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The differential risk of oral contraceptives: the impact of full exposure history*

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Previous discussions have indicated that the small increases of risk of venous thromboembolism (VTE) associated with newer combined oral contraceptives (third generation, containing desogestrel and gestodene) may be attributed to bias due to cohort effects. In a case-control analysis, this may produce an overestimate of risk of newer preparations. In 10 centres in Germany and the UK, the Transnational Study analysed data from 502 women aged 16–44 years with VTE, and from 1864 controls matched for 5-year age group and region. Information on lifetime exposure history from all subjects was added to the dataset used in previous analyses and entered into a Cox regression model with time-dependent covariates. Based on 17 622 continuous exposure episodes comprising 47 914 person-years of observation, the adjusted hazard ratio (equivalent to odds ratio, OR) of VTE for the comparison of current users of third-generation versus current users of second-generation (primarily levonorgestrel compounds) combined oral contraceptives was 0.8 (0.5 to 1.3). The OR obtained in standard case-control analysis had been 1.5 (1.1 to 2.1). Adjustment for past exposures includes more information and appears more valid than the standard cross-sectional analysis. Using this approach, the Transnational Study data show no evidence for an increased risk of VTE with third- compared with second-generation combined oral contraceptives.

Key words: case-control study/Cox regression analysis/epidemiology/oral contraceptive use/venous thromboembolism

Introduction

A good deal of the development of new oral contraceptives (OC) was directed towards reducing the risk of thromboembolic events which were found to be associated with OC use soon after their introduction (Thorogood, 1993). It therefore came as a surprise when studies published in 1995/1996 seemed to show an increased risk of venous thromboembolism (VTE) among users of newer OC compared with users of older OC (Bloemenkamp *et al.*, 1995; Farley *et al.*, 1995; Jick *et al.*, 1995; Spitzer *et al.*; 1996; Farmer *et al.*, 1997). This has engendered considerable discussions on the safety of newer (third-generation) OC in Europe which are still ongoing (Lewis and Heinemann, 1997; Spitzer, 1997a,b; Vandenbroucke and Rosendaal, 1997; Meirik, 1998). Because the differences found between users of newer (third-generation products containing <50 μg ethinyl oestradiol (EE2) and the progestins gestodene and desogestrel) and older (second-generation, containing <50 μg EE2 and primarily levonorgestrel) OC were small, ranging between 1.3 and 2.2 (Table I), and because the population impact of intervention is large, investigators were careful to address and explore sources of potential bias and confounding factors (Farley *et al.*, 1995; Lewis *et al.*, 1996b; Spitzer *et al.*, 1996; Spitzer, 1997b). The biases addressed included physician diagnostic behaviour, preferential prescribing of newer OC to risk groups, and a phenomenon known as depletion or attrition of susceptibles, observed in a variety of epidemiological studies (Miettinen and Caro, 1989; Moride and Abenhaim, 1994; Posthuma *et al.*, 1994).

Although the results of the Transnational Study (Spitzer *et al.*, 1996) were similar to others published at the same time, the first analyses showed that adjustment for duration of use of the current OC reduced the risk estimates for newer-generation OC by about 12% (Spitzer *et al.*, 1996). Additional analyses showed that the magnitude of risk estimates for individual progestins were closely linked with the time of market introduction of the OC, with increasing risk estimates of VTE found for newer OC (Lewis *et al.*, 1996b). Because it seemed unlikely that older, low-dose OC should consistently show a more beneficial risk profile than newer OC, and because it was found that a larger proportion of individuals using older OC were long-term users than of those using newer OC, a 'healthy user' effect was postulated to be active within these studies. This is a cohort effect based on the notion that long-term users are individuals with good tolerance, whereas groups with shorter duration of use may constitute a different risk set. This results in a depletion of susceptibles in the group of older exposures and loading of problem cases in the group of newer exposures (Lewis *et al.*, 1996b). Cross-sectional comparisons of two groups using medications with different market entry points are therefore likely to overestimate the risk associated with the most recently introduced medication, especially when

*For the Transnational Study on Oral Contraceptives and the Health of Young Women — see appendix

Table I. Summary of results of studies comparing risks of venous thromboembolism among users of third-generation oral contraceptives with users of second-generation oral contraceptives. Odds ratios (OR) with 95% confidence intervals (95% C.I.)

Reference	Investigation	OR	95% C.I.
Farley *et al*. (1995)	WHO study (UK; hospital controls)	2.2*	(1.1 to 4.2)
Farley *et al*. (1995)	WHO study (UK; community controls)	1.4	(0.6 to 3.1)
Jick *et al*. (1995)	GPRD; case-control	2.1*	(1.0 to 4.4)
Bloemenkamp *et al*. (1995)	Leiden study	2.2	(0.9 to 5.4)
Spitzer *et al*. (1996)	Transnational Study	1.5*	(1.1 to 2.0)
Farmer *et al*. (1997)	MediPlus Study (age standardized)	1.7*	(1.0 to 2.8)
Farmer *et al*. (1997)	MediPlus Study (age-matched)	1.3	(0.7 to 2.4)

*$P < 0.05$.

an adverse event is not expected to occur immediately after exposure.

Standard case-control analysis considers current risk factors and summary data on past exposures. The Cox proportional hazards model with time-dependent covariates permits multiple episodes of use and non-use of OC, including precise details of duration and nature of each episode, to be used in adjustment of the associations with current exposures. This approach becomes possible through the availability of the lifetime exposure history of all subjects included in our study. We present here the results of the analysis of a Transnational Study dataset, enhanced with information on all prior exposures of the study subjects.

Materials and methods

Study design and conduct

The Transnational Study on oral contraceptives and the Health of Young Women is a matched case-control study designed to assess the risk of oral contraceptives on deep vein thrombosis and pulmonary embolism (i.e. venous thromboembolism; VTE), arterial thrombotic stroke and myocardial infarction. Its methods are almost identical to those of the case-control study of the World Health Organization Human Reproduction Unit, and have been detailed elsewhere (Spitzer *et al*., 1993; Poulter *et al*., 1995; Lewis *et al*., 1996a). The cases were women aged 16–44 years who had a diagnosis of VTE. Deep vein thrombosis was defined by pain and tenderness in the extremities, a precise record of knee circumference, and confirmation with imaging procedures. The diagnosis of pulmonary embolism was based on symptoms of pain in the chest or side, and confirmatory imaging procedures. The cases were accrued in hospital between early 1993 (first case index date 2 January 1993) and 20 October 1995 in centres in Germany and the UK. These were matched by centre and 5-year age-band to at least one community and one hospital control.

A full exposure history was documented by filling in a calendar sheet which identified exposure by month since menarche, indicating the first eligibility to take OC. Exposure periods of interest were the use of an OC and the brand of OC used, pregnancy, and periods of non-exposure. Current use of OC was defined as the OC used within a 3-month window at the time of the event (for a case), the hospital admission (for a hospital control) or the date of interview (for a community control). Prior use of OC was defined as any use that ended before this period. For this analysis, first-generation OC were defined as any preparation that contained ⩾50 μg of EE2, regardless of progestin content. Second-generation OC were defined as those which had ⩽35 μg of EE2 and contained a progestin other than gestodene or desogestrel. Preparations containing norgestimate were included with the second-generation products to retain consistency with other analyses. Third-generation OC were defined as combination products with low doses of EE2 (usually 30 μg or 20 μg) and either gestodene or desogestrel. Separate analyses for individual progestins were conducted. OC classification lists are available from the authors (Lewis *et al*., 1996a).

Data processing and analysis

All data were checked manually and by computer for eligibility and correct matching. The clinical data were coded twice and difficult or unreconciled diagnoses were arbitrated by local and international panels of clinical specialists. All other data were entered twice and verified. Plausibility checks of current and prior exposures were conducted by numerous procedures, including verification of age, periods of pregnancy, and presence of the indicated product on the market. The data on exposure histories from the pill calendar sheet were entered into a separate database and merged with the main Transnational Study dataset. The data were first modelled for the stroke component of the study. This dataset was chosen because it contained adequate exposures of second- and third-generation OC for cases and controls (Heinemann *et al*., 1997). This approach permitted an unbiased configuration and exploration of this complex dataset. The model derived from this work was then applied to the new VTE dataset.

Figure 1 shows the configuration of the new dataset for analysis using the pill calendar data. Ordinarily, cases and controls are captured within a 3-year study period, and their exposures are assessed for the time during which the event occurred. Standard analyses rarely account for prior exposures, which are key for the attrition of susceptibles. These prior exposures may constitute periods of challenge (high-risk periods). To adjust adequately for these periods, the data were analysed using a Cox regression model on a fixed time axis defined by the successive calendar months (Cox and Oakes, 1984; Clayton and Hills, 1993; Collet, 1994). This method is similar to the Poisson regression, but based on much finer subdivisions in time. In using this method, we computed the conditional probability that, given a failure occurred in a set of subjects, it had occurred in the case rather than in some other member of the risk set. The profile log likelihood of a cohort corresponded with the conditional log likelihood obtained for individually matched case-control studies (Breslow and Day, 1980; D'Agostino *et al*., 1990). In our approach, all study subjects were right-censored at the same time by virtue of their being accrued almost simultaneously within a case-control setting. The subject's risks were determined by different exposure periods and likelihood of exposure to various agents.

We defined a calendar axis from 0 to 458 months for the total period of observation. We left-censored the individual members at 9 years of age, this being the age of first exposure to risk of the subject with the earliest exposure to OC or pregnancy. The exposure episodes j of each subject i were arrayed along this time axis by month (1,..., k). Each subject was followed from cohort entry ($t0_{i1}$) to case-control study entry (tm_{iki}) by month through various exposure periods (tm_{ij}, where $j = 1$,..., k). Event status is defined by the outcome variable d, corresponding to case or control status. The time-dependent variable entered into the model was the exposure or non-exposure to specific OC at monthly intervals. We adjusted for non-time-dependent variables shown to influence risk, such as body mass index (BMI), alcohol use, index age and smoking status, as well as for current and previous duration of use by generation and for switching. The analyses

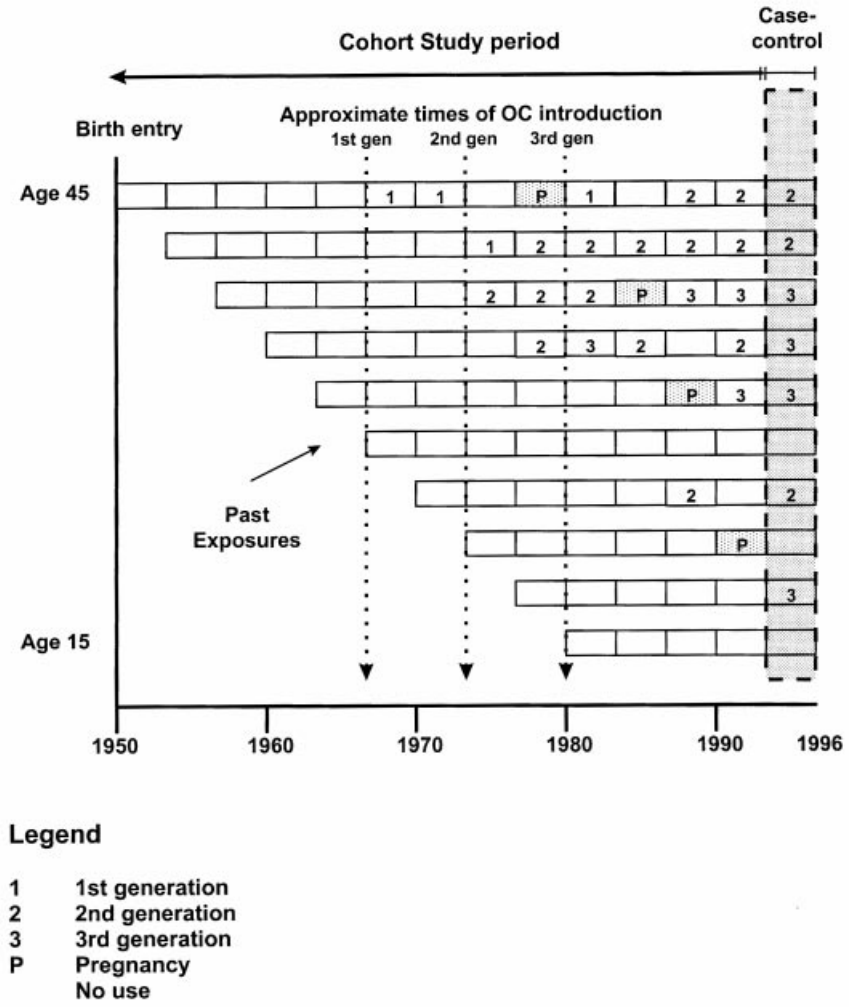

Figure 1. New information added in the Transnational Study 'pill calendar' for longitudinal analysis. In addition to current exposures (case-control setting), past exposure histories and duration of oral contraceptive use were included in a Cox regression model with time-dependent covariates (cohort setting). 1 = first generation (gen); 2 = second generation; 3 = third generation; P = pregnancy, no use; open box = no use.

were performed with STATA 5.0 (StataCorp, 1997). We calculated adjusted hazard ratios expressed as odds ratios (OR; signifying their origin from a case-control study) and their 95% confidence intervals to estimate the risk of VTE associated with use of the various categories of OC investigated.

Results

Data on 2366 women aged 16–44 (502 cases and 1864 controls) were collected from 1 January 1993 to 20 October 1995 in the UK and Germany. Cases differed from controls in that a larger proportion of cases had a BMI >30 (17.7 versus 9.9%), were current smokers (45.8 versus 39.3%), and were current users of oral contraceptives (67.5 versus 41.8%) (see also Spitzer *et al*., 1996). The stratification of current use and previous use by age in Table II shows a predominance of current users of third-generation OC in the age group 16–24 years among cases (41.4% versus 25.4% of controls). Use of third-generation OC is equally distributed among previous users (26.7% of cases and 30.3% of controls) in this age group. Current use of second-generation OC predominates in the age groups 25–44, whereas there is a distinct increase in the proportion of previous users of first-generation OC in the older age groups. Current use of OC decreases considerably with age in both cases and controls (Table II). The proportions of previous use are similar for cases and controls in each age group.

The average current duration of use of all OC increases with age with pronounced age-related differences in length of use by generation (Table III). The total exposure times decline from first to third generation in all age groups for cases (mean times: for first generation 78, second 52, third 30 months) and controls (first generation 71, second 58, third 30 months). The proportion of cases who have used OC for >60 months is lowest in the group of third-generation OC users (12%) compared with cases using second- (20.1%) and first- (48.7%) generation OC. About 16% of cases and 22% of controls were never users, and 41.2% of cases and 42.2% of controls stayed on the same OC throughout. Defined switches from second- to third-generation OC took place in 9.6% of cases and 6.2% of controls. Multiple switches with no clear pattern were found in 26.3% of cases and 23.4% of controls.

A total of 17 622 separate exposure episodes covering 47

Table II. Distribution of current and previous use of oral contraceptives by 10-year age groups and type of oral contraceptive in 502 cases and 1864 controls of the Transnational Study on Oral Contraceptives and the Health of Young Women

	Age 16–24 years		Age 25–34 years		Age 35–44 years	
	n	%	*n*	%	*n*	%
Current use						
Controls						
No current use	217	41.7	388	54.3	480	76.2
First generation	11	2.1	21	2.9	27	4.3
Second generation	154	29.6	186	26.1	84	13.3
Third generation	132	25.4	102	14.3	25	4.0
Progestogen-only	6	1.2	17	2.4	14	2.2
Total	520	100.0	714	100.0	630	100.0
Cases						
No current use	27	19.3	53	27.6	83	48.8
First generation	6	4.3	13	6.8	18	10.6
Second generation	46	32.9	68	35.4	32	18.8
Third generation	58	41.4	53	27.6	30	17.6
Progestogen-only	3	2.1	5	2.6	7	4.1
Total	140	100.0	192	100.0	170	100.0
Previous use[a]						
Controls						
No previous use	172	33.2	189	22.4	215	30.4
First generation	18	3.5	96	11.4	220	31.1
Second generation	171	33.0	418	49.6	249	35.2
Third generation	157	30.3	139	16.5	24	3.4
Total	518	100.0	842	100.0	708	100.0
Cases						
No previous use	36	30.0	60	25.5	59	32.1
First generation	5	4.2	29	12.3	60	32.6
Second generation	47	39.2	110	46.8	54	29.3
Third generation	32	26.7	36	15.3	11	6.0
Total	120	100.0	235	100.0	184	100.0

[a]Multiple mentions possible.

Table III. Duration of current and previous use (months) by age group (years) and by oral contraceptive generation. Absolute numbers (*n*), average durations (mean) and standard deviation (SD) from the mean

	Cases ($n = 502$)			Controls ($n = 1864$)		
	n	Mean	SD	*n*	Mean	SD
Current use						
Overall duration of use						
Age 16–24	113	19.3	19.1	303	24.2	22.3
Age 25–34	139	37.5	37.5	326	37.6	35.3
Age 35–44	87	59.7	64.4	150	63.5	57.8
Duration of first-generation use						
Age 16–24	6	14.5	15.0	11	26.9	30.9
Age 25–34	13	68.2	34.5	21	48.8	39.0
Age 35–44	18	106.2	87.7	27	108.1	71.9
Duration of second-generation use						
Age 16–24	46	18.5	17.1	154	26.7	23.7
Age 25–34	68	38.8	37.5	186	42.6	36.9
Age 35–44	32	55.6	52.5	84	63.1	51.9
Duration of third-generation use						
Age 16–24	58	20.4	20.8	132	21.5	19.9
Age 25–34	53	24.7	28.2	102	27.5	27.9
Age 35–44	30	38.7	47.2	25	28.7	28.0
Previous use						
Overall duration of use						
Age 16–24	79	26.5	22.1	292	30.2	25.1
Age 25–34	165	60.3	42.4	608	64.9	41.4
Age 35–44	144	83.7	61.7	538	88.5	63.6
Duration of first-generation use						
Age 16–24	5	23.4	20.5	18	25.4	20.5
Age 25–34	29	46.8	44.7	96	47.9	41.1
Age 35–44	60	73.2	60.7	220	73.6	56.8
Duration of second-generation use						
Age 16–24	47	22.4	18.6	171	25.4	21.9
Age 25–34	110	46.5	33.4	418	55.3	39.2
Age 35–44	54	56.3	49.8	249	62.1	50.0
Duration of third-generation use						
Age 16–24	32	19.9	16.6	157	20.4	21.1
Age 25–34	36	21.6	23.1	139	31.2	26.1
Age 35–44	11	29.3	27.9	24	27.5	19.1

914 woman-years of observation were included in the Cox regression model with time-dependent covariates. The relative risk (hazard ratio; OR) for the model which included adjustments for exposure in each episode by generation, age, BMI, smoking, alcohol use, duration of current use by generation (first to third) and duration of previous use by generation (first to third) as linear variables, and 'switching' by generation was 2.90 [95% confidence interval (C.I.): 2.06 to 4.09] for any OC use versus non-use, and 8.48 (3.02 to 23.86) for use of first generation versus non-use (Table IV). The OR for second generation versus non-use was 2.85 (1.92 to 4.22) and for third generation it was 2.26 (1.46 to 3.50), all statistically significant. The direct comparison between users of third-generation versus second-generation OC resulted in a risk estimate of 0.79 (95% C.I. 0.50 to 1.26), which was not statistically significant. Estimates comparing users of various progestins with users of levonorgestrel-containing OC show no significant differences (Table IV).

There were no differences in the risk estimates when we stratified by 10-year age groups, nor was there a trend by time of market introduction overall or for any age group. Although there were absolute differences in risk estimates when comparing users with non-users in the UK (2.2; 1.48 to 3.3) and Germany (5.6; 2.9 to 0.8) due largely to the absence of current users of first-generation OC in the UK, there were no important differences in the adjusted comparisons of users of third-generation with users of second-generation OC between countries (UK: 0.85, 0.50 to 1.45; Germany: 0.76, 0.32 to 1.82). No important differences were found either between hospital and community controls when comparing current OC use against no current use (hospital controls: 2.42, 1.74 to 3.38; community controls: 2.19, 1.54 to 3.11), or when comparing users of third- with users of second-generation OC (hospital controls: 0.84, 0.52 to 1.35; community controls: 0.82, 0.51 to 1.33). The model was stable, in that results were altered only slightly as additional adjustment variables were introduced (unadjusted model: 0.84, 0.59 to 1.18; full adjustment: 0.79, 0.50 to 1.26). Concerning other variables which might potentially have influenced the occurrence of VTE, the most pronounced independent risk factors for VTE appeared to be a BMI >30 (2.72, 1.80 to 4.11), current smoking (1.42, 1.12 to 1.79) and diabetes (2.41, 1.07 to 5.42). The use of alcohol was associated with a decreased risk of VTE (0.50, 0.36 to 0.69, versus non-use of alcohol).

Table IV. Main results of Cox regression analysis with time-dependent covariates on the risk of venous thromboembolism (VTE) in young women. Hazard ratios expressed as odds ratios (OR); 95% confidence intervals (95% CI) and *P*-values for the analysis of 502 cases and 1864 controls for exposure in each episode by generation, adjusted for age, body mass index, smoking, alcohol use, duration of current use by generation (1–3) and duration of previous use by generation (1–3) as linear variables, 'switching' by generation. The comparisons of generations and progestins with each other relate to users only (339 cases and 779 controls). In the last four rows, progestins are arranged by sequence of market introduction.

Comparison	OR	95% CI	*P*
No current use of OC (reference group)	1.00	–	–
OC use vs. no current OC use	2.90	2.06 to 4.09	<0.001
First generation vs. no OC use	8.48	3.02 to 23.86	<0.001
Second generation vs. no OC use	2.85	1.92 to 4.22	<0.001
Other second generation vs. no OC	3.25	1.89 to 5.58	<0.001
Levonorgestrel vs. no OC	2.63	1.75 to 3.95	<0.001
Norgestimate vs. no OC	3.65	2.17 to 6.12	<0.001
Third generation vs. no OC use	2.26	1.46 to 3.50	<0.001
Desogestrel 30 vs. no OC	2.52	1.56 to 4.09	0.005
Gestodene vs. no OC	2.25	1.40 to 3.60	0.001
Desogestrel 20 vs. no OC	1.56	0.85 to 2.86	0.150
Second generation (reference group)	1.00	–	–
Third generation vs. second generation	0.79	0.50 to 1.26	0.323
Levonorgestrel (LNG; reference group)	1.00	–	–
>50 μg EE2 vs. LNG	2.89	1.04 to 8.01	0.041
Other second generation vs. LNG	1.08	0.61 to 1.91	0.791
Desogestrel 30 vs. LNG	1.07	0.59 to 1.96	0.818
Gestodene vs. LNG	0.58	0.32 to 1.03	0.063
Norgestimate vs. LNG	1.02	0.50 to 2.05	0.965
Desogestrel 20 vs. LNG	0.71	0.31 to 1.62	0.415

EE2 = ethinyl oestradiol; OC = oral contraceptive; vs. = versus.

Discussion

There are some indications that the studies on oral contraceptives do not meet one of the primary conditions of the case-referent approach, in that the processes which bring the cases to attention and by which controls are selected may not be independent of the exposure (Miettinen and Caro, 1989). This may lead to confounded or biased results when the traditional cross-sectional methods of analysis are used (Lewis *et al*., 1996b; Suissa *et al*., 1997). This is expressed by a variety of inconsistent and implausible results which have led authors to postulate distortion due to heterogeneous exposure groups. A case-control study measures the instantaneous drop-out rate when only individuals (and their controls) who have been healthy up to the time of the index event are included. This approach is best suited for well-defined events which occur soon (preferably days or weeks) after a drug is taken. For an ill-defined and non-specific event such as VTE, this approach becomes problematic when the observed time window of exposure becomes large. The problem is further compounded if there have been previous exposure episodes which can be regarded as high-risk or challenge periods for VTE. For OC, exposure likelihoods additionally differ with age, in that older individuals are more likely to have been exposed to previous generation OC. Lastly, a comparison of older and newer generation OC becomes difficult because high-risk members of the older user group may have dropped out due to events or other intolerances and possibly switched to the apparently more tolerable newer products (Lewis *et al*., 1996b). There is no assurance that the cohort of exposed individuals used as the index population is actually comparable to the cohort of unexposed individuals used as the reference population. There are good reasons indeed to believe that they are not comparable, because the comparison groups for exposure are not homogeneous. In our study, these differences are reflected by differing proportions of users of specific types of OC in the various age groups (Table II), by differences in the lengths of current and previous exposure episodes across age groups and generations (Table III), and by differences in switching patterns between cases and controls.

We adjust for these differences in an enhanced dataset which now includes past exposures and precise duration terms along a time axis. The model used is remarkably stable, and the results appear consistent and plausible. The main effect of the adjustment for prior exposure is a reduction of the risk estimate for users of third-generation OC from 4.8 in the original analysis to 2.3. The comparison of users of third- with users of second-generation OC shows that there is no evidence for an increased risk of third-generation OC (0.79, 0.50 to 1.26; previous estimate 1.5, 1.1 to 2.2) (Lewis *et al*., 1996b; Spitzer *et al*., 1996). The results indicate that the relevant effects of prior exposure for the comparisons between OC user groups are removed. This is demonstrated by the consistency of the results when stratifying by control group and by country, and by the absence of the dependence of risk estimates on the time of market introduction of the various progestins as shown in standard logistic regression (Lewis *et al*., 1996b).

A conventional case-control comparison cannot adequately account for those individuals who have not successfully passed their high-risk periods and who have become cases in the past. The present approach also cannot deal with this issue, but it does use the prior exposure data in as complete a manner as possible. Any estimates achieved with this approach will underestimate the risk in the users who have passed many high-risk periods (i.e. older users of older generation OC) compared with the risk in those who have not traversed as many high-risk periods (i.e. younger users and users of newer products). Recall bias can never be fully excluded in this form of study. However, validity checks of pregnancies and OC market introduction dates showed that women placed their OC brand in the correct time-frame, so that recall bias is unlikely to be an issue. A further limitation is that lifetime histories of other variables, such as BMI and smoking, were not collected, but only data on such variables at the time of entry of the subjects into the case-control study. Their influence cannot be estimated over time, but only in a cross-sectional fashion. However, it should be noted that the unadjusted model yielded virtually identical results, which argues against important distortion by these factors. The full adjustment for past exposures among these healthy women includes more information and provides more precision than the standard cross-sectional analysis.

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Appendix

The Transnational Case-control Study

Overseeing Board and Advisory Groups

Scientific Reference Board: U.Bergman, Karolinska Institute; M.Breckwoldt, U.Freiburg; J.Collins, McMaster University; F.Kemper, U.Munster; J.Le Lorier, University of Montreal; S.MacLeod (Chair), McMaster University; K.MacRae, Charing Cross and Westminster Medical School (until May 1995); W.Ray, Vanderbilt University (since May 1995); J.Schlesselman, University of Pittsburgh.

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Ad hoc Peer Review Task Force: U.Bergmann, Karolinska Institute; J.Daling, Fred Hutchinson Cancer Research Center, University of Washington; M.Elstein, St Mary's Hospital, Manchester; J.Hanley, McGill University; S.Lock (Chair), Wellcome Trust; S.MacLeod, McMaster University; W.Ray, Vanderbilt University; L.Rosenberg, Boston University; S.Suissa, McGill University

British Steering Committee: V.Beral, Oxford University; N.Cherry, Manchester University (until June 1995); M.Elstein (Chair), St Mary's Hospital, Manchester; M.Harrison, UCL Medical School; C.Kay, Royal College of General Practitioners; M.Shipley, University of London.

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The Transnational Case-control Study Group

Potsdam Co-ordinating Centre: Potsdam: V.Anning; A.Assmann; C.Klindworth; D.Kuhl-Habich; M.Lewis (Head of International Data Management); J.Von Rosen.

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Centres

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United Kingdom: Glasgow: L.de Caestecker (Director); E.Hamilton; S.Mitchell; M.Soler-Lopez. London (national co-ordinating centre): D.Curle; J.Gibbs; H.Hemingway; G.Mein; M.Thorogood; N.Poulter; S.Smith. Manchester: P.Hannaford (Director since August 1995); Z.Evans; B.Faragher; S.Ferry; G.McHugh; C.McCollum (Director until August 1995); C.Sutcliffe. Southampton: A.Ascott; N.Dunn; R.Mann (Director); B.Weston.