We conclude that beta-blocking drugs are generally safe to use in insulin-treated diabetics and that hypoglycaemic unconsciousness resulting from their use is rare. Whether selectivity confers any real advantage remains uncertain. It is unnecessary to deny diabetics the therapeutic benefit of beta-blocking drugs.

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Requests for reprints should be sent to AHB.

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Altered haemorheology in oral-contraceptive users

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Summary and conclusions

The haemorheological profile of the menstrual cycle was determined in 12 women who did not take oral contraceptives and compared with that in two groups of women (n = 8 and n = 30) who had been taking oral contraceptives for at least six months. Packed cell volume, platelet count, erythrocyte deformability, plasma fibrinogen concentration, and plasma and whole-blood viscosity varied cyclically throughout the menstrual cycle in the 12 non-users.

This variation was abolished by the use of oral contraceptives, and the values of these indices were raised by an amount likely to predispose to thrombosis.

Introduction

The association between arteriovenous thromboembolism and use of oral contraceptives is well established[1 2] and has stimulated investigation into possible causative mechanisms. Contraceptive steroids increase the concentrations of many coagulation factors and reduce that of antithrombin III,[3-5] increase platelet adhesiveness,[6] and reduce venous flow velocity by increasing venous distensibility[7] and whole-blood viscosity.[8-10] All of these effects increase the risk of thromboembolism, and a full understanding of them must be based on a sound appreciation of the physiological background on which they are imposed. Little attention, however, has as yet been paid to the changes in haemorheological indices in the menstrual cycle. We have determined these changes in both users and non-users of oral contraceptives.

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Patients and methods

Twenty women had blood taken at the same time of day on four occasions one week apart during their menstrual cycle. Twelve were taking no medication, and eight had been taking an oral contraceptive containing 30 μg ethinyloestradiol and 250 μg norgestrel for at least six months. A further 30 women who had been taking the same oral contraceptive for at least six months gave one blood sample between the seventh and twenty-first day of their cycle. All of the women were healthy volunteers, aged from 22 to 34 years, who did not smoke.

Packed cell volume and platelet count were measured with a Coulter Counter S, plasma fibrinogen concentration according to the method of Ratnoff and Menzie,[11] erythrocyte deformability by a microfiltration method,[12] and plasma and whole-blood viscosity with a Deer Rheometer at a shear stress of 0·057 N/m² (0·57 dynes/cm²) at 37°C.

Serial data were analysed using paired *t* tests on the mean differences between stages and cross-sectional data analysed using Student's *t* tests.

Results

The table shows the mean values of all indices in users and non-users of oral contraceptives and the significances of the differences between the means for adjacent stages in each group.

Packed cell volume rose to a peak at ovulation, remained high in the luteal phase, and fell at menstruation in the women who were not taking oral contraceptives. In the women taking oral contraceptives this variability was abolished. Comparing the cross-sectional data from the 30 contraceptive users with data from each stage of the cycle in non-users, the mean packed cell volume was significantly higher in the contraceptive users than in the non-users for all stages (days 1-7, $p < 0.01$; 12-16, $p < 0.05$; 18-21, $p < 0.01$; and 26-28, $p < 0.05$).

Platelet count rose to a peak at ovulation, started to fall before menstruation, and continued to fall during menstruation in non-users. In contraceptive users the count remained steady throughout the cycle, and in the cross-sectional study the mean platelet count was significantly higher in contraceptive users than in non-users on days 1-7 ($p < 0.01$) and 26-28 ($p < 0.01$).

Plasma fibrinogen concentration in non-users rose to a peak just before menstruation and fell after the onset of menstruation but was otherwise constant. In contraceptive users the concentration remained constant during the 21 days of treatment and then fell slightly but

Mean (SE in parentheses) rheological indices in one group of non-users and in two groups of users of oral contraceptives

Indices	Days of cycle								
	Non-users (n = 12)				Users (n = 8)				Users (n = 30)
	1-7	12-16	18-21	26-28	1-7	12-16	18-21	26-28	7-21
Packed cell volume	0·382* (0·005)	0·397† (0·006)	0·390 (NS) (0·007)	0·399 (NS) (0·005)	0·407 (NS) (0·008)	0·405 (NS) (0·007)	0·405 (NS) (0·008)	0·404 (NS) (0·009)	0·417 (0·008)
Platelet count ($\times 10^9$/l)	241‡ (8)	273* (9)	272 (NS) (9)	259‡ (8)	270 (NS) (7)	278 (NS) (7)	282 (NS) (8)	279 (NS) (8)	278 (8)
Plasma fibrinogen (g/l)	2·40† (0·09)	2·45 (NS) (0·08)	2·35 (NS) (0·08)	2·64† (0·10)	2·72 (NS) (0·09)	2·80 (NS) (0·08)	2·82 (NS) (0·08)	2·73† (0·10)	2·79 (0·17)
Erythrocyte deformability index	0·776 (NS) (0·047)	0·783 (NS) (0·075)	0·907‡ (0·007)	0·756† (0·054)	0·861 (NS) (0·064)	0·647† (0·048)	0·788 (NS) (0·066)	0·956‡ (0·059)	0·772 (0·092)
Plasma viscosity (mPa s)	1·74 (NS) (0·024)	1·69 (NS) (0·023)	1·68 (NS) (0·025)	1·74‡ (0·023)	1·75 (NS) (0·033)	1·78 (NS) (0·031)	1·76 (NS) (0·030)	1·71 (NS) (0·049)	1·77 (0·022)
Whole-blood viscosity (mPa s)	9·13* (0·375)	11·05 (NS) (1·230)	10·01 (NS) (1·170)	12·63‡ (0·88)	11·24 (NS) (0·790)	10·62 (NS) (0·717)	12·48 (NS) (1·830)	10·49 (NS) (0·837)	11·90 (1·210)

Statistical comparisons made with paired *t* test.
Difference between mean marked and mean of preceding stage significant at: *$p < 0.001$, †$p < 0.01$, ‡$p < 0.05$.
NS = Not significant.
Conversion: SI to traditional units—Packed cell volume: 0·01 = 1%. Platelets: 10^9/l = 1000/mm³. Fibrinogen: 1 g/l = 100 mg/100 ml. Viscosity: 1 mPa s = 1 cP.

significantly during the seven days without treatment. The 30 contraceptive users had a significantly higher mean plasma fibrinogen concentration than non-users on days 1-7 ($p < 0.01$), 12-16 ($p < 0.01$), and 18-21 ($p < 0.01$).

Erythrocyte deformability in non-users remained constant during the follicular phase, rose to a peak in the early luteal phase, and fell to its lowest value before menstruation. In contraceptive users erythrocyte deformability was at its lowest in mid-cycle and at its highest just before menstruation. The 30 contraceptive users had a significantly lower mean erythrocyte deformability index than the non-users only on days 18-21 ($p < 0.05$).

Plasma viscosity fell slowly in the follicular phase and rose to a peak just before menstruation in non-users. The value was constant in contraceptive users and was significantly higher than in non-users on days 12-16 ($p < 0.05$) and 18-21 ($p < 0.05$).

Whole-blood viscosity in non-users was constant throughout the follicular and early luteal phases, rose to a peak before menstruation, and fell sharply with its onset. In contraceptive users this variability was abolished, and the mean whole-blood viscosity was significantly higher than in non-users on days 1-7 ($p < 0.01$) and 18-21 ($p < 0.05$).

Discussion

The variations in the indices that we have measured are in general agreement with the few studies of individual indices that have been measured in the menstrual cycle[13-17] and show the effect of the changing concentrations of oestrogen and progesterone. When the effect of oral contraceptives on these indices is investigated the timing of sample collection is important. Meade *et al*[2] failed to show any effect of oral contraceptives on platelet count using large, randomly sampled groups, whereas Ygge *et al*[18] showed an increase in platelet count with oral-contraceptive use when, as in our study, sample timing was the same in contraceptive users and controls. Similarly Oski *et al*[19] showed a reduction in erythrocyte deformability in oral-contraceptive users with matched sample timing, whereas Leonhardt *et al*[9] found no reduction with oral-contraceptive use with random sample timing. In none of the published studies has a comparison been made between the values of haemorheological indices in oral-contraceptive users and the various stages of the spontaneous menstrual cycle. Raised packed cell volume, platelet count, plasma fibrinogen concentration, and whole-blood viscosity have been reported in oral-contraceptive users,[8-10] but it has not been noted that during the premenstrual phase of the spontaneous cycle these indices are raised to similar values as those found throughout the cycle in oral-contraceptive users. Thus the increased risk of thromboembolism associated with oral contraceptives of the type studied cannot be attributed to unusual values of haemorheological factors. Treatment with oral contraceptives, however, abolished the cyclical changes in all the indices measured. This loss of variability combined with small but significant increases, seen also in pregnancy[20] with its higher incidence of thromboembolism, may cause sufficient venous stasis and increased coagulability of blood to be responsible for the increased incidence of thromboembolism in oral-contraceptive users.

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