had been obtained. Atypical hyperplasia was diagnosed in one patient by aspiration only, as no curettage specimen was obtained. This was confirmed when an endometrial polyp in the hysterectomy specimen also showed atypical hyperplasia. In another patient adenomatous hyperplasia was diagnosed from the aspirate and histological examination of the hysterectomy specimen showed only a small focus of adenomatous hyperplasia in the glands well below the surface of the uterine cavity. In one patient with postmenopausal bleeding a cytological diagnosis of adenocarcinoma was made but no curettings could be obtained. She was subsequently asymptomatic, but because of the cytological diagnosis a laparotomy was performed three months later when an inoperable ovarian carcinoma was discovered.

Discussion

Our results show that this technique is valuable in assessing endometrial state in unanaesthetised patients. This confirms the results of earlier studies in anaesthetised patients.[8] The technique seems to be even more successful in determining endometrial state than operative curettage in women aged over 40.

In most gynaecology clinics endometrial state is assessed by histological examination of specimens obtained by Vabra curettage. The Isaacs endometrial cell sampler may be more suitable than the Vabra curette for use in outpatient clinics as the cannula is finer, and sounding of the uterine cavity and a suction pump are not required for aspiration. Unlike Vabra curettage,[13 14] pain and bleeding during or after the procedure are slight or absent. Diagnosis of endometrial state was possible in 91% of our patients compared with 77% of patients of similar age assessed by Vabra curettage.[1] Introducing the cannula through the cervical os is sometimes difficult, however, and we recommend that only those experienced in gynaecological procedures should use the aspirator. Nervous patients should perhaps be given premedication with diazepam to reduce the possibility of severe discomfort when the cannula is introduced or during uterine cavity aspiration.

The results of this study suggest that the potential of endometrial cavity aspiration using the Isaacs endometrial cell sampler is considerable. Its use may eliminate the need for many time-consuming inpatient diagnostic curettages. It should also prove invaluable in menopause clinics for monitoring postmenopausal oestrogen treatment. Further experience of endometrial cytology may show that the hormonal state of women with ovulatory disturbances can be similarly assessed.

We thank the medical and nursing staff of the Samaritan hospital for their co-operation, and Dr W O Elson, of the Kendall company, for providing the Isaacs endometrial cell samplers.

References

1 Whitehead, M I, and Campbell, S, in *Proceedings of the Second International Meeting on Endometrial Cancer and Related Topics*, ed R W Taylor, M Brush, and R J King. London, Baillière, Tindall and Cassell. In press.
2 Smith, D C, *et al*, *New England Journal of Medicine*, 1975, **293,** 1164.
3 Ziel, H K, and Finkle, W D, *New England Journal of Medicine*, 1975, **293,** 1167.
4 McDonald, T W, *et al*, *American Journal of Obstetrics and Gynecology*, 1977, **127,** 572.
5 Ayre, J E, *Obstetrics and Gynecology*, 1955, **5,** 137.
6 Gravlee, L C, *Obstetrics and Gynecology*, 1969, **34,** 168.
7 Torres, J E, Holmquist, N D, and Danos, M L, *Acta Cytologica*, 1969, **13,** 163.
8 Isaacs, J H, and Wilhoitte, R W, *American Journal of Obstetrics and Gynecology*, 1974, **118,** 679.
9 Papanicolaou, G N, and Traut, H F, *New York State Journal of Medicine*, 1943, **43,** 767.
10 Reagan, J W, and Ng, A B P, in *Clinical Cytology*, vol 1, ed G L Wied. Basel, Karger, 1965.
11 Dallenbach-Hellweg, G, in *Histopathology of the Endometrium*. Berlin, Springer Verlag, 1975.
12 Jacobs, H S, and Murray, M A F, in *The Management of the Menopause and Post-menopausal Years*, ed S Campbell, p 359. Lancaster, MTP Press, 1976.
13 Holt, E M, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1970, **77,** 1043.
14 Nassler, E, Thomsen, P B, and Weeth, R, *Danish Medical Bulletin*, 1975, **11,** 1165.

(Accepted 8 February 1978)

Transmission of HBsAg from mother to infant in four ethnic groups

A DERSO, ELIZABETH H BOXALL, M J TARLOW, T H FLEWETT

British Medical Journal, 1978, **1,** 949-952

Summary and conclusions

Antenatal screening in the West Midlands during a three-year period identified 297 mothers who were chronic carriers of hepatitis B surface antigen (HBsAg)—a prevalence of about 1 in 850. About half of their infants had HBsAg in the cord blood, but of 122 infants followed up for over three months (mean 8·5 months) only 17 (14%) were still positive for HBsAg. Cord-blood HBsAg-positivity was evenly distributed among different ethnic groups, but the transmission rate was highest among the Chinese, and no carriers were discovered among 39 European infants. Raised serum transaminase concentrations were found in some of the carrier infants who were otherwise healthy.

The results suggest that adequate follow-up of HBsAg-positive infants may be achieved by tests at 4 months and 1 year of age, and that the role of breast-feeding in mother-to-infant transmission of HBsAg is unimportant. The Chinese community may be a suitable population in which to test the effectiveness of specific immunoglobulin administration at birth in preventing the development of the HBsAg carrier state.

University Department of Paediatrics, East Birmingham Hospital, Birmingham B9 5ST

A DERSO, MB, MRCP, research registrar
M J TARLOW, MSC, MRCP, senior lecturer in paediatrics

Regional Virus Laboratory, East Birmingham Hospital, Birmingham B9 5ST

ELIZABETH H BOXALL, BSC, PHD, senior microbiologist
T H FLEWETT, MRCP, FRCPATH, consultant virologist

Introduction

Hepatitis B virus is implicated in various clinical conditions, ranging from different types of hepatitis to immune-complex diseases.[1-3] Its prevalence in the population presents a con-

tinuing source of infection, causing particular problems in renal units, yet the modes of transmission and the mechanisms which maintain the virus in the population are largely unknown. Vertical (mother-to-infant) transmission is known to occur from both mothers with acute type B hepatitis[1-6] and those who are symptomless carriers of hepatitis B surface antigen (HBsAg).[7-10] Some workers have recommended giving specific gammaglobulin[11 12] to the infants at birth, both to prevent possible morbidity in the neonatal period and to reduce the prevalence of the virus in the population. Nevertheless, there is considerable geographical variation in the development of the carrier state[10] and routine use of expensive immune gammaglobulin may not be needed. We undertook a systematic follow-up study in the West Midlands of infants born to mothers who were chronic carriers of HBsAg.

Subjects and methods

Carrier mothers were defined as women without clinical or biochemical evidence of hepatitis who were found to have HBsAg in their blood at screening before and after delivery. Pregnant women attending antenatal clinics in the West Midlands region have been routinely screened for HBsAg by the Regional Blood Transfusion Service in Birmingham since April 1974. This region has a population of about five million and about 80 000 births a year. All sera positive for HBsAg are referred to the Regional Virus Laboratory for confirmation. Initially follow-up of the infants depended on the paediatricians and obstetricians concerned, and only a few infants were adequately followed up. Since October 1976, however, one of us (AD) has tried to see as many of the infants as possible for clinical examination and to obtain blood samples at 6 weeks and 4, 8, and 12 months of age. We have also tried to see as many of the older infants as possible.

Antenatal sera were tested for HBsAg by counterimmunoelectrophoresis (CEP) from April 1974 to July 1976, and since then by reversed passive haemagglutination (RPH; Hepatest, Wellcome Laboratories). In addition to the above tests, all cord-blood and follow-up samples from the infants were tested by solid-phase radioimmunoassay (RIA; Ausria-II-125). Breast-milk samples were tested by RIA, and some were also examined by immune electronmicroscopy (IEM) after initial concentration by ultracentrifugation.[13] Routine tests for hepatitis B surface antibody (anti-HBs) were performed by haemagglutination inhibition using the Hepatest reagents. e Antigen (eAg) and antibody (anti-e)[14] were tested by immunodiffusion using reagents confirmed as specific by the Central Public Health Laboratory, London. Tests for antibody to hepatitis B core antigen (anti-HBc) were performed by CEP against core antigen obtained from the Central Public Health Laboratory.

Liver function tests were performed by routine methods, and autoantibodies (smooth muscle, mitochondrial, antinuclear factor (ANF)) and immunoglobulins (IgG, IgA, IgM) were assayed in several HBsAg-positive and HBsAg-negative infants. Liver function tests were carried out on 26 control infants of the same age undergoing routine minor operations to obtain reference values. Control infants were born to mothers who were HBsAg-negative and were themselves antigen-negative.

Results

VIROLOGICAL STUDIES

HBsAg—In the three years up to May 1977 297 carrier mothers were discovered (a prevalence of approximately 1 in 850). We received cord blood from 219 of the 269 babies delivered. Antigen was detected by solid-phase RIA in 101 of the cord-blood specimens (46%) and 44 of the 85 breast-milk specimens (52%). Six out of 15 samples of breast milk and eight out of 16 samples of cord blood were positive by IEM, and two of the cord blood samples contained intact Dane particles.[15] Although the HBsAg in cord blood was often present only in low titres and may have been due to maternofetal transfusion during delivery, in 25 of the 101 samples of cord blood HBsAg was detectable by RPH in titres ranging from 1/4 to 1/8000. By 6 weeks of age the antigen was present in the serum of fewer infants at a still lower titre. Nevertheless, irrespective of the antigen state at birth and at 6 weeks, some infants developed very high titres of HBsAg at 3-4 months. Of 122 infants followed up beyond the age of 3 months (mean age 8·5 months) 17 (14%) had persistently high titres of HBsAg (usually greater than 1/8000). Table I shows the rough ethnic distribution of chronic HBsAg-carrier mothers: most were "Asians" from India, Pakistan, and Bangladesh, and only 28% were European. The ethnic distribution of the 17 "carrier" infants, however, was different (table II). Chinese infants were much more likely to become carriers (64%) than infants from other ethnic groups. No infants born to European carrier mothers became carriers, though 39 were carefully followed up. The proportion of cord-blood samples containing HBsAg was similar in the different ethnic groups.

e Antigen—Sera from some of the mothers were tested for eAg and anti-e (table III). Six out of 13 of the mothers whose infants had become positive were eAg-positive, whereas only one of the mothers whose infants remained negative had eAg (this woman was Chinese). Table IV shows the ethnic distribution of the eAg carrier state; we were able to include some Chinese mothers whose infants were lost to follow-up and who were not therefore included in table III. As expected[10] the geographical distribution of the eAg carrier state varied considerably, being much more common among those in whom the vertical transmission rate was higher.

Anti-HBc—Tests for the presence of anti-HBc gave predictable results. All cord-blood samples, whether positive or negative for HBsAg, were positive for anti-HBc (maternal). Babies who became negative for HBsAg lost this "maternal" anti-HBc within four to six months. Infants who became carriers continued to be positive for anti-HBc for up to 17 months and began to produce their own antibody.

Anti-HBs—None of the infants produced anti-HBs detectable by passive haemagglutination inhibition, though further investigations using more sensitive tests have yet to be carried out.

TABLE I—*Rough ethnic distribution of symptomless HBsAg-carrier mothers in West Midlands*

Ethnic group	Asian*	European	Afro-Caribbean†	Chinese	Other
Percentage of mothers	45	28	13	11	3

*Mothers from India, Pakistan, and Bangladesh.
†Mothers from West Indies and Africa, excluding those of Asian and European ancestry.

TABLE II—*Ethnic distribution of infants born to HBsAg-carrier mothers, and number of infants positive for HBsAg beyond 3 months of age*

Ethnic group	Total No of infants	No (%) HBsAg-positive
Asian	51	4 (8)
European	39	
Afro-Caribbean	13	4 (30)
Chinese	14	9 (64)
Other	5	
Total	122	17 (14)

TABLE III—*e Antigen (eAg) and antibody (anti-e) in carrier mothers*

	No positive for eAg	No positive for anti-e	No negative for eAg and anti-e	Total No tested
Mothers of babies negative for HBsAg	1	10	7	18
Mothers of babies positive for HBsAg	6	3	4	13

TABLE IV—*Number of mothers positive or negative for eAg or anti-e according to ethnic group*

Ethnic group	No positive for eAg	No positive for anti-e	No negative for eAg and anti-e	Total
European		4	4	8
Asian		3	3	6
Chinese	7	4	2	13
Afro-Caribbean	2	3	1	6

CLINICAL, BIOCHEMICAL, AND IMMUNOLOGICAL FINDINGS

All the infants were healthy with normal growth and development and had no clinical signs of liver disease such as jaundice or hepatomegaly. Some of the HBsAg-positive infants, however, had abnormally high concentrations of serum transaminases, mean concentrations of aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) being nearly twice and three times greater respectively when compared with values in the antigen-negative infants and a group of normal controls (table V).

TABLE V—*Mean concentrations of alanine aminotransferase (SGPT) and aspartate aminotransferase (SGOT) in infants positive or negative for HBsAg compared with controls**

	Controls (n = 26)	HBsAg-negative (n = 97)	HBsAg-positive (n = 15)
Mean age (months)	16·5	9·4	12·5
SGPT† (IU/l)	22·4	25·6	64·1
SGOT‡ (IU/l)	46·9	46·2	80·8

*Controls were HBsAg-negative infants of non-carrier mothers.
†Normal adult value ≤30 IU/l.
‡Normal adult value ≤35 IU/l.

Immunological tests—Tests for autoimmune antibodies in the babies' sera gave negative results. Immunoglobulin concentrations were measured in paired sera from 10 HBsAg-negative infants and from 10 infants who had become carriers; the first sample was taken at about 3 months of age and the second at a mean age of 18 months. When the results were examined with respect to age, only one IgG value was abnormal; this was in a sample from a 17-month-old West Indian child who had become a chronic carrier; her IgA and IgM values were also abnormal. Among the carrier infants, six out of 20 IgA values were considered to be abnormal (200 mg/100 ml) compared with none in the HBsAg-negative infants. Only two IgM values from the HBsAg-negative group were considered to be high (100 mg/100 ml), but in the positive group nine out of 20 were considered to be high.

Discussion

We found an overall transmission rate of 14% in infants followed up beyond the age of 3 months. The babies became strongly positive for HBsAg at 3-4 months of age, which was consistent with infection at birth but did not rule out true infection in utero. The most interesting observation was the great difference in the rate of vertical transmission in different ethnic groups. The Chinese babies were a distinct group with a transmission rate of 64%, rather higher than that expected from the study of Stevens *et al* in Taiwan,[9] where some 40% of the babies born to Chinese carrier mothers became chronic carriers in the first year of life. The Chinese mothers in our study came mainly from Hong Kong and may therefore have constituted a slightly different population from those in Taiwan. The Afro-Caribbean mothers also transmitted the carrier state to their infants, four out of 13 of their children (30%) becoming carriers. More babies were followed up in the Asian group than any other, but the transmission rate was of the order of only 8%, which is close to that expected for the Western World.[10] Nevertheless, although 39 babies of European mothers were followed up, none proved to be positive. This pattern has been observed in other studies of vertical transmission rates. In Taiwan[9] almost half of the babies born to carrier mothers became HBs antigenaemic in the first year of life, but studies in Europe and North America have reported the following transmission rates: 5% in America[8]; 6% in Greece[16]; 6% in Belgium[17]; and none in Denmark.[18]

The Taiwan study also showed that transmission correlated well with the mother's HBsAg titre, the presence of HBsAg in the cord blood, and the presence of HBs antigenaemia in siblings. We did not find a positive correlation between infection in the infant and the titre of the mother's antigen; many of the Asian and European mothers had very high titres but few of their infants became infected. Only 10 out of 62 infants whose cord blood contained HBsAg became carriers, but two without antigen in the cord blood also became carriers. One of these two infants was breast-fed. Among the Chinese families in which a child had become positive for HBsAg in the first year of life, four out of four elder siblings tested were also found to be positive. Nevertheless, we found one West Indian mother whose first infant (age 20 months) became a carrier but whose second baby remained negative at 6 months. In addition to the 17 carrier infants mentioned, three other babies were found to be positive when tested at 4 months—one European, positive by RIA only; one Chinese, positive by RPH to a titre of 1/16; and one Asian, who was positive by RPH to a titre of 1/512. These infants were HBsAg-negative on follow-up, and remained so. We therefore advise anyone interested in following up HBsAg-positive babies to test them at 4 months, but to check again at 1 year.

Factors favouring the development of the carrier state are poorly understood but must ultimately depend on lack of effective host immune response to the virus.[19-21] As in other studies,[17 22 23] the presence of e antigen in the mother's serum correlated well, if not completely, with transmission to the infant. We too have observed a greater proportion of e-antigen reactivity in mothers whose babies became carriers. The prevalence of e antigenaemia was higher among Chinese and Afro-Caribbean mothers, which correlated well with the higher rate of transmission to their infants. We found two mothers who were anti-e positive, one with one carrier baby and the other with two; both these mothers were Chinese. Nevertheless, the exact nature of e antigen is still under discussion,[24] though its prevalence in different ethnic groups may partly explain the different rates of vertical transmission observed in different parts of the world.

The HBsAg-positive infants were clinically healthy, and no case of neonatal hepatitis due to hepatitis B virus has been reported in any of them. There was, however, biochemical evidence of liver damage in some of the infants, whose SGOT and SGPT concentrations reached 212 IU/l and 224 IU/l respectively (the upper limit of normal for infants being taken as 70 IU/l). Some of these abnormalities persisted on serial tests, though other infants had no abnormal concentrations at any time despite their antigenaemia. Two infants had abnormal serum transaminase concentrations at 6 weeks, though they were negative for antigen and antibody. Transaminase concentrations had returned to normal when tested at 4 months, but one infant had a high titre of HBsAg (1/8000) by then, while the other remained negative for antigen and antibody. We considered the question of liver biopsy in the HBsAg-positive infants but rejected it on ethical grounds. If biopsies were done and showed mildly abnormal histological findings then the question of treatment would arise. Should these thriving and apparently healthy infants be treated with potentially dangerous drugs such as corticosteroids and immunosuppressants?

A practical question often asked is whether HBsAg-carrier mothers may safely breast-feed their babies. Among our 17 carrier infants, only four were breast-fed (three cord-blood HBsAg-positive, one negative), 11 certainly were not breast-fed at any stage, and we have no information on the remaining two. Of 64 antigen-negative infants on whom information is available, 28 (44%) were breast-fed for varying periods. Breast milk may contain small amounts of HBsAg, but infection is much more likely to occur from exposure to antigen during birth—for example, ingestion of blood-contaminated liquor or the presence of HBsAg in cord blood. We have not discouraged our HBsAg-carrier mothers from breast-feeding their babies.

Present evidence suggests that giving specific immunoglobulin to babies of Caucasian mothers is not justified. The Chinese community, however, with its high transmission rate, might be a suitable population in which to find out whether administering specific immunoglobulin at birth would prevent the carrier state from developing. A dosage regimen worked out for these infants could be used on the few babies whose mothers have acute serum hepatitis late in pregnancy, and who seem to be at greater risk than the babies whose mothers are carriers.

We acknowledge the invaluable organisational help of our research secretary, Mrs Valerie Shakespeare, who, together with AD, was supported by a project grant from the Medical Research Council. We also thank Staff Nurse Kwai Foong Low for her help in following up the Chinese families; the staff of the hepatitis laboratory at the Regional Blood Transfusion Centre for screening all the antenatal sera; the laboratory staff at East Birmingham Hospital for viral, chemical, and immunological testing; and all the family doctors, obstetricians, paediatricians, and mothers and their babies for co-operating in our study.

Requests for reprints should be sent to Dr Elizabeth Boxall.

References

1 Sherlock, S, *Lancet*, 1976, **2**, 354.
2 Combes, B, *et al*, *Lancet*, 1971, **1**, 234.
3 London, W T, *New England Journal of Medicine*, 1977, **296**, 1528.
4 Wright, R, *et al*, *British Medical Journal*, 1970, **4**, 719.
5 Kattamis, C A, and Demetrios, D, *Pediatrics*, 1974, **54**, 157.
6 Schweitzer, I L, *et al*, *Gastroenterology*, 1973, **65**, 277.
7 Schweitzer, I L, *Proceedings of the National Academy of Sciences*, 1975, **270**, 287.
8 Papaevangelou, G, Hoofnagle, J, and Kremastinou, J, *Lancet*, 1974, **2**, 746.
9 Stevens, C E, *et al*, *New England Journal of Medicine*, 1975, **292**, 771.
10 Boxall, E H, *Biomedicine*, 1977, **26**, 12.
11 Kohler, D F, *et al*, *New England Journal of Medicine*, 1974, **291**, 1378.
12 Holzback, R T, *American Journal of Medicine*, 1976, **61**, 367.
13 Linneman, C C, and Goldberg, S, *Lancet*, 1974, **2**, 155.
14 Magnius, L O, and Espmark, J A, *Journal of Immunology*, 1975, **109**, 1017.
15 Boxall, E H, and Davies, H, *Lancet*, 1974, **2**, 1513.
16 Papaevangelou, G, *et al*, *Archives of Disease in Childhood*, 1974, **49**, 936.
17 Skinhoj, P, Cohn, J, and Bradburne, A F, *British Medical Journal*, 1975, **1**, 10.
18 Skinhoj, P, *et al*, *American Journal of Diseases in Childhood*, 1972, **123**, 380.
19 Eddleston, A L W F, *Postgraduate Medical Journal*, 1974, **50**, 348.
20 Yeung Leiwah, A A C, *Lancet*, 1971, **2**, 470.
21 Dudley, F J, Giustino, V, and Sherlock, S, *British Medical Journal*, 1972, **4**, 754.
22 Okada, K, *et al*, *New England Journal of Medicine*, 1976, **294**, 746.
23 Palmer Beasley, R, *et al*, *American Journal of Epidemiology*, 1977, **705**, 94.
24 Neurath, A R, and Strick, N, *Lancet*, 1977, **1**, 146.

(*Accepted 10 February 1978*)

Dextran and intermittent pneumatic compression in prevention of postoperative deep vein thrombosis: multiunit trial

R C SMITH, R A ELTON, J D ORR, A J L HART, D F GRAHAM, G A G FULLER, J S H RUNDLE, A I S MACPHERSON, C V RUCKLEY

British Medical Journal, 1978, **1**, 952-954

Summary and conclusions

Seven general surgical units co-operated in a clinical trial of dextran 70 and pneumatic calf compression alone and in combination in the prevention of ^{125}I-fibrinogen-detectable deep vein thrombosis in 305 patients.

Both dextran regimens were significantly more effective than pneumatic compression alone. Pulmonary embolism was diagnosed in 14 patients, but there was no significant difference in incidence among the three treatment groups. In patients receiving dextran there was no greater median operative blood loss but there was a significantly greater incidence of postoperative bleeding complications.

Royal Infirmary of Edinburgh, Edinburgh EH3 9YW
R C SMITH, MB, FRCSED, senior surgical registrar
A J L HART, MB, FRCSED, surgical registrar
G A G FULLER, MB, CHB, registrar
A I S MACPHERSON, CHM, FRCSED, FRSED, consultant surgeon

Medical Computing and Statistics Group, University of Edinburgh
R A ELTON, MA, PHD, lecturer in medical statistics

Western General Hospital, Edinburgh, Edinburgh EH4 2XU
J S H RUNDLE, MB, FRCSED, surgical registrar
C V RUCKLEY, CHM, FRCSED, consultant surgeon

Bangour General Hospital, West Lothian EH52 6LR
D F GRAHAM, MB, FRCSED, surgical registrar

Chalmers Hospital, Edinburgh EH3 9HG
J D ORR, MB, FRCSED, surgical registrar

Introduction

Most surgeons agree on the need for prophylaxis against thromboembolism in patients undergoing operation but not on the method of choice. Evidence suggests that the most effective prophylaxis in general surgical patients is low-dose subcutaneous heparin.[1-4] Some surgeons, however, believe that this may cause excessive blood loss during and after operation, and the twice- or thrice-daily injections needed makes it distressing for the patient as well as time-consuming for nursing staff. Thus many centres use dextran infusions or pneumatic calf compression or both as routine methods of prophylaxis, reserving heparin for patients at particular risk.

Use of dextran and pneumatic compression have separately been shown to be effective prophylactic methods.[5-11] We therefore decided to compare the two, used singly and in combination, to see whether there was any additive effect. Seven general surgical units in four hospitals in the Lothians Area Health Board participated in the trial, which in each unit was supervised by a registrar.

Patients and methods

Any patient aged over 40 admitted for an operation likely to last more than 30 minutes was considered for inclusion in the trial. Because of low risk, technical problems of scanning, or the surgeon's preference for a different method of prophylaxis patients in the following groups were excluded: those aged below 40; patients undergoing operations on the head and neck or left chest wall, vascular procedures or operations on the legs, and emergency surgery; women taking the "pill"; and patients with a recent history of venous thromboembolism.

For ethical reasons an untreated control group was not included.

Treatment regimens—Patients admitted to the trial were allocated at random to the three treatment regimens by means of sealed envelopes, numbers being restricted to ensure that the groups were of comparable