GPRG 1968) The adverse effects were nausea, headaches and weight gain. Two studies reported if women experienced any side effect and the there was no evidence of an effect with a pooled OR = 1.45 (95% 0.71, 2.94). There was no evidence of statistical heterogeneity.

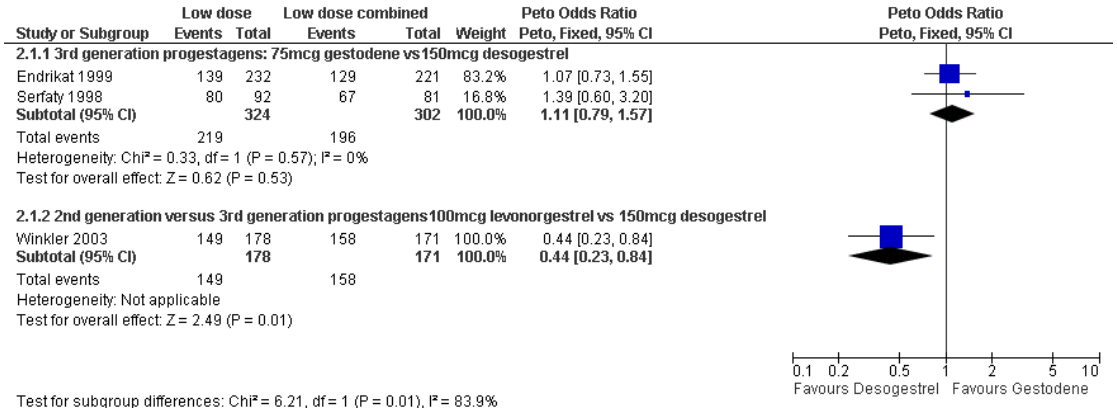
2. Combined OCP versus non steroidal anti-inflammatory drugs

There were no studies identified for this comparison.

3. Combined OCP versus other combined OCP

Pain improvement Figure 9

Figure 9. Forest plot of comparison: 2 Combined low dose OCP versus Combined low doseOCP, outcome: 2.1 Pain improvement.



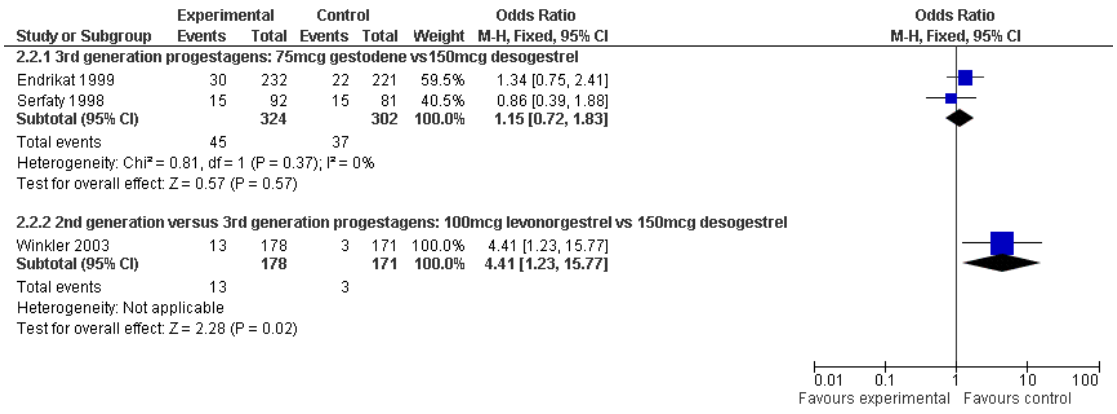
There was no evidence of a difference for the pooled studies for 3rd generation progestagen's (OR = 1.11 (95% CI 0.79 - 1.57)). For the 2nd generation versus 3rd generation the OR was 0.44 (95% CI 0.23-0.84) suggesting benefit of the 3rd generation OCP but this was for a single study (Winkler 2003).

Withdrawals from treatment

Three studies reported this outcome and there was no evidence of a difference for the pooled studies for 3rd generation progestagen's was OR = 1.11 (95% CI 0.79 - 1.57)). and for the 2nd generation versus 3rd generation was OR 0.44 (95% CI 0.23-0.84).

None of studies reported any of the other considered outcomes of additional analgesics required and absence from work or school,or adverse events. Figure 10

Figure 10. Forest plot of comparison: 2 Combined low dose OCP versus Combined low doseOCP, outcome: 2.2 Withdrawals from treatment.



DISCUSSION

The aim of this review was to investigate the effectiveness of combined oral contraceptive pills in the treatment of primary dysmenorrhoea, and to compare the effectiveness of OCPs that use different levels and types of oestrogen and progestogen. The paucity of RCTs investigating oral contraceptives, despite their apparent widespread clinical use, has meant this review is unable to achieve this objective.

Summary of main results

Ten RCTs were included in this review and six compared different OCP preparations with placebo and 4 compared different preparations with each other. No studies compared OCP with the NSAIDs. Only two of our initial hypotheses could be commented on with the available data from the ten trials. The trials included in this review indicate that both low and medium dose oestrogen pills may be more effective than placebo treatment. There is no evidence of a difference between the different pill preparations although the 3rd generation pills may be more effective in pain improvement.

Overall completeness and applicability of evidence

Oral contraceptives are widely advocated as standard treatment for women with primary dysmenorrhoea yet this review has found only scant rigorous clinical evidence to support this practice. The evidence to employ OCPs in clinical practice for dysmenorrhoea seems to stem from studies designed to test the contraceptive efficacy of different brands of oral contraceptives or epidemiological studies. A longitudinal epidemiological study of over 500 nineteen year old Swedish women which compared the occurrence and severity of dysmenorrhoea in those taking combined oral contraceptives with non OCP or IUD users (Milsom 1984). These same women were also re contacted five years later at age twenty-five (Milsom 1990). The original study showed that those taking OCPs had reduced prevalence and severity of dysmenorrhoea compared with non-users. The follow-up study also showed that those women who did not use OCPs in the original study, but were now users had significantly reduced pain. Although changes in parity were controlled for, the overall result could be attributed to the passage of time rather than the efficacy of OCPs for dysmenorrhoea.

Another issue that needs to be considered is that the use of oral contraceptives as treatment for dysmenorrhoea does not just depend on their efficacy but also the suitability of oral contraceptives for the woman. If a woman wants a pregnancy or has contraindications to the OCP, then the OCP would be an unsuitable treatment option at that time.

The lack of reporting of adverse effects experienced by the women in the trials is problematic. Only three placebo controlled trials reported adverse effects.

There are also difficulties in extrapolating the results of this review to modern day populations as the majority of oral contraceptive pills prescribed today include much lower levels of oestrogen and progestogen and often different types of progestogens than some of the trials included in this review.

Quality of the evidence

The trials in the meta-analysis had various quality ratings, only three trials (Cullberg 1972; Hendrix 2002; Davis 2005) had adequately concealed the way the treatment was allocated, but the other trials were of poor quality in this respect, or did not report enough information to make an adequate assessment. Not all of the trials were double-blind and the one trial with a negative result had an error in the marking of the pills and identification may have been possible, although it was stated that double-blinding was used. Women with different levels of severity of dysmenorrhoea were included in the trials and different ways of assessing pain or pain relief were also used. Follow-up length and the timing of outcome assessment also differed, with one trial in the meta-analysis only reporting pain relief after one month of treatment, one trial after two months, and two trials after three months. These are all aspects that could contribute to the statistical heterogeneity in the meta-analysis, although when inspecting the results of the meta-analysis the only trial that differs significantly in results is the GPRG trial.

Overall, three trials were methodologically sound (Cullberg 1972; Hendrix 2002; Davis 2005), but all of the other trials were of poor methodological quality and, in addition to that, three of them (GPRG 1968; Nakano 1971; Buttram 1969a) had small sample sizes.

Potential biases in the review process

There were methodological problems associated with quantifying and grading the pain of dysmenorrhoea. Assessment instruments used in quantifying dysmenorrhoea are based on patient's self report and as such are subject to obvious bias. In addition all the trials categorised pain using different scales, which may be a significant source of heterogeneity in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Combined oral contraceptive pills of medium and low dose oestrogen with 2nd and 3rd generation progestogens may be more

effective than placebo treatment for dysmenorrhoea but the interpretation of the results is limited because the variable quality of the RCTs included in this review.

Implications for research

There is a paucity of RCTs of the combined OCP for dysmenorrhoea. There is only one trial of a low dose oestrogen OCP and further placebo controlled trials of the low dose OCP for pain improvement of dysmenorrhoea would be welcome. Comparisons with other standard medical treatments such as nonsteroidal anti-inflammatories would also be useful. Any future trials would need to be double blind, randomised controlled trials with adequate sample sizes, and use objective pain outcome measures such as the visual analogue scale or Moos Menstrual Distress Questionnaires (MMDQ).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bassol 2000

Methods	Randomisation list was prepared with random number tables. Open trial 342 participants randomised which included 156 women with dysmenorrhoea. Withdawals: 98(44 from gestodene group and 54 from desogestrel group)
Participants	Inclusion: aged 18 to 35 years old, require contraception for at least 12 months, sexually active, healthy. Exclusion: unclassified genital bleeding, pregnancy, pathologic conditions, used parental depot-contraceptives during the previous 6 months. Age: Argentina: 24.79 +/- 4.8, Brazil: 25.13 +/- 5.5, Chile: 26.63 +/- 4.91, Mexico: 24.53 +/- 3.9 Location: Argentina, Brazil, Chile, Mexico
Interventions	1. Ethinyl estradiol 0.03mg, 0.075mg gestodene 2. Ethinyl estradiol 0.02mg, 0.15mg desogestrel Duration: 12 cycles
Outcomes	Dysmenorrhoea (slight, moderate, severe) Adverse events.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random list of 20 blocks of 20 and 5 blocks of 10.
Allocation concealment?	Yes	Women received a package of pills they agreed to use in accordance with a progressive random number of the list
Blinding? All outcomes	No	Open
Incomplete outcome data addressed? All outcomes	Unclear	Although there were 98 dropouts it is unclear if they were included in the final analysis
Free of selective reporting?	Yes	
Power calculations?	Yes	

Bassol 2000 (*Continued*)

Dropouts reported?	Yes	98 dropouts (44 from the 30 mcg/gestodene group and 54 in the 20 mcg/150 mcg group)
Baseline comparability?	Yes	

Buttram 1969a

Methods	Random - unstated Double blind, parallel trial 40 participants randomised
Participants	Inclusion: severe primary dysmenorrhoea (incapacitating pain for 2 or more days per cycle), pelvic exam to confirm no pathology. Exclusion: mild pain, dysmenorrhoea due to organic causes Age: groups 1 and 2 - average 20; group 3 - average 22 Location: USA
Interventions	1. Norinyl 2 - norethindrone 2mg with mestranol 0.1mg from day 5 to 25 (equivalent to 70mcg of ethinyl oestradiol) 2. Sequential regimen with mestranol 0.08mg from day 5 for 11 days then chlormadinone acetate 2mg added for last 10 days of cycle. (This is equivalent to 56 mcg of ethinyl oestradiol) 3. Placebo - day 5 to 25 Duration: 3 cycles
Outcomes	Duration and severity of dysmenorrhoea - measured pre, during and post. No adverse events were collected
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No method stated
Allocation concealment?	Unclear	B - Unclear, stated randomised
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Yes	
Power calculations?	No	

Buttram 1969a (*Continued*)

Dropouts reported?	No	
Baseline comparability?	Yes	

Buttram 1969b

Methods	Random - unstated Double blind, parallel trial 40 participants randomised
Participants	Inclusion: severe primary dysmenorrhoea (incapacitating pain for 2 or more days per cycle), pelvic exam to confirm no pathology. Exclusion: mild pain, dysmenorrhoea due to organic causes Age: groups 1 and 2 - average 20; group 3 - average 22 Location: USA
Interventions	1. Norinyl 2 - norethindrone 2mg with mestranol 0.1mg from day 5 to 25 (equivalent to 70mcg of ethinyl oestradiol) 2. Sequential regimen with mestranol 0.08mg from day 5 for 11 days then chlormadinone acetate 2mg added for last 10 days of cycle. (This is equivalent to 56 mcg of ethinyl oestradiol) 3. Placebo - day 5 to 25 Duration: 3 cycles
Outcomes	Duration and severity of dysmenorrhoea - measured pre, during and post. No adverse events were collected
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No method stated
Allocation concealment?	Unclear	B - Unclear, stated randomised
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	No data provided
Free of selective reporting?	Unclear	No data provided
Power calculations?	Unclear	No data provided
Dropouts reported?	Unclear	No data provided

Buttram 1969b (*Continued*)

Baseline comparability?	Unclear	No data provided

Cullberg 1972

Methods	Randomisation was done statistically by the pharmaceutical company, allocation concealment was via a secure code not broken until after all data was collected. Double blind 322 women initially randomised, 23 drop outs (5 pregnancies, 6 disappeared, 4 somatic complaints such as bleeding skin troubles or nausea, 3 interfering illness, 4 change of mind). 213 of the initial group randomised had dysmenorrhoea, with 203 women with dysmenorrhoea analysed
Participants	Inclusion: women aged between 18 to 45, absence of actual known disease, normal menstrual cycle, no actual or planned pregnancy. Exclusion: use of oral contraceptive in last 3 months Age: 27.5 (7.7) Source: female personnel from the general post office, the general telephone company, 4 nursing schools, 2 hospitals, the psychological institute at the local university Location: Stockholm, Sweden.
Interventions	1. norgestrel 1mg, ethinyl oestradiol 0.05mg 2. norgestrel 0.5mg, ethinyl oestradiol 0.05mg (Ovral) 3. norgestrel 0.06mg, ethinyl oestradiol 0.05mg 4. placebo Treatment was for 2 months and 1 tablet free month follow up
Outcomes	Dysmenorrhoea (improved, worse, unchanged, none prior to treatment)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Pharmaceutical company provided the sequence
Allocation concealment?	Yes	A - Adequate, via a secure code not broken until after all data was collected
Blinding? All outcomes	Yes	Double
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Unclear	No data provided

Cullberg 1972 (*Continued*)

Power calculations?	No	
Dropouts reported?	No	
Baseline comparability?	Yes	

Davis 2005

Methods	Randomisation list was prepared with random number tables. Double blind 76 participants randomised, 74 analysed.
Participants	Inclusion: aged 19 years or younger with moderate or severe dysmenorrhoea, regular menstrual cycles for at least 1 year, 21 to 35 days of menstrual cycle length, condom users. 300 adolescents were screened for eligibility. Exclusion: pregnancy, history of pelvic pathology, abnormal genital bleeding, recent miscarriage or abortion, use of other medications likely to interfere with metabolisms of oral contraceptives. Age: OC group: 16.7 +/- 2, Placebo group: 16.9 +/- 2 Source: medical centre, college campuses Location: USA
Interventions	1. Ethinyl estradiol 0.02mg, 0.1mg levonorgestrel 2. Placebo Duration: 3 cycles
Outcomes	Pain severity (5 point scale) Rating of worst pain intensity Use of analgesic medication Absence from work or study Adverse events Discontinuation rate
Notes	3 publications from one study

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random numbers table
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double
Incomplete outcome data addressed? All outcomes	Yes	76 randomised and 74 analysed

Davis 2005 (*Continued*)

Free of selective reporting?	Yes	
Power calculations?	Yes	Sample size was calculated for power to detect differences in main outcome of dysmenorrhoea between the OC group and the placebo group
Dropouts reported?	Yes	7/ 150 (4 from OCP and 3 from placebo group)
Baseline comparability?	Yes	

Endrikat 1999

Methods	Randomisation method not stated. Open trial 1563 participants randomised which included women with no dysmenorrhoea. Withdawals: 449(228 from gestodene group and 221 from desogestrel group)
Participants	Inclusion: aged 18 to 35 years old, desire for contraception for at least 12 months Exclusion: contraindications to OC use, various pathologies, unclassified genital bleeding, history of migraine accompanying menstrual bleeding, pregnancy. Age: GSD group - 25.5, DSG group - 25.1 Location: France, Austria, United Kingdom, the Netherlands, Switzerland and Italy
Interventions	1. Ethinyl estradiol 0.02mg, 0.15mg desogestrel 2. Ethinyl estradiol 0.02mg, 0.075mg gestodene Duration: 12 cycles
Outcomes	Dysmenorrhoea (did or did not experience pain relief)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information provided
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	Open
Incomplete outcome data addressed? All outcomes	No	87 women were excluded from the analysis because of protocol violations

Endrikat 1999 (*Continued*)

Free of selective reporting?	Unclear	Did not report adverse events
Power calculations?	Yes	
Dropouts reported?	Yes	449/1563 (228 from gestodene group and 221 from desogestrel group)
Baseline comparability?	Yes	

GPRG 1968

Methods	Administration of medicine was random however due to error each treatment had different numbers so were not identical Double blind 93 participants randomised
Participants	Inclusion: all cases of dysmenorrhoea except mild pain Age: 10 to 40 Location: UK
Interventions	1. Norinyl 1 - norethisterone 1mg, mestranol 0.05mg 2. Placebo Duration: 2 cycles
Outcomes	Relief of pain Duration of pain Days off work/in bed Analgesics required Side effects
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Unequal numbers because of errors
Allocation concealment?	Unclear	B
Blinding? All outcomes	Yes	Double blinding but the placebo group had packaging that was different different from treatment group although the patients were unaware which group they were assigned to
Incomplete outcome data addressed? All outcomes	No	

GPRG 1968 (*Continued*)

Free of selective reporting?	Yes	
Power calculations?	No	
Dropouts reported?	No	
Baseline comparability?	Yes	

Hendrix 2002

Methods	Randomisation list was generated by computer. Double blind 77 participants randomised, 59 analysed.
Participants	Inclusion: history of Grade 2 or Grade 3 dysmenorrhoea for at least 4 cycles, regular menstrual cycles, pelvic exam to confirm no pathology, no older than 32 years old. Exclusion: secondary dysmenorrhoea, suspected pregnancy, drugs use, sexually transmitted disease. Age: mean 24.2 +/- 4.9 Location: USA
Interventions	1. 21 days of desogestrel 0.15mg, ethinyl estradiol 0.02mg followed by 2 days of placebo and 5 days of ethinyl estradiol 0.01mg 2. Placebo Duration: 4 cycles
Outcomes	Pain severity (5 point scale)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated list
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	No adverse events
Power calculations?	No	

Hendrix 2002 (*Continued*)

Dropouts reported?	Yes	25/77 (14 from the desogestrel group and 11 from the placebo group)
Baseline comparability?	Yes	

Nakano 1971

Methods	Randomisation by 'envelope method' Double blind 22 participants randomised, 18 analysed
Participants	Inclusion: severe primary dysmenorrhoea that required absence from duty Location: Japan
Interventions	1. SH-850 - 0.5mg norgestrel, 0.05mg ethinyl estradiol from day 5-25 2. Placebo Duration: 44 cycles experimental group, 31 cycles placebo group (between 3-6 cycles for each participant)
Outcomes	Degree of symptomatic relief - 3 point scale for each women and cycle Menstrual flow
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No data provided
Allocation concealment?	Yes	A "envelope method"
Blinding? All outcomes	Yes	Double
Incomplete outcome data addressed? All outcomes	No	
Free of selective reporting?	Unclear	No adverse events
Power calculations?	No	
Dropouts reported?	Yes	4/22
Baseline comparability?	Yes	

Serfaty 1998

Methods	Randomisation method not stated. Open trial - no blinding used. 1016 women initially randomised, 182 drop outs (bleeding irregularities, adverse effects,). 213 of the initial group randomised had dysmenorrhoea, with 173 women with dysmenorrhoea analysed
Participants	Inclusion: regular menstrual cycles (24-35 days cycles), aged 18-45 years old, BMI of 18-29 kg/m2 Exclusion: smokers, contraindications to OC use, drugs use, women who had just given birth or had an abortion. Age: DSG group - 26.2, GSD group - 26.3 Location: France
Interventions	1. Ethinyl estradiol 0.02mg, 0.15mg desogestrel 2. Ethinyl estradiol 0.02mg, 0.075mg gestodene Duration: 6 cycles.
Outcomes	Dysmenorrhoea (mild, moderate, severe)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No data provided
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Unclear	No data provided
Free of selective reporting?	Unclear	No adverse events
Power calculations?	Yes	
Dropouts reported?	Yes	182/1016 (85 from desogestrel and 97 from gestodene group)
Baseline comparability?	Yes	

Winkler 2003

Methods	Randomisation list was generated by computer. Open trial 1027 women initially randomised, 239 dropouts (unacceptable bleeding problems, adverse events). 349 of the initial group randomised had dysmenorrhoea and no dropouts reported
Participants	Inclusion: aged 18 to 45 years old, BMI of 18 to 29 kg/m2 Exclusion: smoking, concomitant medication or addictive drugs, psychiatric disorders, using injectable hormonal contraceptives within 6 months of enrolment Age: DSG group - 28.2, LNG group - 28.5 Location: Germany and the Netherlands
Interventions	1. Ethinyl estradiol 0.02mg and 0.15mg desogestrel 2. Ethinyl estradiol 0.02mg and 0.01mg levonorgestrel Treatment was for 6 months and 5 months follow up
Outcomes	Dysmenorrhoea (improved/ not improved)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Unclear	B -
Blinding? All outcomes	No	Open
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	No adverse events reported
Power calculations?	No	
Dropouts reported?	Yes	239/1027
Baseline comparability?	Yes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Creatsas 1998	Study participants did not have dysmenorrhoea
Foidart 2000	Only small number of women with dysmenorrhoea included in the study
Iannotti 1991	Not a randomised or controlled clinical trial. No information on the oestrogen/progestagen compound used. Trial published in Italian, translated by Riccardo Fontani.
Karasawa 1968	Trial compared norethindrone/mestranol combination with placebo, however combination of OCP studied is no longer available. 2mg norethindrone, 0.1mg mestranol. Trial published in Japanese.
Kaunitz 2000	Only small number of women with dysmenorrhoea included in the study
Kremser 1971	Trial compared Norinyl - norethisterone 2mg and mestranol 0.1mg combination with placebo, this combination of OCP is no longer available
Kristjansdottir 2000	Not a randomised or controlled clinical trial.
Kwiecien 2003	Only small number of women with dysmenorrhoea included in the study
La Guardia 2003	The objective of the study was to compare the efficacy and safety of 5 different OCPs and only reported dysmenorrhoea as an adverse event in approximately 25% of patients. (Table 3)
Matthews 1968	Not a randomised controlled trial
Moore 1999	Only small number of women with dysmenorrhoea included in the study
Reisman 1999	No women clearly with dysmenorrhea in the study
Tallian 1994	Not an RCT. Allocation to treatment groups was retrospective. Trial published in Hungarian, methods and results sections translated by Gabor Kovacs

DATA AND ANALYSES

Comparison 1. Combined OCP versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain improvement	7	497	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [1.32, 3.08]
1.1 low dose oestrogen and 1st/2nd generation progestagen	1	76	Odds Ratio (M-H, Fixed, 95% CI)	1.83 [0.69, 4.83]
1.2 low dose oestrogen and 3rd generation progestagen	1	73	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 medium dose oestrogen and 1st/2nd generation progestagen	5	348	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [1.28, 3.30]
2 Pain score (mean change)	2	150	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.46, -0.12]
2.1 Low dose oestrogen and 1st/2nd generation progesterone	1	74	Mean Difference (IV, Fixed, 95% CI)	1.50 [-0.78, 3.78]
2.2 Low dose oestrogen and 3rd generation progestagen	1	76	Mean Difference (IV, Fixed, 95% CI)	-0.3 [-0.47, -0.13]
2.3 Medium dose oestrogen and 1st/2nd generation progestagen	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Additional analgesia required	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 low dose oestrogen and 1st/2nd generation progestagen	1	74	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.13, 0.85]
3.2 low dose oestrogen and 3rd generation progestagen	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 medium dose oestrogen and 1st/2nd generation progestagen	1	89	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [0.66, 4.72]
4 Absence from school or work	2	148	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.17, 0.88]
4.1 low dose oestrogen and 1st/2nd generation progestagen	1	59	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.92]
4.2 medium dose oestrogen and 1st/2nd generation progestagen	1	89	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.18, 0.99]
5 Withdrawals from treatment	2	134	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.18, 23.72]
5.1 low dose oestrogen and 1st/2nd generation progestagen	1	74	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.18, 23.72]
5.2 low dose estrogen and 3rd generation progestagen	1	60	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 medium dose oestrogen and 1st/2nd generation progestagen	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adverse events	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Nausea	3	225	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.41, 2.03]
6.2 Headaches	2	135	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.67, 3.67]

6.3 Weight gain	1	76	Odds Ratio (M-H, Fixed, 95% CI)	2.17 [0.71, 6.65]
6.4 Experienced any side effect	2	165	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.71, 2.94]

Comparison 2. Combined low dose OCP versus Combined low doseOCP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain improvement	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 3rd generation progestagens: 75mcg gestodene vs150mcg desogestrel	2	626	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.79, 1.57]
1.2 2nd generation versus 3rd generation progestagens100mcg levonorgestrel vs 150mcg desogestrel	1	349	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.23, 0.84]
2 Withdrawals from treatment	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 3rd generation progestagens: 75mcg gestodene vs150mcg desogestrel	2	626	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.72, 1.83]
2.2 2nd generation versus 3rd generation progestagens: 100mcg levonorgestrel vs 150mcg desogestrel	1	349	Odds Ratio (M-H, Fixed, 95% CI)	4.41 [1.23, 15.77]

Analysis 1.1. Comparison 1 Combined OCP versus placebo or no treatment, Outcome 1 Pain improvement.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 1 Combined OCP versus placebo or no treatment

Outcome: 1 Pain improvement

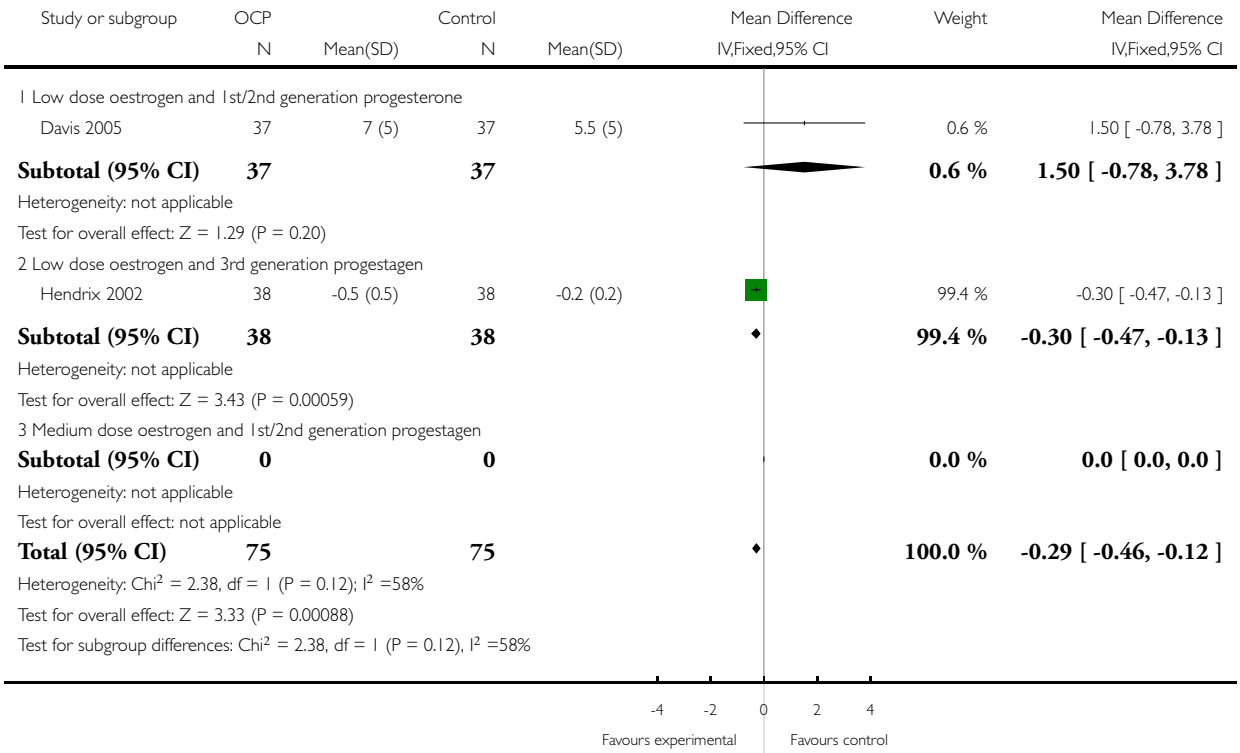
Study or subgroup	OCP n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 low dose oestrogen and 1st/2nd generation progestagen				
Davis 2005	15/38	10/38		1.83 [0.69, 4.83]
Subtotal (95% CI)	**38**	**38**		**1.83 [0.69, 4.83]**
Total events: 15 (OCP), 10 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.21 (P = 0.22)				
2 low dose oestrogen and 3rd generation progestagen				
Hendrix 2002	0/38	0/35		0.0 [0.0, 0.0]
Subtotal (95% CI)	**38**	**35**		**0.0 [0.0, 0.0]**
Total events: 0 (OCP), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 medium dose oestrogen and 1st/2nd generation progestagen				
Buttram 1969a	12/15	5/13		6.40 [1.18, 34.61]
Buttram 1969b	7/12	5/13		2.24 [0.45, 11.11]
Cullberg 1972	96/154	15/49		3.75 [1.88, 7.48]
GPRG 1968	9/38	15/36		0.43 [0.16, 1.18]
Nakano 1971	3/12	1/6		1.67 [0.13, 20.58]
Subtotal (95% CI)	**231**	**117**		**2.06 [1.28, 3.30]**
Total events: 127 (OCP), 41 (Control)				
Heterogeneity: Chi^2 = 14.00, df = 4 (P = 0.01); I^2 =71%				
Test for overall effect: Z = 3.00 (P = 0.0027)				
Total (95% CI)	**307**	**190**		**2.01 [1.32, 3.08]**
Total events: 142 (OCP), 51 (Control)				
Heterogeneity: Chi^2 = 14.06, df = 5 (P = 0.02); I^2 =64%				
Test for overall effect: Z = 3.23 (P = 0.0012)				

Analysis 1.2. Comparison 1 Combined OCP versus placebo or no treatment, Outcome 2 Pain score (mean change).

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 1 Combined OCP versus placebo or no treatment

Outcome: 2 Pain score (mean change)

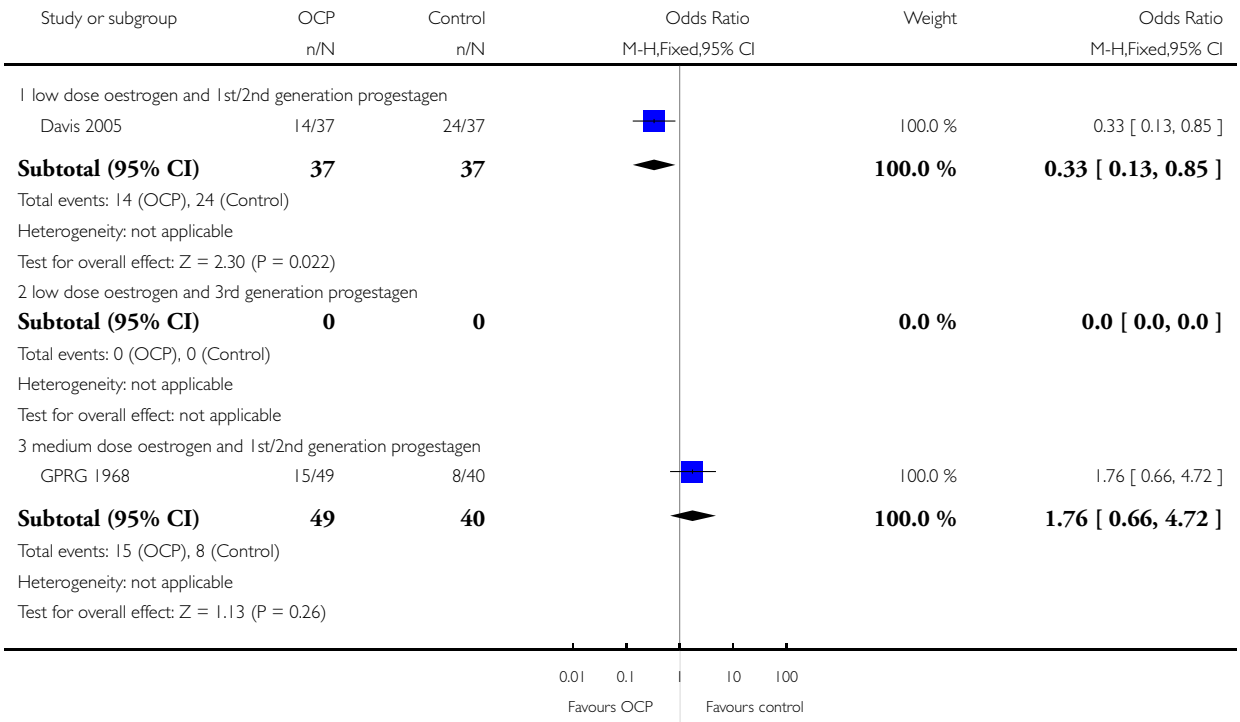


Analysis 1.3. Comparison 1 Combined OCP versus placebo or no treatment, Outcome 3 Additional analgesia required.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 1 Combined OCP versus placebo or no treatment

Outcome: 3 Additional analgesia required

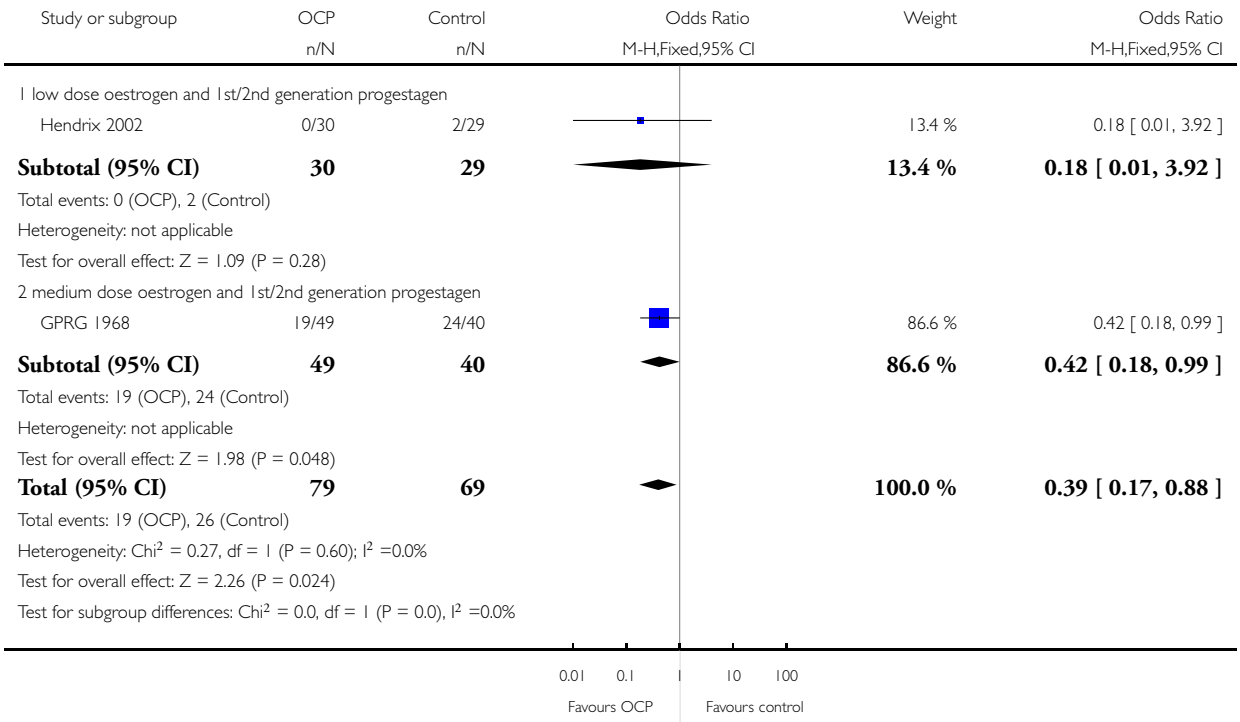


Analysis 1.4. Comparison 1 Combined OCP versus placebo or no treatment, Outcome 4 Absence from school or work.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 1 Combined OCP versus placebo or no treatment

Outcome: 4 Absence from school or work



Analysis 1.5. Comparison 1 Combined OCP versus placebo or no treatment, Outcome 5 Withdrawals from treatment.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 1 Combined OCP versus placebo or no treatment

Outcome: 5 Withdrawals from treatment

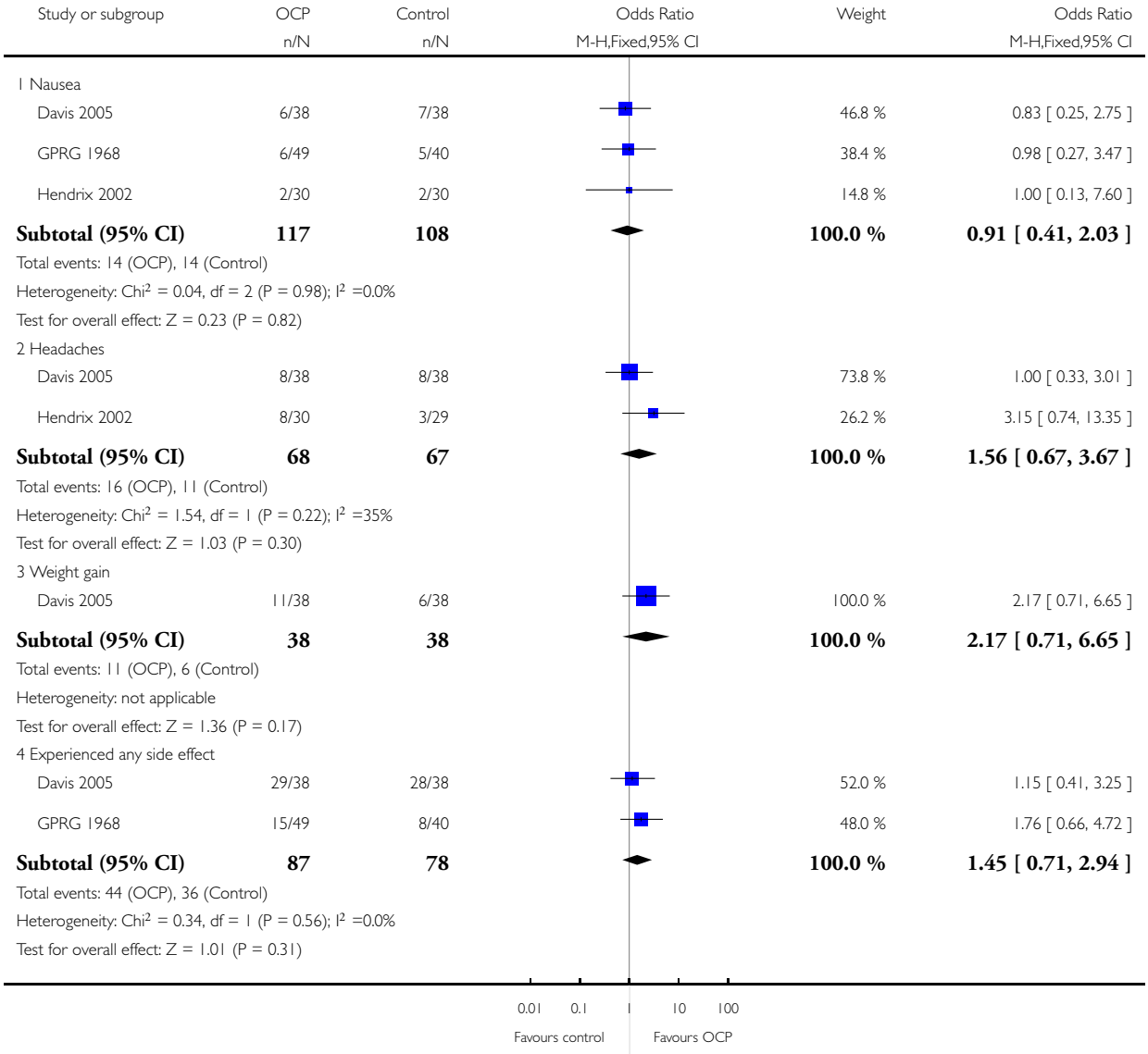
Study or subgroup	OCP n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 low dose oestrogen and 1st/2nd generation progestagen				
Davis 2005	2/37	1/37		2.06 [0.18, 23.72]
Subtotal (95% CI)	**37**	**37**		**2.06 [0.18, 23.72]**
Total events: 2 (OCP), 1 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.58 (P = 0.56)				
2 low dose estrogen and 3rd generation progestagen				
Hendrix 2002	0/30	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**30**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (OCP), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 medium dose oestrogen and 1st/2nd generation progestagen				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (OCP), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**67**	**67**		**2.06 [0.18, 23.72]**
Total events: 2 (OCP), 1 (Control)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				
Test for subgroup differences: Not applicable				

Analysis 1.6. Comparison 1 Combined OCP versus placebo or no treatment, Outcome 6 Adverse events.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 1 Combined OCP versus placebo or no treatment

Outcome: 6 Adverse events

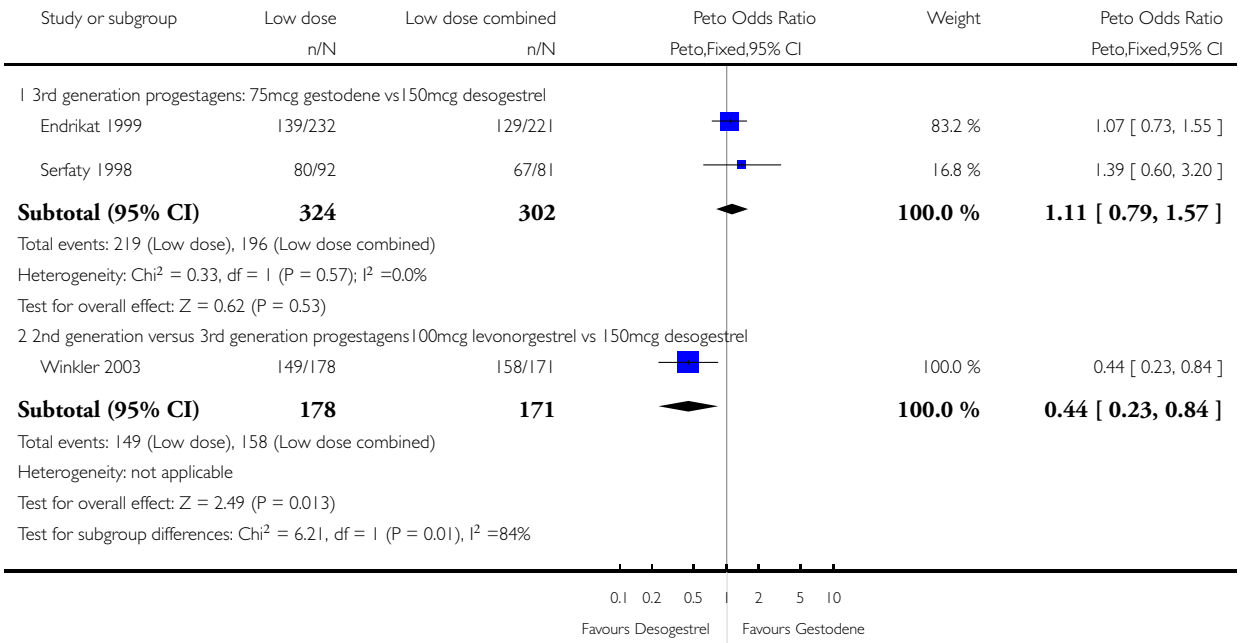


Analysis 2.1. Comparison 2 Combined low dose OCP versus Combined low doseOCP, Outcome 1 Pain improvement.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 2 Combined low dose OCP versus Combined low doseOCP

Outcome: 1 Pain improvement

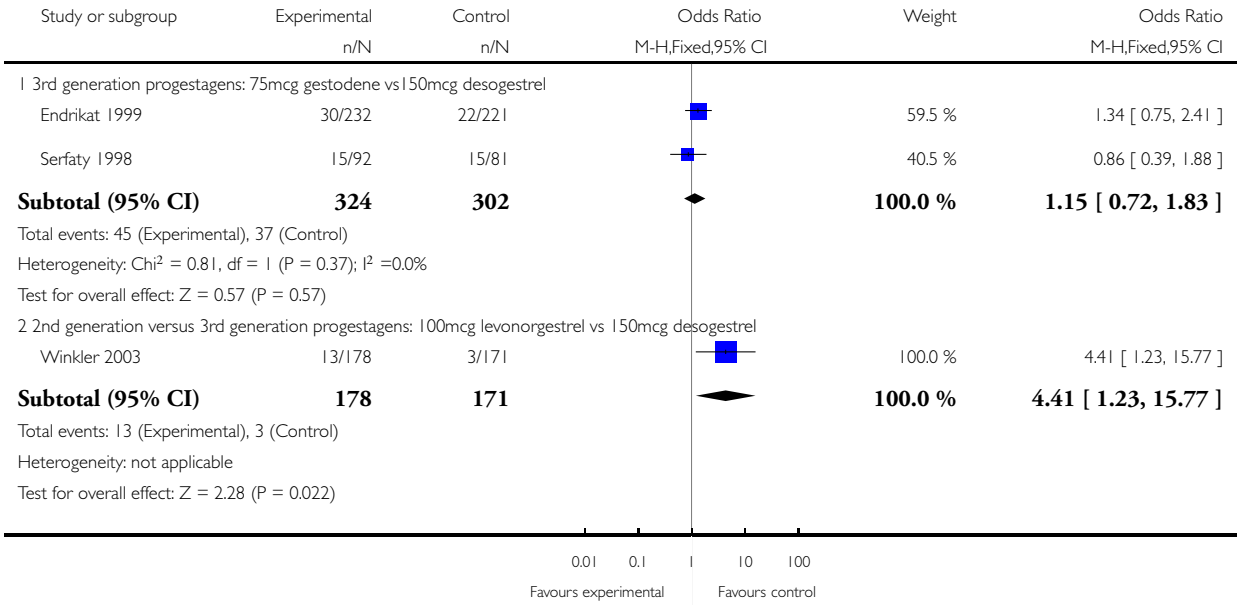


Analysis 2.2. Comparison 2 Combined low dose OCP versus Combined low doseOCP, Outcome 2 Withdrawals from treatment.

Review: Oral contraceptive pill for primary dysmenorrhoea

Comparison: 2 Combined low dose OCP versus Combined low doseOCP

Outcome: 2 Withdrawals from treatment



APPENDICES

Appendix 1. Embase search strategy

1 exp Dysmenorrhea/ (3308)
2 dysmenorrh$.tw. (2044)
3 (pain$ adj5 menstr$).tw. (522)
4 (pain$ adj5 period$).tw. (2579)
5 (primary adj5 dysmenorrh$).tw. (470)
6 (menstr$ adj5 cramp$).tw. (68)
7 (pelvic adj5 pain$).tw. (3820)
8 or/1-7 (9848)
9 exp contraceptive agents/ or exp contraceptive agents, female/ or exp contraceptives, oral/ or exp contraceptives, oral, combined/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ (63848)
10 (combin$ adj5 oral adj5 contracep$ adj5 pill$).tw. (239)
11 OCP$.tw. (999)
12 exp estrogens/ or exp estrogens, non-steroidal/ or exp progestins/ (147954)
13 exp estradiol/ or exp estriol/ or exp estrone/ (54835)
14 estr$.tw. (95102)

15 oestr$.tw. (19800)
16 exp ethinyl estradiol/ or exp ethinyl estradiol-norgestrel combination/ or exp mestranol/ (10564)
17 (ethinyl adj5 estr$).tw. (1703)
18 mestra$.tw. (263)
19 xenoestr$.tw. (586)
20 phytoestr$.tw. (2023)
21 progest$.tw. (47411)
22 (chlormadinone adj5 acetate$).tw. (304)
23 norethisterone$.tw. (1285)
24 (progest$ adj5 norgestrel$).tw. (71)
25 exp norgestrel/ or exp levonorgestrel/ (7287)
26 norethisterone/ (4169)
27 exp Desogestrel/ (1875)
28 gestodene.tw. (557)
29 norgestimate.tw. (225)
30 dienogest.tw. (173)
31 exp Anti-Inflammatory Agents, Non-Steroidal/ (238189)
32 non-steroidal anti-inflammatory agent$.tw. (767)
33 non-steroidal anti-inflammatory compound$.tw. (46)
34 or/9-33 (441795)
35 8 and 34 (2759)
36 Clinical trial/ (490967)
37 Randomized controlled trials/ (154143)
38 Random Allocation/ (25024)
39 Single-Blind Method/ (7349)
40 Double-Blind Method/ (68122)
41 Cross-Over Studies/ (19921)
42 Placebos/ (109705)
43 Randomi?ed controlled trial$.tw. (27644)
44 RCT.tw. (2147)
45 Random allocation.tw. (602)
46 Randomly allocated.tw. (9551)
47 Allocated randomly.tw. (1309)
48 (allocated adj2 random).tw. (552)
49 Single blind$.tw. (7022)
50 Double blind$.tw. (80822)
51 (treble or triple) adj blind$).tw. (126)
52 Placebo$.tw. (103693)
53 Prospective Studies/ (72343)
54 or/36-53 (646507)
55 Case study/ (5301)
56 Case report.tw. (110283)
57 Abstract report/ or letter/ (458214)
58 or/55-57 (571816)
59 54 not 58 (624088)
60 animal/ (18226)
61 human/ (6020154)
62 60 not 61 (14460)
63 59 not 62 (623992)
64 35 and 63 (1072)

Appendix 2. Embase search strategy

1 exp Dysmenorrhea/ (2343)
2 dysmenorrh$.tw. (2482)
3 (pain$ adj5 menstr$).tw. (567)
4 (pain$ adj5 period$).tw. (2832)
5 (primary adj5 dysmenorrh$).tw. (502)
6 (menstr$ adj5 cramp$).tw. (79)
7 (pelvic adj5 pain$).tw. (3897)
8 or/1-7 (9899)
9 exp contraceptive agents/ or exp contraceptive agents, female/ or exp contraceptives, oral/ or exp contraceptives, oral, combined/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ (52363)
10 (combin$ adj5 oral adj5 contracep$ adj5 pill$).tw. (249)
11 OCP$.tw. (1035)
12 exp estrogens/ or exp estrogens, non-steroidal/ or exp progestins/ (144546)
13 exp estradiol/ or exp estriol/ or exp estrone/ (68986)
14 estr$.tw. (116728)
15 oestr$.tw. (27719)
16 exp ethinyl estradiol/ or exp ethinyl estradiol-norgestrel combination/ or exp mestranol/ (8407)
17 (ethinyl adj5 estr$).tw. (1990)
18 mestra$.tw. (616)
19 xenoestr$.tw. (547)
20 phytoestr$.tw. (1960)
21 progest$.tw. (61689)
22 (chlormadinone adj5 acetate$).tw. (493)
23 norethisterone$.tw. (1427)
24 (progest$ adj5 norgestrel$).tw. (110)
25 exp norgestrel/ or exp levonorgestrel/ (4191)
26 norethisterone/ (3729)
27 exp Desogestrel/ (899)
28 gestodene.tw. (548)
29 norgestimate.tw. (228)
30 dienogest.tw. (114)
31 exp Anti-Inflammatory Agents, Non-Steroidal/ (119997)
32 non-steroidal anti-inflammatory agent$.tw. (1004)
33 non-steroidal anti-inflammatory compound$.tw. (58)
34 or/9-33 (365184)
35 8 and 34 (1649)
36 randomised controlled trial.pt. (246988)
37 controlled clinical trial.pt. (76091)
38 randomised controlled trials as topic/ (51973)
39 random allocation/ (59478)
40 double blind method/ (94335)
41 single blind method/ (11560)
42 or/36-41 (416903)
43 animals/ not (animals/ and humans/) (3143455)
44 42 not 43 (390618)
45 clinical trial.pt. (439641)
46 exp clinical trials as topic/ (197300)
47 (clinic$ adj25 trial$).ti,ab. (138994)
48 cross-over studies/ (21186)
49 (crossover or cross-over or cross over).tw. (39586)
50 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (93606)

51 placebos/ (26539)
52 placebo$.ti,ab. (106409)
53 random$.ti,ab. (393741)
54 research design/ (50670)
55 or/45-54 (892971)
56 55 not 43 (827111)
57 44 or 56 (848022)
58 35 and 57 (642)

Appendix 3. Cinahl search strategy

exp Dysmenorrhea/ (277)
2 dysmenorrh$.tw. (233)
3 (pain$ adj5 menstr$).tw. (100)
4 (pain$ adj5 period$).tw. (427)
5 (primary adj5 dysmenorrh$).tw. (76)
6 (menstr$ adj5 cramp$).tw. (32)
7 (pelvic adj5 pain$).tw. (525)
8 or/1-7 (1325)
9 exp contraceptive agents/ or exp contraceptive agents, female/ or exp contraceptives, oral/ or exp contraceptives, oral, combined/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ (6729)
10 (combin$ adj5 oral adj5 contracep$ adj5 pill$).tw. (44)
11 OCP$.tw. (53)
12 exp estrogens/ or exp estrogens, non-steroidal/ or exp progestins/ (4347)
13 exp estradiol/ or exp estriol/ or exp estrone/ (773)
14 estr$.tw. (3134)
15 oestr$.tw. (309)
16 exp ethinyl estradiol/ or exp ethinyl estradiol-norgestrel combination/ or exp mestranol/ (0)
17 (ethinyl adj5 estr$).tw. (88)
18 mestra$.tw. (1)
19 xenoestr$.tw. (10)
20 phytoestr$.tw. (197)
21 progest$.tw. (1117)
22 (chlormadinone adj5 acetate$).tw. (3)
23 norethisterone$.tw. (34)
24 (progest$ adj5 norgestrel$).tw. (0)
25 exp norgestrel/ or exp levonorgestrel/ (344)
26 norethisterone/ (0)
27 exp Desogestrel/ (0)
28 gestodene.tw. (15)
29 norgestimate.tw. (12)
30 dienogest.tw. (6)
31 exp Anti-Inflammatory Agents, Non-Steroidal/ (7636)
32 non-steroidal anti-inflammatory agent$.tw. (19)
33 non-steroidal anti-inflammatory compound$.tw. (0)
34 or/9-33 (17126)
35 8 and 34 (174)
36 exp clinical trials/ (50105)
37 Clinical trial.pt. (24633)
38 (clinic$ adj trial$1).tw. (11842)
39 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (6873)
40 Randomi?ed control$ trial$.tw. (10291)
41 Random assignment/ (16979)

42 Random$ allocat$.tw. (1113)
43 Placebo$.tw. (9720)
44 Placebos/ (3902)
45 Quantitative studies/ (3633)
46 Allocat$ random$.tw. (66)
47 or/36-46 (70614)
48 35 and 47 (73)

Appendix 4. Specialised register

1 exp Dysmenorrhea/ (247)
2 dysmenorrh$.tw. (493)
3 (pain$ adj5 menstr$).tw. (127)
4 (pain$ adj5 period$).tw. (1386)
5 (primary adj5 dysmenorrh$).tw. (254)
6 (menstr$ adj5 cramp$).tw. (19)
7 (pelvic adj5 pain$).tw. (339)
8 or/1-7 (2201)
9 exp contraceptive agents/ or exp contraceptive agents, female/ or exp contraceptives, oral/ or exp contraceptives, oral, combined/ or exp contraceptives, oral, hormonal/ or exp contraceptives, oral, sequential/ or exp contraceptives, oral, synthetic/ (4193)
10 (combin$ adj5 oral adj5 contracep$ adj5 pill$).tw. (29)
11 OCP$.tw. (36)
12 exp estrogens/ or exp estrogens, non-steroidal/ or exp progestins/ (4084)
13 exp estradiol/ or exp estriol/ or exp estrone/ (2900)
14 estr$.tw. (6269)
15 oestr$.tw. (1727)
16 exp ethinyl estradiol/ or exp ethinyl estradiol-norgestrel combination/ or exp mestranol/ (887)
17 (ethinyl adj5 estr$).tw. (522)
18 mestra$.tw. (49)
19 xenoestr$.tw. (1)
20 phytoestr$.tw. (136)
21 progest$.tw. (3176)
22 (chlormadinone adj5 acetate$).tw. (61)
23 norethisterone$.tw. (507)
24 (progest$ adj5 norgestrel$).tw. (18)
25 exp norgestrel/ or exp levonorgestrel/ (629)
26 norethisterone/ (605)
27 exp Desogestrel/ (269)
28 gestodene.tw. (198)
29 norgestimate.tw. (69)
30 dienogest.tw. (45)
31 exp Anti-Inflammatory Agents, Non-Steroidal/ (10844)
32 non-steroidal anti-inflammatory agent$.tw. (113)
33 non-steroidal anti-inflammatory compound$.tw. (3)
34 or/9-33 (21858)
35 8 and 34 (480)

WHAT'S NEW

Last assessed as up-to-date: 17 February 2008.

Date	Event	Description
12 January 2009	New citation required but conclusions have not changed	New author added Chooi Ling Wong Title changed from 'Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhoea' to 'Oral contraceptive pill for primary dysmenorrhoea

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2001

Date	Event	Description
8 November 2008	New search has been performed	There were 5 studies in the first version of this review published in 2001. In the 2008 update one study was removed as not truly a RCT Matthews 1968 and 6 new studies were added. Bassol 2000; Davis 2005; Winkler 2003; Endrikat 1999; Serfaty 1998
25 June 2008	Amended	Converted to new review format.
18 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Michelle Proctor: Took the lead in writing the initial protocol and review, performed initial searches of databases for trials, was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, was responsible for statistical analysis and interpretation of the data.

Helen Roberts: Commented on drafts of the protocol and review, and added clinical expertise to the discussion.

Sarah Hetrick: performed independent data extraction and quality assessment of the included trials for the 1st review.

Chooi Ling Wong: performed updated searches of electronic databases for trials, was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, was responsible for statistical analysis and interpretation of the data.

Cindy Farquhar:initiated and conceptualised the review, commented on drafts of the protocol and original review. She involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials for the update in 2008 and rewrote the review after receiving the editorial feedback.

DECLARATIONS OF INTEREST

Helen Roberts has received funding from Schering, Wyeth, Pharmaco Organanon, and Pharmacia Upjohn in the past.

SOURCES OF SUPPORT

Internal sources

- University of Auckland, School of Medicine, Auckland, New Zealand.

External sources

- Princess of Wales Memorial Trust Fund administered by the Mercia Barnes Fund 1991-2002, New Zealand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the update in 2008, the comparisons were restructured.

The outcome of pain relief was changed to pain improvement in the 2008 update.

The title was changed from 'Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhoea' to 'Oral contraceptive pill as treatment for primary dysmenorrhoea'.

A new author was added Chooi Ling Wong.

INDEX TERMS

Medical Subject Headings (MeSH)

Contraceptives, Oral, Combined [adverse effects; *therapeutic use]; Dysmenorrhea [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans