Primary care management of abnormal uterine bleeding
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CRD summary
The authors concluded that two interventions for irregular bleeding and three for heavy cyclic bleeding had low or moderate strength of evidence for effectiveness. One intervention had high strength of evidence for reduction of heavy cyclic bleeding. These conclusions reflect the evidence and appear reliable but the small proportion of good quality trials should be borne in mind.

Authors' objectives
To evaluate the effectiveness and potential harms of non-surgical interventions for improving long and short-term outcomes in women with irregular uterine bleeding and women with abnormal cyclic uterine bleeding.

Searching
MEDLINE, EMBASE and CINAHL were searched from January 1980 to June 2012 for articles published in English. Reference lists of included publications and recent systematic reviews were handsearched to locate further studies. For evidence of harms the authors searched PubMed from January 1980 to June 2012 (strategy reported in appendix) and scanned standard drug package inserts.

Study selection
Randomised controlled trials that evaluated non-surgical interventions for non-pregnant women with irregular or abnormal cyclic uterine bleeding for three months or more were eligible for inclusion. Studies of women with polycystic ovarian syndrome were included with studies of irregular bleeding as long as the patient baseline and outcome data included information regarding cycle regularity. Studies of women with abnormal uterine bleeding caused by coagulation defects, systemic disease, structural abnormalities, cancer, medication side-effects or infertility (with a primary treatment goal of conception) were excluded. Outcomes of interest included bleeding profile, quality of life, pain, sexual function and patient satisfaction with treatment outcomes. For evidence of harms, observational studies with at least 1,600 participants/records were included.

Interventions evaluated by the included trials included levonorgestrel-releasing intrauterine system (LNG-IUS) combined oral contraceptive pills, nonsteroidal anti-inflammatory drugs (NSAID), progestogens, lifestyle/behavioural changes, acupuncture and decision aids. Most studies were head-to-head comparisons; a smaller proportion were placebo-controlled. Studies were performed in North America, Europe (including one UK study for irregular uterine bleeding and two UK studies for abnormal cyclic uterine bleeding), South America, Africa and Asia. The duration of most studies was six months or less.

Two reviewers independently screened studies for inclusion at the full text stage; any discrepancies were resolved by discussion with senior investigators.

Assessment of study quality
Study quality was assessed using the Cochrane Collaboration's risk of bias tool. Risk of bias was assessed as being low, high or unclear for each of randomisation, allocation concealment, blinding, outcome data reporting and reporting bias. A pre-established threshold was used to rate the overall quality of each study as good (low risk of bias), fair (medium risk of bias) or poor (high risk of bias).

Study quality was assessed independently by two reviewers; any discrepancies were resolved by discussion with senior investigators.

Data extraction
Date on outcomes were extracted using standardised forms. Two reviewers independently extracted data; a senior investigator checked the extracted data for accuracy and completeness.

Methods of synthesis
Data were presented in a narrative synthesis. Results were reported separately for irregular or abnormal cyclic uterine bleeding according to the type of intervention used. The overall strength of evidence for each outcome was assessed using slightly modified GRADE criteria.

**Results of the review**

Thirty-nine studies from 41 publications were included in the review: 10 studies on irregular uterine bleeding and 29 studies on abnormal cyclic uterine bleeding. Studies of irregular uterine bleeding were classified as being of good (two studies), fair (two studies) and poor quality (six studies). Studies on abnormal cyclic uterine bleeding were classified as being of good (four studies), fair (eight studies) and poor quality (17 studies).

**Women with irregular uterine bleeding (10 studies):** Metformin, metformin with exenatide and tricyclic oral contraceptive all improved menstrual regularity. All of the studies on metformin recruited women with polycystic ovary syndrome or oligomenorrhoea (four studies). Metformin (with or without exenatide) was the only intervention to show benefit across a number of studies. Other treatments showed potentially promising results in singular/small studies (details in the report).

**Women with abnormal cyclic uterine bleeding (29 studies):** All comparisons of LNG-IUS versus other treatments including NSAIDS, combined oral contraceptives, progestogens and usual care (seven studies) favoured LNG-IUS for reduction of menstrual blood loss, which ranged from 70% to 87% less than baseline. NSAIDS were always found to be better than placebo or progestogens for reduction of menstrual blood loss (six studies) but the degree of improvement varied greatly. Reduction of menstrual bleeding was demonstrated more with tranexamic acid compared with progestogens and NSAIDs (in three out of four studies). High strength evidence was found for the reduction of menstrual bleeding and days of menstrual bleeding with combined oral contraceptives compared with placebo (two studies).

Further results, including potential adverse effects of the different interventions, were reported in the report.

**Authors’ conclusions**

Two interventions for reduction of irregular bleeding (metformin and combined oral contraceptives) and three interventions for reduction of heavy cyclic bleeding (LNG-IUS, NSAIDS and tranexamic acid) had low or moderate strength of evidence for effectiveness. One intervention (combined oral contraceptives) had high strength of evidence for reduction of heavy cyclic bleeding.

**CRD commentary**

The review questions were clear and the inclusion criteria were sufficiently replicable. Relevant databases were accessed. The restriction to studies in English meant that some relevant studies may have been missed. Efforts were made throughout the review process to minimise reviewer error and bias. A well known quality assessment tool was used and revealed that the quality of most studies was poor. The authors acknowledged that most of the included trials were small and of short duration with a lack of standard terminology and diagnostic criteria for identifying and enrolling women with abnormal uterine bleeding. It was also stated that tools for collecting outcome data were crude and may have affected attrition rates. Given the diversity between the included trials, the narrative method of synthesis seemed appropriate.

This appeared to be a well conducted review. The authors’ conclusions reflect the evidence and appear reliable. The small proportion of good quality trials should be borne in mind.

**Implications of the review for practice and research**

**Practice:** The authors stated that contraceptive options such as LNG-IUS and combined oral contraceptives were proven options for helping with management of abnormal uterine bleeding. Agents like metformin may also be considered for women with polycystic ovary syndrome. Tranexamic acid may be considered for those with heavy bleeding. The authors stated that clinicians should be made aware of the constraints of literature for these populations and utilise more information to guide decisions and discuss potential side-effects and harms.

**Research:** The authors stated that future research was required on possible benefits of exercise and weight loss and insulin sensitising and glycaemic control agents (such as metformin, exenatide) on irregular bleeding patterns. Carefully
controlled trials of complementary and alternative medicine were suggested as were randomised controlled trials designed specifically to assess heaviness and intervals of irregular bleeding. Recommendations for abnormal cyclic uterine bleeding included assessment of the acceptability and cost-effectiveness of various treatments in primary care settings within the United States and research to determine which individuals were likely to respond to each intervention.

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