Fortnightly review

Management of abnormal bleeding in women receiving hormone replacement therapy

C P Spencer, A J Cooper, M I Whitehead

Hormone replacement therapy relieves climacteric symptoms and reduces the risk of cardiovascular disease and osteoporosis. Less than 10% of postmenopausal women, however, have ever taken hormone replacement therapy.¹ Studies report a high degree of non-compliance, with about 70% of women stopping hormone replacement therapy after a year.² One of the main reasons for non-compliance is vaginal bleeding, which occurs in 30-80% of women who stop treatment.^{3 4}

Postmenopausal women who still have a uterus are given progestogens to protect the endometrium.^{5 6} Table 1 shows the types and doses of oral progestogens in current use. Progestogens can be administered sequentially for at least 10-12 days of each 28 day treatment cycle or calendar month. Sequential regimens are prescribed to perimenopausal and early postmenopausal women with intermittent and unpredictable ovarian function. About 85% of women receiving such sequential progestogen will experience withdrawal bleeding towards the end of, or immediately after, the progestogen phase (when the progestogen is added). Most women taking sequential therapy continue to bleed each month for as long as hormone replacement therapy is prescribed; a minority (often older women) develop amenorrhoea.

To overcome the re-establishment of vaginal bleeding, progestogens are increasingly being administered continuously in combination with the oestrogen. The aim is to achieve amenorrhoea by rendering the endometrium atrophic.⁷ It is hoped that women who have been postmenopausal for many years and are used to not bleeding regularly will accept continuous combined therapies more readily than sequential ones. In some women additional factors may need to be

Summary points

Up to 80% of causes of non-compliance with hormone replacement therapy are related to bleeding

Uterine pathology is responsible for up to 30% of cases of abnormal bleeding associated with hormone replacement therapy

Perimenopausal women should be advised to take sequential hormone replacement therapy regimens rather than continuous combined therapies to minimise breakthrough bleeding from erratic endogenous ovarian activity

Postmenopausal women starting "bleed free" hormone replacement therapy regimens should be counselled about erratic bleeding during the first few months of treatment

Abnormal bleeding associated with continuous combined therapy that persists for more than six months and that continues after treatment is withdrawn should be investigated with ultrasound scanning or hysteroscopy, or both

Menopause Clinic, King's College Hospital, London SE5 9RS

C P Spencer, research fellow

A J Cooper, research fellow

M I Whitehead, consultant gynaecologist

Correspondence to: Dr Spencer.

BMJ 1997;315:37-42

Table 1 Progestogens in current use with hormone replacement therapy

	Dose range (daily)
C19 androgenic progestogens (nortestosterone derived)	
Norethisterone acetate (Micronor, Noriday, Micronor HRT, Primolut N)	0.7-2.5 mg
Norgestrel (Neogest)	75-150 µm
C21 non-androgenic progestogens (progesterone derived)	
Medroxyprogesterone acetate (Provera)	5-10 mg
Dydrogesterone (Duphaston)	10-20 mg

considered: there are no data to show that continuous combined hormone replacement therapy reduces the risk of heart disease, so that sequential regimens are advised in women with cardiovascular risk factors such as a family history, hypertension, established coronary heart disease, and hypercholesterolaemia.

Methods

We performed a Medline search for all papers about causes and management of abnormal bleeding associated with hormone replacement therapy between 1966 and 1996. We identified eight papers, and table 2 summarises their content and limitations.

MIW coauthored two of these papers, in which a classification of causes of bleeding and an approach to investigation were proposed.^{10 11} Because of developments in hormone replacement therapy, both now

Table 2 Papers published on abnormal bleeding associated with hormone replacement therapy

Paper	Content	Limitations
Thornycroft 1995 ⁸	Types of hormone replacement therapy available Investigations of abnormal bleeding	No information on causes of abnormal bleeding
Sporrong et al 1992 ⁹	Determination of volume of blood loss during use of hormone replacement therapy as measured by alkaline haematin method compared to subjective method	
Marsh et al 1993 ¹⁰	Comprehensive list of causes and management of abnormal bleeding during hormone replacement therapy	Indications for endometrial biopsy in women taking "bleed free" hormone replacement therapy need updating
Marsh et al 1992 ¹¹	Types of hormone replacement therapy and side effects Causes of abnormal bleeding during hormone replacement therapy	Limited information about investigations
Akkad et al 1995 ¹²	Hysteroscopic study of organic causes of abnormal bleeding during hormone replacement therapy in 106 women	
Udoff et al 1995 ¹³	A meta-analysis of studies examining incidence of bleeding in women taking continuous combined hormone replacement therapy	No information on causes or management of bleeding
Evans et al 1995 ¹⁴	Brief information on management of abnormal bleeding during hormone replacement therapy	No information on causes of bleeding
Rosenfeld 1994 ¹⁵	Incidence of bleeding during continuous combined hormone replacement therapy Information on management of bleeding problems	

need updating, and this article provides a revised classification of causes of abnormal bleeding and guidelines on their investigation and treatment.

Patterns of abnormal bleeding

Bleeding associated with sequential hormone replacement therapy

There are two types of abnormal bleeding. The first is characterised by heavy or prolonged bleeding at the appropriate time of the cycle (that is, towards the end of, or immediately after, the progestogen phase). The second type of abnormal bleeding is breakthrough bleeding that occurs at any other time.

Bleeding associated with continuous combined hormone replacement therapy

In theory bleeding should not occur during continuous combined therapy or with gonadomimetic drugs such as tibolone. In practice, however, about 40% of postmenopausal women starting continuous, combined oestrogen and progestogen regimens will experience bleeding during the first four to six months of treatment. Some women may bleed for between seven and 18 months after the start of hormone replacement therapy. One in 10 women taking tibolone will bleed for the first four to six months of treatment.¹⁶ Such bleeding is usually light. Amenorrhoea is more likely if treatment is not started until at least 12 months after the menopause¹⁷ so that endogenous ovarian function has diminished.

Valid interpretation of any study of bleeding patterns with continuous combined therapies depends on two analyses that are often overlooked. The first involves the way in which the proportion of women achieving amenorrhoea is presented. If this is expressed only as a percentage of those remaining in a study it is possible to obtain rates of 90-95% over a period of 12-18 months.¹⁸ However, when the number achieving amenorrhoea is expressed as a percentage of those starting the study, this figure is reduced to 40-55%.^{17 19} The main reasons for discontinuation are chronic bleeding and side effects from continuous administration of the progestogen. A recent meta-analysis of continuous combined therapies shows that, after six months of treatment, 62-100% of women who

continued taking treatment became amenorrhoeic irrespective of the therapy used.¹³ Importantly, these studies reported drop out rates of up to 65%, which are similar to those from sequential therapies.^{3 4}

The second analysis that is of most use to clinicians is the predictive value of amenorrhoea after a particular duration of therapy. One of the few studies addressing this issue showed that women who were amenorrhoeic after six months of therapy had a 90% chance of remaining amenorrhoeic during the rest of the 12 month trial. Only 40-50% of those women still bleeding after six to eight months of treatment eventually achieved amenorrhoea at 12 months.¹⁹ Other authors have reported similarly.¹⁷

There are no accepted criteria for "abnormal" bleeding with continuous combined therapies. In theory any bleeding with a treatment designed to induce amenorrhoea could be considered abnormal. In practice the ideal of immediate and universal amenorrhoea has not been achieved. Some data are available from placebo controlled studies on which to base clinical guidelines. In postmenopausal women (at least 12 months beyond their last menstrual period) tibolone (Livial) did not seem to cause endometrial stimulation, and the incidence of bleeding was no higher than that with placebo.¹⁶

Interim data for a study of continuous treatment with conjugated equine oestrogens and medroxyprogesterone acetate (Premique) showed that the drop out rate at 12 months was just under 50%.¹⁹ The current recommendation for this preparation is that follow up examinations are performed every six to 12 months, with all patients being monitored annually for symptoms of endometrial abnormality (Premique data sheet).

We are still waiting for long term data from a large multicentre study in Britain of oestradiol with progestogen (Kliofem): however, according to the manufacturers, after three months of therapy over 80% of women experienced amenorrhoea or light spotting (Kliofem Product Monograph, Novo Nordisk, Crawley, 1996). This monograph also advises that further investigations of bleeding are not necessary provided that it subsides completely within three weeks of stopping treatment.

With any “no bleed” therapy, endometrial assessment should be considered if light bleeding continues after the first six months of treatment or if bleeding recurs after amenorrhoea has been established and there is no obvious explanation for the bleeding.

Causes of abnormal bleeding

There are no data on what are the most common causes of abnormal bleeding. Attempts to quantify poor compliance are fraught with difficulty since patients may dissemble or be confused by the instructions on the drug packaging.

Poor compliance

This may be due to any failure to take progestogen or oestrogen therapy correctly. If hormone replacement therapy causes side effects poor compliance is more likely. This seems to be more common with the progestogen, and this component of treatment may be omitted unless included in a single tablet preparation. Women who miss taking progestogen may bleed irregularly and, if the omission of progestogen is chronic, have an increased risk of developing endometrial hyperplasia and carcinoma. This risk persists for at least 15 years after stopping unopposed oestrogen therapy,²⁰ and such women should be considered for gynaecological review if abnormal bleeding occurs after hormone replacement therapy has been discontinued.

Poor gastrointestinal absorption

In theory bowel disorders such as gastroenteritis, malabsorption syndromes (such as coeliac disease, Whipple's disease, etc), and inflammatory bowel disorders (such as ulcerative colitis, Crohn's disease, etc) may all affect the absorption of oral oestrogen and progestogen and could lead to abnormal bleeding. In such patients oestrogens can be administered via the percutaneous, transdermal, or subcutaneous route, and progestogens can be administered transdermally, rectally, vaginally, or intrauterine.

Failure to synchronise endogenous ovarian activity with exogenous hormone treatment

This problem occurs almost exclusively in premenopausal and perimenopausal women. In premenopausal women with a regular 28 day cycle it is important to start administration of progestogens on day 17 of the cycle (counting the first day of normal bleeding with the period as day 1) to coincide with endogenous production of progesterone. In patients with a 20 day cycle the progestogen is added from day 8 to day 19, in those with a 42 day cycle it is added from day 30 to day 41, and so on. Failure to do so will result in patients bleeding twice during the month—one bleed will be due to ovarian function and the second to exogenous administration of hormone.

Perimenopausal women may bleed erratically because their own ovarian function is intermittent and unpredictable. All forms of sequential oestrogen and progestogen hormone replacement therapy are then associated with irregular bleeding. In such patients the combined oral contraceptive should be considered if there are no contraindications. Unlike hormone replacement therapy, the combined oral contraceptive

Table 3 Gynaecological disorders that may cause abnormal bleeding in association with hormone replacement therapy

Site	Pathology
Uterus	Submucous fibroids, endometrial polyps, endometrial hyperplasia (simple, complex, focal, or atypical), adenomyosis, endometritis, adenocarcinoma, sarcoma
Cervix	Polyps, erosions, carcinoma
Ovary	Oestrogen-secreting tumours
Vagina and vulva	Atrophic vaginitis, vaginal intraepithelial neoplasia, primary and secondary neoplasms, advanced vulval carcinoma

also suppresses ovarian function and thus gives good control of the cycle in perimenopausal women with an erratic cycle.

Gynaecological disorders

These include uterine, ovarian, cervical, vaginal, and vulval pathologies (see table 3). Uterine abnormalities may be responsible for up to 27% of cases of abnormal bleeding with hormone replacement therapy¹²; they include, in order of prevalence, submucous fibroids, endometrial polyps, and endometrial hyperplasia. Adenomyosis may cause menorrhagia with hormone replacement therapy and is usually confirmed only after hysterectomy or endometrial resection, when pathological examination allows the diagnosis to be confirmed.

Previous oestrogen implant therapy

Oestradiol implants can continue to release oestradiol for up to three and a half years after insertion.²¹ Because such implants can produce higher concentrations of oestradiol in the plasma than tablets or patches the risk of endometrial hyperplasia may well be increased if the progestogen is not taken properly. This may explain why one study reported a 55% incidence of endometrial hyperplasia with oestrogen implant therapy.²² Furthermore, higher doses of progestogens may be required to ensure adequate endometrial protection. Patients should be advised to continue to take the progestogen for 10-12 days per calendar month until amenorrhoea has been achieved for three consecutive months. Only then is further endometrial stimulation by the implant unlikely.

Drug interactions

In theory antibiotics, particularly broad spectrum drugs, may cause abnormal bleeding because of intestinal hurry and altered bacterial gut flora affecting absorption of oral oestrogen and progestogen.

Enzyme inducers such as griseofulvin, rifampicin, barbiturates, phenytoin, carbamazepine, and primidone all affect oestrogen metabolism and may, in theory, cause irregular bleeding. In clinical practice, however, patients often become amenorrhoeic while taking these drugs, presumably because of enhanced oestrogen metabolism. This will often lead to a higher dose of oestrogen being needed to alleviate symptoms.

Coagulation defects

These include thrombocytopenia, von Willebrand's disease, and the leukaemias. Warfarin or high dose aspirin therapy also affect the clotting mechanisms and, depending on the severity, may be associated with heavy bleeding.

Important questions to ask patients about abnormal bleeding during hormone replacement therapy

- When does bleeding occur with respect to the oestrogen and the progestogen phase?
- How long does the bleeding last and how heavy is it?
- Was there a period of amenorrhoea before hormone replacement therapy was started?
- Is there a problem that suggests poor compliance (such as progestogens causing premenstrual tension, incorrect administration of drug, poor adherence of skin patches)?
- Has there been any concomitant drug treatment?

Bleeding from an “unstable” or “atrophic” endometrium

This is seen almost exclusively in patients taking continuous combined hormone replacement therapy and is the commonest cause of abnormal bleeding on such treatment. It cannot be identified by ultrasound examination, but the diagnosis is made by excluding other pathologies and by typical hysteroscopic features.

Concomitant use of tamoxifen

Treatment with tamoxifen is associated with an increased risk of endometrial carcinoma and development of polyps.²³⁻²⁷ Ultrasound examination of the endometrium in patients taking tamoxifen often shows irregular thickening of the endometrium with cystic spaces and sometimes fluid in the endometrial cavity.²⁸⁻²⁹ Currently, there is no established correlation between endometrial histology and ultrasonic findings. Consequently, for patients who are taking or who have taken tamoxifen, a hysteroscopy or ultrasound scan with saline infusion is advised if these women experience any degree of abnormal bleeding while taking hormone replacement therapy.

Assessing abnormal bleeding associated with hormone replacement therapy

The box lists important questions that should be asked when taking a patient's history. With sequential therapies, women who experience bleeding too early during the phase of progestogen treatment may benefit from an increased dose of progestogen. Completely erratic bleeding suggests the presence of a submucous fibroid, endometrial polyp, or carcinoma. The first two may be missed at dilatation and curettage, and hysteroscopy can be an invaluable diagnostic tool. Postcoital bleeding suggests the presence of cervical pathology, and a careful speculum examination, including the taking of a cervical smear, should be performed. Atrophic vaginitis is usually obvious on direct inspection of the vaginal walls, when contact bleeding with the Cusco's speculum may occur.

Investigations

Three types of specialised investigation are commonly used if more obvious causes for the abnormal bleeding, such as poor compliance, have been confidently excluded.

Outpatient endometrial biopsy

This should be considered in women taking sequential therapies if any of the following criteria are met:

- Heavy withdrawal bleeding
- Prolonged withdrawal bleeding
- Breakthrough bleeding during two or more cycles.

Heavy or prolonged bleeding is bleeding that is heavier or more prolonged than that experienced premenopausally, or which is heavier or more prolonged than that experienced when the patient first started hormone replacement therapy. Thus, changes in the bleeding pattern during hormone replacement therapy may be important.

Most endometrial biopsies can be performed on an outpatient basis. The two commonly used methods are the Pipelle and the Vabra aspiration biopsy. The sampling error of the Pipelle is greater than that of the Vabra,³⁰ but the Vabra procedure causes more discomfort.³¹ It is preferable to obtain the endometrial specimen during the oestrogen and progestogen phase of the cycle because it is easier to differentiate between hyperplastic and secretory phase endometrium. Additionally, the degree of secretory change can also be ascertained, which may help in future management with respect to altering the dose of progestogen or the duration of administration.

These methods have limitations. Both are “blind” procedures, and thus not all of the endometrium will be sampled. About 4% and 42% of the endometrium is sampled by the Pipelle and Vabra devices respectively.³⁰ Additionally, endometrial polyps may be missed. Identical limitations apply to formal dilatation and curettage performed under a general anaesthetic. Thus, if an adequate outpatient biopsy has been performed yet abnormal bleeding continues with a sequential hormone replacement therapy, hysteroscopic assessment should also be considered. The value of both outpatient and inpatient endometrial biopsy has yet to be established with continuous combined hormone replacement therapy.

Ultrasound scanning

Ultrasound examination is used to assess endometrial thickness, endometrial and myometrial homogeneity or heterogeneity, and abnormalities of endometrial morphology. Measurements of endometrial thickness are of most value in patients taking continuous combined therapies, in whom the endometrial thickness (double measurement) is often less than 5 mm because the endometrium is atrophic. A measurement greater than 5 mm or irregularities in endometrial morphology whereby one area is thicker than another suggests the need for biopsy or hysteroscopy. Measurements of endometrial thickness are of much less value with sequential therapies.

Ultrasound scanning can be used to diagnose submucous fibroids and endometrial polyps. Both may be demonstrated more easily if saline is infused into the endometrial cavity at the same time (saline infusion sonography).³²⁻³⁴ Figures 1 and 2 show the appearances of an endometrial polyp and submucous fibroid respectively with saline infusion sonography.

Hysteroscopy

This represents the optimal endometrial assessment because the whole surface of the endometrium can be

Fig 1 Endometrial polyp as seen with sonohysterography

visualised,^{35, 36} and the technique is useful with both sequential and continuous combined hormone replacement therapy. It can detect small polyps or submucous fibroids that have been missed by endometrial biopsy procedures, dilatation and curettage, or ultrasound investigations.

Treating abnormal bleeding associated with hormone replacement therapy

Any underlying cause should be treated—for example, polyps need to be surgically removed.

Absence of secretory transformation in patients taking sequential therapy

In this condition an endometrial biopsy taken during the progestogen phase of treatment fails to show secretory activity. The current dose of progestogen should be increased and the patient reviewed with a menstrual calendar three months later.

Submucous fibroids

These may have been diagnosed by ultrasound scanning or hysteroscopy. Because they are “oestrogen

dependent,” the lowest dose of oestrogen required for the abolition of menopausal symptoms or for bone preservation should be prescribed. If the fibroids enlarge and the patient wishes to continue taking hormone replacement therapy then surgical treatment is warranted. This may take the form of hysterectomy or minimally invasive surgery.³⁷⁻³⁹

Abnormal bleeding with no obvious cause during sequential therapy

In a minority of women who have abnormal bleeding while taking sequential hormone replacement therapy no organic pathology can be found despite appropriate and thorough investigation. In perimenopausal and early postmenopausal women intermittent ovarian activity may be responsible. The problem is self limiting as ovarian function will eventually fail completely. Poor compliance may be reduced by a thorough explanation of why and how to take both the oestrogen and progestogen; the use of a preparation containing both hormones in a single tablet may be helpful. Alternatively, changing the type of progestogen (see table 1) may improve compliance. If all progestogens cause side effects then the levonorgestrel-containing intrauterine contraceptive (Mirena) may be useful, though it is not currently licensed for this type of use.

Bleeding from an “unstable” endometrium in patients taking continuous combined therapy

In the absence of any pathology, bleeding that continues after six months of continuous combined therapy usually comes from an atrophic endometrium. It may be more common in patients who switch directly from sequential combined hormone replacement therapy to continuous combined treatment as compared with previously untreated patients. Thus, a 28 day break of all hormone replacement therapy (“wash out” period) between treatments is often recommended, though this strategy has not been evaluated. Alternatives include increasing the oestrogen dose, the progestogen dose, or using sequential hormone replacement therapy.

Conclusions

Abnormal bleeding reduces compliance with both sequential and continuous combined hormone replacement therapies. There are many different causes, but the most important seem to be intrauterine structural abnormalities such as submucous fibroids and endometrial polyps. Women taking continuous combined therapies may have chronic, erratic bleeding during the first four to six months of treatment and should be so counselled before contemplating therapy.

We thank Dr Anil Taylor, Department of Gynaecological Ultrasound, King's College Hospital, London, for supplying the sonohysterographic prints.

Funding: None.

Conflict of interest: None.

- 1 Bryce FC, Lilford RJ. General practitioners' use of hormone replacement therapy in Yorkshire. *Eur J Obstet Gynaecol* 1990;37:55-61.
- 2 Ravnkar VA. Compliance with hormone replacement therapy. *Am J Obstet Gynecol* 1987;156:1332-4.
- 3 Ryan PJ, Harrison R, Blake GM, Fogelman I. Compliance with hormone replacement therapy (HRT) after screening for postmenopausal osteoporosis. *Br J Obstet Gynaecol* 1992;99:325-8.

Fig 2 Submucous fibroid as seen with sonohysterography

- 4 Hahn RG, Nachtigall RD, Davies TC. Compliance difficulties with progestin-supplemented estrogen replacement therapy. *J Fam Pract* 1984;18:411-4.
- 5 Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85:304-13.
- 6 Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJB. Effects of oestrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *N Engl J Med* 1981;305:1599-605.
- 7 Hawthorn RJS, Spowart K, Walsh D, McKay Hart D. The endometrial status of women on long term continuous combined hormone replacement therapy. *Br J Obstet Gynaecol* 1991;98:939-42.
- 8 Thornycroft IH. Practical aspects of hormone replacement therapy. *Prog Cardiovasc Dis* 1995;38:243-55.
- 9 Sporrang T, Rybo G, Mattsson LA, Vilbergson G, Crona N. An objective and subjective assessment of uterine blood loss in postmenopausal women on hormone replacement therapy. *Br J Obstet Gynaecol* 1992;99:399-401.
- 10 Marsh MS, Whitehead MI. The practicalities of hormone replacement therapy. *Baillieres Clin Endocrinol Metab* 1993;7:183-202.
- 11 Marsh MS, Whitehead MI. Management of the menopause. *Br Med Bull* 1992;48:426-57.
- 12 Akkad AA, Habiba MA, Ismail N, Abrams K, Al-Azzawi F. Abnormal bleeding on hormone replacement: the importance of intrauterine structural abnormalities. *Obstet Gynecol* 1995;86:330-4.
- 13 Udoff L, Langenberg P, Adashi EY. Combined continuous hormone replacement therapy: a critical review. *Obstet Gynecol* 1995;86:306-16.
- 14 Evans MP, Fleming KC, Evans JM. Hormone replacement therapy: management of common problems. *Mayo Clin Proc* 1995;70:800-5.
- 15 Rosenfeld JA. Update on continuous estrogen-progestin replacement therapy. *Am J Obstet Gynecol* 1994;50:1510-23.
- 16 Rymer J, Fogelman I, Chapman MG. The incidence of vaginal bleeding with tibolone treatment. *Br J Obstet Gynaecol* 1994;101:53-6.
- 17 Hillard TC, Siddle NC, Whitehead MI, Fraser DI, Pryse-Davies J. Continuous combined conjugated equine estrogen-progestogen therapy: effects of medroxyprogesterone acetate and norethindrone acetate on bleeding patterns and endometrial histologic diagnosis. *Am J Obstet Gynecol* 1992;167:1-7.
- 18 Magos AL, Brincat M, Studd JWW, Wardle P, Schlesinger P, O'Dowd T. Amenorrhoea and endometrial atrophy with continuous oral estrogen and progestogen therapy in postmenopausal women. *Obstet Gynecol* 1985;65:496-99.
- 19 Archer DF, Pickar JH, Bottiglion F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. *Obstet Gynecol* 1994;83:686-92.
- 20 Paganini-Hill A, Ross RK, Henderson BE. Endometrial cancer and patterns of use of oestrogen replacement therapy: a cohort study. *Br J Cancer* 1989;59:445-7.
- 21 Gangar K, Cust M, Whitehead MI. Symptoms of oestrogen deficiency associated with supraphysiological plasma oestradiol concentrations in women with oestradiol implants. *BMJ* 1989;299:601-2.
- 22 Paterson MEL, Wade-Evans T, Sturdee DW, Thom MH, Studd JWW. Endometrial disease after treatment with oestrogens and progestogens in the climacteric. *BMJ* 1980;280:822-4.
- 23 Van Leeuwen FE, Benraadt J, Coebergh JWW, Klijmeney LALM, Gimbrère CHF, Otter R, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet* 1994;343:448-52.
- 24 Friedl A, Jordan VC. What we know and what we don't know about tamoxifen in the human uterus. *Br Cancer Res Treat* 1994;31:27-39.
- 25 Kedar RP, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet* 1994;343:1318-21.
- 26 Ismail SM. Pathology of endometrium treated with tamoxifen. *J Clin Pathol* 1994;47:827-33.
- 27 Ross D, Whitehead M. Hormonal manipulation and gynaecological cancer: the tamoxifen dilemma. *Curr Opin Obstet Gynecol* 1995;7:63-8.
- 28 Bornstein J, Auslender R, Pascal B, Gutterman E, Isakov D, Abramovici H. Diagnostic pitfalls of ultrasonographic uterine screening in women treated with tamoxifen. *J Reprod Med* 1994;39:674-8.
- 29 Goldstein SR. Unusual ultrasonographic appearance of the uterus in patients receiving tamoxifen. *Am J Obstet Gynecol* 1994;170:447-51.
- 30 Rodriguez GC, Yaqub N, King ME. A comparison of the Pipelle device and the Vabra aspirator as measured by endometrial denudation in hysterectomy specimens: the Pipelle device samples significantly less of the endometrial surface than the Vabra aspirator. *Am J Obstet Gynecol* 1993;168:55-9.
- 31 Kaunitz AM, Masciello A, Ostrowski M, Rovira EZ. Comparison of endometrial biopsy with the endometrial Pipelle and Vabra aspirator. *J Reprod Med* 1988;33:427-31.
- 32 Cohen JR, Luxman D, Sagi J, Yovel I, Wolman I, David MP. Sonohysterography for distinguishing endometrial thickening from endometrial polyps in postmenopausal bleeding. *Ultrason Obstet Gynecol* 1994;4:227-30.
- 33 Parsons AK, Lense JJ. Sonohysterography for endometrial abnormalities: preliminary results. *J Clin Ultrasound* 1993;21:87-95.
- 34 Gaucherand P, Piacenza JM, Salle B, Rudigoz RC. Sonohysterography of the uterine cavity: preliminary investigations. *J Clin Ultrasound* 1995;23:339-48.
- 35 Gimpleson RJ, Rappold HO. A comparative study between panoramic hysteroscopy with directed biopsies and dilatation and curettage: a review of 276 cases. *Am J Obstet Gynecol* 1988;158:489-92.
- 36 Downes E, Al-Azzawi F. The predictive value of outpatient hysteroscopy in a menopause clinic. *Br J Obstet Gynaecol* 1993;100:1148-9.
- 37 Indman PD. Hysteroscopic treatment of menorrhagia associated with uterine leiomyomas. *Obstet Gynecol* 1993;81:716-20.
- 38 Spaulding LB. Endometrial ablation for refractory postmenopausal bleeding with continuous hormone replacement therapy. *Fertil Steril* 1994;62:1181-5.
- 39 Brooks PG, Serden SP. Endometrial ablation in women with abnormal bleeding aged fifty and over. *J Reprod Med* 1992;37:682-4.

Correction

Fortnightly review: Seasonal allergic rhinitis

An error occurred in this article by Abhi Parikh and Glenis K Scadding (10 May, pp 1392-5). In the box of drug treatments for children (top of p 1394) the age limit for treatment with azelastine should have been for children aged 5 years and over (rather than over 9 years).

The music makers

Harmonisation in South Africa

As a foreigner in South Africa you are not alone. Most people in the country are in a similar position. The old system kept different racial groups apart so effectively that they are now as strange to each other as different nations.

My first realisation of this was that only after three weeks on the men's ward did one of the nurses ask me if I came from overseas. In every other country I have been to, my Englishness has stuck out like a sore thumb, usually before uttering a word of any language; but in Zululand a white man from England is no more alien than a white man from Johannesburg. I used to reckon that a man from Mars would not be regarded as any more foreign either, but that is probably a slight exaggeration.

There is now going to be a cultural mixing, but one gem that really should not get lost in the melée is Zulu music. The Zulus and Swazis are glorious singers and do not even seem to know it. A group can break into harmony as easily as we might recite a nursery rhyme. Women who have been given a spinal anaesthetic usually sing as the operation is about to begin, with theatre staff joining in harmony. My colleague, when asked what they were

singing, replied: "They are not singing, they are praying." "Praying we don't goof up?" "That as well."

The singing and praying after giving a spinal anaesthetic is very helpful in telling whether a patient is still alive. Those that do not break into melody are scolded until they do. Visiting medical students tell us that this does not happen in Durban, but they are missing out. Last year, after doing well in the local elections, a group of African National Congress supporters sang so well outside the treatment room that we almost forgave them for needing stitches at midnight.

A worry is that as the local, and mainly not wealthy, population get more televisions and radios they may change to a mediocre Western style of music. On the positive side, South African Broadcasting is working hard to be fair to every language and culture in the country and the African song "Shosholoz" did manage to become the unofficial anthem of the Rugby World Cup.

C H Vaughan Williams, *principal medical officer, Mosvold Hospital, Ingwavuma, South Africa*