Danazol for heavy menstrual bleeding (Review)

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[Intervention Review]

Danazol for heavy menstrual bleeding

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ABSTRACT

Background

Heavy menstrual bleeding (HMB) is an important cause of ill health in pre menopausal women. Medical therapy, with the avoidance of possibly unnecessary surgery is an attractive treatment option, but there is considerable variation in practice and uncertainty about the most effective therapy. Danazol is a synthetic steroid with anti-oestrogenic and anti progestogenic activity, and weak androgenic properties. Danazol suppresses oestrogen and progesterone receptors in the endometrium, leading to endometrial atrophy (thinning of the lining of the uterus) and reduced menstrual loss and to amenorrhoea in some women.

Objectives

To determine the effectiveness and tolerability of danazol when used for heavy menstrual bleeding in women of reproductive years.

Search strategy

We searched the Menstrual Disorders and Subfertility Group's Specialised Register of controlled trials (6 Nov 2001). We also searched the Cochrane Controlled Trials Register (Cochrane Library, Issue 3, 2001), MEDLINE (1966 to Oct 2001), EMBASE (1980 to Oct 2001), Current Contents (1993 to Oct 2001), CINAHL (1982 to Sept 2001), and the National Research Register (Issue 3, 2001). Attempts were also made to identify trials from citation lists of included trials and relevant review articles. In most cases the first author of each included trial was contacted for unpublished additional information.

Selection criteria

Randomised controlled trials of danazol versus placebo, any other medical (non-surgical) therapy or danazol in different dosages for heavy menstrual bleeding in women of reproductive age with regular HMB measured either subjectively or objectively. Trials that included women with post menopausal bleeding, intermenstrual bleeding and pathological causes of heavy menstrual bleeding were excluded.

Data collection and analysis

Nine RCTs, with 353 women, were identified that fulfilled the inclusion criteria for this review. Quality assessment and data extraction were performed independently by two reviewers. The main outcomes were menstrual blood loss, the number of women experiencing adverse effects, weight gain, withdrawals due to adverse effects and dysmenorrhoea. If data could not be extracted in a form suitable for meta-analysis, they were presented in a descriptive format.

Main results

Most data were not in a form suitable for meta analysis, and the results are based on a small number of trials, all of which are underpowered. Danazol appears to be more effective than placebo, progestogens, NSAIDs and the OCP at reducing MBL, but confidence intervals were wide. Treatment with danazol caused more adverse events than NSAIDs (OR 7.0; 95% CI 1.7, 28.2) and progestogens (OR 4.05, 95% CI 1.6, 10.2), but this did not appear to affect adherence to treatment. Danazol was shown to significantly lower the duration of menses when compared with NSAIDs (WMD -1.0; 95% CI -1.8, -0.3) and a progesterone releasing IUD (WMD -6.0; 95% CI -7.3, -4.8). There were no randomised trials comparing danazol with tranexamic acid or the levonorgestrel-releasing intrauterine system.

Authors' conclusions

Danazol appears to be an effective treatment for heavy menstrual bleeding compared to other medical treatments, though it is uncertain whether it is acceptable to women. The use of danazol may be limited by its side effect profile, its acceptability to women and the need for continuing treatment. Overall no strong recommendations can be made due to the small number of trials, and the small sample sizes of the included trials.

PLAIN LANGUAGE SUMMARY

Danazol is an effective treatment for the reduction of heavy menstrual bleeding, but the adverse effects may be unacceptable to women

Options to help avoid surgery can be important for many women who are having problems with heavy menstrual bleeding. One of the drug options is danazol. Danazol suppresses the hormones that increase the endometrium (the lining of the uterus that is shed during menstruation). However, danazol can also produce male characteristics and some menopause-like symptoms, as well as weight gain and acne. The review found that although danazol is effective at reducing menstrual blood loss there are not enough trials to show whether this treatment is acceptable to women with heavy menstrual bleeding.

BACKGROUND

Heavy menstrual bleeding (menorrhagia) can have a significant impact on women's lives. In the UK, one in 20 women aged 30-49 consult their general practitioner each year with heavy menstrual bleeding (Vessey 1992) and it accounts for 12% of all gynaecological referrals (Bradlow 1992). Once referred to a gynaecologist, surgical intervention is highly likely (Coulter 1991).

Heavy menstrual bleeding (HMB) or menorrhagia is clinically defined as greater than or equal to 80 ml blood loss per menstrual cycle (Hallberg 1966; Cole 1971). It is, however, the woman's perception of her own menstrual loss which is the key determinant in a referral and, indeed, subsequent treatment. The main aim of the treatment of menorrhagia is to reduce blood loss in order to improve quality of life and prevent anaemia.

Many factors can cause HMB for example coagulation disorders, endocrine disorders, uterine abnormalities and other pelvic pathology. These disorders should be excluded before decisions are made about treatment as they may require different management. However, in most cases, there is no pathological cause of the heavy bleeding, and the condition is labelled dysfunctional uterine bleeding (EHCB 1995). Eighty percent of women treated for menorrhagia have no uterine abnormality and over a third of the women undergoing hysterectomies for HMB have a normal uterus removed (Gath 1982; Clarke 1995). Although patient satisfaction with hysterectomies is high (Coulter 1994), there are complications and occasional death associated with hysterectomy (Dicker 1982). Complications are more likely when the hysterectomy is performed by the open abdominal route, as is usually the case (Hospital 1995). Effective medical therapy, that avoids unnecessary surgery, is therefore an attractive alternative.

A wide variety of medications are available to reduce HMB but their effectiveness has been questioned (Coulter 1995). The aim of this review is to see if danazol is an effective therapy for HMB. Danazol is chemically derived from testosterone (a naturally occurring hormone). It inhibits ovulation and reduces oestrogen levels. It also causes endometrial atrophy (thinning of the lining of the uterus), reduced menstrual loss and leads to amenorrhoea (absence of periods) in some women (Chimbira 1980b). Danazol has

a dramatic effect on increasing haemoglobin and serum ferritin levels and may therefore be valuable in women who need effective therapy to stop very heavy bleeding and restore their haemoglobin and iron status to normal (Ford 1994; Chimbira 1979). Danazol has androgenic properties (a tendency to cause male characteristics) which may result in acne, seborrhoea (greasy skin) and hirsutism (excessive hair growth). Other side effects include weight gain, irritability, musculoskeletal pains, hot flushes and breast atrophy (loss of breast tissue). Longer term treatment with danazol may cause liver effects (including benign hepatic adenomas) in some women.

OBJECTIVES

To determine the effectiveness and tolerability of danazol when given for heavy menstrual bleeding in women of reproductive years.

We wished to investigate:

1. Whether treatment with danazol is more effective than placebo in reducing heavy menstrual blood loss.

2. Whether treatment with danazol is more effective than other medical therapies (antifibrinolytics, NSAIDs, progestogens) in reducing heavy menstrual blood loss.

3. If effective, what is the optimum dosage of danazol.

4. Whether treatment with danazol leads to an improved quality of life for women with heavy menstrual blood loss.

5. Whether women tolerate treatment with danazol and find it an acceptable treatment.

RESULTS

Overall nine studies compared the use of danazol with placebo, other medical treatments or different doses of danazol for the treatment of heavy menstrual bleeding. The studies contained a total of 353 participants.

DANAZOL VS. PLACEBO

One study with 66 participants compared danazol 200 mg once daily with a matched placebo once daily for three months of treatment (Lamb 1987).

Menstrual blood loss (objective/subjective)

This study did not assess objective MBL, and subjective MBL was assessed using an unidentified scoring system. It was not possible to include data for the menstrual blood loss scores, as the type of scoring system used and the figures were poorly reported in the paper. The authors report no significant differences in blood loss scores for the placebo group when comparing before and after treatment scores. A significant difference in blood loss scores was reported for the danazol group compared to the pre-treatment scores, but it is unclear how this was calculated.

Duration of menses

The data for duration of menses could not be included in this review as the figures were inadequately reported in the paper. The author reported no difference in duration of menses for the placebo group comparing pre and post treatment figures. A significant difference in duration of menses was reported for the danazol group (when comparing before and after treatment figures), but the authors do not indicate how this was calculated.

Withdrawals due to side effects

The number of withdrawals due to side effects during the intervention did not significantly differ between the two groups (OR 2.06, 95% CI 0.18, 23.94).

Body weight

The trial reported data on the mean body weight for each group. After three months treatment the mean weight (kg) of the danazol group was significantly greater than that of the placebo group (WMD 6.70, 95% CI 0.98, 12.42).

DANAZOL VS. PROGESTOGENS

Five of the included studies involving a total of 131 women compared 200 mg danazol with a progestogen. For four of the studies the comparison intervention was norethisterone, and in one study the progestogen was medroxyprogesterone acetate.

Menstrual blood loss (objective/subjective)

Four of the studies comparing danazol with a progestogen reported data on MBL. In two trials MBL was measured objectively using the alkaline haematin method. One small parallel trial comparing danazol with norethindrone in the meta analysis (n=37) showed no significant difference between the two groups for menstrual blood loss after treatment (WMD -35.60 , 95% CI -102.20, 31.00) (Higham 1993). The other trial reporting objectively measured MBL, contained data which was not reported in a form suitable for pooling. This trial reported MBL as medians and ranges, rather than means and standard deviations and is included as descriptive data in the Other Data section (Cameron 1987). In this trial the groups were not comparable at baseline, and the study compared MBL after treatment to MBL at baseline for the different treatment groups. There was no significant difference between the before and after treatment values for the progestogen group ($p>0.05$), where as MBL after treatment was significantly lower than that at baseline for the danazol group ($p<0.05$) (Cameron 1987).

Two studies comparing danazol with a progestogen reported subjective measures of MBL. Both are included as descriptive data in the other data section due to skewing of the data in one (Dunphy 1998) and use of a non-standard bleeding scale in the

other (Bonduelle 1991). One trial used the pictorial chart method described by Higham (1990) to record monthly blood loss and reported that MBL after three months treatment was significantly lower in the danazol group compared to the medroxyprogesterone acetate group (p=0.0128) (Dunphy 1998). The other study used a seven point scoring system where daily bleeding scores were combined to give a score for each menstrual period. The trial compared bleeding scores after three months treatment and showed a significant difference between the two groups in favour of danazol (p<0.05).

One study (n=18) included the outcome of MBL three months after the intervention. The trial showed that MBL (assessed by the pictorial chart method) was significantly lower in the progestogen group three months after treatment was stopped (WMD 203.00, 95%CI 25.65, 380.35) (Dunphy 1998).

Side effects

Four trials reported the number of women in each of the two treatment groups experiencing side effects. The four studies in the meta analysis showed that significantly more women in the danazol group experienced side effects compared to the progestogen group (OR 4.05, 95% CI 1.61, 10.21) (Bonduelle 1991; Buyru 1995; Dunphy 1998; Higham 1993). Commonly reported side effects for danazol treatment included acne, weight gain, headache, nausea and tiredness. One study found that adverse effects were reported with a similar frequency and were of a similar nature in both treatment groups (Bonduelle 1991). Commonly reported side effects in this study were weight gain, bloating, gastro-intestinal symptoms, skin changes, lethargy, depression and reduced concentration. Buyru 1995 found that headaches and muscle cramps were reported with similar frequency in both groups, but the danazol group also complained of weight gain, acne, nausea and intermenstrual bleeding. The Higham (1993) study found that both groups reported the adverse effects of muscle cramps and depression with similar frequency. In this study, other commonly reported side effects amongst the danazol group included headache, weight gain, nausea and vomiting and acne, where as other adverse effects reported amongst the progestogen group were premenstrual tension symptoms (Higham 1993).

Withdrawals due to side effects

Four trials comparing danazol with a progestogen reported the number of withdrawals due to side effects. Pooling of data from these studies showed that there was no significant difference between the two groups in terms of withdrawals due to side effects (OR 1.67, 95% CI 0.53, 5.23).

Duration of menses

Four studies comparing danazol with a progestogen assessed the duration of menses. The Chi square test for heterogeneity showed there is significant heterogeneity within the comparison (19.52, df=3, p=0.0002). To consider this heterogeneity, the data was analysed using a random effects model to take into account the variability between the studies when calculating the summary statistic. Pooling of data from these trials shows that there was no significant difference between the groups in the duration of menses after treatment (WMD -0.74, 95%CI -2.31, 0.82).

Dysmenorrhoea

One of the studies comparing danazol with a progestogen reported this outcome (Bonduelle 1991). Abdominal pain and backache were assessed using a three point scoring system. The study compared before and after treatment scores for both measures of pain for the two groups. For the danazol group there was no significant difference in the before and after treatment scores on either of these measures of dysmenorrhoea (p>0.05). The post treatment backache score was significantly lower than that at baseline for the norethisterone group (p<0.05), but there was no significant difference in the before and after treatment abdominal pain scores (p>0.05). This trial was included as descriptive data in the other data section due to the use of a non standard pain scale.

Weight gain

Three studies comparing danazol with a progestogen reported weight gain as an outcome measure. One trial reported weight gain as mean weight gain, and showed that the mean weight gain was significantly higher in the danazol group (WMD 2.80, 95% CI 1.60, 4.00) (Dunphy 1998). One study reported the number of women with a weight gain of >2kg and the another reported the number of women with weight gain of >3kg. For weight gain as a dichotomous variable there was no significant difference between the danazol and progestogen groups. Where the number of women with weight gain >2kg was assessed the OR was 2.86 (95% CI 0.48, 17.11) (Higham 1993) and where the numbers with weight gain >3kg was reported the OR was 5.57 (95% CI 0.48, 64.09) (Bonduelle 1991). But the reported results are imprecise with wide confidence intervals.

Efficacy of intervention

Three studies included this outcome. One study assessed this objectively, reporting the number in each group with MBL of <80 ml at the end of the intervention, and the other two studies assessed efficacy subjectively. The study assessing efficacy objectively showed a significant difference in favour of danazol. Significantly more women in the danazol group had a MBL of less than 80 ml at the end of the intervention (OR 7.20 95% CI 1.28, 40.37) (Higham 1993).

For subjective efficacy of medication, where efficacy was measured as the number of women rating the treatment as highly or moderately effective, subjective efficacy was significantly better after danazol treatment than after norethisterone (OR 4.33, 95% CI 1.09, 17.17) (Higham 1993). Where efficacy was assessed by the numbers rating their MBL as none or moderate, there was no sig-

nificant difference between the two groups (OR 5.83, 95% CI 0.70, 48.87) (Bonduelle 1991).

DANAZOL VS. NSAIDS

Three studies compared danazol with a NSAID for the treatment of heavy menstrual bleeding. All three studies compared danazol with mefenamic acid, but one trial also used naproxen as a comparison intervention.

Menstrual blood loss (objective/subjective)

All three studies reported this outcome, and all assessed MBL using the alkaline haematin method. One small parallel trial (n=39) in the meta-analysis showed that mean MBL after two months treatment was significantly lower in the danazol group compared to the mefenamic acid group (WMD -96.70, 95% CI -138.80, -54.60) (Dockeray 1989). Two other trials are included as descriptive data in the other data section as one reported MBL in a form unsuitable for inclusion in the meta analysis and in the other the data showed significant skewness. One trial included in the other data section, compared danazol with mefenamic acid and reported MBL as medians and ranges. In this trial the groups were not comparable at baseline and the study compared MBL after treatment to MBL at baseline for the different treatment groups, rather than comparing MBL across the groups. MBL after treatment was significantly lower than that at baseline for the danazol group ($p<0.05$), but there was no significant difference between the before and after treatment MBL values for the mefenamic acid group ($p>0.05$) (Cameron 1987). The other trial was a cross-over trial which compared danazol with both mefenamic acid and naproxen. When the mean and standard deviation were calculated from the individual participant data and put into the meta-analysis, mean MBL after two months treatment was significantly lower in the danazol group compared to both the mefenamic acid group ($p=0.001$) and the naproxen group ($p=0.02$) (Fraser 1991). These figures refer to data prior to participants crossing over to the other treatment .

Side effects

One study which compared danazol with mefenamic acid reported this outcome. There were significantly more adverse effects in the danazol group compared to the mefenamic acid group 75% compared to 30% (OR 7.00, 95% CI 1.74, 28.17) (Dockeray 1989). The mefenamic acid group complained mainly of nausea, vomiting and diarrhoea; the danazol group complained of more serious adverse effects such as musculoskeletal pains, dizziness, flushes, acne, behavioural changes, tiredness, breast atrophy, hirsutism and hoarseness.

Withdrawals due to side effects

None of the studies comparing danazol with a NSAID reported this outcome.

Duration of menses

Two trials in both of which mefenamic acid was the comparison intervention assessed this outcome. Pooling of data from these trials showed the duration of menses was significantly shorter in the danazol groups after two months of treatment (WMD -1.03; 95% CI -1.78 -0.28).

Dysmenorrhoea

One parallel study reported this outcome. Dysmenorrhoea was assessed in two ways in the study; according to the number of women in each intervention group who reported an improvement in dysmenorrhoea after two months treatment, and using a three point pain scale scoring system. The number reporting an improvement in dysmenorrhoea showed no significant difference between the two interventions (OR 1.20; 95% CI 0.20, 7.31). The dysmenorrhoea scores showed no significant difference between the two groups after two months of treatment ($p>0.05$) (Dockeray 1989). The data for the dysmenorrhoea scores was included in the Other Data section due to the use of a non-standard pain scale.

Acceptability of treatment

One study included the outcome of the numbers in each group unwilling to continue that particular treatment. This small parallel trial (n=39) compared danazol with mefenamic acid and showed no significant difference between the two groups with regard to the number unwilling to continue the treatment (OR 1.11; 95% CI 0.32, 3.90) (Dockeray 1989).

DANAZOL VS. ORAL CONTRACEPTIVE

One small cross-over study involving 12 women compared danazol 200 mg with an oral contraceptive (ethinyl oestradiol 30ug and levonorgestrel 150ug) (Fraser 1991). Only the data prior to the cross-over were included in the analysis.

Menstrual blood loss (objective/subjective)

Blood loss was measured objectively using the alkaline haematin method. After two months treatment mean MBL for the danazol group was significantly lower than that for the oral contraceptive group ($p=0.02$). The trial was included in the Other Data section as descriptive data due to skewness of the data.

Other outcomes

The only trial comparing danazol with an oral contraceptive did not report any other outcome measures.

DANAZOL VS. PROGESTERONE RELEASING IUD

One trial with 14 participants compared danazol with a progesterone releasing intrauterine device (releasing 65ug progesterone daily) for two months treatment.

Menstrual blood loss (objective/subjective)

MBL was measured objectively using the alkaline haematin method. The study compared MBL after the intervention with

that at baseline for each of the interventions, rather than making comparisons between the groups as the groups were not comparable at baseline. For both groups MBL after the intervention was significantly lower than that at baseline $p<0.05$ and $p<0.01$ for the danazol and progesterone releasing IUD interventions respectively (Cameron 1987). The trial was included as descriptive data in the Other Data section as the data was not reported in a form suitable for inclusion in the meta-analysis.

Duration of menses

The one trial comparing danazol with a progesterone releasing IUD reported data on the duration of menses after two months treatment compared with that at baseline for each group. The results show that the mean duration of menses was significantly shorter in the danazol group (WMD -6.00; 95% CI -7.25, -4.75).

DANAZOL 200 mg VS. DANAZOL 100 mg

One study involving 32 participants compared danazol 200 mg with danazol 100 mg for the treatment of heavy menstrual bleeding (Chimbira 1980a).

Menstrual blood loss (objective/subjective)

MBL was reported objectively after three months treatment and compared with mean MBL at baseline for each group. For both groups mean MBL after three months treatment was significantly lower than mean MBL at baseline ($p<0.01$). There was no significant difference between the two groups after three months of treatment ($p=0.2$) (Chimbira 1980a). This trial was reported in the Other Data section as descriptive data as the data showed significant skewness.

Duration of menses

The mean duration of menses was included as one of the outcome measures in the study comparing danazol 200 mg with danazol 100 mg. The authors reported that the duration of menses after three months treatment with danazol 200 mg was significantly less than that at baseline ($p<0.01$). There was no significant difference in the duration of menses after three months treatment with danazol 100 mg compared to that at baseline ($p>0.05$). The trial was reported as descriptive data in the Other Data section as the figures were inadequately reported in the paper.

Dysmenorrhoea

The study assessed the outcome of the numbers in each group reporting an improvement in dysmenorrhoea after three months treatment. For this outcome there was no significant difference between the two groups (OR 0.68; 95% CI 0.12, 3.83) (Chimbira 1980a).

Weight gain

The trial comparing danazol 200 mg with danazol 100 mg reported the mean gain in weight for the two groups, danazol 200 mg (mean weight gain 2.3 kg after three months of treatment), danazol 100 mg (mean of 2.1 kg) (Chimbira 1980a). No standard deviations were reported in the trial so a WMD could not be calculated.

DANAZOL 200 mg VERSUS REDUCING DOSE DANAZOL

One small parallel trial compared danazol 200 mg with a reducing dose of danazol for three months treatment. Thirty six women were involved in this comparison. The reducing dose danazol was a regime of danazol 200 mg/day for one month, 100 mg/day the next month and danazol 50 mg/day for the third month.

Menstrual blood loss (objective/subjective)

Mean MBL was measured objectively after three months treatment, and there was no significant difference in mean MBL between the two groups (WMD 33.50; 95% CI -32.38, 99.38) (Higham 1993).

Side effects

The number of women in each intervention group experiencing adverse effects was reported as an outcome measure. For this outcome there was no significant difference between the two groups (OR 1.13, 95% CI 0.14, 9.07) (Higham 1993).

Withdrawals due to side effects

The number of withdrawals due to side effects showed no significant difference between the danazol 200 mg group and the group taking a reducing dose of danazol (OR 0.88, 0.15,5.05) (Higham 1993).

Weight gain

The study comparing danazol 200 mg with a reducing dose of danazol assessed the number of women in each group who had a weight gain of >2kg after three months treatment. There was no significant difference between the two groups on this outcome measure (OR 0.32, 95% CI 0.08, 1.28) (Higham 1993).

Duration of menses

The mean duration of menses for women in the two intervention groups was assessed after three months treatment. The only trial in the meta-analysis showed no significant difference between the two intervention groups (WMD 1.30, 95%CI -0.76, 3.36) (Higham 1993).

Subjective efficacy of intervention

Subjective efficacy was measured as the number of women rating the treatment as highly or moderately effective in each of the intervention groups. There was no significant difference between the two groups after three months of daily treatment (OR 1.18, 95% CI 0.30, 4.73) (Higham 1993).

DISCUSSION

The aim of this review was to assess the effectiveness and tolerability of danazol for the treatment of heavy menstrual bleeding. Despite the fact that danazol has been available for the treatment of menorrhagia for a considerable length of time, there is a general lack of well-designed research to evaluate the effectiveness and tolerability of this therapy. The results of this review are based on a small number of trials which are underpowered and with unclear allocation concealment.

The largest trial had 20 women in each arm. A power calculation for sample size based on a (alpha)=0.05 and b (beta)=0.80 where danazol treatment is compared to either progestogen or NSAID therapy (the most common medical treatments) indicated that at least 30 women in each arm would be required to show an acceptable increase in benefit (30%) in the proportion of women having their menstrual bleeding reverting to normal (<80 mls/cycle). It was not feasible to consider a benefit of treatment in terms of the actual quantity of blood loss, mls/cycle, that women find satisfactory and no data were available to assess satisfaction with treatment. Therefore, where no differences between interventions are reported, it may be that the trials are too small to show any difference.

MENSTRUAL BLOOD LOSS: objective measurement

Danazol was shown to be no more effective than progestogens at reducing MBL by one trial included in the meta-analysis. If response to treatment is defined as reduction of menstrual blood loss to <80 ml/cycle, significantly more women in the danazol group had their MBL reduced to below 80 ml/cycle. Another trial, included as descriptive data, suggested that danazol may be more effective than progestogens at reducing MBL. One limitation of the studies comparing danazol with a progestogen is that in all these studies, the progestogen was given in the luteal phase of the cycle (days 19-26). Progestogens given during the luteal phase of the cycle in women with ovulatory HMB may increase, rather than reduce menstrual blood loss (Preston 1995).

Danazol was shown to be more effective at reducing MBL than mefenamic acid by the one trial included in the meta-analysis and two other trials. Danazol was also shown to be more effective than naproxen at reducing MBL by one small trial included in the meta-analysis. Thus there is consistent evidence that danazol is more effective than NSAIDs in reducing MBL.

Danazol was shown to be more effective at reducing MBL than the oral contraceptive pill by one small trial included as Other Data. The results of one trial included as descriptive data indicate danazol is no more effective than a progestogen releasing IUD in reducing MBL.

On the available evidence, a 200 mg daily danazol regime appears to be no more effective in reducing MBL compared to danazol 100 mg or a reducing dose danazol regimen. There are some limitations to this evidence. The results are based on one trial and small numbers of participants for all comparisons and the data for some comparisons are heavily skewed.

It is possible that the differences found were underestimated. Trials were included in this review if women had a subjective complaint of heavy menstrual bleeding and/or if they had objectively determined heavy menstrual bleeding. In all of the included studies, participants had a subjective complaint of heavy menstrual bleeding and in five studies, women had their MBL objectively measured by the alkaline haematin method. To comply with the definition of objectively defined menorrhagia, trials would have to include only women with MBL>80 ml/cycle. However in one study participants were included if their objectively defined MBL was>50 ml/cycle (Cameron 1987) and another included women with a MBL of >60 ml/cycle. Menorrhagia was correctly defined as objectively determined MBL of >80 ml/cycle in three studies (Dockeray 1989; Dunphy 1998; Higham 1993).

Many women who seek medical help for heavy menstrual bleeding have normal blood loss (Fraser 1984; Haynes 1977) and results from one RCT have suggested that there is little response to therapy in women with MBL <35 ml (Fraser 1981). Since a proportion of the study participants with a complaint of heavy menstrual bleeding may have had normal menstrual blood loss, it is likely that some reported differences between treatment and placebo groups have been underestimated.

MENSTRUAL BLOOD LOSS: subjective measurement

Whilst the alkaline haematin extraction method is the most accurate method for assessment of blood loss and is used as the standard, a woman's own perception of her MBL is important in the evaluation of effectiveness of treatment on MBL. Therefore a woman's subjective assessment is an important outcome measure.

Three studies recorded MBL according to subjective measures. One trial compared danazol 200 mg daily and a placebo and the authors reported that danazol was significantly more effective after two months treatment. Danazol was shown to be significantly more effective than progestogens at reducing MBL by one study which used a pictorial bleeding chart method to assess MBL and by one study which used a bleeding intensity score to assess MBL.

The subjective assessment of MBL is an important outcome measure, as most diagnoses and interventions for heavy menstrual bleeding are based on clinical evidence, in the absence of objectively determined heavy menstrual bleeding. It is therefore important in practice that any intervention results in a significant improvement in the woman's own perceived cyclical loss.

MENSTRUAL BLOOD LOSS AFTER CESSATION OF THERAPY

It has been reported that danazol has a significant 'carry-over' effect and many women have reduced MBL for up to four months

after cessation of therapy (Shaw 1994), suggesting that danazol could be used intermittently. Danazol might be more acceptable in clinical use if it could be effectively used intermittently. There are no studies assessing intermittent danazol use for HMB, but two of the included studies (Dunphy 1998; Lamb 1987) assessed whether danazol has a significant 'carry-over' effect. Lamb (1987) reported that a reduction in blood loss score was maintained for four months after treatment ceased, but insufficient information was provided for these data to be included in the review. This finding was not confirmed in one study which compared danazol with a progestogen, and found there to be no significant carry-over effect of danazol 3 months after treatment was stopped (Dunphy 1998).

As danazol has a rapid and significant effect on increasing haemoglobin and serum ferritin (Chimbira 1979; Ford 1994), it may be valuable in women who need a highly effective short term treatment to stop very heavy bleeding and restore their haemoglobin and iron status to normal. One of the potential short term uses of danazol is to use it intermittently, however there is currently insufficient evidence to assess whether danazol can be effectively used on an intermittent basis.

ADVERSE EVENTS

There were no significant differences in reported adverse effects with danazol 200 mg in comparison with a reducing dose danazol. No data are available for whether women treated with danazol experience more adverse effects than those treated with the oral contraceptive or a progestogen releasing IUD. However, women treated with danazol experienced significantly more adverse effects than those treated with a progestogen and those treated with mefenamic acid.

Danazol has weak androgenic properties, and hence can cause side effects related to this. These side effects spontaneously resolve after cessation of treatment. None of the included trials reported data on numbers experiencing specific adverse events in a suitable form for inclusion in this review, but commonly reported side effects for danazol treatment included acne, weight gain, headache, nausea and tiredness. One study comparing danazol with mefenamic acid, reported that women in the mefenamic acid group experienced mostly gastrointestinal side effects such as nausea/vomiting and diarrhoea, whereas women in the danazol group experienced more serious side effects such as musculoskeletal pains, flushes, behavioural changes, lethargy, and androgenic effects such as acne, breast atrophy, hirsutism and hoarseness (Dockeray 1989).

Women using danazol for heavy menstrual bleeding are likely to require long term treatment, so any adverse events which affect adherence to treatment or treatment safety are particularly important. One study reported that for the women treated with danazol, the side effects of breast atrophy, hirsutism and hoarseness did not develop until the second month of treatment (Dockeray 1989). As the studies included in this review all involved two to three months treatment, data on the side effect profile of danazol for longer term treatment with danazol would be useful. A longer period of treatment would enable the longer term liver effects of danazol to be assessed. These potential liver effects may be an important factor limiting the long term use of danazol and they have not been evaluated by any of the studies.

WEIGHT GAIN

Weight gain is one of the androgenic side effects of danazol which may limit its use (Irvine 1999), and is therefore an important outcome measure. When compared to placebo, the mean weight of the danazol group was significantly greater than that of the placebo group after two months treatment. Three studies assessed weight gain for danazol compared with a progestogen. The mean weight gain of the danazol group was significantly greater than that of the progestogen group. However when weight gain was assessed in terms of the number of women with a weight gain of > 2kg (Higham 1993) and the number of women with a weight gain of >3kg (Bonduelle 1991), there was no significant difference between the two interventions. There was no significant difference in terms of the number of women with weight gain of >2kg when danazol 200mg was compared with a reducing dose of danazol. However assessment of weight gain by a dichotomous outcome may not be sensitive to determine real differences between the groups. One study compared mean weight gain for danazol 200mg versus 100 mg. There appears to be no difference in terms of mean weight gain between these regimens, however there is currently insufficient evidence to answer this question.

WITHDRAWALS DUE TO SIDE EFFECTS

There was no significant difference in withdrawals due to side effects when danazol 200 mg daily was compared to placebo, progestogens or a reducing dose danazol. However, due to the small number of women involved in the studies, there is insufficient evidence to evaluate this outcome adequately. It may be that the numbers are too small to reveal any differences between the groups. The large drop out rates of several trials (five studies had drop out rates of more than 10%) points towards the treatment being unacceptable to women. Some of these may be unreported withdrawals due to side effects.

DYSMENORRHOEA

There was no significant difference between danazol 200 mg/day, NSAIDs and a reducing dose of danazol in terms of the number of women reporting an improvement in dysmenorrhoea. There is insufficient evidence to determine whether there is any difference between danazol and progestogens with regards to improvement in dysmenorrhoea. One study has evaluated this, and the results indicate that progestogens may produce a greater improvement in dysmenorrhoea (Bonduelle 1991).

DURATION OF MENSES

A significant reduction in the duration of menses in favour of danazol is shown for those trials comparing danazol with NSAIDs and a progesterone releasing IUD. The results of one trial indicate that the duration of menses may be shorter after treatment with a 200mg danazol regimen when compared with a 100 mg regimen. Another study showed that the duration of menses is significantly shorter for women treated with a reducing dose of danazol compared to those treated with danazol 200 mg/day. There is no significant difference in the duration of menses when danazol is compared to progestogens. The results from one trial comparing danazol with a progestogen, indicate that danazol may cause substantially more protracted bleeding in some women, whereas this is not the case for norethisterone (Higham 1993). The reason for this is unknown.

EFFICACY OF INTERVENTION

Two studies comparing danazol with a progestogen evaluated subjective efficacy of treatment. One study showed subjective efficacy was significantly greater for danazol, where as the second found no difference between the two interventions.

ACCEPTABILITY OF INTERVENTION

One study comparing danazol and mefenamic acid assessed the acceptability of treatment , and found there was no difference between the two treatments in terms of the number of women unwilling to continue treatment. However, it may be that too few participants were included in the analysis to show any difference between the groups. The study reported that the reason women were unwilling to continue treatment differed between the two groups. For the mefenamic acid group, the reason most women gave for being unwilling to continue treatment was due to a lack of efficacy, whereas for women in the danazol group it was largely due to side effects (Dockeray 1989).

DOSAGE

One of the objectives of this review is to determine the optimum dosage of danazol as a treatment for HMB. Two small trials compared the standard dose of danazol for HMB, 200 mg/day with a lower dose of 100 mg and a reducing dose regimen. No differences in effectiveness or frequency of adverse events were reported, but women treated with 200 mg/day had a shorter duration of menses when compared with a reducing dose regimen. Numbers of women in the trials were insufficient to adequately assess this outcome.

It is important to note that there are no studies comparing danazol with tranexamic acid and the levonorgestrel-releasing intrauterine system (Mirena). These treatments may be as effective as danazol, but an objective comparison has not been carried out.

No study has included changes in quality of life or resource cost as outcome measures. Danazol has a contraceptive effect in doses of above 200 mg/day, however it is not licensed for use as a contraceptive, and therefore women not wishing to conceive require additional contraception. This is particularly important with danazol as it is has a teratogenic effect and there is a risk of masculinisation of a female fetus if exposure to danazol is continued between 8 and 18 weeks of gestation. This means that the acceptability of danazol to women, and quality of life outcomes are very important and they have not been properly addressed by any of the trials.

SUMMARY OF THESE RESULTS IN TERMS OF THE OBJECTIVES

1. Is danazol more effective than placebo in reducing heavy menstrual blood loss?

One small trial assessed this outcome, and danazol appears to be more effective than placebo, but the data are poorly reported.

2. Is danazol more effective than other medical therapies?

Danazol is more effective than progestogens, NSAIDs and the OCP, although the results are imprecise with wide confidence intervals.

3. What is the optimum dosage of danazol?

The standard dose of 200 mg/day of danazol does not appear to differ in effectiveness and frequency of adverse events when compared to 100 mg/day or a reducing regimen. However these results are based on one small trial for each comparison.

4. Does treatment with danazol lead to an improved quality of life for women with HMB?

The included trials only assessed improvement in dysmenorrhoea and there were insufficient data to address this outcome adequately.

5. Do women tolerate treatment with danazol and find it acceptable?

There was an increased frequency of adverse events when danazol was compared with other medical therapies. This did not appear to affect the acceptability of the treatment. However this comparison was only reported by one small study.

AUTHORS' CONCLUSIONS

Implications for practice

The results do not give clear indications for recommending danazol as a treatment for heavy menstrual bleeding. Danazol appears to be an effective treatment for heavy menstrual bleeding when compared to other medical treatments, though it is uncertain whether it is acceptable to women. The use of danazol may be limited by its side effect profile, its acceptability to women and the need for continuing treatment.

Implications for research

Additional well designed RCTs with sufficient power are needed to test the efficacy of danazol compared to other medical therapies. Future trial design needs to include outcomes such as quality of life measures and a longer period of treatment (at least six months) to adequately evaluate adverse events and participant satisfaction. However, there may be difficulties in doing long term research because of the side effects of danazol and the existence of more acceptable alternatives.

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