Skin disorders in relation to oral contraception and other factors, including age, social class, smoking and body mass index. Findings in a large cohort study

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Summary

Background Over the years, a substantial number of scientific papers has been published considering the possible relationship between oral contraceptive use and various skin disorders.

Objectives We aimed to investigate the possible effects of oral contraceptives and other factors including age, social class, smoking and body mass index on the occurrence of hospital referral for skin disorders within the Oxford Family Planning Association (Oxford-FPA) contraceptive study. Methods We carried out a cohort study with long-term follow up of 17,032 women aged 25–39 years recruited at 17 family planning centres in England and Scotland between 1968 and 1974. The main outcome measure was the pattern of referral to hospital for skin disorders among the participants. The conditions considered (number of women affected in parentheses) were: malignant melanoma (48); other skin cancers (83); benign skin neoplasms (384); boils and cellulitis (334); eczema and dermatitis (327); erythematous disease (54); psoriasis (92); hypertrophic and atrophic conditions (59); diseases of the nails (80); diseases of the hair and hair follicles (74); diseases of the sebaceous glands (362); pigmented naevi (383); and unspecified eruptions (199). Some of these disease categories are broad, which complicates interpretation of the findings.

Results As the data relate to hospital referrals, while most skin disorders are largely managed within primary care, it is difficult to know to what extent our findings can be generalized to disease patterns in the community. None the less, a number of interesting results emerged. These included increased risks (approximately twofold) of referral to hospital for boils and cellulitis in heavy women, for psoriasis in women who smoke, and for pigmented naevi in women of higher social class. Referral for pigmented naevi was reduced by about half in women with a high body mass index. Of the oral contraceptive associations studied, we consider that only an increased risk of referral for eczema or dermatitis in current or recent pill users (relative risk $1\cdot6$, 95% confidence interval $1\cdot2-2\cdot1$) might reflect a causal relationship. There was no increased risk in past users nor was the risk related to duration of use. These findings are very similar to those reported from the Royal College of General Practitioners oral contraception study.

Conclusions Hospital referral for certain skin disorders was related to age, social class, smoking and body mass index within the Oxford-FPA study. Hospital referral for skin disorders generally seems to be unrelated to oral contraceptive use within the study, the possible exception being eczema and dermatitis, which occur more commonly in current and recent pill users than in non-users.

Key words: cohort study, oral contraception, skin disorders

Over the years, a substantial number of scientific papers has been published considering the possible relationship between oral contraceptive use and various skin disorders. Many of these have been concerned

Correspondence: Professor M.P.Vessey. E-mail: martin.vessey@dphpc.ox.ac.uk with malignant melanoma; we reported our findings in the Oxford Family Planning Association (Oxford-FPA) contraceptive study in relation to this disease in 1991. Others, however, have concentrated on non-neoplastic conditions: a review by Ridley² drew attention to possible associations between pill use and acne, thinning of

the hair, chloasma, photosensitivity, herpes gestationis and a number of other conditions.

Referral to hospital for diagnosis and management of skin disorders (both neoplastic and non-neoplastic) has been a frequent event in the Oxford-FPA study. We considered it would be of value to analyse the available data to see if we could detect any important associations between oral contraceptive use and the range of skin conditions covered by the study. We also decided to investigate the effects of age and a number of other factors including social class, smoking and body mass index on the risk of skin disorders in view of the paucity of epidemiological information on these topics.

Subjects and methods

A detailed description of the methods used in the Oxford-FPA study has been given elsewhere.³ In brief, 17,032 women were recruited at 17 large family planning clinics in England and Scotland between 1968 and 1974. At the time of recruitment, each woman had to be: (i) aged 25-39 years; (ii) married; (iii) white and British; (iv) willing to co-operate; and (v) either a current user of oral contraceptives of ≥ 5 months standing or a current user of a diaphragm or an intrauterine device of ≥ 5 months standing without previous exposure to the pill. Among other items, each woman was asked questions at entry to the study about her age, child-bearing history, contraceptive history, height and weight, social class, smoking behaviour and past medical history.

During follow-up, each woman was questioned by a doctor or a nurse at return visits to the clinic and certain items of information were noted. These included details of pregnancies and their outcome, changes in contraceptive practices and reasons for the changes, and particulars of any referrals to hospital either as an out-patient or an in-patient. Diagnoses on discharge from hospital after an in-patient spell were confirmed by obtaining copies of discharge letters, summaries and pathology reports. Women who stopped attending the clinic were sent a postal version of the follow-up form and, if this was not returned, were interviewed by telephone or at a home visit. The work was co-ordinated by a part-time research assistant in each clinic and yearly follow-up was maintained until age 45 years, with an annual loss of contact of only about 0.4%. All diagnostic coding throughout the study was done by one of us (M.P.V.) to avoid interobserver variation.

On reaching the age of 45 years, each woman was

allocated to one of three groups: (i) oral contraceptives never used; (ii) oral contraceptives used for a total of ≥8 years; and (iii) other durations of oral contraceptive use. Only the women in the first two groups were followed up annually in the detailed way already described until the end of the study in mid-1994. Accordingly, women in the third group have been omitted from the present analysis from age 45 years onwards.

This analysis is based on the computation of woman years of observation terminated by the occurrence of the first referral to hospital for the skin condition under consideration, by release from follow-up (emigration, death, short-term pill users reaching age 45 years), by loss to follow-up, by withdrawal of co-operation or by the end of the study (July 1994). Information about social class, smoking, height, weight and body mass index was available only from the initial recruitment form. Information about age, parity and contraceptive practices was, however, also available from the followup forms, and this information was taken into account in the computation of woman years of observation. Both in-patient and out-patient referrals to hospital were included in the analysis. Out-patient diagnoses for conditions other than malignant tumours were generally self-reported by the women concerned without confirmation being sought from the consultant. Indirectly standardized disease rates were calculated by the method described by Vessey et al.3 and tests of significance and the calculation of 95% confidence intervals (CIs) were based on methods described by Breslow and Day.4

Results

A decision was made at the outset to focus on disease categories including 50 or more affected women. The only exception to this rule concerns the data on malignant melanoma, which have been included even though only 48 women developed this disease.

Table 1 shows the skin disorders under consideration and the numbers of women with hospital referral for the different disorders. The most commonly occurring conditions within the heading erythematous disease (International Classification of Diseases, ICD rubric 695) were erythema nodosum and rosacea. Within the heading hypertrophic and atrophic conditions (ICD rubric 701), the most common conditions were localized scleroderma and keloid scar. Alopecia made up almost 90% of the disorders coded to ICD rubric 704 (diseases of the hair and hair follicles), while over 90%

Table 1. Summary of associations between first referral rates for skin diseases (International Classification of Diseases 8 rubrics in parentheses) and age, parity, social class, smoking, height, weight and body mass index. The rates on which the table is based were standardized for age

	No. of			Social				Body mass
Disease or disease group	women	Age	Parity	class	Smoking	Height	Weight	index
Malignant melanoma (172)	48	11	_	_	_	_	_	_
Other skin cancers (173)	83	† ††	_	1	_	_	_	_
Benign skin neoplasms (216)	384	111	_	1	_	_	_	_
Boils and cellulitis (680-682)	334	_	_	_	1	1	111	11
Eczema and dermatitis (692)	327	$\downarrow\downarrow\downarrow$	_	_	_	_	_	_
Erythematous disease (695)	54	_	_	_	_	_	_	_
Psoriasis (696)	92	_	_	_	111	_	_	_
Hypertrophic and atrophic conditions (701)	59	_	_	_	_	_	_	_
Diseases of nails (703)	80	† ††	_	1	_	_	111	_
Diseases of hair and hair follicles (704)	74	_	_	_	_	_	_	_
Diseases of sebaceous glands (706)	362	_	_	_	1	_	_	_
Pigmented naevus (757·1)	383	11	_	111	_	1	_	‡ ‡
Skin eruption not otherwise specified (788·2)	199	1	_	_	-	_	_	_

1, Positive association; \downarrow , negative association; \neg , no association; one arrow P < 0.05; two arrows P < 0.01; three arrows P < 0.001 (based on χ^2 trend). Groupings used in trend analysis: age (years) 25–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60+. Parity (term births) 0, 1, 2, 3, 4+. Social class (Registrar General's Classification) lower (IV–V plus armed forces, unemployed), middle (III), higher (I–II). Smoking (cigarettes per day) never, ex-smoker, 1–14, 15+. Height (cm) < 155, 155–164, \geq 165. Weight (kg) < 51, 51–57, 58–63, 64–70, > 70. Body mass index (kg m⁻²) < 20, 20–21·9, 22–23·9, 24–25·9, 26–27·9, \geq 28.

of the disorders coded to ICD rubric 706 (diseases of the sebaceous glands) were reported to be (sebaceous) cysts.

Table 1 also shows in summary form which relationships between the various first hospital referral rates and a range of other factors of potential interest reached statistical significance. The direction of the significant relationships is also indicated. Highly significant (P < 0.001) positive associations with age were found for other skin cancers (ICD rubric 173), benign skin neoplasms (ICD rubric 216) and diseases of the nails (ICD rubric 703). Eczema and dermatitis (ICD rubric 692) showed a highly significant negative association with age. Highly significant positive associations were also found with body weight for boils and cellulitis (ICD rubric 680-682) and for diseases of the nails (ICD rubric 703), with cigarette smoking for psoriasis (ICD rubric 696) and with social class for pigmented naevi (ICD rubric 757·1). Various other less highly significant associations were also found (see Table 1).

Table 2 provides some information concerning the

magnitude of the associations between first hospital referral rates for boils and cellulitis, psoriasis, diseases of the nails and pigmented naevi and the factors considered in Table 1. Relative risks are given for each condition, contrasting the extreme groups of each classification variable. These four conditions were chosen for inclusion in Table 2 because highly significant (P < 0.001) associations were found between them and factors other than age in Table 1. Only four of the relative risks given in Table 2 have a value of two or more, namely those for boils and cellulitis in relation to weight and for diseases of the nails in relation to age, social class and weight. Only two relative risks have a value of 0.5 or less, namely those for psoriasis in relation to age and for pigmented naevi in relation to body mass index.

The relationships between the various skin disorders and some simple measures of oral contraceptive use (adjusted for age) are summarized in Table 3. Only seven of the comparisons given in the table reached the

Table 2. Associations between first hospital referral rates for boils and cellulitis, psoriasis, diseases of the nails and pigmented naevi and the factors considered in Table 1. Data are relative risks and 95% confidence intervals (in parentheses) adjusted for age

Variable	Baseline group	Comparison group	Boils and cellulitis	Psoriasis	Diseases of nails	Pigmented naevi
Age (years)	25-34	55-59 ^a	1.0 (0.5-1.7)	0.2 (0.0-6.8)	4.9 (1.6-14.3)	1.5 (0.9-2.5)
Parity (no. of births)	0	4+	0.6 (0.3-1.1)	1.0 (0.4-2.5)	1.4 (0.4 - 6.4)	0.8 (0.5-1.4)
Social class	I–II	IV-V	$1 \cdot 1 \ (0 \cdot 7 - 1 \cdot 6)$	1.4 (0.6-2.9)	$2 \cdot 2 \ (1 \cdot 1 - 4 \cdot 2)$	0.6 (0.4 - 0.8)
Smoking (cigarettes per day)	Never	15+	1.3 (1.0-1.8)	1.9 (1.0 - 3.6)	$1 \cdot 1 \ (0 \cdot 5 - 2 \cdot 2)$	0.8 (0.6-1.1)
Height (cm)	< 155	≥ 165	1.5 (0.9 - 2.4)	0.6 (0.3-1.2)	1.9 (0.7 - 7.2)	1.3 (0.9 - 2.1)
Weight (kg)	< 51	> 70	$2 \cdot 0 \ (1 \cdot 2 - 3 \cdot 4)$	0.7 (0.2-2.2)	3.5 (1.2-12.2)	0.9 (0.6-1.5)
Body mass index (kg m ⁻²)	< 20	≥ 28	1.5 (0.9 - 2.7)	$1 \cdot 3 \ (0 \cdot 4 - 4 \cdot 0)$	1.6 (0.5-4.9)	0.5 (0.3-1.0)

 $^{^{\}rm a}$ This group was chosen for comparison because the 60+ group was small.

Table 3. Relative risks and 95% confidence intervals (in parentheses) for referral to hospital for various skin disorders in relation to oral contraceptive use. Women who had never used oral contraceptives have been taken as the reference category. Relative risks are adjusted for age (5-year groups)

	No. of	Oral contraceptive use				
Condition	women	Ever used ^a	Recently used ^b	Used in past ^c		
Malignant melanoma	48	0.8 (0.4-1.4)	0.1 (0.0-0.6)*	1.1 (0.6-2.0)		
Other skin cancers	83	$0.9 \ (0.6-1.4)$	$0.4 \ (0.1-1.2)$	1.0 (0.6-1.6)		
Benign skin neoplasms	384	$1 \cdot 2 \ (1 \cdot 0 - 1 \cdot 5)$	$0.9 \ (0.6-1.2)$	1.3 (1.0-1.6)*		
Boils and cellulitis	334	$1 \cdot 1 \ (0 \cdot 9 - 1 \cdot 4)$	$1 \cdot 2 \ (0 \cdot 9 - 1 \cdot 6)$	1.1 (0.8-1.4)		
Eczema and dermatitis	327	1.3 (1.0-1.6)*	1.6 (1.2-2.1)*	1.0 (0.8-1.4)		
Erythematous disease	54	1.1 (0.6-2.0)	1.2 (0.6-2.5)	1.0 (0.5-2.0)		
Psoriasis	92	1.5 (1.0-2.4)	1.7 (1.0-2.9)	1.4 (0.8-2.4)		
Hypertrophic and atrophic conditions	59	$0.9 \ (0.5-1.6)$	1.0 (0.5-2.1)	0.9 (0.5-1.7)		
Nail disease	80	0.7 (0.5-1.2)	$0.9 \ (0.5-1.7)$	0.7 (0.4-1.1)		
Diseases of hair and hair follicles	74	1.9 (1.1-3.4)*	2.2 (1.2-4.3)*	1.6 (0.8-3.1)		
Sebaceous gland disease	362	$1.0 \ (0.8-1.3)$	$1 \cdot 1 \ (0 \cdot 9 - 1 \cdot 5)$	1.0 (0.8-1.3)		
Pigmented naevus	383	1.0 (0.8-1.2)	0.8 (0.6-1.1)	1.1 (0.9-1.4)		
Skin eruption not otherwise specified	199	1.3 (0.9-1.7)	1.5 (1.1-2.2)*	1.1 (0.8–1.6)		

^a Use at any time; ^b current use or use within the preceding 12 months; ^c last use more than 12 months ago; *P < 0.05.

5% level of statistical significance. Of these, the findings for eczema and diseases of the hair and hair follicles are of the greatest interest. There was also a relationship of similar magnitude between psoriasis and oral contraceptive use that did not, however, quite reach statistical significance.

Various other analyses were undertaken in addition to those given in Table 3. First, in order to take into account the possible confounding effects of variables in addition to age (see Table 1), we recomputed the relative risks for boils and cellulitis adjusting for age, smoking and body weight; for psoriasis adjusting for age and smoking; for diseases of the nails adjusting for age, social class and body weight; and for pigmented naevi adjusting for age, social class and body mass index. These analyses produced relative risk estimates closely similar to those shown in Table 3, although those for psoriasis were very slightly reduced. Secondly, we examined the data for each skin disorder in relation to total duration of oral contraceptive use (non-user, user for up to 12 months, 13–24 months, 25–48

months, 49-72 months, 73-96 months, 97 or more months). Only one statistically significant trend was found, namely that for diseases of the hair and hair follicles (P = 0.01). For this condition, relative risks for the seven duration of use categories previously listed were as follows: 1.0, 1.8 (95% CI 0.3-6.3), 0.9 (95% CI 0·1-3·6), 2·2 (95% CI 1·0-4·8), 1·9 (95% CI 0·8-4.1), 1.1 (95% CI 0.3-3.1) and 2.3 (95% CI 1.2-4.6). The explanation for the significant trend lies in the difference between those ever using and those never using oral contraceptives rather than differences between different categories of duration of oral contraceptive use. Finally, we examined the relationship between risk and recency of oral contraceptive use, in more detail than is shown in Table 3, for eczema and dermatitis, psoriasis, diseases of the hair and hair follicles and skin eruptions not otherwise specified. The results are given in Table 4. For eczema and dermatitis and skin eruptions not otherwise specified, the highest elevation of risk was in current or recent users, while for psoriasis and diseases of the hair and hair follicles,

Table 4. Relative risks and 95% confidence intervals (in parentheses) for selected skin disorders in relation to recency of oral contraceptive use. Relative risks are adjusted for age

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Interval since oral contraceptives last used (months)	Eczema and dermatitis $(n = 327)$	Psoriasis $(n = 92)$	Diseases of hair and hair follicles $(n = 74)$	Skin eruption not specified $(n = 199)$		
Never used	1.0	1.0	1.0	1.0		
≤ 12	1.6 (1.2-2.1)	1.7 (1.0-2.9)	$2 \cdot 2 \ (1 \cdot 2 - 4 \cdot 3)$	1.5 (1.1-2.2)		
13-24	0.7 (0.3-1.4)	_	1.4 (0.3 - 4.7)	1.4 (0.6-2.8)		
25-48	1.1 (0.6-1.7)	1.3 (0.4 - 3.1)	1.7 (0.6 - 4.5)	1.4 (0.8-2.5)		
49-72	0.8 (0.4-1.3)	1.6 (0.5 - 3.9)	0.7 (0.1-2.9)	1.1 (0.5-2.0)		
73-96	1.0 (0.6-1.8)	1.6 (0.5-4.1)	2.9 (1.0-7.4)	0.9 (0.4-1.9)		
97-120	1.1 (0.5-1.9)	2.3 (0.8-5.6)	1.6 (0.3 - 5.4)	0.8 (0.3-1.8)		
≥ 121	1.4 (0.9 - 2.2)	$1.6 \ (0.6-3.5)$	1.5 (0.4-4.1)	1.0 (0.6-1.8)		

risk was elevated fairly generally across the different recency of use groups.

Discussion

Extensive analysis of the Oxford-FPA study over the years has indicated that the quality of the data is high.^{3,5,6} In addition, a satisfactory level of follow-up has been maintained and no indication has emerged that women using oral contraceptives are more likely to present for medical attention or to be referred to hospital than users of other contraceptive methods.^{3,5,6}

The data reported here do, none the less, have some important limitations and require cautious interpretation. First, only those episodes of disease requiring referral to hospital were recorded in the Oxford-FPA study. Many skin disorders are managed entirely in general practice, with referral to hospital being reserved for severe or intractable cases. It is thus difficult to know to what extent our findings can be generalized to disease patterns in the community. Secondly, the diagnoses for those episodes managed entirely on an out-patient basis were, in general, self-reported by the women concerned. Thirdly, some of the disease categories considered are broad, for example 'erythematous disease' (ICD rubric 695) and 'hypertrophic and atrophic conditions' (ICD rubric 701). Fourthly, the numbers of women affected are small for some disease categories, despite the fact that we limited our analyses to categories including at least 50 women (save for malignant melanoma). Fifthly, the analyses presented were not, in general, testing pre-existing hypotheses, but were rather of an exploratory type. Accordingly, in view of the large number of significance tests undertaken, some 'significant' results would be expected to occur by the play of chance alone. Finally, about 75% of the exposure to the pill in the Oxford-FPA study concerns preparations containing 50 µg oestrogen or more, which are now rarely used. It follows that our findings should be extrapolated with extreme caution to the oral contraceptives used today.

Relationships between the different disease groups and age were broadly as expected. Some of the other general findings, however, were of considerable interest. First, hospital referral for boils and cellulitis showed a strong positive association with body weight. This was not attributable to clinically recognized diabetes mellitus as only a few of the women with boils or cellulitis had such a hospital diagnosis during follow-up. A similar strong relationship between diseases of the nails (mostly in-growing toenail) and body weight

was an expected finding. Secondly, hospital referral for psoriasis was strongly associated with cigarette smoking. This relationship has been reported previously, with relative risks of a similar magnitude to those we have found. 7,8 Finally, hospital referral for pigmented naevi was strongly positively associated with social class and strongly negatively associated with body mass index. There are a number of possible explanations for the first of these findings. Women in the higher social classes may have a greater awareness of the relationship between moles and melanoma (and a greater willingness to act when in doubt). Another possibility is that women in the higher social classes may have been more likely than other women to take action over moles which they considered to be cosmetically undesirable. Again, sun exposure, particularly during continental holidays, may have been more common among higher social class women than other women. The negative relationship between hospital referral for pigmented naevi and body mass index is, however, harder to explain. It is not attributable to the fact that lower social class women tend to have a higher body mass index than women of higher social class. One possible explanation is that women with a higher body mass index might not be able to see all their skin as easily as leaner women.

With regard to possible effects of oral contraceptive use on the various skin disorders, we have found no indication of any harmful influence of the pill on the risk of malignant melanoma. This was the conclusion of our earlier report, but it was based on only 32 cases, while our present analysis includes 48 cases. Although there has been some variation in the results obtained in other studies, most have reached similar conclusions to our own. 9,10

Some positive findings have, however, emerged from the present study. In particular, statistically significant increases in risk in recent users of oral contraceptives have been found for eczema and dermatitis, diseases of the hair and hair follicles and skin eruptions not otherwise specified. In addition, the corresponding relative risk for psoriasis was very close to statistical significance.

Clearly, it is difficult to evaluate the findings for skin eruptions not otherwise specified which must cover an array of different inadequately described disorders. The other three conditions, however, require more careful consideration. Findings for each of them have been reported from the Royal College of General Practitioners (RCGP) oral contraception study, 11 but no useful data are available from the Walnut Creek contraceptive drug

study¹² and nothing relevant has been published from the Nurses' Health Study. 13 In the RCGP oral contraception study, elevated relative risks of eczema were found among current users of the pill in comparison with non-users in each of the different eczema categories examined, namely due to detergents (relative risk 1.5, not significant), due to drugs (relative risk 2.2, P < 0.05), due to photosensitivity (relative risk 4.3, P < 0.01), due to other specific agents (relative risk 1.5, P < 0.05) and due to unspecified agents (relative risk 1·2, P < 0.01). In every case, there was little evidence of any elevation of risk when ex-users of the pill were compared with non-users. These findings are entirely consistent with our own and it seems possible that oral contraceptive use can lead to eczematous eruptions in some women. With regard to diseases of the hair and hair follicles, the RCGP oral contraception study provided data only for alopecia. There were 149 cases in current users, 46 in ex-users and 161 in nonusers. There was no suggestion of any association between alopecia and pill use, the relative risk comparing current users with non-users being 1.1 (not significant) and that comparing ex-users with non-users being 1.2 (not significant). Although we found some statistically significant associations between diseases of the hair and hair follicles and pill use, including a relative risk of $2 \cdot 2$ comparing recent users with non-users, there was no clear trend in risk in relation to duration of oral contraceptive use or in relation to the interval since oral contraceptives were last used. Viewed together with the RCGP findings, our data do not provide convincing evidence of a causal association. There was also little evidence of any effect of oral contraceptive use on psoriasis in the RCGP oral contraception study. With a total of 380 cases, the relative risk comparing current users with non-users was 1.2 (not significant) and that comparing ex-users with non-users was 1.3 (not significant). Again, our data (based on 92 cases) show no relationship to duration of oral contraceptive use or to interval since last oral contraceptive use. This pattern is not what would be expected with a causal relationship.

In conclusion, this analysis has shown up some interesting relationships between certain skin diseases and a number of variables. These include an increased rate of referral to hospital for boils and cellulitis in heavy women, for psoriasis in women who smoke, and for pigmented naevi in women of higher social class.

Referral for pigmented naevi was reduced in women with a high body mass index. Of the oral contraceptive associations studied, only an increased risk of hospital referral for eczema or dermatitis in current or recent users may perhaps reflect a causal relationship.

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