ORIGINAL RESEARCH ARTICLE

ELSEVIER

The Use of Oral Contraceptives and the Occurrence of Acute Myocardial Infarction in Young Women

Results From the Transnational Study on Oral Contraceptives and the Health of Young Women

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The objective of this study was to assess the risk of myocardial infarction (MI) associated with the use of new and old combination oral contraceptives (OC). A matched case-control study in 16 centers in Germany, the United Kingdom, France, Austria, and Switzerland explored the association of current use of combination OC with the occurrence of MI. Our subjects were 182 women aged 16–44 years with MI; the controls were 635 women without MI (at least one hospital control and one community control per case) matched for 5-year age group and region. The main outcome measures were odds ratios comparing current use of a specific group of OC against current use of other groups or against no current use.

The adjusted overall odds ratio (OR; 95% confidence intervals) for MI for second generation OC versus no current use was 2.35 (1.42 to 3.89) and 0.82 (0.29 to 2.31) for third generation OC (low dose ethinyl estradiol, gestodene, and desogestrel). A direct comparison of third generation users with second generation users yielded an OR of 0.28 (0.09 to 0.86). In subgroup analyses, the odds ratio for the UK alone was 1.25 (0.36 to 4.29), while for continental Europe it was 0.10 (0.02 to 0.48). For hospital controls, the risk estimated was 0.98 (0.22 to 4.44), and 0.18 (0.04 to 0.65) for community controls. The independent risk of MI among current smokers adjusted for OC use was 7.21 (4.58 to 11.36). Among users of third generation OC, the OR for current smokers was 3.75 (0.65 to 21.74) and among users of second generation it was 9.50 (2.93 to 30.96). A comparison of OC use in the UK for the time before and after regulatory action was taken in October 1995 shows that the likelihood of a control (last control accrued June 1996) being treated with second generation OC is seven times higher after 1 November 1995 than it was before.

Third generation OC are the first to be associated with no excess risk of MI. A significantly lower risk of MI is found when comparing use of third generation OC with use of second generation OC. There seems to be an impressive amelioration of risk among smokers using newer OC. An impact of regulatory action in the UK was found in the OC use spectrum of controls. CONTRACEPTION 1997;56: 129–140 © *1997 Elsevier Science Inc. All rights reserved.*

KEY WORDS: oral contraceptives, myocardial infarction, epidemiology, case-control study, gestodene, desogestrel, levonorgestrel, ethinyl estradiol

Introduction

Since the introduction of oral contraceptives (OC), their use has been associated with risk both to the venous and the arterial systems.[1] Thus, studies have shown risk associations of OC use related to the occurrence of venous thromboembolism (deep vein thrombosis and pulmonary embolism), ischemic stroke, and acute myocardial infarction.[2] These conditions, primarily affecting healthy young women, can be serious and should be explored thoroughly to prevent harm to this population if the exposure is causally related to outcome events. Because the main risk was initially thought to be due to the estrogen component contained in OC, various progestogens were developed to enable a reduction of

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Submitted for publication June 24, 1997
Accepted for publication July 7, 1997

655 Avenue of the Americas, New York, NY 10010

ISSN 0010-7824/97/$17.00
PII S0010-7824(97)00118-2

the amount of estrogen exposure in users.[3] Although there has been a secular decline in risk estimates for OC over the years, concerns have been voiced in the European regulatory agencies about the thrombophilic properties of newer agents. The results of several studies regarding venous thromboembolisms (VTE) in 1995 and 1996 from three different sources showed a small increase in risk for VTE associated with the use of newer OC.[4–8] Because a letter advising physicians to discontinue newer prepartions was circulated by the Commission on the Safety of Medicines (CSM) in the UK almost immediately, these results met with considerable public[9] and scientific[10] reaction. Parallel to the results on the association between VTE and newer OC use, two communications had indicated that there is no excess risk of myocardial infarction among users of third generation OC.[11,12] A more recent publication corroborates this result.[13]

Our own study, the Transnational Study on Oral Contraceptives and the Health of Young Women, incorporated three matched case-control studies with virtually identical methods for which the exposure factor of particular interest was the use of newer generation OC. The outcomes for the three studies were, respectively, venous thromboembolism (VTE), myocardial infarction (MI), and ischemic (thrombotic) stroke (IS). We report here the final results of the case-control study component assessing and contrasting the relationship between the use of older (second) and newer (third) generation OC and MI in young women.

Study Subjects and Methods

The methods of the Transnational Study have been published as study protocols in detail elsewhere.[14,15] Women aged 16–44 were accrued in sixteen centers of five countries (Austria, France, Germany, Switzerland, and the UK) according to definitions, questionnaires, and field operations very similar to those of the case-control study of the World Health Organization (WHO) Human Reproduction Unit.[16] This worldwide study in 19 countries was almost completed at the outset of the Transnational Study, which was conducted only in Europe.

The cases were women with a first-ever event of MI who were not pregnant at the time of the event. An average of three controls were matched to each case; at least one control was hospitalized and at least one was from the community. Controls were matched to the cases within 5-year age bands and by participating center. The cases of MI (International Classification of Diseases, Ninth Revision [ICD9] 410) met the WHO criteria of chest pain, changes in electrocardiogram (ECG), and cardiac enzyme elevation. Controls were identified and interviewed within 4 months of the MI of the index case. Hospital controls were obtained from the case hospitals according to a list of predefined diagnoses. Community controls were obtained from the same group general practice as the corresponding case in UK and by a similar approach in France, and from population registers in Germany, Austria, and Switzerland. Both groups were interviewed by trained interviewers from each center using a standardized approach and questionnaire. Current OC use was defined as use within 3 months before the event for a case. The date of hospital admission (hospital controls) or the date of interview (community controls) was considered to be the analogous index date to the case. The field work, beginning with feasibility and pilot projects, started in July 1991. Case accrual began in August 1993 and was suspended in early March 1996; the field work was completed in June 1996.

Exposure to oral contraceptives was confirmed by inspecting the patients' packet of pills. Clinical data were verified with medical records. All data were checked manually and by computer on site and in the central data management facility of the study. Pill use and medical codes were coded twice by different coders, and all data were entered twice for verification and correction. Unreconciled diagnoses were checked by local and international panels.

We assessed the current use of third generation OC containing low-doses of ethinyl estradiol (usually 30 or 20 μg) and one of two progestogens, gestodene or desogestrel. Second generation OC (the main reference group) are other low-dose ethinyl estradiol preparations (under 50 μg) combined with progestogens (primarily levonorgestrel) that had been introduced to the market earlier. In the main analysis, the progestogen norgestimate, which can be classified as either third or second generation, was classified as second generation to be consistent with the WHO. However, the impact of classifying norgestimate as third generation was also assessed.

We report unmatched odds ratios with 95% confidence intervals (CI) to estimate the risk of myocardial infarction with the use of the various categories of oral contraceptives. The combination of community controls and hospital controls had been declared to be our main reference group in the published protocol,[14,15] but we also stratified by hospital and community controls. Odds ratios were calculated using unconditional logistic regression with the statistical package Stata 4.0[17] to adjust for the potential confounding variables (linear age, center, smoking status, hypertension, hypercholesterol, diabetes mellitus, family history of MI, and duration of use of cur-

Table 1. Distribution of selected baseline variables among study subjects by events and type of control; numbers and percentages of subjects with the characteristic

	Cases (n = 182)		Hospital Controls (n = 274)		Community Controls (n = 361)	
	n	%	n	%	n	%
Country						
UK	102	56.0	148	54.0	207	57.3
Germany	47	25.8	84	30.7	98	27.1
Southern Rim*	33	18.1	42	15.3	56	15.5
Age group (years)						
16–24	2	1.1	2	0.7	5	1.4
25–34	40	22.0	59	21.5	75	20.8
35–44	140	76.9	213	77.7	281	77.8
Current smoker	146	80.2	97	35.4	136	37.7
Hypertension	42	23.3	27	9.9	23	6.4
Aspirin use	40	22.1	62	22.6	95	26.3
Diabetes mellitus	14	7.7	6	2.2	6	1.7
High lipids	20	11.3	6	2.2	8	2.2
Family history of acute myocardial infarction	39	21.7	22	8.1	18	5.0
Family history of stroke	8	4.5	7	2.6	4	1.1
High alcohol use	35	19.2	44	16.1	108	29.9
Parity	167	91.8	221	80.7	305	84.5
Current user	57	31.3	67	24.5	89	24.7
First user	8	4.4	14	5.1	2	0.6
Body mass index						
≤20	17	9.8	41	15.0	56	15.6
21–25	64	36.8	131	48.0	198	55.2
26–30	51	29.3	57	20.9	74	20.6
>30	42	24.1	44	16.1	31	8.6
Outpatient contacts						
Never	23	12.7	15	5.5	37	10.3
1–3 times	77	42.5	117	42.7	189	52.5
4–12 times	61	33.7	112	40.9	117	32.5
>12 times	20	11.0	30	10.9	17	4.7
Hospital physician contacts						
Never	128	71.1	143	52.4	268	74.4
1–3 times	37	20.6	97	35.5	78	21.7
4–12 times	11	6.1	32	11.7	13	3.6
>12 times	4	2.2	1	0.4	1	0.3
Pre-eclampsia	11	6.1	12	4.4	14	3.9

*Countries designated as "Southern Rim" include Austria, France, and Switzerland.

rent OC) after modeling variables individually and through a backward elimination process. We also estimated the independent effect of major variables, of which current smoking was deemed to be the most important. Matched analyses were also done as a sensitivity check and to determine whether overmatching may have occurred.

Results

A total of 182 cases of MI (13 of them fatal) and 635 controls were enrolled. One-hundred-two cases were identified in the UK, 47 in Germany, 6 in Switzerland, 7 in Austria, and 20 in France (Table 1). Cases differed considerably from controls in that the prevalence of risk indicators was higher for almost all categories in cases. Thus, the group of women with events showed a higher proportion of smoking (80% among cases versus 37% among controls), hypertension (cases: 23%; controls: 8%), hypercholesterolemia, diabetes mellitus, family history of MI, pregnancies, and body mass index >25. Educational level and alcohol use was slightly lower among cases than among controls (data not shown). There seem to be no major differences between hospital and community controls with respect to the distribution of baseline characteristics with the exception of the proportion of first users (5% in hospital and 0.6% in community controls), lower alcohol use, lower educational status, and a higher number of hospital physician contacts (Table 1).

Table 2. Distribution of exposures by age groups and type of study participant; norgestimate-containing compounds are defined as second generation OC

	Cases		Hospital Controls		Community Controls	
	n	%	n	%	n	%
Age 16–24						
1st generation	0	0.0	0	0.0	0	0.0
2nd generation	1	50.0	0	0.0	0	0.0
3rd generation	0	0.0	1	50.0	3	60.0
POP	1	50.0	0	0.0	0	0.0
Nonusers	0	0.0	1	50.0	2	40.0
Total	2	100.0	2	100.0	5	100.0
Age 25–34						
1st generation	2	5.0	3	5.1	3	4.0
2nd generation	11	27.5	14	23.7	16	21.3
3rd generation	5	12.5	10	16.9	9	12.0
POP	0	0.0	1	1.7	1	1.3
Nonusers	22	55.0	31	52.5	46	61.3
Total	40	100.0	59	100.0	75	100.0
Age 35–44						
1st generation	12	8.6	5	2.3	11	3.9
2nd generation	16	11.4	20	9.4	21	7.5
3rd generation	2	1.4	7	3.3	19	6.8
POP	7	5.0	6	2.8	6	2.1
Nonusers	103	73.6	175	82.2	224	79.7
Total	140	100.0	213	100.0	281	100.0

POP, progestogen only pills.

Among all 817 study subjects, we found 57 cases and 156 controls exposed to OC, of whom 7 cases and 49 controls were exposed to third generation OC. The age distribution by OC use shows that third generation OC are given preferentially to younger age groups and that OC use is very low in the 35–44-year-old age groups (Table 2). Unless otherwise indicated, "third generation" in the following comparisons is defined as low-dose estrogen combined with either desogestrel or gestodene as the progestogen. All comparisons of OC use versus nonuse show statistically significantly increased adjusted risk estimates for the association with MI (Table 3), with the exception of third generation OC (OR of MI for use of third generation versus no use: 0.82; 95% CI: 0.29 to 2.31; p = 0.711). The analysis for linear trend in proportions shows a significant decline in risk from first generation to third generation (χ^2 = 8.537; p = 0.0035). When comparing current use of third generation OC to second generation OC as risk factors for the occurrence of myocardial infarction, the fully adjusted odds ratio is OR = 0.28 (CI: 0.08 to 0.86; p = 0.026). The crude OR for this comparison was 0.36 (CI: 0.15 to 0.89), and the comparison using a larger model incorporating age by year, center, smoking status, hypertension, diabetes mellitus, alcohol use, parity, body mass index, study year, family history of MI, and current duration of use resulted in an OR of 0.27 (CI: 0.08 to 0.91). Based on the sample size calculations, our study was designed for the summary analysis of all participating centers and all controls. In a subgroup analysis not prespecified in the protocol, we partitioned women who were controls into two groups: hospital controls and those matched in the community. In the comparison of third generation OC users versus second generation OC users, we estimated an OR = 0.99 (CI: 0.22 to 4.49; p ~1.000) when the unmatched results are confined to the hospital-matched sets, and an OR = 0.15 (CI: 0.04 to 0.52; p = 0.003) for data confined to cases and community controls (Table 3). The matched analysis using conditional logistic regression showed an odds ratio of 0.28 (CI: 0.09 to 0.87) for the comparison of third versus second generation OC (Table 4). For second generation versus no use, the matched OR = 2.99 (CI: 1.51 to 5.91), and for third generation versus no current use, the matched OR = 0.85 (CI: 0.30 to 2.39). Because of conflicting opinions about the classification of norgestimate, we also show that the reclassification of users of OC containing norgestimate (1 case, 4 controls) as third generation users has little or no impact on the main comparison of third versus second generation OC (Table 5). When we stratified for age, the crude OR for the comparison of third versus second generation OC was 0.71 (CI: 0.22 to 2.39) for women aged 25–34, and 0.20 (CI: 0.04 to 0.93) for women aged 35–44.

A further unplanned subgroup analysis was di-

Table 3. Comparisons of oral contraceptive use and risk of acute myocardial infarction (AMI); odds ratios (OR) unmatched analysis adjusted for linear age, center, smoking status, hypertension, hypercholesterol, diabetes mellitus, family history of AMI, and duration of use of current OC with 95% confidence intervals (95% CI); norgestimate-containing compounds defined as second generation OC

Comparison	Exposed		OR	95% CI
	Cases	Controls		
All controls				
No current OC use (reference)	125	479	1.00	— —
Any OC use vs. no use	57	156	2.35	1.42 to 3.89
1st gen. OC use vs. no use	14	22	4.32	1.59 to 11.74
2nd gen. OC use vs. no use	28	71	2.96	1.54 to 5.66
Levonorgestrel vs. no use	22	57	2.99	1.47 to 6.11
3rd gen. OC use vs. no use	7	49	0.82	0.29 to 2.31
3rd gen. vs. 2nd gen use	7	49	0.28	0.09 to 0.86
3rd gen. vs. levonorgestrel use	7	49	0.27	0.08 to 0.89
Hospital controls				
No current OC use (reference)	125	207	1.00	— —
Any OC use vs. no use	57	67	3.17	1.63 to 6.15
1st gen. OC use vs. no use	14	8	6.97	1.84 to 26.47
2nd gen. OC use vs. no use	28	34	2.92	1.27 to 6.69
Levonorgestrel vs. no use	22	28	3.12	1.27 to 7.70
3rd gen. OC use vs. no use	7	18	2.92	0.72 to 11.84
3rd gen. vs. 2nd gen use	7	18	0.99	0.22 to 4.49
3rd gen. vs. levonorgestrel use	7	18	0.93	0.20 to 4.37
Community controls				
No current OC use (reference)	125	272	1.00	— —
Any OC use vs. no use	57	89	2.06	1.17 to 3.63
1st gen. OC use vs. no use	14	14	3.35	1.05 to 10.70
2nd gen. OC use vs. no use	28	37	3.24	1.53 to 6.84
Levornogestrel vs. no use	22	29	3.32	1.46 to 7.57
3rd gen. OC use vs. no use	7	31	0.49	0.16 to 1.48
3rd gen. vs. 2nd gen use	7	31	0.15	0.04 to 0.52
3rd gen. vs. levonorgestrel use	7	31	0.15	0.04 to 0.53

rected at determining potential regional differences. If we combine the four countries on the European continent (Gemany, Austria, Switzerland, and France), the estimates and confidence intervals become: third versus second generation OR = 0.10 (CI: 0.02 to 0.48; p = 0.004); third generation versus no use OR = 0.34 (CI: 0.08 to 1.50; p = 0.155); and second generation versus no current use OR = 3.3 (CI: 1.71 to 6.42; p < 0.0001). By comparison, the odds ratios for the UK are: third versus second generation OR = 1.25 (CI: 0.36 to 4.29; p = 0.723); third generation versus no use OR = 0.80 (CI: 0.29 to 2.18; p = 0.662); and second generation versus no current use OR = 0.64 (CI: 0.29 to 1.42; p = 0.270).

Current smoking was a significant risk factor for MI (OR = 9.72; CI: 5.58 to 16.93), but no risk was shown for past smoking (Table 6). After adjustment for OC use, the OR was 7.21 (CI: 4.58 to 11.36). There was no risk difference when nonsmoking OC users were compared with nonsmoking nonusers (OR = 1.32; CI: 0.51 to 3.45). Among third generation OC users, the crude odds ratio for current smoking was 3.75 (CI: 0.65 to 21.74). For second generation OC users, it was 9.50 (CI: 2.92 to 30.96) and 19.50 (CI: 2.11 to 179.89) for first generation OC users. For women who were not current users of OC, the equivalent risk estimate was 6.66 (CI: 3.88 to 11.43). For never-smokers (26 cases and 300 controls), the comparison of women who used third generation (2 cases, 24 controls) with those who used second generation (4 cases, 38 controls) resulted in a crude odds ratio of 0.79 (CI: 0.13 to 4.66). The same comparison done for current smokers (146 cases, 233 controls) showed an OR of 0.31 (CI: 0.10 to 1.00; p = 0.049). The individual risk of the group of former smokers (10 cases, 102 controls, no third generation exposure among cases) could not be estimated in our data.

Other known risk factors, like diabetes mellitus, hypertension, and self-reported high lipids are shown to be important independent contributors to MI in our study (Table 6). Information on blood pressure measurement prior to administration of an

Table 4. Matched analysis; comparisons of oral contraceptive use and risk of acute myocardial infarction (AMI); matched odds ratios (OR) adjusted for smoking status, hypertension, hypercholesterol, diabetes mellitus, family history of AMI, and duration of use of current OC with 95% confidence intervals (95% CI)

Comparison	Exposed		OR	95% CI
	Cases	Controls		
All controls				
No current OC use (reference)	125	479	1.00	— —
Any OC use vs. no use	57	156	2.26	1.32 to 3.86
1st gen. OC use vs. no use	14	22	4.66	1.52 to 14.33
2nd gen. OC use vs. no use	28	71	2.99	1.51 to 5.91
Levonorgestrel vs. no use	22	57	3.38	1.63 to 7.00
3rd gen. OC use vs. no use	7	49	0.85	0.30 to 2.39
3rd gen. vs. 2nd gen. use	7	49	0.28	0.09 to 0.87
3rd gen. vs. levonorgestrel use	7	49	0.24	0.07 to 0.78
Hospital controls				
1st gen. OC use vs. no use	14	8	4.84	1.14 to 20.64
2nd gen. OC use vs. no use	28	34	2.64	1.09 to 6.40
3rd gen. OC use vs. no use	7	18	2.59	0.58 to 11.65
3rd gen. vs. 2nd gen. use	7	18	0.98	0.22 to 4.44
Community controls				
1st gen. OC use vs. no use	14	14	4.49	1.18 to 17.00
2nd gen. OC use vs. no use	28	37	3.15	1.38 to 7.16
3rd gen. OC use vs. no use	7	31	0.55	0.17 to 1.81
3rd gen. vs. 2nd gen. use	7	31	0.18	0.05 to 0.65

Norgestimate-containing compounds defined as second generation OC.

OC was acquired only for current users. This information was unavailable for 13% of cases and 6% of controls who used OC at the time of interview, so that this variable cannot be adequately evaluated. Crude analysis shows that risk of MI among women without a blood pressure measurement is 1.81 (CI: 1.20 to 2.73) compared with women who did have their blood pressure checked. The risk associated with MI was 1.07 (CI: 0.66 to 1.74) for the comparison of users versus nonusers of OC among women who had their blood pressure checked and 2.76 (CI: 1.36 to 5.61) among women who did not have their blood pressure measured prior to OC prescription.

Table 5. Comparisons of oral contraceptive use and risk of acute myocardial infarction (AMI); odds ratios (OR) unmatched analysis adjusted for linear age, center, smoking status, hypertension, hypercholesterol, diabetes mellitus, family history of AMI, and duration of use of current OC with 95% confidence intervals (95% CI); norgestimate-containing compounds defined as third generation OC

Comparison	Exposed		OR	95% CI
	Cases	Controls		
All controls				
2nd gen. OC use vs. no use	27	67	3.21	1.65 to 6.21
3rd gen. OC use vs. no use	8	53	0.79	0.30 to 2.11
3rd gen. vs. 2nd gen. use	8	53	0.25	0.08 to 0.74
3rd gen. vs. levonorgestrel use	8	53	0.27	0.09 to 0.83
Hospital controls				
2nd gen. OC use vs. no use	27	32	3.41	1.46 to 7.09
3rd gen. OC use vs. no use	8	20	1.81	0.46 to 7.97
3rd gen. vs. 2nd gen. use	8	20	0.53	0.12 to 2.36
3rd gen. vs. levonorgestrel use	8	20	0.58	0.13 to 2.68
Community controls				
2nd gen. OC use vs. no use	27	35	3.37	1.57 to 7.24
3rd gen. OC use vs. no use	8	33	0.55	0.19 to 1.56
3rd gen. vs. 2nd gen. use	8	33	0.16	0.05 to 0.53
3rd gen. vs. levonorgestrel use	8	33	0.16	0.05 to 0.57

Table 6. Selected determinants for acute myocardial infarction (AMI); adjustments are for linear age, center, parity, smoking, hypertension, hypercholesterol status, diabetes mellitus, body mass index, family history of AMI, and study year; the respective determinant under study is excluded from the adjustment

Comparison	Exposed		OR	95% CI
	Cases	Controls		
Current use	57	156	2.34	1.36 to 4.05
First user	8	16	10.58	2.82 to 39.73
Risk factors				
Diabetes mellitus	14	12	2.53	0.80 to 7.96
Hypertension	42	50	3.31	1.74 to 6.31
High lipids (self-reported)	20	14	4.24	1.68 to 10.68
Smoking				
Never smoker	26	300	1.0	— —
Former smoker	10	102	1.11	0.46 to 2.69
Current smoker	146	233	9.72	5.58 to 16.93
Body mass index				
≤20	17	97	1.0	— —
20–24	64	329	1.73	0.84 to 3.57
25–29	51	131	3.72	1.68 to 8.25
≥30	42	75	4.79	2.07 to 11.05
Family history of AMI	39	40	3.69	1.91 to 7.14
Parity	167	526	2.80	1.29 to 6.09
Age groups (years)				
16 to 24	2	7	1.0	— —
25 to 34	40	134	2.76	0.26 to 29.14
35 to 44	140	494	2.21	0.21 to 22.52

In our study, the first case of MI was collected in August 12, 1993, the last case on March 7, 1996; the first control was accrued on September 23, 1993, the last on June 12, 1996. Given that in the intervening time between October 1995 and June 1996 changes in OC use may have occurred due to regulatory pressures, we show a table stratified by before and after 1 November 1995 for the UK and the Southern Rim countries (Table 7). The likelihood of a control being treated with second generation OC in the UK is seven times higher (OR of second generation use after November 1995 = 7.1; 95% CI: 1.5 to 34.6) in the time between November 1, 1995, and June 1996 than before November 1, 1995. There is a slight rise in overall pill use in the UK attributable largely to an increase in the 25–34-year-olds (from 43% to 53% among controls), with a slight decrease noted among 35–44-year-olds (20% versus 14% among controls). On the other hand, the Southern Rim countries show a proportionate increase in third generation use (OR of second generation after November 1, 1995 = 0.7; 95% CI: 0.1 to 3.2). The German centers were discontinued in June 1996 due to a lack of gestodene exposure, as shown by the continuous surveillance of exposure among controls. Therefore, those centers could not enter this component of the analysis. These data do not lend themselves to a detailed analysis, so that no risk estimates by period are presented.

Discussion

Compared with noncurrent users, we find a risk of MI associated with prior generations of oral contraceptives, but not with the third generation OC containing desogestrel or gestodene. The overall results show a clear gradient of decreasing risk from first to third generation of OC ($p = 0.0035$). The risk estimates comparing third generation with second generation OC are based on seven cases of MI and 49 controls exposed to third generation OC and on 28 cases and 71 controls exposed to second generation OC. The overall, fully adjusted OR for all five countries is 0.28 (CI: 0.09 to 0.86), which is statistically significant. For this comparison, crude odds ratios, unmatched OR using a small and a complete model, and matched OR were calculated. The fact that all show statistical significance without large differences in either the point estimates or the confidence intervals indicate that these results, although based on a small number of exposed cases and controls, are fairly stable. Compared with second generation users, the point estimates are consistent with a benefit in the range of two- to four-fold for users of the third generation progestogens.

Although the protocol of the study and sample size calculations specified summary risk ratios for cases and controls irrespective of the type of control or the country that they came from, we also did subgroup

Table 7. Proportion of use of oral contraceptives by generation and type of study participant before and after 1 November 1995

	Before November 1, 1995				After November 1, 1995			
	Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%
UK								
3rd generation	4	4.9	19	7.1	1	4.8	2	2.3
2nd generation	5	6.2	24	9.0	3	14.3	18	20.7
POP	4	4.9	7	2.6	1	4.8	3	3.4
No use	68	84.0	218	81.3	16	76.2	64	73.6
Total	81	100.0	268	100.0	21	100.0	87	100.0
Southern Rim*								
3rd generation	1	3.6	9	16.4	0	0.0	9	20.9
2nd generation	8	28.6	6	10.9	1	20.0	4	9.3
1st generation	2	7.1	1	1.8	1	20.0	0	0.0
POP	1	3.6	1	1.8	0	0.0	1	2.3
No use	16	57.1	38	69.1	3	60.0	29	67.4
Total	28	100.0	55	100.0	5	100.0	43	100.0
Germany†								
3rd generation	1	2.1	10	5.5	—	—	—	—
2nd generation	11	23.4	19	10.4	—	—	—	—
1st generation	11	23.4	21	11.5	—	—	—	—
POP	2	4.3	2	1.1	—	—	—	—
No use	22	46.8	130	71.4	—	—	—	—
Total	47	100.0	182	100.0	—	—	—	—

*Countries designated as "Southern Rim" include Austria, France, and Switzerland.

†Accrual in Germany until June 1995 only due to low prevalences of gestodene use presumably caused by publicity related to regulatory actions. Figures for Germany are not given because German centers were discontinued in July 1995.

analyses focusing on control type and the country of origin. The small numbers exposed are reflected in the crude OR found for the individual study components, which range from 0.06 (CI: 0.01 to 0.56; 1 case, 18 controls) in the Southern Rim (Austria, France, Switzerland) to 1.25 (CI: 0.36 to 4.29; 5 cases, 21 controls) in the UK, with Germany intermediate at 0.17 (CI: 0.02 to 1.54; 1 case, 10 controls), so that the combined OR for the continental European component is 0.10 (CI: 0.02 to 0.48; 2 cases, 16 controls). This may be a reflection of the way health care is provided in the different areas. Clearly, the regulatory mechanisms in the UK that also led to the premature termination of the field work of our study have had a pronounced effect on the distribution of OC use in the UK. Thus, three (75%) of the UK controls using norgestimate were collected after November 1995, and second generation OC use had escalated significantly.

The stratification by type of control produced different risk estimates by control type, with the primary benefit apparent in the comparison using community controls only. While hospital controls are intermediate between cases and community controls in terms of risk profile, they differ from both in their use of hospital physicians. As could be suspected, our data suggest that hospital controls are individuals with a higher likelihood of being in the hospital at any given time than either community controls or cases who came into the hospital for treatment of an acute medical condition. This important difference indicates that the community controls may be the more appropriate comparison group for young women with a first event of myocardial infarction. The poorer response rate among community controls, however, may also introduce bias in this group. It is important to emphasize that all controls, hospital-based and community, had been specified to be the main reference in the published protocol.[14,15]

Potential biases in case-control studies include diagnostic bias, exposure selection bias, as well as attrition of susceptibles.[18] All of these also include characteristics linked to a differential risk of incurring an event. It is unlikely that these will come to bear as strongly in the MI study as they can be assumed to have had an impact on the study on venous thromboembolism. MI is a much more robust diagnosis and all surviving cases are likely to enter the hospital, so that diagnostic bias is improbable. Because the distinction between venous and arterial risk factors is not entirely clear in the literature, physicians hardly differentiate between the two. Exposure selection bias based on physician risk perception may be an issue, as evidenced by the influence of

blood pressure checking prior to OC prescription.[13] But this would tend to lead to an overestimate of the association if newer exposures advertised as having improved safety profiles are be allocated to the high-risk group. The results shown for MI differ from those for VTE, so that one may assume that the high risk of venous thromboembolism found for the specific risk population with Factor V Leiden mutation is not active here.[19,20] The results of matched analyses demonstrate that overmatching did not occur.

From the initial discussion about the association of OC use and MI, there has been a sharp decline in the risk patterns reported in the epidemiologic studies on OC of the mid-1970s. Risk ratios found in the US in 1978 ranged between 4.0 and 14.0 for the association of OC use and MI, with smoking found to be an important confounding factor.[21–23] A similar magnitude of risk for MI and for death from ischemic heart disease was found in the UK with conflicting results concerning former use and duration of use.[24,25] Some investigations found pill use to be only associated with risk of MI among smokers with no risk evident among nonsmokers.[26] The Nurses' Health Study, an 8-year observational cohort of 119,061 women aged 30 to 55 years, found an increased risk among current users (RR = 2.5; 95% CI: 1.3 to 4.9) with the excess risk concentrated among cigarette smokers, but no increase among former users and no relationship with duration of use.[27] The lack of association with duration of use indicates that oral contraceptives do not promote atherosclerosis, and that any acute processes related to platelet function and coagulation[28] are affected in a reversible manner.

The incidence rates estimated for young women range from 0 to 3/100,000/year in 25–34-year-olds, and from 6 to 14/100,000/year in 25–34-year-old women in Germany.[29] The overall case fatality of MI is approximately 50%; about 30% of MI events are fatal out of hospital, and about 40% do not survive the first 24 h after the event.[30] A hospital-based case-control study concerned primarily with survivors might, therefore, not provide an appropriate estimate. Our study, which includes 13 fatal events among 182 total cases, reflects the situation among those who have survived longer than 24 h after the event. However, the risk estimates for fatal MI events and OC use have generally been similar to those of surviving events, and have shown a similar decline over the years. In 1975, a nearly three-fold (2.8) increase of risk associated with OC use and death of MI was found for women under the age of 50,[31] with a similar risk shown among survivors as for fatal events.[32] The relationship of fatal events to OC use in women aged under 40 was estimated as a relative risk of 1.9 (CI: 0.7 to 4.9) for 1986 to 1988.[33] The most recent study of a UK database that included all fatal and nonfatal events produced a statistically nonsignificant estimate of 0.6 to 0.7 for the risk of MI incurred with use of third generation OC compared with levonorgestrel.[12]

The following points become clear when the literature is reviewed: there is a continuous decrease of the risk observed for the association between MI and OC use; there is a consistent link with cigarette smoking, much more so than with other risk factors; and other risk factors carry an independent risk. The central importance of cigarette smoking for the occurrence of MI in young women has long been known.[34] Calculations based on the early results showed that the contribution of smoking to MI risk is much larger than that of OC use.[35] Our own results appear to be at the end of a progression from an observed risk increase to no risk shown for recently introduced progestogens. Our results show that cigarette smoking was associated with a much higher risk of heart attack than the use of either generation of OC. Overall, nonsmoking OC users showed no increased risk of acute myocardial infarction (AMI) when compared with nonsmoking nonusers. However, the analyses on the impact of smoking by use of second and third generation OC showed a greater elevation of MI risk for smokers who use second generation progestogens compared with those who use third generation compounds. Experimental research is needed to show whether the apparent attenuation of the risk posed by smoking among users of third generation OC is due to the action of the newer progestogens. Clinical risk factors play a larger role in the risk of MI than OC use. Although our data on blood pressure measurements prior to the prescription of an OC are not adequate, our crude results point in a similar direction to the ones shown by the WHO study.[13] Women with prior blood pressure checks are on the whole at less risk of MI than those who did not have their blood pressure measured. This result is difficult to interpret, but possibly indicates that guidance of high-risk patients is an effective intervention measure.

The pathophysiologic mechanism for a reduction of risk of MI with the newer progestogens is not entirely clear. Compared with levonorgestrel, desogestrel—the most extensively examined third generation progestogen—has a lower affinity for androgen receptors[36] and does not inhibit the estrogen-related increase in sex-hormone-binding globulin (SHBG).[37] Gestodene is known to act in a similar fashion. Low levels of SHBG were found to be associated with an increase of hypertension and cardiovascular mortality.[38] The lack of inhibition of SHBG by the newer progestogens might, therefore, provide some of the

explanation of the observed effect. The new progestogens are also known to have a positive influence on lipid metabolism by increasing HDL-cholesterol.[39,40] It seems unlikely that this effect should become apparent in a population of young women, because the risk posed by hypercholesterolemia tends to act in the long-term. On the other hand, women with MI events in our study show a significantly different profile of arterial risk factors than do the controls, and the main benefit was found among women in the older age group, where the risk of MI is higher. The epidemiologic evidence implies that there is no adverse effect of third generation OC on the arterial side, the physiologic background for which needs to be more firmly established.

Although the baseline morbidity of MI in the population of 16–44-year old women is low, the risk of mortality following events is high, with a case fatality of around 50%.[29,30] The fact that three independent studies[10,12,13] now show that the newer generation oral contraceptives are not associated with a risk of MI could, therefore, translate into clinically important lives saved, particularly when we observe that the main effect lies in the older age group. However, our study also shows that the main risk for MI is due to the known arterially mediated risk factors. Clearly, intensive risk counseling should precede prescription of any medication, and if an oral contraceptive is chosen, then it appears that the newer progestogens are the appropriate choice for women with a cardiovascular risk.

Acknowledgments

This study was financially supported with an unconditional grant made by Schering AG Berlin. Accountability of the investigators was only to the Scientific Reference Board (SRB) who approved the protocol, received periodic reports, conducted audits on the field, and conducted audits of the data before submission. On statistical issues, the SRB was advised by the Statistical Advisory Group (SAG).

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Appendix

The Transnational Case-Control Study:

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