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Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation (Review)

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Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD001895.
DOI: 10.1002/14651858.CD001895.pub3.

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[Intervention Review]

Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation

Martha Hickey[1], Jenny M Higham[2], Ian Fraser[3]

[1]The University of Melbourne, The Royal Women's Hospital, Melbourne, Australia. [2]Faculty of Medicine, Imperial College of Science, London, UK. [3]Professor in Reproductive Medicine, The University of Sydney, Sydney, Australia

Contact address: Martha Hickey, The University of Melbourne, The Royal Women's Hospital, Level 7, Research Precinct, Melbourne, Victoria, Parkville 3052, Australia. Martha.Hickey@thewomens.org.au.

Editorial group: Cochrane Gynaecology and Fertility Group
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2012.

Citation: Hickey M, Higham JM, Fraser I. Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD001895. DOI: 10.1002/14651858.CD001895.pub3.

ABSTRACT

Background

Irregular menstrual bleeding may arise due to exogenous sex steroids, lesions of the genital tract or be associated with anovulation. Irregular bleeding due to oligo/anovulation (previously called dysfunctional uterine bleeding or DUB) is more common at the extremes of reproductive life, and in women with ovulatory disorders such as polycystic ovary syndrome (PCOS). In anovulatory cycles there may be prolonged oestrogen stimulation of the endometrium without progesterone withdrawal and so cycles are irregular and bleeding may be heavy. This is the rationale for using cyclical progestogens during the second half of the menstrual cycle, in order to provoke a regular withdrawal bleed. Continuous progestogen is intended to induce endometrial atrophy and hence to prevent oestrogen-stimulated endometrial proliferation. Progestogens, and oestrogens and progestogens in combination, are widely used in the management of irregular menstrual bleeding, but the regime, dose and type of progestogen used vary widely, with little consensus about the optimum treatment approach.

Objectives

To determine the effectiveness and acceptability of progestogens alone or in combination with oestrogens in the regulation of irregular menstrual bleeding associated with oligo/anovulation.

Search methods

We searched the following databases in February 2012: Cochrane Menstrual Disorders and Subfertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and reference lists of articles.

Selection criteria

All randomised controlled trials of progestogens (via any route) alone or in combination with oestrogens in the treatment of irregular menstrual bleeding associated with oligo/anovulation.

Data collection and analysis

Study quality assessment and data extraction were carried out independently by two review authors. All authors were experts in the content of this review.

Main results

No randomised trials were identified that compared progestogens with oestrogens and progestogens or with placebo in the management of irregular bleeding associated with oligo/anovulation.

Authors' conclusions

There is a paucity of randomised studies relating to the use of progestogens and of oestrogens and progestogens in combination in the treatment of irregular menstrual bleeding associated with anovulation. There is no consensus about which regimens are most effective. Further research is needed to establish the role of these hormonal treatments in the management of this common gynaecological problem.

PLAIN LANGUAGE SUMMARY

Progestogens with or without oestrogen for irregular menstrual bleeding

Irregular bleeding associated with infrequent or no ovulation occurs most commonly in adolescents and in women approaching the menopause. It may also occur in those with polycystic ovary syndrome. This irregular bleeding may also be heavy. Hormonal treatments are commonly given to these women, but there is insufficient evidence to recommend whether progestogens alone or progestogens in combination with oestrogen are most effective for irregular uterine bleeding associated with infrequent or no ovulation.

BACKGROUND

Description of the condition

Disturbances of menstrual bleeding manifest in a wide range of presentations. The term “abnormal uterine bleeding” or AUB is used to describe any departure from normal menstruation or from a normal menstrual cycle pattern (Munro 2011). Abnormal bleeding is defined in terms of disturbances of regularity, of frequency and of heaviness and duration of flow. The term 'dysfunctional uterine bleeding' is no longer used.

Disturbances of bleeding regularity include irregular menstrual bleeding and absent bleeding (amenorrhoea). The definition of irregular menstrual bleeding has been controversial, but current consensus recommendations are >20 days of variation in individual cycle length over a period of one year (Munro 2011). Irregular menstrual bleeding may be due to infrequent or absent ovulation (oligo/anovulation). The most common cause of oligo/anovulation is polycystic ovary syndrome (PCOS), which affects around 6% of women of reproductive age (Azziz 2004). In addition, women at the extremes of reproductive life – in the early years following menarche and in the menopause transition, are more likely to have disturbed ovulation and hence irregular menstrual bleeding (Harlow 2012).

When regular ovulation does not occur, unopposed oestrogen exposure may result in a persistent proliferative or hyperplastic endometrium (Lacey 2009). Exactly why disturbances of ovulation cause irregular and/or heavy menstrual bleeding is not well understood, but is likely to be due to local endometrial changes. Irregular menstrual bleeding in the early years after menarche is thought to be due to immaturity of the hypothalamic-pituitary-gonadal axis. However, in some young women this irregular bleeding may be an early presentation of PCOS, particularly in girls with a high body mass index (van Hooff 2004).

It was previously thought that irregular cycles in the menopause transition were largely due to oligo/anovulation, but recent data indicate that at least a third of irregular cycles in the mid-to-late menopause transition are ovulatory but with a disturbed ovulation pattern. These distinct endocrine disturbances have been termed “luteal out of phase” or “LOOP” cycles due to the development of a new preovulatory follicle during the preceding luteal phase (Hale 2009). This is often followed by a luteinising hormone (LH) peak and ovulation during subsequent menstruation. These LOOP cycles are usually found during phases of irregular menstrual bleeding and can also lead to heavy bleeding (Hale 2011). The truly anovulatory cycles were associated with the lightest bleeding in this study.

Description of the intervention

Menstrual bleeding that is irregular or excessive is often highly inconvenient for women. The medical management of irregular menstrual bleeding aims to regulate bleeding and to reduce heavy menstrual bleeding. Progestogens and oestrogens and progestogens in combination are already widely used in the management of irregular or heavy bleeding due to disturbed ovulation, but the regime, dose and type of progestogen used vary widely, with little consensus about the optimum treatment approach. The unwanted effects of progestogens vary according to the type and dose of progestogen, whether the preparations are given cyclically (for up to three weeks in a month) or continuously, and also vary between individuals. Common non-menstrual unwanted effects of progestogens include headaches, weight gain and breast tenderness. Irregular bleeding and spotting are common side effects of progestogens of all types and regimes, particularly continuous low-dose preparations (Hickey 2008).

How the intervention might work

Women with irregular menstrual bleeding can be broadly considered in three main groups: adolescents who have not yet established regular menstrual cycles; those with anovulation due to PCOS; and women in the menopause transition, who may have disturbances of ovulation. Effective treatment approaches are likely to differ in these groups, with the emphasis on regulation of bleeding in adolescent girls, establishing regular bleeding or amenorrhoea during the menopause transition and greater consideration of fertility and induction of ovulation in those with PCOS. Treatments for anovulatory infertility such as clomiphene may induce regular bleeding, but this is not their primary aim and clomiphene is not a long-term treatment option.

Changes in the length of the menstrual cycle generally imply disturbances of the hypothalamo-pituitary-gonadal (HPG) axis (the hormonal interaction between the brain and the ovaries). In irregular menstrual bleeding due to oligo/anovulation there will be no progesterone withdrawal from oestrogen-primed endometrium and so cycles are irregular. Prolonged oestrogen stimulation may cause a build up of endometrium with erratic bleeding as it breaks down and is expelled. This is the rationale for using cyclical progestogens during the second half of the menstrual cycle, in order to provoke a regular withdrawal bleed. Continuous progestogen is intended to induce endometrial atrophy and hence to prevent oestrogen-stimulated endometrial proliferation. Unopposed oestrogen (without progesterone) may cause the endometrium to thicken and potentially to develop endometrial hyperplasia or even endometrial cancer (Lacey 2009). Exogenous progestogens can induce secretory transformation of proliferative or hyperplastic endometrium associated with anovulation (Gellersen 2007).

Why it is important to do this review

Abnormal uterine bleeding creates significant morbidity for women of reproductive age and imposes major medical, social and economic problems for women, their families, the workplace and health services. Heavy menstrual bleeding (HMB) affects up to 30% of women (www.nice.org.uk). In the UK and USA, 5% of women of reproductive age consult their general practitioner annually with a menstrual complaint.

Hysterectomy is an effective treatment for abnormal uterine bleeding, but is not appropriate for many women, particularly those who wish to preserve their fertility. Sex steroid preparations may be effective, but more information is needed about the comparative efficacy of sex steroids, particularly for irregular menstrual bleeding.

OBJECTIVES

To determine the effectiveness and acceptability of progestogens alone or in combination with oestrogens in the regulation of irregular menstrual bleeding associated with oligo/anovulation.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We planned to exclude non-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias.

Types of participants

Criteria for inclusion

Women with irregular and/or heavy menstrual bleeding associated with oligo/anovulation.

All age groups from adolescent to perimenopausal women were included.

Criteria for exclusion

Women with:

- irregular menstrual bleeding secondary to systemic or pelvic pathology
- irregular bleeding associated with exogenous sex steroid use
- non-endocrine (non-hormonal) causes of irregular menstrual bleeding
- post-menopausal bleeding (more than one year from the last menstrual period).

Types of interventions

Criteria for inclusion

- Comparisons of progestogens via any route versus placebo or no treatment
- Comparisons of progestogens and oestrogens versus placebo or no treatment
- Comparisons of progestogens via any route versus progestogens and oestrogens in combination.

All types of progestogens and oestrogens in all doses and combinations, via any route (for example oral, injectable, patches etc.) and by any regime were considered.

Types of outcome measures

Primary outcomes

1. Persistence of irregular menstrual bleeding, assessed subjectively using patient's observations, or objectively using menstrual charts
2. Adverse events, including non-menstrual unwanted effects such as headaches, nausea, bloating, breast tenderness and (objectively documented) weight gain; changes in mood and libido associated with treatment.

Secondary outcomes

1. Intermenstrual bleeding or spotting
2. Amenorrhoea
3. Dissatisfaction with treatment (from the woman's perspective)
4. Need for surgical treatment for irregular bleeding in women previously treated with progestogens or oestrogens and progestogens in combination.

Search methods for identification of studies

We searched for all published and unpublished RCTs of progestogens alone or in combination with oestrogens to regulate menstrual bleeding in women with irregular menstrual bleeding without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator. Please see Appendices 1-8 for full search strategies.

Electronic searches

For the 2012 update of this review we searched the following electronic databases, trial registers and websites in February 2012: The Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials (Appendix 1), the Cochrane Central Register of Controlled Trials (Appendix 2), MEDLINE (Appendix 3), EMBASE (Appendix 4) and PsycINFO (Appendix 5).

For the 2007 update of the review we searched the following databases in May 2007: CINAHL (Appendix 6), EBM reviews (Appendix 7), and Current Contents (Appendix 8).

Searching other resources

We hand-searched reference lists of articles retrieved by the search and contacted experts in the field to seek additional data. Studies of perimenopausal hormone therapy were also searched.

Data collection and analysis

The review was undertaken by three review authors (MH, JH and ISF), all of whom were content experts. The search strategy described previously was employed to obtain titles and, where possible, abstracts of studies potentially relevant to the review.

Selection of studies

The titles and abstracts were screened by MH who discarded any studies that were clearly ineligible but who aimed to be overly inclusive rather than risk losing relevant studies. MH obtained copies of the full text articles and made copies for JH and ISF in which the authors and institutions were struck out and the results section removed. The review authors assessed independently whether the studies met the inclusion criteria. Any disagreements were resolved by discussion. Where papers contained insufficient information to make a decision about eligibility, further information was sought from study investigators.

Data extraction and management

It was planned that two review authors would independently extract data from eligible studies. Any disagreements would be resolved by discussion or by a third review author. We attempted to correspond with study investigators for further data on methods and/or results, as required.

Assessment of risk of bias in included studies

It was planned that two review authors would independently assess the included studies for risk of bias using the Cochrane risk of bias assessment tool (www.cochrane-handbook.org) to assess: allocation (random sequence generation and allocation

concealment); blinding of participants and personnel, blinding of outcome assessors; incomplete outcome data; selective reporting; and other bias. Disagreements would be resolved by discussion or by a third review author. We planned to describe all judgements fully and present the conclusions in a Risk of Bias table, which would be incorporated into the interpretation of review findings by means of sensitivity analyses (see below).

Measures of treatment effect

It was planned that for dichotomous data (e.g. adverse events), we would use the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). For continuous data (e.g. menstrual bleeding scores), if all studies reported exactly the same outcomes we would calculate mean differences (MDs) between treatment groups. If similar outcomes were reported on different scales (e.g. change in weight) we would calculate standardised mean differences (SMDs). We planned to present 95% confidence intervals for all outcomes.

Unit of analysis issues

We planned to include only first-phase data from crossover trials.

Dealing with missing data

We planned to analyse the data on an intention-to-treat basis as far as possible and to attempt to obtain missing data from the study investigators. Where these were unobtainable, only the available data would be analysed.

Assessment of heterogeneity

We planned to consider whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We planned to assess statistical heterogeneity by the measure of the I^2 statistic. An I^2 measurement greater than 50% would be taken to indicate substantial heterogeneity.

Assessment of reporting biases

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

Data synthesis

If the studies were sufficiently similar, we planned to combine the data using a fixed effect model.

Subgroup analysis and investigation of heterogeneity

We did not plan any subgroup analyses. If we detected substantial heterogeneity, we planned to explore possible explanations in sensitivity analyses. We planned to take any statistical heterogeneity into account when interpreting the results, especially if there were any variation in the direction of effect.

Sensitivity analysis

We planned to conduct sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis. These analyses would include consideration of whether the review conclusions would have differed if:

- eligibility were restricted to studies without high risk of bias
- a random effects model had been adopted
- the summary effect measure had been relative risk rather than odds ratio.

Overall quality of the body of evidence: Summary of Findings Table

We planned to generate a Summary of Findings Table using GRADEPRO software. This table would evaluate the overall quality of the body of evidence for main review outcomes, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) would be justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

The search strategy described previously was employed to obtain titles and, where possible, abstracts of studies that were potentially relevant to the review. No randomised trials of progestogens alone or in combination with oestrogens for irregular menstrual bleeding were identified.

Included studies

No eligible studies were identified.

Excluded studies

Seven studies were excluded from the review for the following reasons:

- Four were not randomised controlled trials (Aksu 1997; Bishop 1960; Falcone 1994; Fraser 1990)
- Two did not include the population of interest (Munro 2006; Wollter 1997)
- One did not include any comparison of interest (Saarikoski 1990).

Risk of bias in included studies

No eligible studies were identified.

Effects of interventions

No eligible studies were identified.

DISCUSSION

Overall completeness and applicability of evidence

We found no randomised evidence relevant to our clinical question. Clinical studies of sex steroids in the management of irregular

menstrual bleeding associated with oligo/anovulation are not easy to perform, and bleeding patterns may be erratic and highly variable. In addition, management is likely to be affected by patient age, medical history and fertility wishes.

Agreements and disagreements with other studies or reviews

Objective evidence for the role of progestogens for irregular bleeding was found in two trials. Neither met the inclusion criteria for this review.

Saarikoski 1990 compared the effects of two progestogen regimes on endometrial histology in 80 women with a variety of menstrual disorders, seven of whom had irregular bleeding. This randomised study investigated the effects of cyclical norethisterone (NET, 5 mg three times daily) and natural micronised progesterone (NMP, 100 mg three times daily) on endometrial histology in 80 women with menstrual disorders including heavy, frequent and irregular bleeding; 18 women also had fibroids. They reported that only seven women had irregular bleeding but that 89% had anovulatory cycles. It was unclear how anovulation was confirmed. The authors stated that endometrial histology indicated the need for progestogens in all women because of cystic glandular hyperplasia in 41, proliferative endometrium in 30 (normal endometrial cellular pattern seen under the influence of oestrogen in the first half of the menstrual cycle) and "incomplete maturation" of the endometrium in nine; the term "incomplete maturation" was not defined. The outcome measures were endometrial histology, serum oestradiol, progesterone, prolactin, follicle stimulating hormone (FSH), LH and sex hormone binding (SHB) levels. Endometrial biopsies at three and six months of treatment, and again three months after cessation of treatment, showed that cystic glandular hyperplasia had resolved in all except one woman (in the NET group) by three months of treatment. Proliferative endometrium was seen in seven of 30 women following treatment, all of whom were in the NET group. The quantity or regularity of bleeding following treatment was not reported but the authors noted that 19 women discontinued treatment (14 NMP users and five NET users), mainly (six women) because of amenorrhoea. A further three women using NMP complained of breakthrough bleeding.

Fraser 1990 showed a reduction in menstrual blood loss (MBL) and decrease in the number of bleeding days in six women with objectively demonstrated anovulation and heavy menstrual bleeding who were treated with oral progestogens; three with NET 5 mg three times daily, and three with medroxyprogesterone acetate (MPA) 10 mg three times daily for 14 days from day 12 to 25 inclusive. Women were allocated rather than randomised to these treatment groups. Using participants as their own controls, the study demonstrated a significant reduction in menstrual blood loss from a pretreatment mean of 131 ± 40 mL (mean ± SD) to 80 ± 31 mL during the first treatment cycle, and 64 ± 14 mL in the second cycle (paired t test, t = 4.638, P < 0.005 in the first cycle and t = 4.025, P = < 0.01 in the second). The duration of bleeding was also reduced following treatment, from a mean of 8.5 ± 2.4 days before treatment to 6.2 ± 1.7 days in the first treatment cycle, and 5.5 ± 1.1 days in the second (t = 3.105, P = 0.027). No obvious difference was observed between the two progestogens. This study suggests that cyclical oral progestogens are effective in regulating and reducing irregular bleeding due to oligo/anovulation. However larger, randomised studies are needed to confirm this role and to compare progestogen types, regimes, dosages and routes of administration.

There was little long-term effect of progestogens on endometrial histology. Three months after cessation of treatment, 34% of women showed a hyperplastic or proliferative endometrial appearance; and a secretory appearance (normal endometrial cellular pattern under the influence of oestrogen followed by progesterone seen in the second half of the menstrual cycle) was seen in only 25%.

AUTHORS' CONCLUSIONS

Implications for practice

It remains unclear how irregular menstrual bleeding associated with oligo/anovulation should best be treated. No randomised evidence is currently available about the most effective type, dose, regime and administration route of progestogen, or the relative efficacy of progestogens used alone or in combination with oestrogens.

Implications for research

Randomised controlled trials of progestogens alone or in combination with oestrogens are needed in order to define the relative efficacy and acceptability of these interventions in regulating menstrual bleeding. In particular, trials are needed to compare different cyclical progestogens with combined oral contraceptives in irregular bleeding associated with PCOS, and oral versus intrauterine progestogens in perimenopausal irregular bleeding.

ACKNOWLEDGEMENTS

Thanks to the Menstrual Disorders and Subfertility Group (MSDG) editorial base for renewing the search strategy and updating the review in 2007 and 2012.

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References to studies excluded from this review

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Bishop 1960 *{published data only}*

* Bishop PMF. Treatment of functional menstrual disorders with norethisterone. *British Medical Journal* 1960;**9**:1103-5.

Falcone 1994 *{published data only}*

* Falcone T, Desjardins C, Bourque J, Granger L, Hemmings R, Quiros E. Dysfunctional uterine bleeding in adolescents. *Journal of Reproductive Medicine* 1994;**39**(10):761-4.

Fraser 1990 *{published and unpublished data}*

Fraser IS. Treatment of ovulatory and anovulatory dysfunctional uterine bleeding with oral progestogens. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 1990;**30**:353-6.

Munro 2006 *{published data only}*

Munro M, Mainor N, Basu R, Brisinger M, Barreda L. Oral medroxyprogesterone acetate and combination oral contraceptives for acute uterine bleeding. *Obstetrics and Gynecology* 2006;**108**(4):924-9.

Saarikoski 1990 *{published data only}*

Saarikoski S, Yliskoski M, Penttila I. Sequential use of norethisterone and natural progesterone in pre-menopausal bleeding disorders. *Maturitas* 1990;**12**:89-97.

Wollter 1997 *{published data only}*

* Wollter-Svensson LO, Stadberg E, Andersson K, Mattsson L-A, Odlind V, Persson I. Intrauterine administration of levonorgestrel 5 and 10 mcg/24 hours in perimenopausal hormone replacement therapy. *Acta Obstetricia Gynecologica Scandinavica* 1997;**76**:449-54.

Additional references

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Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004;**89**(6):2745-9.

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Harlow 2012

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Hickey 2008

Hickey M, Salamonsen LA. Endometrial structural and inflammatory changes with exogenous progestogens.. *Trends in Endocrinology and Metabolism* 2008;**19**(5):167-74.

Lacey 2009

Lacey JVJ, Chia VM. Endometrial hyperplasia and the risk of progression to carcinoma. *Maturitas* 2009;**63**(1):39-44.

Munro 2011

Munro MG, Critchley HO, Fraser IS. The flexible FIGO classification concept for underlying causes of abnormal uterine bleeding. *Seminars in Reproductive Medicine* 2011;**29**(5):391-9.

van Hooff 2004

van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasing RA, Koppenaal C, Schoemaker J. Predictive values of menstrual cycle pattern, body mass index, hormone levels and polycystic ovaries at aged 15 years for oligo-amenorrhoea at aged 18 years. *Human Reproduction* 2004;**19**(2):383-92.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Aksu 1997	Twenty-four adolescents with heavy vaginal bleeding leading to anaemia were treated with high dose progestogens for 10 days (20-120 mg of medroxyprogesterone acetate per day). There were

Study	Reason for exclusion
	no comparison or control groups. There was no discussion of whether bleeding was regular or irregular, although the mean duration of bleeding was prolonged at 15.6 12.3 days. Underlying haematological disorders were excluded. The adolescents were not sexually active. The main outcome measure was immediate cessation of bleeding. No follow up was reported.
Bishop 1960	Five to 25 mg of norethisterone was given to 35 women with "metropathia haemorrhagica", diagnosed by heavy and irregular menstrual bleeding in women with cystic glandular hyperplasia on endometrial curetting. There was no comparison group and no control group. Withdrawal bleeds occurred within a few days of discontinuing treatment in 180/182 treatment cycles. There was no report of menstrual bleeding patterns during treatment and no follow-up data.
Falcone 1994	A retrospective study of 61 adolescents admitted to hospital with dysfunctional uterine bleeding. Approximately half of these participants had irregular menstrual bleeding (55.7%). Oestrogens and progestogens alone and in combination were used according to the preference of the physician. Five patients underwent dilation and curettage. Five patients had underlying haematological abnormalities. The study reported that 93% responded to steroid therapy with cessation or decrease in bleeding, but did not compare therapies or provide any follow-up data.
Fraser 1990	Non-randomised trial of two progestogen regimes in objectively demonstrated anovulatory dysfunctional uterine bleeding. Included six women with anovulation and menorrhagia who received norethisterone 5 mg 3 times daily from days 12 to 25 inclusive, or medroxyprogesterone acetate 10 mg 3 times daily for 2 cycles. Outcomes were reduction in number of bleeding days and in objectively measured menstrual blood loss.
Munro 2006	Randomised open label trial of 40 women with acute uterine bleeding. This review focused on irregular bleeding. Twenty women were given medroxyprogesterone acetate (MA) 20 mg and twenty were given monophasic combination OC. Cessation of bleeding occurred in 88% of the OC group and 76% of the MA group. The results were limited by sample size.
Saarikoski 1990	Prospective randomised trial of 80 women with a variety of menstrual disorders; seven had irregular bleeding although 41 had endometrial cystic glandular hyperplasia. They received norethisterone 5 mg 3 times daily or natural micronised progesterone, 100 mg 3 times daily. Outcomes of interest were endometrial histology after 6 months of treatment. Attempts were made to contact the authors in January 1998 to request further details but no reply was received.
Wollter 1997	Prospective study of 108 perimenopausal women with vasomotor symptoms. Women were randomised to levonorgestrel (5 or 10 mcg/24 hours) from an intrauterine system with either oestradiol valerate (2 mg) or transdermal oestradiol (50 mcg/24 hours). There was no mention of bleeding patterns before treatment, only that fewer than twelve months had elapsed since their last menstrual period. Bleeding patterns following treatment were reported, frequent bleeding was the most common reason for discontinuation. At the end of the study, 62% of subjects were amenorrhoeic. No significant differences between the groups were seen. The study did not clearly investigate the effects of these treatments on bleeding patterns associated with anovulation.

APPENDICES

Appendix 1. MDSG search strategy

MDSG search for MH301 2012 update

Keywords CONTAINS "progestagen"or"Progesterone" or "progestin" or "progestins" or "progestogens" or "progestogen" or "estrogen" or "*Estrogens" or "oestrogen" or "oral contraceptive" or "oral contraceptives" or "oral estrogen" or "*Medrogestone" or "medroxyprogesterone" or "desogestrel" or "lynestrenol" or "noresthisterone" or "norethindrone" or "Norethisterone" or "Levonorgestrel" or "OCP" or "contraceptive agents" or "contraceptives agent" or Title CONTAINS"progestagen"or"Progesterone" or "progestin" or "progestins" or "progestogens" or "progestogen" or "estrogen" or "*Estrogens" or "oestrogen" or "oral contraceptive"

or "oral contraceptives" or "oral estrogen" or "*Medrogestone" or "medroxyprogesterone" or "desogestrel" or "lynestrenol" or "noresthisterone" or "norethindrone" or "Norethisterone" or "Levonorgestrel" or "OCP" or "contraceptive agents" or "contraceptives agent"
AND
Title CONTAINS "menorrhagia" or "menstrual distress" or "Menstruation Disorders" or "metrorrhagia" or "irregular bleeding" or "irregular menstrual cycles" or "dysfunctional bleeding" or "dysfunctional uterine bleeding" or "dysfunctional uterus" or "anovulation" or "Polycystic Ovary Syndrome" or "PCOS" or "uterine hemorrhage" or Title CONTAINS "menorrhagia" or "menstrual distress" or "Menstruation Disorders" or "metrorrhagia" or "irregular bleeding" or "irregular menstrual cycles" or "dysfunctional bleeding" or "dysfunctional uterine bleeding" or "dysfunctional uterus" or "anovulation" or "Polycystic Ovary Syndrome" or "PCOS" or "uterine hemorrhage"

Appendix 2. CENTRAL search strategy

CENTRAL search for 2012 update:

1 exp progestins/ or exp progesterone/ (2613)

2 (progestogen$ or Progestin$ or progesterone$).tw. (3293)

3 exp Estrogens/ (5381)

4 (estro$ or oestro$).tw. (5881)

5 exp Contraceptives, Oral, Hormonal/ or exp Contraceptives, Oral/ (2756)

6 (oral adj5 contracept$).tw. (1548)

7 exp Medroxyprogesterone/ or exp Medroxyprogesterone Acetate/ (979)

8 exp desogestrel/ or exp lynestrenol/ or exp norethindrone/ or exp norgestrel/ or exp ethinyl estradiol-norgestrel combination/ or exp levonorgestrel/ (1488)

9 Medroxyprogesterone$.tw. (1225)

10 desogestrel.tw. (357)

11 (lynestrenol or norethindrone).tw. (250)

12 (norgestrel or ethinyl estradiol).tw. (659)

13 levonorgestrel.tw. (665)

14 OCP.tw. (46)

15 or/1-14 (11604)

16 exp uterine hemorrhage/ or exp menorrhagia/ or exp metrorrhagia/ (905)

17 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (135)

18 (dysfunction$ adj5 uter$ bleed$).tw. (90)

19 DUB.tw. (23)

20 menorrhagi$.tw. (281)

21 metrorrhagi$.tw. (40)

22 exp Anovulation/ (90)

23 Anovulat$.tw. (276)

24 exp Polycystic Ovary Syndrome/ (577)

25 (Polycys$ adj5 Ovar$).tw. (839)

26 (PCOS or PCOD).tw. (583)

27 (menstrua$ adj2 disorder$).tw. (41)

28 (uter$ adj3 hemorrhage$).tw. (24)

29 (bleeding adj2 disorder$).tw. (79)

30 or/16-29 (2394)

31 15 and 30 (816)

32 limit 31 to yr="2007 -Current" (130)

Appendix 3. MEDLINE search strategy

MEDLINE search for 2012 update:

1 exp progestins/ or exp progesterone/ (66620)

2 (progestogen$ or Progestin$ or progesterone$).tw. (69303)

3 exp Estrogens/ (129915)

4 (estro$ or oestro$).tw. (123552)

5 exp Contraceptives, Oral, Hormonal/ or exp Contraceptives, Oral/ (38704)

6 (oral adj5 contracept$).tw. (20882)

7 exp Medroxyprogesterone/ or exp Medroxyprogesterone Acetate/ (6138)

8 exp desogestrel/ or exp lynestrenol/ or exp norethindrone/ or exp norgestrel/ or exp ethinyl estradiol-norgestrel combination/ or exp levonorgestrel/ (9218)

9 Medroxyprogesterone$.tw. (4855)

10 desogestrel.tw. (925)

11 (lynestrenol or norethindrone).tw. (1454)

12 (norgestrel or ethinyl estradiol).tw. (3748)

13 levonorgestrel.tw. (2911)

14 OCP.tw. (1075)

15 or/1-14 (258070)

16 exp uterine hemorrhage/ or exp menorrhagia/ or exp metrorrhagia/ (14609)

17 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (1852)

18 (dysfunction$ adj5 uter$ bleed$).tw. (724)

19 DUB.tw. (328)

20 menorrhagi$.tw. (2260)

21 metrorrhagi$.tw. (850)

22 exp Anovulation/ (1824)

23 Anovulat$.tw. (4041)

24 exp Polycystic Ovary Syndrome/ (8236)

25 (Polycys$ adj5 Ovar$).tw. (8096)

26 (PCOS or PCOD).tw. (4432)

27 (menstrua$ adj2 disorder$).tw. (1660)

28 (uter$ adj3 hemorrhage$).tw. (827)

29 (bleeding adj2 disorder$).tw. (3022)

30 or/16-29 (35294)

31 15 and 30 (8145)

32 randomized controlled trial.pt. (299815)

33 controlled clinical trial.pt. (81739)

34 randomized.ab. (216055)

35 placebo.tw. (129233)

36 clinical trials as topic.sh. (152163)

37 randomly.ab. (159585)

38 trial.ti. (92531)

39 (crossover or cross-over or cross over).tw. (49471)

40 or/32-39 (733494)

41 exp animals/ not humans.sh. (3533551)

42 40 not 41 (677881)

43 31 and 42 (1128)

44 (2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed. (3440010)

45 43 and 44 (221)

MEDLINE Search for 2007 update

MEDLINE (1966 to May 2007)

1 exp Progestins/ (51573)
2 (progestogen$ or Progestin$ or progesterone$).tw. (57686)
3 exp Estrogens/ (58300)
4 (estro$ or oestro$).tw. (99414)
5 exp Contraceptives, Oral/ (35851)
6 (oral adj5 contracept$).tw. (15729)
7 exp Menstrual Cycle/de [Drug Effects] (3351)

8 or/1-7 (196006)
9 uterine hemorrhage/ or menorrhagia/ or metrorrhagia/ (9813)
10 (uter$ adj5 bleed$).tw. (2555)
11 (menstrua$ adj5 bleed$).tw. (1098)
12 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (1226)
13 (dysfunction$ adj5 uter$ bleed$).tw. (576)
14 DUB.tw. (208)
15 or/9-14 (12745)
16 randomized controlled trial.pt. (234701)
17 controlled clinical trial.pt. (74869)
18 Randomized Controlled Trials/ (48464)
19 Random allocation/ (57810)
20 Double-blind method/ (91140)
21 Single-blind method/ (10900)
22 or/16-21 (397972)
23 clinical trial.pt. (435563)
24 exp clinical trials/ (190865)
25 (clin$ adj25 trial$).ti,ab,sh. (129687)
26 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (90476)
27 Placebos/ (26144)
28 placebo$.ti,ab,sh. (114654)
29 random$.ti,ab,sh. (491011)
30 Research design/ (47354)
31 or/23-30 (867947)
32 animal/ not (human/ and animal/) (3097854)
33 22 or 31 (875276)
34 33 not 32 (801923)
35 8 and 15 and 34 (764)
36 (2004$ or 2005$ or 2006$ or 2007$).ed. (2299763)
37 35 and 36 (137)
38 review.pt. (1275632)
39 letter.pt. (589482)
40 retrospective.tw. (130797)
41 observational.tw. (24425)
42 or/38-41 (2004596)
43 37 not 42 (101)
44 from 43 keep 1-101 (101)

Appendix 4. EMBASE search strategy

EMBASE search for 2012 update:

1 exp gestagen/ (119362)

2 (progestogen$ or Progestin$ or progesterone$).tw. (69990)

3 gestagen$.tw. (1555)

4 exp PROGESTERONE/ (61214)

5 exp estrogen/ (183122)

6 (estro$ or oestro$).tw. (131141)

7 exp oral contraceptive agent/ (45867)

8 (oral adj5 contracept$).tw. (20006)

9 exp MEDROXYPROGESTERONE ACETATE/ or exp MEDROXYPROGESTERONE/ (15591)

10 exp DESOGESTREL/ (2427)

11 exp LYNESTRENOL/ (1639)

12 exp norethisterone/ (6073)

13 exp NORGESTREL/ (3536)

14 exp LEVONORGESTREL/ (7231)

15 Medroxyprogesterone$.tw. (5108)

16 desogestrel.tw. (985)

17 (lynestrenol or norethindrone).tw. (1084)

18 (norgestrel or ethinyl estradiol).tw. (2953)

19 levonorgestrel.tw. (3090)

20 OCP.tw. (1209)

21 or/1-20 (316121)

22 exp uterus bleeding/ (6541)

23 exp "MENORRHAGIA AND METRORRHAGIA"/ or exp MENORRHAGIA/ (8373)

24 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (1800)

25 (dysfunction$ adj5 uter$ bleed$).tw. (820)

26 DUB.tw. (387)

27 menorrhagi$.tw. (2630)

28 metrorrhagi$.tw. (825)

29 (menstrua$ adj2 disorder$).tw. (1812)

30 (uter$ adj3 hemorrhage$).tw. (800)

31 (bleeding adj2 disorder$).tw. (3746)

32 or/22-31 (22082)

33 exp ANOVULATION/ (3429)

34 Anovulat$.tw. (4287)

35 exp ovary polycystic disease/ (12597)

36 (Polycys$ adj5 Ovar$).tw. (9810)

37 (PCOS or PCOD).tw. (5657)

38 or/33-37 (17683)

39 21 and 32 and 38 (491)

40 Clinical Trial/ (826949)

41 Randomized Controlled Trial/ (289563)

42 exp randomization/ (53430)

43 Single Blind Procedure/ (13891)

44 Double Blind Procedure/ (101543)

45 Crossover Procedure/ (30153)

46 Placebo/ (175282)

47 Randomi?ed controlled trial$.tw. (59740)

48 Rct.tw. (6464)

49 random allocation.tw. (1020)

50 randomly allocated.tw. (15182)

51 allocated randomly.tw. (1693)

52 (allocated adj2 random).tw. (683)

53 Single blind$.tw. (10753)

54 Double blind$.tw. (116144)

55 ((treble or triple) adj blind$).tw. (234)

56 placebo$.tw. (155319)

57 prospective study/ (163667)

58 or/40-57 (1119455)

59 case study/ (11206)

60 case report.tw. (197169)

61 abstract report/ or letter/ (770730)

62 or/59-61 (975395)

63 58 not 62 (1087005)

64 39 and 63 (118)

65 (2010$ or 2011$).em. (1298269)

66 64 and 65 (13)

Appendix 5. PsycINFO search strategy

PsycINFO search for 2012 update

1 exp Hormone Therapy/ (1323)

2 (progestogen$ or Progestin$ or progesterone$).tw. (3188)

3 gestagen$.tw. (13)

4 exp Progesterone/ (1591)

5 exp Estrogens/ (4323)

6 (estro$ or oestro$).tw. (6893)

7 exp Oral Contraceptives/ (592)

8 (oral adj5 contracept$).tw. (998)

9 exp Progestational Hormones/ (1748)

10 (lynestrenol or norethindrone).tw. (17)

11 (norgestrel or ethinyl estradiol).tw. (63)

12 levonorgestrel.tw. (35)

13 OCP.tw. (57)

14 or/1-13 (10976)

15 exp Menstrual Disorders/ (877)

16 METRORRHAGIA.tw. (1)

17 METRORRHAGIA.tw. (1)

18 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (132)

19 (dysfunction$ adj5 uter$ bleed$).tw. (18)

20 DUB.tw. (71)

21 (menstrua$ adj2 disorder$).tw. (159)

22 (uter$ adj3 hemorrhage$).tw. (0)

23 (bleeding adj2 disorder$).tw. (25)

24 Anovulat$.tw. (106)

25 exp Endocrine Sexual Disorders/ (723)

26 (Polycys$ adj5 Ovar$).tw. (179)

27 (PCOS or PCOD).tw. (98)

28 or/15-27 (2093)

29 14 and 28 (251)

30 limit 29 to ("0830systematic review" or "2000treatment outcome/randomized clinical trial") (8)

Appendix 6. CINAHL search strategy

CINAHL search for 2007 update

1 exp Progestins/ (1159)
2 (progestogen$ or Progestin$ or progesterone$).tw. (958)
3 exp Estrogens/ (3564)
4 (estro$ or oestro$).tw. (2624)
5 exp Contraceptives, Oral/ (4781)
6 (oral adj5 contracept$).tw. (1107)

7 exp Menstrual Cycle/de [Drug Effects] (107)
8 or/1-7 (7510)
9 uterine hemorrhage/ or menorrhagia/ or metrorrhagia/ (572)
10 (uter$ adj5 bleed$).tw. (173)
11 (menstrua$ adj5 bleed$).tw. (90)
12 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (74)
13 (dysfunction$ adj5 uter$ bleed$).tw. (53)
14 DUB.tw. (14)
15 or/9-14 (738)
16 8 and 15 (152)
17 limit 16 to yr="2004 - 2007" (61)
18 exp clinical trials/ (43840)
19 Clinical trial.pt. (20772)
20 (clinic$ adj trial$1).tw. (10271)
21 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (6120)
22 Randomi?ed control$ trial$.tw. (8968)
23 Random assignment/ (15190)
24 Random$ allocat$.tw. (1026)
25 Placebo$.tw. (8576)
26 Placebos/ (3492)
27 Quantitative studies/ (3206)
28 Allocat$ random$.tw. (60)
29 or/18-28 (61489)
30 17 and 29 (27)
31 review.tw. (52537)
32 retrospective.tw. (11331)
33 observational.tw. (4484)
34 or/31-33 (64061)
35 30 and 34 (15)
36 from 35 keep 1-15 (15)

Appendix 7. EBM Reviews search strategy

EBM Reviews search for 2007 update

1 exp Progestins/ (973)
2 (progestogen$ or Progestin$ or progesterone$).tw. (2888)
3 exp Estrogens/ (3537)
4 (estro$ or oestro$).tw. (5003)
5 exp Contraceptives, Oral/ (3178)
6 (oral adj5 contracept$).tw. (1356)
7 exp Menstrual Cycle/de [Drug Effects] (605)
8 or/1-7 (9652)
9 uterine hemorrhage/ or menorrhagia/ or metrorrhagia/ (608)
10 (uter$ adj5 bleed$).tw. (290)
11 (menstrua$ adj5 bleed$).tw. (166)
12 (irregular adj5 (period$ or menstrua$ or bleed$ or blood loss)).tw. (119)
13 (dysfunction$ adj5 uter$ bleed$).tw. (73)
14 DUB.tw. (20)
15 Polycystic Ovary Syndrome/ (386)
16 (Polycys$ adj5 Ovar$).tw. (554)
17 (PCOS or PCOD).tw. (369)
18 Anovulation/ (70)
19 Anovulat$.tw. (221)
20 or/15-19 (762)
21 or/9-14 (941)
22 8 and 20 and 21 (8)
23 from 22 keep 1-8 (8)

Appendix 8. Current Contents search strategy

Current Contents search for 2007 update:

These databases were searched using the following subject headings and keywords:

Dysfunctional uterine bleeding
DUB
anovulatory DUB
Irregular menstrual bleeding/
Menstrual cycle/drug therapy
Progestogen/
Progestogen/
Progestin/
Progest$/
Oestrogen/
Estrogen/
Oestr$/
Polycystic ovar$
PCOS
PCOD
Cystic ovar$
Polycystic ovary syndrome/therapy
(dysfunctional adj5 uter$).tw
exp contraceptives, oral/
contracept$.tw
Contraception oral
Intermenstrual bleeding.tw
Spotting.tw

WHAT'S NEW

Date	Event	Description
12 September 2012	Review declared as stable	As no studies are expected, this review will no longer be updated.

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 1, 2000

Date	Event	Description
10 August 2012	New citation required but conclusions have not changed	Review updated. No change to conclusions.
22 February 2012	New search has been performed	Search updated. No studies found.
21 September 2010	Amended	Contact details updated.
6 November 2008	Amended	Converted to new review format.
19 July 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Martha Hickey: initiated and conceptualised the review; took the lead in writing the 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, and was responsible for statistical analysis and interpretation of the data.
Jenny Higham: was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, contributed to discussion and interpretation of results and writing of the protocol and review.
Ian Fraser: performed independent data extraction, commented on drafts of the protocol and review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- not detailed by review author, Not specified.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Anovulation [*complications]; Drug Therapy, Combination [methods]; Estrogens [*therapeutic use]; Menorrhagia [*drug therapy] [etiology]; Progestins [*therapeutic use]

MeSH check words

Adult; Female; Humans