Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid

John Bonnar, Brian L Sheppard

Abstract

***Objective*—To compare the efficacy and acceptability of ethamsylate, mefenamic acid, and tranexamic acid for treating menorrhagia.**

***Design*—Randomised controlled trial.**

***Setting*—A university department of obstetrics and gynaecology.**

***Subjects*—76 women with dysfunctional uterine bleeding.**

***Interventions*—Treatment for five days from day 1 of menses during three consecutive menstrual periods. 27 patients were randomised to take ethamsylate 500 mg six hourly, 23 patients to take mefenamic acid 500 mg eight hourly, and 26 patients to take tranexamic acid 1 g six hourly.**

***Main outcome measures*—Menstrual loss measured by the alkaline haematin method in three control menstrual periods and three menstrual periods during treatment; duration of bleeding; patient's estimation of blood loss; sanitary towel usage; the occurrence of dysmenorrhoea; and unwanted events.**

***Results*—Ethamsylate did not reduce mean menstrual blood loss whereas mefenamic acid reduced blood loss by 20% (mean blood loss 186 ml before treatment, 148 ml during treatment) and tranexamic acid reduced blood loss by 54% (mean blood loss 164 ml before treatment, 75 ml during treatment). Sanitary towel usage was significantly reduced in patients treated with mefenamic acid and tranexamic acid.**

***Conclusions*—Tranexamic acid given during menstruation is a safe and highly effective treatment for excessive bleeding. Patients with dysfunctional uterine bleeding should be offered medical treatment with tranexamic acid before a decision is made about surgery.**

Trinity College Department of Obstetrics and Gynaecology, Trinity Centre for Health Sciences, St James' Hospital and the Coombe Women's Hospital, Dublin
John Bonnar, *professor and head of department*
Brian L Sheppard, *associate professor of human reproduction*

Correspondence to: Professor John Bonnar, Trinity College Department of Obstetrics and Gynaecology, Trinity Centre for Health Sciences, St James' Hospital, Dublin 8, Ireland.

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Introduction

Excessive menstrual bleeding is a common complaint and in any year around 5% of women in the 30-49 year age range consult their family doctors with this problem.[1] In 1993, 821 700 prescriptions were issued in England and Wales for menorrhagia at a cost of £7.2m.[2] Menorrhagia accounts for 15% of gynaecological referrals and half of the 90 000 hysterectomies performed every year in the United Kingdom.[3] A further 10 000 women are currently treated every year for menorrhagia by endometrial ablation. Most patients complaining of menorrhagia have no detectable pelvic disease and are diagnosed as cases of dysfunctional uterine bleeding.

The mechanisms controlling menstrual bleeding are poorly understood. In the past decade studies have shown increased endometrial fibrinolysis and an alteration in prostaglandin balance as local uterine abnormalities present in dysfunctional uterine bleeding.[4-7] Antifibrinolytic drugs are effective in decreasing excessive menstrual bleeding.[5 8 9] The prostaglandin synthetase inhibitor mefenamic acid[10-12] and the haemostatic ethamsylate[13 14] have also been widely used to control excessive menstrual bleeding. To our knowledge there has been no comparative study of these three treatments. We compared the effects of tranexamic acid (an antifibrinolytic), mefenamic acid, and ethamsylate in a randomised study of women with objective evidence of menorrhagia.

Patients and methods

Patients were aged 35-46 years and complained of regular heavy menstrual bleeding (table 1). Organic causes of menorrhagia were excluded by gynaecological investigation, which included hysteroscopy, endometrial biopsy, and a cervical smear test three to 12 months before entry into the study. We excluded patients with a history of renal or hepatic impairment, previous thromboembolic disease, inflammatory bowel disease, peptic or intestinal ulceration, or coagulation or fibrinolytic disorders.

When planning the study we estimated the number of patients required assuming that the interpatient standard deviation of the difference in average menstrual blood loss before and during treatment would be roughly 50 ml. A test based on normality assumptions with $\alpha = 0.05$ would have a power >0.80 for treatment differences of at least 40 ml if there were at least 26 patients per treatment group. Assuming a 15% drop out frequency after randomisation we estimated the required number of patients in the study as 90, to be recruited at 45 a year.

Over two years 81 patients qualified for treatment out of over 400 who were seen complaining of excessive menstrual bleeding. Of these 81 patients, five withdrew during treatment cycle 1 (two randomised to treatment with mefenamic acid, two to treatment with ethamsylate, and one to treatment with tranexamic acid) and did not provide any follow up data. Seventy six patients were therefore included in an intention to treat analysis of efficacy and safety. Data on these patients were included if they were known to have taken at least one dose of the study drug and if they provided any follow up data for one or more key efficacy variables.

The 76 women with dysfunctional uterine bleeding had a mean menstrual loss greater than 80 ml measured over three consecutive menstrual periods before treatment. They were allocated by a computer generated randomisation list to one of the three treatments taken for five days from day 1 of bleeding during the three subsequent menstrual periods. Twenty seven patients were allocated to receive ethamsylate 500 mg six hourly, 23 patients to receive mefenamic acid 500 mg eight hourly, and 26 patients to receive tranexamic acid 1 g six hourly.

Menstrual blood loss was measured by the alkaline haematin method.[15] The influence of treatment on the

Table 1—*Characteristics of patients in the three drug treatment groups. Values are means (SD)*

	Ethamsylate (n = 27)	Mefenamic acid (n = 23)	Tranexamic acid (n = 26)	Total (n = 76)
Age (years)	37 (8)	38 (8)	40 (5)	39 (7)
Height (cm)	164 (7)	161 (6)	160 (6)	162 (7)
Weight (kg)	64 (9)	66 (12)	66 (10)	65 (10)

duration of bleeding, the patient's estimation of blood loss, the number of sanitary towels used, the occurrence of dysmenorrhoea, and the nature, duration, incidence, and severity of unwanted events were recorded. At the end of the study patient acceptability was assessed by asking, "Would you be prepared to continue with this treatment?" If the patient answered "no" the reasons were recorded.

Patients gave fully informed consent and the study was approved by the hospital ethics committee.

Statistical methods—Paired and unpaired *t* tests were used to compare menstrual blood loss in the three control and three treatment cycles (see fig 1). All final data processing and statistical analyses were carried out with SAS (version 6.06; SAS Institute Inc, Chicago) run on a VAX 6320 computer system and StatXact (version 2.04; CYTEL Software Corporation, Chicago). For each efficacy variable the arithmetic means of the three pretreatment (control) and three treatment periods were calculated. Quantitative efficacy variables were analysed by fitting a linear model with treatment as a factor with the three levels (tranexamic acid, mefenamic acid, and ethamsylate). Logarithmic transformation was carried out when appropriate. Comparisons were bases on an *F* distribution and if the overall *F* test result was significant tests for differences between treatment groups were carried out.

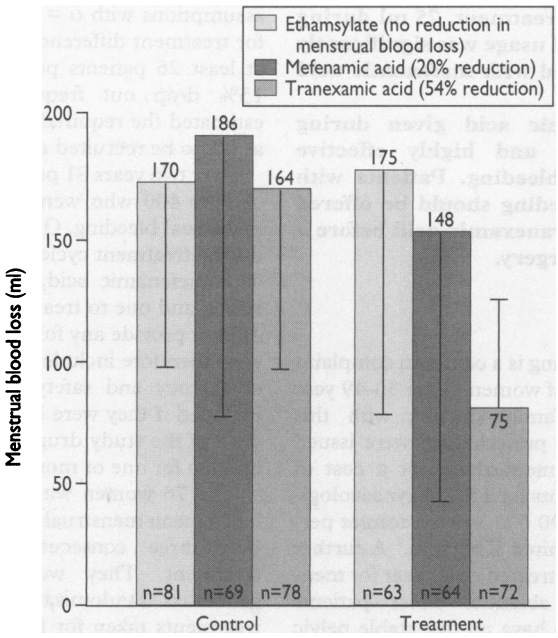

Fig 1—*Mean menstrual blood loss of 27 patients during three pretreatment (control) cycles and three cycles during treatment with ethamsylate, 23 patients during three pretreatment cycles and three cycles during treatment with mefenamic acid, and 26 patients during three pretreatment cycles and three cycles during treatment with tranexamic acid. Bars are SD*

Table 2—*Effect of the three drugs on duration of bleeding, sanitary towel usage, and patient's assessment of menstrual blood loss and dysmenorrhoea. Except where stated otherwise values are numbers (percentages) of patients*

	Ethamsylate (n = 27)	Mefenamic acid (n = 23)	Tranexamic acid (n = 26)
Menstrual blood loss:			
Less	12 (44)	13 (57)	18 (69)
Same	5 (19)	5 (22)	4 (15)
Greater	8 (30)	4 (17)	4 (15)
Dysmenorrhoea:			
Better	1 (4)	3 (13)	5 (19)
Same	19 (70)	11 (48)	14 (54)
Worse	4 (15)	8 (35)	7 (27)
Mean duration (days) (SD):			
Control	5.7 (1.1)	5.8 (1.3)	5.5 (1.4)
Treatment	5.7 (2.0)	5.3 (1.3)	4.9 (1.8)
Mean No of sanitary towels (SD):			
Control	25 (9.0)	25 (7.0)	23 (7.0)
Treatment	25 (9.0)	23 (9.0)*	20 (6.0)**

*P<0.05. **P<0.01.

Results

EFFECT ON MENSTRUAL LOSS

Figure 1 shows the effects of treatment on menstrual blood loss. Treatment of 27 patients with ethamsylate during three menstrual periods had no effect on blood loss. Mean blood loss during the three control menstrual periods ranged from 157 to 185 ml and during the three treated menstrual periods from 161 to 185 ml. In 23 patients treated with mefenamic acid the mean menstrual loss in the control cycles ranged from 159 to 199 ml and in the three treatment cycles from 138 to 168 ml. In 26 patients treated with tranexamic acid the mean menstrual loss during the three control cycles ranged from 143 to 178 ml; during treatment the mean loss fell to 72-75 ml (fig 1).

Figure 2 compares the mean menstrual blood loss during the three control and three treatment cycles. Ethamsylate had no effect on reducing blood loss, mefenamic acid reduced blood loss by 20% (P<0.001), and tranexamic acid reduced blood loss by 54% (P<0.001). The change in mean blood loss between the control and treatment cycles consisted of an increase of 8 ml (range 280 to 103 ml) with ethamsylate, a decrease of 43 ml (range 82 to 179 ml) with mefenamic acid, and a decrease of 89 ml (range 24 to 214 ml) with tranexamic acid. Comparing the results of treatment on absolute changes in blood loss showed that tranexamic acid reduced the mean loss by 97 ml more than with ethamsylate (95% confidence interval 140 to 54 ml; P<0.001) and by 56 ml more than with mefenamic acid (90 to 2 ml; P<0.05) whereas mefenamic acid reduced blood loss by 51 ml more than with ethamsylate (-96 to -6 ml; P<0.05).

DURATION OF BLEEDING AND SANITARY TOWEL USAGE

There was no difference between the treatments in the duration of menstrual bleeding (table 2). Patients treated with ethamsylate used the same number of sanitary towels as in the control cycles. A significant reduction in the number of sanitary towels used was found in patients treated with mefenamic acid (P<0.05) and tranexamic acid (P<0.01).

PATIENT ASSESSMENT OF BLOOD LOSS AND DYSMENORRHOEA

The women were asked whether their menstrual blood loss during treatment was less, the same, or greater. Twelve (44%) taking ethamsylate, 13 (57%)

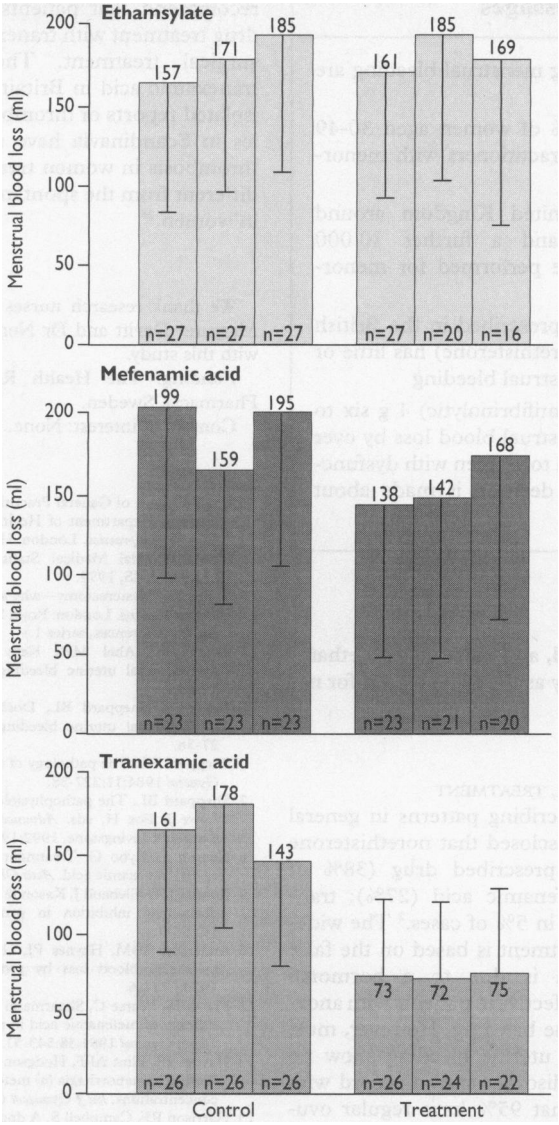

Fig 2—*Mean menstrual blood loss during three control and three treatment cycles in patients treated with ethamsylate (no reduction in blood loss), mefenamic acid (20% reduction in blood loss), and tranexamic acid (54% reduction in blood loss). Bars are SD*

taking mefenamic acid, and 18 (69%) taking tranexamic acid thought their menstrual loss was less. Eight (30%) patients taking ethamsylate thought their menstrual loss was greater during treatment (table 2).

An improvement in dysmenorrhoea was reported by one (4%) patient in the ethamsylate group, three (13%) patients in the mefenamic acid group, and five (19%) patients in the tranexamic acid group. There was no change in dysmenorrhoea in 19 (70%) patients in the ethamsylate group, 11 (48%) in the mefenamic acid group, and 14 (54%) in the tranexamic acid group (table 2).

PATIENT CONTINUATION OF TREATMENT

Eighteen women stopped treatment during the study—11 of the 27 taking ethamsylate, three of the 23 taking mefenamic acid, and four of the 26 taking tranexamic acid. Eleven of the 18 patients withdrew after the first cycle of treatment. Poor efficacy was given as the reason for withdrawal by five women taking ethamsylate and one woman taking mefenamic acid. Four other women taking ethamsylate, one of three taking mefenamic acid, and three of five taking tranexamic acid described an unwanted event such as nausea, headache, and dizziness as the reason for withdrawing from treatment.

PATIENT ACCEPTABILITY OF TREATMENT

At the end of the study 17 (74%) patients taking mefenamic acid and 20 (77%) taking tranexamic acid wished to continue the treatment. By contrast, 18 (67%) patients taking ethamsylate did not wish to continue. Poor efficacy was given as the reason for not continuing by nine of the 18 patients taking ethamsylate, four of six taking mefenamic acid, and two of six taking tranexamic acid. Nausea, headache, and dizziness were reported by another eight women not wishing to continue treatment—five taking ethamsylate, one taking mefenamic acid, and two taking tranexamic acid.

Discussion

EFFECT OF TREATMENT ON MENSTRUAL BLOOD LOSS

In women with objective evidence of menorrhagia we have shown a significant reduction of menstrual blood loss with mefenamic acid (20%) and tranexamic acid (54%) but no effect with ethamsylate. Treatment with tranexamic acid during menstruation had the highest patient acceptance and reduced the mean menstrual blood loss to 75 ml. The 20% reduction in blood loss with mefenamic acid was less than adequate in our patients, the mean menstrual loss during treatment being 148 ml—that is, over three times normal.[16] Our failure to show a reduction of the mean blood loss in patients treated with ethamsylate is even more surprising, as five patients withdrew from the study during the treatment phase because of poor efficacy.

Few comparative studies have been undertaken on the medical treatment of menorrhagia using objective measurement of menstrual blood loss. In a previous study we found that mefenamic acid reduced the mean menstrual loss by 20% compared with 60% with danazol over two consecutive menstrual periods; adverse side effects were significantly more common with danazol (75% of patients) than with mefenamic acid (30%).[17] The percentage reduction in menstrual blood loss reported with mefenamic acid is usually in the range 20-35%,[11 18 19] though reductions of up to 46% have been reported.[20]

The reduction in menstrual blood loss during treatment with mefenamic acid and tranexamic acid was associated with a significant decrease in the number of sanitary towels used but the duration of bleeding was not affected. A previous study of ethamsylate recorded a significant reduction in the number of tampons and duration of bleeding[21] but we found no effect of ethamsylate on these variables.

PATIENT ACCEPTABILITY

The frequency of unwanted events was slightly increased during treatment. Many such events reported during treatment for menorrhagia are symptoms arising during menstruation and may not be related to the treatment. The frequency of nausea, however, was increased with tranexamic acid and mefenamic acid. Other workers have reported up to 30% of patients experiencing headache and gastrointestinal disturbance with mefenamic acid[17] and tranexamic acid.[8] An important part of any treatment evaluation is patient acceptability. Patient satisfaction as shown by willingness to continue treatment after the study was high for both tranexamic acid (77%) and mefenamic acid (74%) and low in patients taking ethamsylate (33%). Patients

Key messages

- Mechanisms controlling menstrual bleeding are poorly understood
- In any year around 5% of women aged 30-49 years visit their general practitioners with menorrhagia
- Every year in the United Kingdom around 45 000 hysterectomies and a further 10 000 endometrial ablations are performed for menorrhagia
- The commonest drug prescribed in the British Isles for menorrhagia (norethisterone) has little or no effect in reducing menstrual bleeding
- Tranexamic acid (an antifibrinolytic) 1 g six to eight hourly reduces menstrual blood loss by over half and should be offered to women with dysfunctional bleeding before a decision is made about surgery

treated with mefenamic acid, and more so with ethamsylate, reported poor efficacy as the main reason for not continuing.

COMPARISON WITH HORMONAL TREATMENT

A recent analysis of prescribing patterns in general practice for menorrhagia disclosed that norethisterone was the most commonly prescribed drug (38% of patients), followed by mefenamic acid (27%); tranexamic acid was prescribed in 5% of cases.[2] The widespread use of hormone treatment is based on the false premise that menorrhagia is due to a hormonal imbalance. Progestogen is effective in patients with anovulatory dysfunctional uterine bleeding. However, most women with dysfunctional uterine bleeding show no evidence of any hormonal disorder and in accord with other studies[22 23] we find that 95% have regular ovulatory cycles. A report on treating objectively proved menorrhagia with norethisterone showed no significant reduction of menstrual loss.[24] Another study of norethisterone showed a decrease of 10-15% in menstrual bleeding compared with a 30% reduction with mefenamic acid.[18] In a recent comparative study of ovulatory menorrhagia tranexamic acid reduced the mean menstrual blood loss by 45% and norethisterone increased mean blood loss by 20%.[25]

Prescribing ineffective medical treatment for excessive menstrual bleeding seems to be widespread. This must contribute to the large number of patients having hysterectomy for menorrhagia in the United Kingdom on the indication of failed medical treatment. In Scandinavia, where tranexamic acid is the most widely used drug for menorrhagia, the hysterectomy rate is less than half that in the United Kingdom.

Conclusion

Over 90% of menstrual blood loss occurs during the first three days of menstruation both in normal menstruation and in menorrhagia.[22 23] Treatment to reduce menstrual blood loss will have maximal effect if given during these three days. Tranexamic acid 1 g every six to eight hours during these three days would reduce menstrual blood loss by over half and return menstrual bleeding to normal for most women. We recommend that patients should be offered effective drug treatment with tranexamic acid before deciding on surgical treatment. The reluctance to prescribe tranexamic acid in Britain may be partly due to a few isolated reports of thromboembolism. Large scale studies in Scandinavia have shown that the incidence of thrombosis in women treated by tranexamic acid is no different from the spontaneous incidence of thrombosis in women.[26]

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1 Royal College of General Practitioners, Office of Population Censuses and Surveys, Department of Health and Social Security. *Morbidity statistics from general practice.* London: HMSO, 1986.
2 Intercontinental Medical Statistics Ltd. *United Kingdom and Ireland.* London: IMS, 1994.
3 Smith SK. Hysterectomy—why and when? In: Smith SK, ed. *Dysfunctional uterine bleeding.* London: Royal Society of Medicine Press, 1994:107. (Key paper conferences, series 1.)
4 Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandins and dysfunctional uterine bleeding. *Research and Clinical Forums* 1983;**5**: 39-43.
5 Bonnar J, Sheppard BL, Dockeray CJ. The haemostatic system and dysfunctional uterine bleeding. *Research and Clinical Forums* 1983;**5**: 27-36.
6 Sheppard BL. The pathology of dysfunctional uterine bleeding. *Clin Obstet Gynecol* 1984;**11**:227-38.
7 Sheppard BL. The pathophysiology of dysfunctional uterine bleeding. In: Lowe J, Fox H, eds. *Advances in gynaecological pathology.* Edinburgh: Churchill Livingstone, 1992:191-206.
8 Nilsson L, Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid. *Acta Obstet Gynecol Scand* 1967;**46**:572-80.
9 Bonnar J, Guillebaud J, Kasonde JM, Sheppard BL. Clinical applications of fibrinolytic inhibition in gynaecology. *J Clin Pathol* 1980;**33**(suppl 14):55-9.
10 Anderson ABM, Haynes PJ, Guillebaud J, Turnbull AC. Reduction in menstrual blood loss by prostaglandin synthetase inhibitors. *Lancet* 1976;i:774-6.
11 Fraser IS, Pearse C, Shearmann RP, Elliott PM, McIpveen J, Mokham R. Efficacy of mefenamic acid in patients with a complaint of menorrhagia. *Obstet Gynecol* 1981;**58**:543-51.
12 Haynes PJ, Flint APF, Hodgson H, Anderson BM, Fray F, Turnbull AC. Studies in menorrhagia (a) mefenamic acid (b) endometrial prostaglandin concentrations. *Int J Gynaecol Obstet* 1980;**17**:567-72.
13 Harrison RF, Campbell S. A double-blind trial of ethamsylate in the treatment of primary and intra-uterine device menorrhagia. *Lancet* 1976;i:283-5.
14 Chamberlain G, Freeman R, Price F, Kennedy A, Green D, Eve L. A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. *Br J Obstet Gynaecol* 1991;**98**: 707-10.
15 Hallberg L, Nilsson L. Determination of menstrual blood loss. *Scand J Clin Lab Invest* 1964;**16**:244-8.
16 Hallberg L, Hogdahl A, Nilsson L, Rybo G. Menstrual blood loss—a population study. *Acta Obstet Gynecol Scand* 1966;**45**:320-51.
17 Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. *Br J Obstet Gynaecol* 1989;**96**:840-4.
18 Cameron IT, Haining R, Linsden M-A, Thomas VR, Smith SK. The effects of mefenamic acid and norethisterone on measured menstrual blood loss. *Obstet Gynecol* 1990;**76**:85-8.
19 Anderson ABM, Hagnes PJ, Guillebaud J, Turnbull AC. Reduction of menstrual blood loss by prostaglandin synthetase inhibitors. *Lancet* 1976;i:774-6.
20 Hall P, MacLachlin N, Thorn N. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. *Br J Obstet Gynaecol* 1987;**94**:554-8.
21 Jaffe G, Wickham A. A double-blind pilot study of Dicynene in the control of menorrhagia. *J Int Med Res* 1973;**1**:127-9.
22 Haynes PJ, Anderson ABM, Turnbull AC. Patterns of menstrual blood loss in menorrhagia. *Research and Clinical Forms* 1979;**1**:73-8.
23 Haynes PJ, Hodgson H, Anderson ABM, Turnbull AC. Measurement of menstrual blood loss in patients complaining of menorrhagia. *Br J Obstet Gynaecol* 1977;**84**:763-8.
24 Cameron IT, Leusk R, Kelly RW, Baird DT. The effect of danazol, mefenamic acid, norethisterone and a progesterone impregnated coil on endometrial prostaglandin levels in women with menorrhagia. *Prostaglandins* 1988;**34**:99-110.
25 Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995;**102**:401-6.
26 Rybo G. Tranexamic acid therapy is effective treatment in heavy menstrual bleeding. *Clinical Update on Safety Therapeutic Advances* 1991;**4**:1-8.

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