the LDL receptor sites[15] may provide the basis for a test with greater discriminating capacity than the determination of total serum cholesterol or LDL cholesterol.

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Requests for reprints should be addressed to Dr J V Leonard, Department of Child Health, Institute of Child Health, London WC1.

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Fluctuations of serum and bile lipid concentrations during the menstrual cycle

T S LOW-BEER, A C B WICKS, K W HEATON, P DURRINGTON, J YEATES

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Summary

We measured fasting serum and bile lipid concentrations at three intervals during the normal menstrual cycles of 11 healthy women not taking oral contraceptives. In nine of them cholesterol saturation of bile, and therefore presumably the risk of developing gall stones, was higher nine days after midcycle than at the end of menstruation. This change in bile cholesterol saturation was preceded by a significant fall in serum lipid concentrations: during the nine days after mid-cycle serum triglyceride and cholesterol concentrations fell in nine and eight of the 11 women respectively. Changes in the composition of serum and biliary lipids during the menstrual cycle are presumably due to a direct effect of sex hormones on the liver.

Introduction

Women are more likely to develop gall stones than men.[1] The gall stones commonly found in affluent societies are rich in cholesterol.[2] There is much to suggest that this sex-related difference is partly due to sex hormones. For example—oral contraceptives encourage the oversaturation of bile with cholesterol[3 4] and gall stones seem to be commoner in women taking oestrogens either as part of the contraceptive pill[5] or for relief of post-menopausal symptoms.[6] Pregnancy appears to predispose to gall stones.[1 7] Cholesterol saturation of both monkey and rat bile may be altered by changing sex-hormone concentrations in the blood.[8-10]

Blood concentrations of oestrogen and progestogen fluctuate considerably during the normal menstrual cycle. We thought that bile cholesterol saturation might also fluctuate, and consequently the risk of forming gall stones. We therefore decided to study biliary lipid composition during normal menstrual cycles, and in view of the relationship between serum and biliary lipids,[11] and between serum lipids and sex hormones,[12] we also measured fasting serum cholesterol and triglyceride concentrations.

Subjects and methods

Twelve healthy female volunteers aged 20-43 years were accepted for these studies. All had a history of regular 26-30 day menstrual cycles and had not taken any hormone preparations for three months before the study. One woman had a cycle which was abnormally long for her so she was excluded.

Each woman was studied on three occasions during her menstrual cycle: the day after menstruation had ceased (usually the fifth or sixth day after starting), when oestrogen and progesterone concentrations are generally low; at mid-cycle (assessed as 14 days before the predicted date of menstruation), when oestrogen concentrations are normally at their highest; and eight to nine days later, at the expected progesterone peak. To ensure that the order of study did not influence the results, seven women began the study at the end of menstruation, and the other four at mid-cycle. On each of the three occasions bile and blood samples were collected after an overnight fast of nine hours. The women swallowed a duodenal tube, and 5-8 ml of bile was aspirated after intravenous pancreozymin injection (Boots Co Ltd). The aspirate was immediately divided into aliquots and stored at $-20°C$ for subsequent estimation of concentrations of cholesterol and phospholipid, total bile-salt content, the bile-salt composition, and the ratio of glycine to taurine conjugation. All samples from each subject were always analysed in the same batch.

Biliary cholesterol concentrations were assayed by gas-liquid chromatography, using a pure cholesterol standard.[13] Phospholipid concentrations were measured by the method of King[14] without prior lipid extraction. For total bile salts, the 3-α-hydroxysteroid dehydrogenase enzyme system was used.[15] The relative concentrations of these three lipids were expressed as a cholesterol saturation index.[16-18] The

University Department of Medicine, Royal Infirmary, Bristol BS2 8HW

T S LOW-BEER, BM, MRCP, lecturer in medicine (present appointment: consultant physician and gastroenterologist Selly Oak Hospital, Birmingham B29 6JD)
A C B WICKS, MD, MRCP, research fellow
K W HEATON, MD, FRCP, consultant senior lecturer in medicine
P DURRINGTON, MB, MRCP, senior house officer in medicine
J YEATES, technician

relative amounts of cholate, chenodeoxycholate, and deoxycholate in the samples, and the ratio of glycine to taurine conjugates, were measured using the 3-α and 7-α-hydroxysteroid dehydrogenase enzymes[15 19 20] after thin-layer chromatographic separation.[21]

Serum cholesterol and triglyceride concentrations were measured on the Technicon Autoanalyser; cholesterol by a modification of the Liebermann-Burchardt reaction[22]; and triglycerides by the standard semi-automated Technicon method.[23] Statistical differences were assessed by the two-tailed paired *t* test.

Results

In nine of the eleven women the cholesterol saturation index of bile was higher eight to nine days after mid-cycle than at the end of menstruation (fig 1). There were no significant differences between cholesterol saturation indices at the other two intervals. Cholesterol content of bile, expressed as a percentage of total biliary lipid concentration, changed significantly in parrallel with the saturation index, but there were no significant changes in the proportions of bile salts or phospholipid (table). The total concentration of biliary lipids in the duodenal aspirates did not fluctuate significantly. The proportions of cholate, chenodeoxycholate, and deoxycholate and their conjugation with glycine and taurine did not vary significantly in the three samples, and fell within the generally reported range for normal subjects.

Serum lipid concentrations showed significant fluctuations (fig 2). During the eight or nine days after mid-cycle, nine of the eleven women showed a fall in triglyceride concentrations, and eight a fall in cholesterol concentrations. Mean serum triglyceride concentrations (±standard error of mean) were 0·59±0·07 mmol/l (52·2±6·2 mg/100 ml) at the end of menstruation, 0·67±0·06 mmol/l (59·3±5·3 mg/100 ml) at mid-cycle, and 0·52±0·04 mmol/l (46·0±3·5 mg/100 ml) eight to nine days later. Serum cholesterol concentrations on the same occasions were 3·97±0·01 mmol/l (153·3±0·4 mg/100 ml), 3·92±0·16 mmol/l (151·4±6·2 mg/100 ml), and 3·63±0·16 mmol/l (140·2±6·2 mg/100 ml).

Women whose biliary cholesterol concentrations did not fall during the last part of the cycle were not the same as those with no fall in serum lipid concentrations during the eight to nine days after mid-cycle.

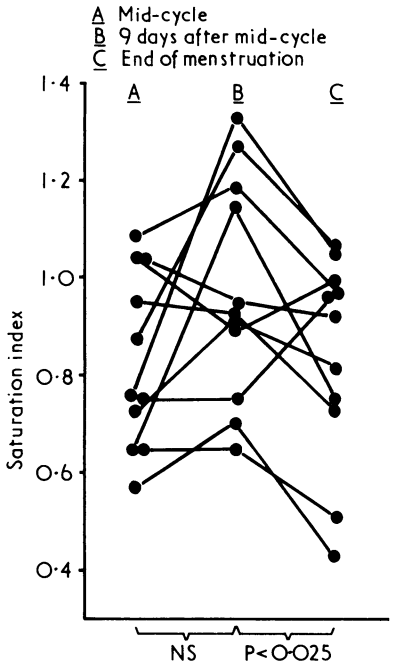

FIG 1—Bile cholesterol saturation index during menstrual cycle. (Index calculated according to equation of Thomas and Hofmann,[16] based on data of Hegart and Dam,[17] and Holzbach *et al.*[18])

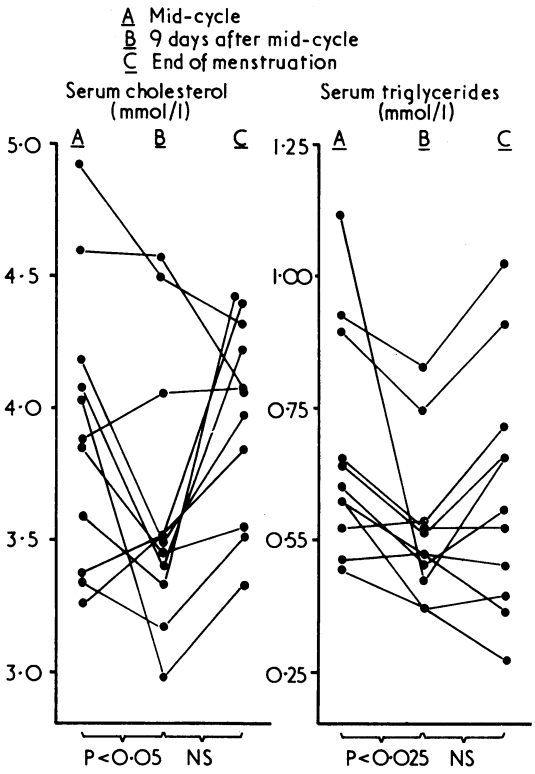

FIG 2—Serum cholesterol and triglyceride concentrations during menstrual cycle.

Conversion: SI to traditional units—Serum cholesterol 1 mmol/l ≈ 38·6 mg/100 ml; triglyceride 1 mmol/l ≈ 88·5 mg/100 ml.

TABLE I—*Mean biliary lipid concentration (±standard error of mean) in 11 women at three intervals during normal menstrual cycle. Relative concentrations of lipids are expressed as cholesterol saturation index*

	End of bleeding	Mid-cycle	Eight to nine days after mid-cycle
Total (mmol/l)	40·9 ± 7·5	41·3 ± 8·4	45·1 ± 13·6
Cholesterol (% of total)	5·3 ± 0·4	5·1 ± 0·5	6·3 ± 0·5*
Phospholipid (% of total)	20·5 ± 0·7	19·7 ± 1·3	21·5 ± 1·7
Bile salt (% of total)	74·3 ± 0·9	75·2 ± 1·8	72·2 ± 1·9
Cholesterol saturation index	0·83 ± 0·06	0·83 ± 0·05	0·98 ± 0·07*

*Significantly different from end of bleeding ($P < 0·025$).

Discussion

This study shows that saturation of bile with cholesterol, and therefore the tendency for cholesterol-rich gall stones to form, fluctuates during the menstrual cycle. The average saturation index of bile was 18% greater eight to nine days after mid-cycle than at the end of bleeding. Bennion *et al*[24] could find no appreciable variation in bile composition during the menstrual cycle, but they studied only six women and the average cholesterol concentration fell during the same part of the cycle as in our study. Serum cholesterol and triglyceride concentrations also fluctuated, serum lipid concentrations falling during the eight to nine days after mid-cycle, after which time bile cholesterol concentrations had generally reached a peak and were themselves about to fall. More frequent sampling would be necessary to show the precise timing and extent of the cyclical changes, and to relate the fluctuations we have observed to each other or to individual hormone concentrations.

The changes in serum and biliary lipid composition during the menstrual cycle are probably due to a direct effect of sex hormones on the liver. Conceivably fluctuations in the efficiency of gall bladder emptying with the different phases of the

menstrual cycle might also affect bile lipid secretion, since the gall bladder acts both to concentrate bile and to regulate its flow into the intestine. Indeed, emptying of the gall bladder in response to injected cholecystokinin has been shown to be less during the second half of the cycle.[25] Variable gall bladder function probably did not contribute to the variations in biliary cholesterol saturation which we found, since there were no significant differences in the total concentration of lipid in the bile samples (table I).

It has long been known that serum cholesterol concentrations fluctuate during the menstrual cycle. In two reports serum cholesterol concentrations were found to be highest at about ovulation, falling subsequently,[26 27] as in the present study. A cyclical fluctuation in serum triglyceride concentrations averaging more than 20% appears to be a new finding. This is compatible with the observation of a mid-cycle peak in the concentration of very low-density lipoprotein (VLDL), the principal lipoprotein carrying endogenous triglycerides.[28] The same workers also showed a mid-cycle peak in the concentration of high-density lipoproteins, and, since these, together with VLDL, normally contain a third to a half of the total cholesterol in serum, fluctuations in the concentrations of these lipoproteins probably account for the serum cholesterol findings.

The changes in the concentrations of lipids in serum and bile during the menstrual cycle raise the fascinating question of whether one is dependent on the other or whether both are independently related to changes in sex hormones. In view of these cyclical variations, we recommend that in any studies requiring measurements of serum and bile lipid concentrations in women of childbearing age, samples should be taken at standard points in the menstrual cycle.

Requests for reprints should be addressed to: T S Low-Beer, Department of Gastroenterology, Selly Oak Hospital, Birmingham B29 6JD.

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Treatment of atopic eczema in children: clinical trial of 10% sodium cromoglycate ointment

S A HAIDER

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Summary

In a double-blind randomised group-comparative trial 21 children with chronic atopic eczema were treated twice daily for up to 12 weeks with an ointment containing 10% sodium cromoglycate (SCG) in white soft paraffin. A similar group of 21 children was treated for up to 12 weeks with a placebo ointment consisting of the white soft-paraffin base only. The number of patients who withdrew from the trial because treatment was ineffective was significantly greater in the placebo group (16) than in the SCG group (four). Comparison between the two groups also showed significant improvement in inflammation, lichenification, and cracking, and the symptoms of itching and sleep disturbance among those on SCG treatment. At the end of treatment significantly more patients in the SCG group (16) had benefited from treatment compared with only two patients in the placebo group. No patients experienced side effects. I conclude that SCG ointment may be a safe alternative to topical steroids in the treatment of atopic eczema in children.

Bury General Hospital, Bury, Lancs BL9 6PG
S A HAIDER, MRCPE, DCH, consultant paediatrician

Introduction

Sodium cromoglycate (SCG) is effective in the treatment of asthma[1] (Intal), rhinitis[2] (Rynacrom, Lomusol), vernal keratoconjunctivitis[3] (Opticrom), and proctocolitis.[4] The drug acts by inhibiting the release of the chemical mediators of the immediate (type I) hypersensitivity reaction. Inhibition of type III reactions has also been shown in asthma.[5]

Eczema is a skin disorder often associated with a high incidence of atopy.[6] Initial investigations[7] in the treatment of a few patients with atopic eczema and contact dermatitis using up to 4% SCG, either as an aqueous solution injected intra-