ORAL CONTRACEPTIVE USE AND MALIGNANCIES OF THE GENITAL TRACT

Results from The Royal College of General Practitioners' Oral Contraception Study

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Summary Of 47 000 women followed since 1968, those who had used oral contraceptives (ever-users) had a significantly higher incidence rate of cervical cancer than never-users. After standardisation of rates by age, parity, smoking, social class, number of previously normal cervical smears, and history of sexually transmitted disease, the excess was 41 per 100 000 woman-years for carcinoma-in-situ and 8 per 100 000 woman-years for invasive cervical cancer. Incidence increased with increasing duration of use: the standardised incidence rate for cervical cancer in women who had taken the pill for more than 10 years was four times that in never-users. Ever-users had a lower incidence of other uterine cancers (deficit 5 per 100 000 woman-years); a lower incidence of ovarian cancer was also found (deficit 4 per 100 000), but was not statistically significant. Overall, ever-users had an excess incidence for genital tract cancers of 37 per 100 000 woman-years. This excess was mainly from carcinoma-in-situ of the cervix; the excess incidence of invasive cervical cancer was offset by the deficits in other uterine and ovarian cancers. Standardised mortality rates from genital cancer were similar in ever-users and never-users. Of relevance to clinical practice is the substantially different distribution of primary cancer sites: cervical cancer accounted for 75% of the invasive genital cancers and 74% of deaths from genital cancer in ever-users, but only 31% of the invasive cancers and 30% of deaths in never-users.

Introduction

WOMEN who have used oral contraceptives (ever-users) have a higher risk of cancer of the uterine cervix,[1-4] and a lower risk of endometrial[5-8] and ovarian[9-11] cancer than women who have never used the pill (never-users). The observed excess of cervical cancer in ever-users is thought to be balanced by the reduction in ovarian and endometrial cancer, but no data have been available to permit direct comparison of the incidence of, or mortality from, these cancers in a population.[12] We report the incidence and mortality rates from cancers of the genital tract among 47 000 women in the United Kingdom followed from May, 1968, until April, 1987.

Methods

The Royal College of General Practitioners' Oral Contraception Study has been described in detail.[13] Briefly, during a 14-month period beginning in May, 1968, over 23 000 women taking oral contraceptives and an equal number of controls who had never taken the pill were recruited by 1400 general practitioners throughout the UK. Twice a year, the general practitioners report details on contraceptive use and morbidity and mortality for each of their study subjects who remain under observation. Data are coded according to the 8th Revision of the International Classification of Diseases (ICD).[14]

For each month of observation, women are classified as current-users, former-users, or never-users of oral contraceptives. In this analysis, current-users and former-users are grouped together as ever-users. Never-users who later began to use the pill are included in the ever-user group from the time of change. For analyses of incidence rates, periods of observation and associated events are excluded after women have a hysterectomy. The total time of observation in this analysis is 257 028 woman-years for ever-users and 182 866 woman-years for never-users. Morbidity and mortality rates are adjusted by indirect standardisation, the total study population being taken as the standard:[15] rates are adjusted for age (15–19, 20–24, &c); parity (0, 1, 2–3, 4+); cigarette consumption at entry (0, 1–14, 15+ cigarettes per day); social class at entry (I with II, III, IV with V, and other); number of previously normal Papanicolaou smears (0, 1, 2, 3+); and history of sexually transmitted disease (ICD 098–099).

Ever-users and never-users are compared by estimation of both the ratio of and the difference between the standardised rates in the two groups, with adjustments for the same factors. Statistical significance is calculated as a two-sided χ^2 test and confidence intervals are estimated by Miettinen's method.[16] Tests of linear trend are obtained by comparison of the mean exposure observed with that expected if no trend occurred, with a standard normal deviate.

Data on the number of previously normal cervical smears were checked in 1987 by a survey of a random sample of 100 general practitioners who still participated in the study. They were asked to list all the cervical smears noted in their clinical records for 2 randomly selected study subjects. Replies for 189 (95%) women were obtained and were compared with information previously reported for the same women.

For analysis of mortality trends, rates were calculated from data for England and Wales from the Office of Population Censuses and Surveys. Age-specific mortality rates were calculated for 5-year periods, beginning in 1950–54, and ending in 1980–84. The causes of death examined were cervical cancer (ICD 180); uterine cancer other than cervical cancer (ICD 7th and 8th: 181, and 182; 9th: 179, 181, and 182); and ovarian cancer (ICD 183).

TABLE I—INCIDENCE OF MALIGNANCIES OF GENITAL TRACT BY ORAL CONTRACEPTIVE USE

Cancer site (ICD)	Incidence (no)		Ever-users *vs* never-users	
	Ever-users	Never-users	Relative incidence (95% CI)	Difference in incidence (95% CI)
Cervix—invasive (180)	18 (49)	10 (16)	1·8 (1·0, 3·3)	8 (0·3, 15·7)
—carcinoma-in-situ (234·0)	62 (173)	21 (34)	2·9 (2·0, 4·1)	41 (27·3, 54·7)
Uterus, except cervix (181–182)	1 (2)	6 (16)	0·2 (0·0, 0 7)	−5 (−8·9, −1 1)
Ovary (183)	5 (12)	9 (18)	0·6 (0·3, 1·4)	−4 (−10·6, +2·6)
Vagina (184·0)	0·4 (1)	0 (0)	. .	. .
Vulva (184·1)	0·3 (1)	1 (1)	. .	. .
Total—all	87 (234)	50 (85)	1·7 (1·4, 2·2)	37 (20·4, 53·6)
—excluding cervical carcinoma-in-situ	26 (65)	27 (51)	1·0 (0·5, 1·7)	−1 (−14·9, +12·0)

Incidence per 100 000 woman years (number of cases), standardised for age, parity, smoking, social class, number of previously normal cervical smears, and history of sexually transmitted diseases.
. . Inadequate numbers to calculate risk.
(Women with more than 1 primary cancer counted only once in the totals.)

TABLE II—INCIDENCE OF CERVICAL AND OVARIAN MALIGNANCIES BY ORAL CONTRACEPTIVE USE ACCORDING TO AGE, PARITY, SMOKING, AND SOCIAL CLASS

—	Cervical carcinoma-in-situ			Cervical invasive cancer			Ovarian cancer		
	Ever-users	Never-users	Relative incidence	Ever-users	Never-users	Relative incidence	Ever-users	Never-users	Relative incidence
Age (yr)									
<25	19 (4)	0 (0)	∞	0 (0)	8 (1)	0·0	0 (0)	0 (0)	–
25–34	71 (68)	21 (13)	3·4*	15 (14)	8 (5)	1·8	3 (3)	3 (2)	1·0
35–44	83 (82)	18 (13)	4·5*	24 (24)	6 (4)	4·3*	5 (5)	10 (7)	0·5
45–54	45 (17)	24 (8)	1·9	24 (9)	9 (3)	2·7	11 (4)	24 (8)	0·4
55+	44 (2)	0 (0)	∞	33 (2)	84 (3)	0·4	0 (0)	9 (1)	0·0
Parity									
0	11 (2)	8 (1)	1·4	45 (2)	0 (0)	∞	15 (1)	0 (0)	∞
1	71 (24)	6 (2)	12·5*	7 (2)	7 (3)	1·0	5 (1)	9 (5)	0·5
2–3	61 (111)	22 (20)	2·8*	14 (25)	10 (9)	1·4	4 (6)	11 (12)	0·4
4+	76 (36)	59 (11)	1·3	41 (20)	23 (4)	1·8	8 (4)	5 (1)	1·5
No cigarettes smoked/day†									
0	44 (59)	9 (10)	4·8*	14 (18)	3 (3)	5·4*	6 (6)	8 (12)	0·7
1–14	70 (55)	20 (8)	3·6*	19 (15)	17 (7)	1·1	4 (3)	7 (3)	0·6
15+	99 (59)	79 (16)	1·3	27 (16)	29 (6)	0·9	6 (3)	12 (3)	0·5
Social class†									
I & II	47 (27)	12 (5)	3·9*	13 (8)	9 (3)	1·5	4 (2)	14 (6)	0·3
III	59 (94)	23 (20)	2·6*	18 (28)	10 (9)	1·9	6 (8)	7 (8)	0·9
IV & V	89 (50)	30 (9)	3·0*	21 (11)	12 (4)	1·8	5 (2)	8 (4)	0·7
Other	38 (2)	0 (0)	∞	39 (2)	0 (0)	∞	0 (0)	0 (0)	–

Incidence per 100 000 woman-years (no), standardised for age, parity, smoking, social class, number of previously normal cervical smears, and history of sexually transmitted diseases.
*$p < 0.05$.
†At recruitment.

Results

Ever-users of oral contraceptives had an excess of invasive cervical cancer and of carcinoma-in-situ of the cervix, and a deficit of all other cancers of the uterus ($p < 0.05$, see table I; all but one of the cancers in the "uterus, except cervix" category were described as endometrial cancer). The deficit of ovarian cancer is not statistically significant. When the rates for all cancers of the genital tract are combined there is a significant excess of 37 cases per 100 000 woman-years in ever-users but, if carcinoma-in-situ of the cervix is excluded, the total incidence of invasive cancers is similar in ever-users and never-users.

Cervical cancer accounted for 75% of the invasive genital cancers in ever-users but only 31% of such malignancies in never-users. Ovarian cancer accounted for 18% of the invasive cancers in ever-users, but 35% in never-users ($p < 0.001$ for the different distribution of primary sites).

Table II shows the standardised incidence rates for cervical cancer (invasive and carcinoma-in-situ) and ovarian cancer in oral contraceptive ever-users and never-users according to age, parity, smoking, and social class, respectively. There are too few cases of other genital cancers for individual analysis. When ever-users and never-users are examined separately, cervical cancer incidence tends to increase with age, parity, amount smoked, and social class. Ovarian cancer incidence also increases with age, but shows little relation to parity, smoking habit, or social class. Rates for carcinoma-in-situ and invasive cancer of the cervix are, with few exceptions, higher in ever-users than never-users; ovarian cancer rates are generally lower in ever-users. These differences in incidence do not vary appreciably between the age, parity, smoking-habit, and social-class groups.

Table III shows the standardised incidence rates of cervical cancer, other cancers of the uterus, ovarian cancers, and all genital tract cancers combined, according to duration of oral contraceptive use. The incidence of carcinoma-in-situ and invasive cancer of the cervix increases significantly with an increasing duration of oral contraceptive use; after more than 10 years of use, the incidence is more than four times that in never-users. The incidence of other uterine and of ovarian cancer declines with increasing duration of use, but the trends are not statistically significant. For all genital cancers combined there is a significant increase with duration of use, but only when carcinoma-in-situ of the cervix is included. The contribution of cervical cancer to the total incidence of invasive genital cancer increases with duration of oral contraceptive use: invasive cervical cancer

TABLE III—INCIDENCE OF GENITAL TRACT CANCERS BY DURATION OF ORAL CONTRACEPTIVE USE

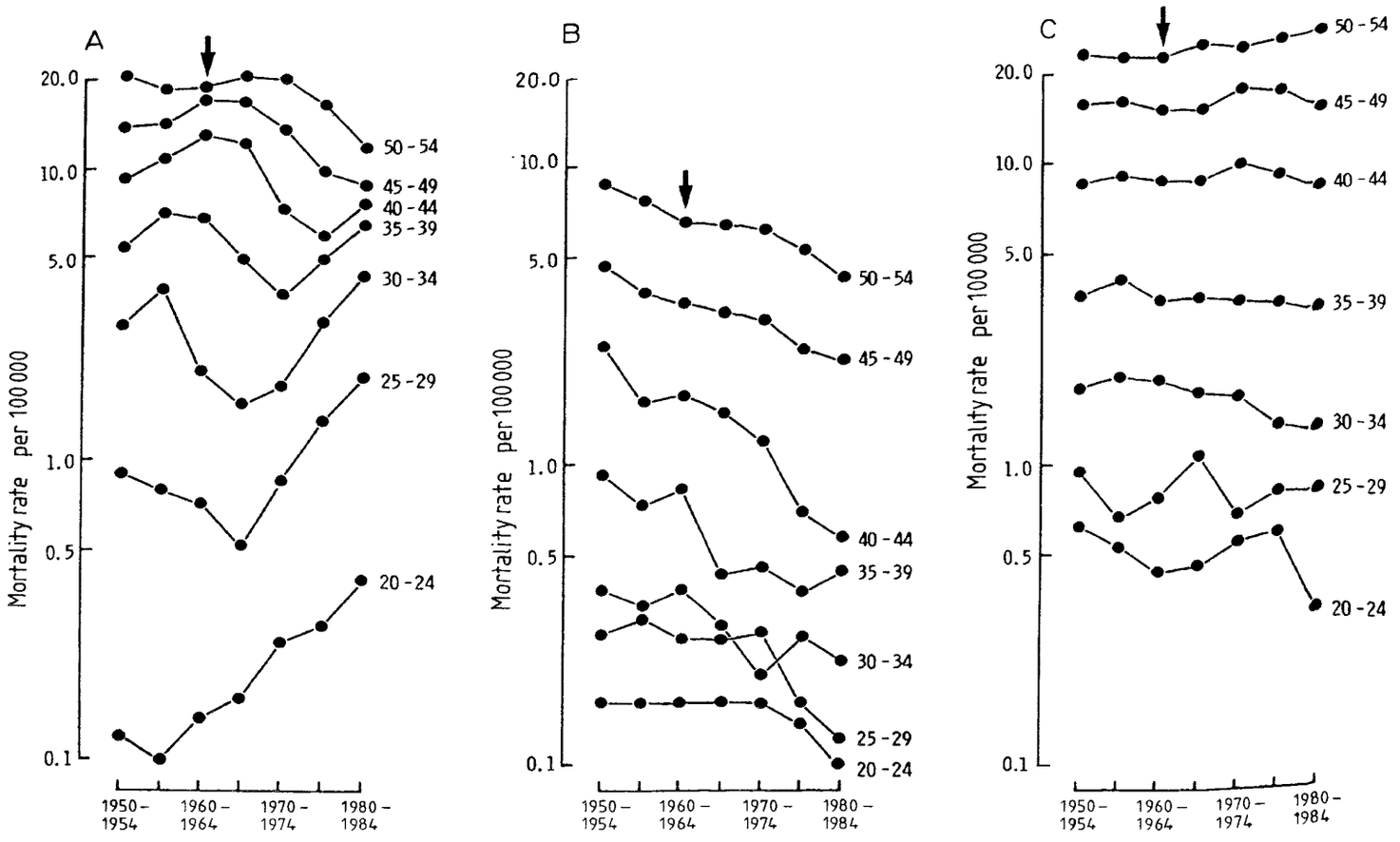
Duration of use (yr)	Incidence (no)					
					Total	
	Cervical carcinoma -in-situ	Cervical invasive cancer	Uterus except cervical cancer	Ovarian cancer	All genital cancer	Excluding in-situ cervical cancer
0	21 (34)	10 (16)	6 (16)	9 (18)	50 (85)	27 (51)
<5	50 (84)	13 (21)	1 (1)	7 (9)	72 (115)	23 (33)
5–9	76 (66)	20 (17)	1 (1)	3 (2)	101 (84)	26 (20)
10+	101 (23)	44 (11)	0 (0)	3 (1)	140 (35)	41 (12)
Z (trend, 1 df)	+7·36	+3·73	−1·20	−1·64	+5·86	+0·50
p	<0·001	<0·001	0·23	0·10	<0·001	0·62

Incidence per 100 000 woman-years (no), standardised for age, parity, smoking, social class, and number of previously normal cervical smears.

TABLE IV—INCIDENCE OF INVASIVE CERVICAL CANCER ACCORDING TO ORAL CONTRACEPTIVE USE AND NUMBER OF PREVIOUSLY NORMAL CERVICAL SMEARS

No previous normal smears	Incidence (no)	
	Ever-users	Never-users
0	19 (22)	11 (14)
1	25 (20)	6 (2)
2	8 (4)	0 (0)
3+	8 (3)	0 (0)
Z (trend, 1 df)	−1·61	−1·86
p	0·07	0·06

Incidence per 100 000 woman-years (no), standardised for age, parity, smoking, social class, and history of sexually transmitted diseases.



Age-specific mortality rates per 100 000 women in England and Wales, 1950–54 to 1980–84.
For cervical cancer (A); other uterine cancers (B); and ovarian cancer (C).
Arrows indicate the time when oral contraceptives were first introduced to the UK.

accounted for 64% of the invasive genital cancers in women who used the pill for less than 5 years, but for 88% of the cancers in women who used the pill for more than 5 years.

In ever-users and never-users the incidence of invasive cervical cancer tends to decline with the number of previous Papanicolaou smears (see table IV). In ever-users, however, the decline is not regular. In the retrospective survey to check the accuracy of the number of cervical smears recorded there was 89% agreement with the study records; agreement was similar for ever-users and never-users with no systematic differences between the two groups.

Table V shows mortality rates from genital cancers in ever-users and never-users. The patterns described for incidence—an excess of cervical cancer and a deficit of other uterine and ovarian cancers—persist for deaths, but the differences are no longer statistically significant. 5-year survival rates from cervical cancer were 67% in ever-users and 59% in never-users; and for ovarian cancer 50% and 41%, respectively. The total death rate from all genital cancers is similar in ever-users and never-users.

TABLE V—MORTALITY FROM MALIGNANCIES OF GENITAL TRACT BY ORAL CONTRACEPTIVE USE

Cancer site (ICD)	Mortality (no deaths)		Ever-users *vs* never-users	
	Ever-users	Never-users	Relative mortality (95% CI)	Difference in mortality (95% CI)
Cervix (180)	5·6 (14)	3·2 (6)	1·8 (0·5, 5 6)	2·4 (−2 6, +7·4)
Uterus, except cervix (181, 182)	0·0 (0)	0 7 (2)	. .	. .
Ovary (183)	2·6 (5)	4·4 (11)	0·6 (0·1, 2·3)	−1 8 (−6·7, +2·9)
Vulva (184·1)	0·0 (0)	0·8 (1)	. .	. .
Total	8·4 (19)	9·3 (20)	0·9 (0·2, 3·4)	−0·9 (−13·4, +11·6)

Mortality per 100 000 woman-years (no), standardised for age, parity, smoking, social class, number of previously normal cervical smears, and history of sexually transmitted diseases.
. . Inadequate numbers to calculate risk.

The figure shows female mortality trends by age in England and Wales since 1950 for cervical cancer, other uterine cancers, and ovarian cancer. The arrows indicate the time when oral contraceptives were first available in England and Wales, although they were not widely used until the late 1960s.[17] There has been a striking increase in mortality from cervical cancer in young women since the 1960s, which was first seen in 20- to 24-year-olds and has spread to progressively older women—characteristic of a birth-cohort effect. Mortality from uterine cancer other than cervical cancer (mainly endometrial cancer) has declined at all ages, the downward trend being evident before the 1960s and greatest below 45 years of age since then. Mortality from ovarian cancer has decreased for women under 50 years old, especially since the early 1970s.

Discussion

The findings from this cohort study of 47 000 women confirm other published data that women who have used oral contraceptives have a higher incidence of cervical cancer and a lower incidence of endometrial and ovarian cancer than women who have never used oral contraceptives.[1-11] No special group could be identified in which the overall excesses or deficits differed substantially from the rest. Incidence rates were standardised by age, parity, smoking,

social class, number of previously normal cervical smears, and history of sexually transmitted disease; therefore the differences observed between ever-users and never-users are not due to these factors. The Oral Contraception Study relies on data collected by general practitioners during normal consultations; information on sexual practices was not collected, although a woman's past history of sexually transmitted disease was included as a potential confounding factor and this should, in part at least, adjust for differences in exposure to sexually transmitted agents. Information on social class and cigarette consumption was recorded at the time of recruitment but not since then. Changes in these characteristics should not greatly bias the comparisons because past social and behavioural factors are probably more important for cancer induction than are recent ones.

By April, 1987—the end of the follow-up period for this analysis—63% of the women enrolled in the study were no longer under observation, largely because patients had left the general practitioner who recruited them. Those who have left still contribute to the total period of observation up to that time, therefore the loss of woman-years of observation is less. Moreover, the groups of ever-users and never-users who left had almost identical characteristics, so their loss should not materially bias the results.

The incidence of cervical cancer increases steadily with an increased duration of oral contraceptive use: in women who had taken the pill for more than 10 years, the incidence was more than 4 times the rate in never-users. In this study, information on oral contraceptive use was obtained before the diagnosis of cancer was made, in contrast with the case-control data collection for most other investigations of the relation between genital cancer and oral contraceptive use.[3-11] Our findings cannot therefore be attributed to bias in reporting of oral contraceptive use.

Women who have never used the pill may have a low rate of cervical cancer because they have used barrier methods of contraception. Data on the use of other methods of contraception were collected at recruitment, and women who reported use of barrier methods can be excluded. For the remaining never-users, the incidence of cervical cancer was 9 per 100 000 woman-years for invasive disease (10 cases) and 17 per 100 000 woman-years for carcinoma-in-situ (18 cases): these rates are lower than the corresponding rates of 18 and 62 per 100 000, respectively, in ever-users (table I). Differential use of barrier methods of contraception is therefore unlikely to explain the difference in cervical cancer rates between ever-users and never-users, although data on use of barrier methods were only collected at recruitment.

Our data allow direct comparison of the incidence and mortality from cancers of the genital tract in women who have and have not used oral contraceptives. For all malignancies of the genital tract combined, there is an excess incidence in oral contraceptive users of 37 per 100 000 woman-years, mainly because of an excess of carcinoma-in-situ of the cervix. When cervical carcinoma-in-situ is excluded, incidence rates are roughly similar (table I), as are mortality rates (table V). However, the distribution of primary sites differs substantially according to history of oral contraceptive use. Cervical cancer accounted for only one-third of the invasive cancers and deaths in never-users but three-quarters of the invasive cancers and deaths in ever-users. In long-term pill users, the contribution of cervical cancer to the total is greater still.

Since invasive cervical cancer is potentially preventable by effective screening, special attention should be given to its early detection in ever-users of the pill. The data in table IV are based on small numbers, but suggest that screening by Papanicolaou smears may not be as effective in ever-users as in never-users. Other studies have shown a halving of the rate of invasive cervical cancer in women who have had one negative smear compared with women who have never had a smear, and a further reduction if two smears have been negative.[18,19] The finding here in never-users is consistent with those data, but in ever-users the trend is irregular. However, firm conclusions cannot be drawn because of the small numbers and the lack of comparable information from elsewhere. Further evaluation of the effect of pill use on the effectiveness of screening for cervical cancer is needed.

Are the associations between oral contraceptives and genital cancer causal, or secondary to other factors? It has been argued that the raised incidence of cervical cancer in oral contraceptive users is not a direct effect of the hormonal agents, but secondary to different sexual practices between oral contraceptive users and non-users; the lower incidence of ovarian and endometrial cancer in oral contraceptive users may be attributable to never-users including a disproportionate number of infertile women, who have increased risks of ovarian and endometrial cancer. However, in this and other studies,[1-11] the associations with oral contraceptive use persist after adjustment for other known risk factors. There might, however, still be residual confounding. Similar relations have been found irrespective of the population surveyed and type of study design. That the incidence rates are related to duration of pill use suggests a causal association. Moreover, national mortality trends are in the direction expected if oral contraceptives were to increase the risk of cervical cancer and to reduce the risk of endometrial and ovarian cancers, although changes in sexual practices, childbearing patterns, and other factors may well have influenced these trends. None of these considerations is conclusive alone, but taken together they suggest a causal association between oral contraceptives and a changed incidence of genital cancers. The clinical implications remain the same, regardless of whether or not the associations are causal.

Genital cancers are not the only conditions affected by oral contraceptive use. An excess overall mortality rate in oral contraceptive users of 20 per 100 000 woman-years has been described in this study population,[20] almost entirely because of circulatory diseases. Knowledge of the long-term effects of oral contraceptives is still incomplete, especially for breast cancer; the overall effects of oral contraceptive use cannot yet be fully assessed.

We thank the 1400 general practitioners who contributed data for this survey. The study is supported by the Medical Research Council. The costs of pilot trials and supplementary expenditure have been met by the Scientific Foundation Board of the Royal College of General Practitioners. The Board thanks Organon, Ortho, Schering, Searle, Syntex, and Wyeth for financial support. We are grateful to Ms Lucy Carpenter for help with the statistical analysis and to Ms Nina Saroi for preparing the typescript.

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EFFECTS OF SIMVASTATIN AND CHOLESTYRAMINE ON LIPOPROTEIN PROFILE IN HYPERLIPIDAEMIA OF NEPHROTIC SYNDROME

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Summary The efficacy, safety, and tolerability of simvastatin (20 mg twice a day) in the treatment of hyperlipidaemia due to unremitting nephrotic syndrome was compared with that of cholestyramine (8 g twice a day) in a crossover trial in ten patients. Two patients were taken off the protocol, one because he could not tolerate cholestyramine and one because of non-compliance with the cholestyramine regimen. No clinical or laboratory adverse experiences were noticed during the study in the other eight patients. Simvastatin was significantly more effective than cholestyramine in reducing the hyperlipidaemia—it produced a 36% decrease in total cholesterol and a 39% decrease in low density (LDL)-cholesterol, whereas cholestyramine reduced total cholesterol by 8% and LDL-cholesterol by 19%. With simvastatin the apolipoprotein B level decreased by 30%, whereas the apolipoprotein A level increased by 10%.

Introduction

THERE is no unanimity on the clinical consequences of the hyperlipidaemia of the nephrotic syndrome, which is characterised by raised total and low-density (LDL) cholesterol levels with normal or reduced high-density lipoprotein (HDL) cholesterol,[1,2] an abnormality associated with accelerated atherosclerosis in non-nephrotic patients.[3] Studies demonstrating accelerated atherosclerosis were confounded by inclusion of patients with diabetes mellitus, on steroid treatment, or with renal failure,[4] whereas studies that did not establish a relation between nephrotic hyperlipidaemia and accelerated atherosclerosis can be criticised for inclusion of patients who were in remission and for not specifying death due to chronic renal failure.[5]

Hyperlipidaemia may also be regarded as a pathogenic factor in the development of focal and segmental glomerulosclerosis.[6] Recent studies have shown that lipid-lowering therapy reduced the incidence of focal glomerulosclerosis in a remnant kidney model[7] and in obese rats in which glomerulosclerosis develops spontaneously.[8] In addition, cholesterol supplementation accelerated the development of focal glomerulosclerosis and aggravated proteinuria in a rat model of the nephrotic syndrome.[9]

Few controlled studies have been carried out to assess the efficacy of lipid-lowering drugs in nephrotic hyperlipidaemia, and none of the drugs investigated restored to normal the lipid abnormalities associated with nephrotic syndrome.[10,11] Recently, inhibition of the rate-controlling enzyme of cholesterol synthesis (3-hydroxy-3-methylglutaryl coenzyme A reductase, or HMG CoA reductase) has proved to be a very effective treatment in primary hypercholesterolaemia[12,13] and secondary hypercholesterolaemia due to diabetes mellitus.[14] Here we describe a crossover trial comparing the effects of 6 weeks' treatment with the HMG CoA reductase-inhibitor simvastatin[13] with those of the bile-acid binding resin cholestyramine on the lipoprotein pattern in ten patients with long-standing unremitting nephrotic syndrome.

Patients and Methods

Patients

The subjects were ten patients with nephrotic syndrome as defined by proteinuria in excess of 3 g per day. Informed consent was obtained and the study was approved by the University Hospital Committee for Studies in Humans. All patients had a total cholesterol of 8·5 mmol/l or more at the start of the study. Subjects were aged 30–75 years; seven were men. The diagnoses (biopsy proven) were: membranous glomerulonephritis (6), focal glomerulosclerosis (2), mesangiocapillary glomerulonephritis (1), and lupus nephritis (1). None of the patients had diabetes mellitus. No patient was known to have a family history of lipid abnormalities. Thyroid function was normal in all patients. The known duration of the nephrotic syndrome ranged from 8 to 46 months. In all patients oedema was treated with diuretics. One patient also received steroids. Dosages of diuretic and steroid medication were unchanged during the study period.

TABLE I—EFFECTS OF SIMVASTATIN AND CHOLESTYRAMINE ON LIVER FUNCTION AND CREATININE KINASE IN 8 PATIENTS WITH NEPHROTIC SYNDROME

—	Placebo	Simva-statin	Placebo	Cholesty-ramine	Ref range
ALT (U/l)	13·6 (3·4)	16·4 (7·7)	16·0 (7·8)	20·7 (16·5)	2–30
AST (U/l)	15·2 (1·7)	15·7 (5 1)	16·9 (6 2)	22·6 (8 1)	2–30
Alkaline phophatase (U/l)	69·5 (21·1)	66·9 (17·8)	67·5 (22·4)	72·2 (28·1)	35–140
Total bilirubin (μmol/l)	5·5 (2·5)	6·0 (2·3)	5·3 (2·7)	5·9 (3 1)	0–17
Creatinine kinase (U/l)	53 6 (17·7)	57·4 (24·2)	53 9 (23·8)	56·7 (25 7)	10–120

Findings given as means (SD).
There were no significant changes between the various treatment periods.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Ref range = reference range.

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