as the one in Stratford-on-Avon (NATC/RCGP Distance Learning Course, National Asthma Training Centre). Reducing the dose of antipsychotic drugs increases the risk of death or near death. Therefore mechanisms need to be in place that enable early identification of patients who have reduced their medication. The community psychiatric nurse is probably best placed to do this. Repeat prescription policies in general practice need to be revised in the light of this study. Patients on combined therapy (asthma and psychosis) should not be provided with repeat prescriptions without attending the surgery. The results of this study indicate that these patients should be seen for their asthma on at least a monthly basis. Failure to attend agreed appointments could serve as a warning system and appropriate measures can be taken.

Some health professionals erroneously believe that asthma is caused by stress and may be misled into treating the psychological symptoms at the expense of good asthma management. This paper brings together important issues related to shared care, compliance, and mortality from asthma. A more holistic approach to care needs to be implemented for this group of asthmatic patients requiring antipsychotic or sedative drugs.

1 Proceedings of the Asthma Mortality Task Force, 1986. Sheffer AL, Buist S, eds. *J Allergy Clin Immunol* 1987:80 (3):361-486.

Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study

Walter O Spitzer, Michael A Lewis, Lothar A J Heinemann, Margaret Thorogood, Kenneth D MacRae on behalf of Transnational Research Group on Oral Contraceptives and the Health of Young Women

See p 88 and editorial by McPherson

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Abstract

***Objective*—To test whether use of combined oral contraceptives containing third generation progestogens is associated with altered risk of venous thromboembolism.**

***Design*—Matched case-control study.**

***Setting*—10 centres in Germany and United Kingdom.**

***Subjects*—Cases were 471 women aged 16-44 who had a venous thromboembolism. Controls were 1772 women (at least 3 controls per case) unaffected by venous thromboembolism who were matched with corresponding case for age and for hospital or community setting.**

***Main outcome measures*—Odds ratios derived with stratified analyses and unconditional logistic regression to adjust for potential confounding variables.**

***Results*—Odds ratios (95% confidence intervals) for venous thromboembolism were: for any oral contraceptives versus no use, 4·0 (3·1 to 5·3); for second generation products (low dose ethinyloestradiol, no gestodene or desogestrel) versus no use, 3·2 (2·3 to 4·3); for third generation products (low dose ethinyloestradiol, gestodene or desogestrel) versus no use, 4·8 (3·4 to 6·7); for third generation products versus second generation products, 1·5 (1·1 to 2·1); for products containing gestodene versus second generation products, 1·5 (1·0 to 2·2); and for products containing desogestrel versus second generation products, 1·5 (1·1 to 2·2). Probability of death due to venous thromboembolism for women using third generation products is about 20 per million users per year, for women using second generation products it is about 14 per million users per year, and for non-users it is five per million per year.**

***Conclusions*—Risk of venous thromboembolism was slightly increased in users of third generation oral contraceptives compared with users of second generation products.**

Introduction

Oral contraceptives have been linked with a small absolute increase in the incidence of vascular disease in many epidemiological studies. Several reviewers have weighed the evidence on the safety of early oral contraceptives and have concluded that their risks are balanced by benefits.[1-4] Since their introduction, oral contraceptives have undergone considerable development intended to reduce the risk of adverse effects. In the 1970s second generation drugs were introduced that contained a lower dose of ethinyloestradiol, which it was believed would reduce the risk of vascular disease. More recently, third generation drugs were introduced that contained gonane progestogens—desogestrel, gestodene, and norgestimate.

Later events have led to a reappraisal of the safety of these third generation drugs. Results of a pharmacokinetic study of 22 women in Germany suggested that gestodene, but not desogestrel, may increase the risk of vascular events.[5,6] This led the German regulatory authorities to alert doctors to drugs containing gestodene and to require an epidemiological study of vascular disease. In October 1995 unpublished results from three studies, including the one reported here, led the Committee on Safety of Medicines in the United Kingdom to warn doctors of a potentially increased risk of venous thromboembolism in users of oral contraceptives containing desogestrel or gestodene.

The transnational case-control study of oral contraceptives is a multinational study of oral contraceptives and vascular disease undertaken at the request of German regulatory authorities in response to concern about gestodene. This first report has been prepared earlier than planned in response to the expressed needs of the medicines regulatory authorities in Europe and the wider medical community.

Methods

GENERAL PLAN AND DESIGN

Our design and all definitions, questionnaires, and field operations were virtually identical to those of the case-control study of the World Health Organisation Human Reproduction Unit,[7] which was under way as we started. This was done to allow the results to be combined at a later date if necessary. The transnational project encompasses three simultaneous case-control studies, with respective outcomes of deep vein thrombosis and pulmonary embolism (that is, venous thromboembolism), arterial thrombotic stroke, and myocardial infarction. Sudden death attributable to any of these outcomes was included. The initial

protocol was published before the studies began, and revisions to the protocol were also published.[8,9] The field work was done in 16 centres in five countries (Austria, France, Germany, Switzerland, and the United Kingdom). Field work is continuing in 10 centres.

The required ratio of three controls per case included at least one community control and one hospital control. We originally planned to have a minimum of four controls per case, but examination of the distribution of variables among controls in early 1994 showed that we could attain adequate statistical power with three controls. We did not use enrolled cases for whom we failed to match at least one control from the community and one from hospital. The British community controls were recruited from the same group general practice as the corresponding case (not necessarily the same general practitioner). In Germany population lists from the same neighbourhood were used. In France the matching method was similar to that in the United Kingdom, while in Switzerland and Austria the matching was based on neighbourhood population lists. The age range for both cases and controls was 16-44 years, with cases and controls matched for age within five year age bands. The other inclusion and exclusion criteria for both cases and controls are published separately.[7-9]

SUBJECTS

Enrolment of cases was concurrent, defined as within four months of the venous thromboembolism event or its diagnosis. All cases were identified in hospital. In addition, the appropriate authorities were contacted in order to identify all deaths diagnosed as due to venous thromboembolism that occurred in women aged 16-44 in the geographical area of the study. Diagnosis of deep vein thrombosis relied on pain and tenderness in the extremities, a precise record of knee circumference, and confirmation with imaging procedures. Diagnosis of pulmonary embolism was based on symptoms of pain in the chest or the side and confirmatory imaging procedures. Necropsy reports of the fatal events were reviewed. Log books of all cases enrolled and rejected were kept in all centres.

CONTRACEPTIVE USE

Current use of oral contraceptives was defined as use within the three months before the event (for a case), hospital admission (for a hospital control), or date of interview (for a community control). Only current use was considered to be a risk factor in the analyses; prior use was considered only for adjustment purposes

For the purpose of this analysis, we defined first generation oral contraceptives as any preparation that contained 50 μg or more of ethinyloestradiol, regardless of progestogen content. Second generation oral contraceptives were defined as those containing 35 μg or less of ethinyloestradiol and a progestogen other than gestodene or desogestrel. Preparations containing norgestimate were included with the second generation products, to retain consistency with the World Health Organisation analysis. There were 18 cases and 28 controls who used these products. Third generation oral contraceptives were defined as products containing low doses of ethinyloestradiol (usually 30 μg or 20 μg) and either gestodene or desogestrel. Progesterone only pills containing no oestrogen were used by 17 cases and 34 controls. Precise definitions of the classifications of oral contraceptives are available from the authors.

INTERVIEWS

Interviews were conducted personally. We confirmed exposure to oral contraceptives by inspecting individual patients' packets of pills in samples of the cases and controls. Clinical data were verified with medical records when they were coded. All data were checked manually and by computer for eligibility and correct matching. We did double coding of clinical data and double entry with verification of all other data. Local and international panels of clinical specialists checked all difficult or unreconciled diagnoses.

The original research questions for the case control study on venous thromboembolism were: (1) What is the relative risk of venous thromboembolism for current use of all oral contraceptives now on the market in the countries where the investigation was conducted, compared with no current use? (2) In the same countries what is the relative risk of venous thromboembolism for current use of low dose combinations of gestodene and ethinyloestradiol compared with all other low dose ethinyloestradiol oral contraceptives not containing gestodene or desogestrel?

In the light of the newly expressed concern about third generation products we added two other comparisons for analysis. (3) What is the relative risk of venous thromboembolism for current use of all third generation oral contraceptives compared with all second generation products? (4) What is the relative risk of venous thromboembolism for current use of oral contraceptives containing desogestrel compared with all second generation products?

DATA ANALYSIS

After the quality assurance described above, we created a file of predetermined variables that we deemed essential or important: table 1 lists these "cardinal variables."

We used stratified analyses and unconditional logistic regression, with simultaneous adjustment performed with STATA 4.0 (Stata, College Station, TX, USA) were used to adjust for potential confounding variables (linear age, study centre, body mass index, smoking, alcohol use, and duration of use of oral contraceptives before the current exposure). Tables 1 and 2 show the categories in each variable. We did additional stratified analyses to search for unsuspected confounding variables and potential biases and also performed conditional logistic regression to assess whether overmatching had occurred.

Table 1—*Cardinal variables used in logistic regression analysis*

Variable	Category
Major variables	
Age	In five year bands
Diagnosis for cases	As per protocol
Confidence of diagnosis	Possible, probable, certain
Diagnosis for controls	As per protocol
Area of residence	By centre and subcentre
Type of control	Community or hospital
Exposure to oral contraceptives	
User status	Never used, former user, current user
Type of contraceptive	Code
How recent the exposure	By month
Duration of exposure	By month
Potential confounders	
Life style:	
Smoking	Never, former, current
Alcohol consumption	No of drinks a day, a week, a month
Body mass index (kg/m²)	<20, 20-30, ≥30
Medical history:	
Hypertension	Yes or no
Diabetes	Yes of no
Any pregnancies	Yes or no
Rheumatic heart disease	Yes or no
Family history:	
Stroke	Yes or no
Acute myocardial infarction	Yes or no
Educational status	Years of education

Table 2—*Distribution of selected variables from cardinal data set among study subjects in United Kingdom and Germany. Values are numbers (percentages) of subjects*

	Cases (n=471)	Hospital controls (n=789)	Community controls (n=983)
Age group (years):			
16-24	133 (28·2)	244 (30·9)	255 (25·9)
25-34	188 (38·4)	310 (39·3)	376 (38·3)
35-44	157 (33·3)	235 (29·6)	352 (35·8)
Risk factors:			
Body mass index ≥30	77 (16·4)	88 (11·2)	84 (8·6)
Current smoker	215 (45·7)	346 (43·9)	343 (34·9)
Alcohol intake (No of drinks):			
>1 monthly and <1 weekly	166 (35·2)	285 (36·1)	364 (37·0)
>1 weekly	71 (15·1)	140 (17·7)	218 (22·2)
Medical history:			
Hypertension	27 (5·7)	36 (4·6)	68 (6·9)
Diabetes	11 (2·3)	13 (1·7)	8 (0·8)
Pre-eclampsia	22 (4·7)	40 (5·1)	37 (3·8)
Current use of oral contraceptive	318 (67·5)	329 (41·7)	437 (44·5)
Year of accession:			
1993	71 (15·1)	85 (10·8)	108 (11·0)
1994	286 (60·7)	455 (57·7)	599 (60·9)
1995	114 (24·2)	249 (31·6)	276 (28·1)

For this report, we calculated adjusted odds ratios and their 95% confidence intervals to estimate the risk of venous thromboembolism associated with use of the various categories of oral contraceptives. To assist in the interpretation of the data and to examine how several possible biases might affect the estimates, we stratified by age and by first use of an oral contraceptive versus subsequent use. We also assessed how much the estimates were affected when controls were only from hospital or only from the community.

SOURCE OF DATA

This paper includes data primarily from the United Kingdom and Germany, where three years of field work have been completed, and is based on accrual of subjects up to 3 October 1995. At the time that this data set was created, field work had been in progress for less than one year in Austria, Switzerland, and France. Nevertheless, we also report the key odds ratios for all five nations combined.

The German data were affected by highly publicised regulatory actions taken by the Federal Institute for Drug Safety and Medical Products in 1989-90 with respect to a prominent third generation oral contraceptive, just as we were starting field work. This was reflected in low exposure rates to third generation products in our German data and thus very unstable point estimates. Accordingly, some analyses, mainly those relating to potential biases, were confined to the British data set. Similar analyses for Germany alone will be published in a German medical journal.

We calculated aetiologic fractions separately for the United Kingdom and Germany by the method of Miettinen.[10] The fractions permitted calculation of rates of attributable deaths for each country based on national mortality registries. The total number of deaths occurring in each exposure category could then be determined by multiplying the overall total number of deaths by the proportion applying to that exposure category. The number of deaths in an exposure category with an odds ratio of OR_1 that would be saved by switching to another category with an odds ratio of OR_2 is:

$(OR_1-OR_2)/OR_1 \times$ total number of deaths in the category to which OR_1 applies[11 12]

This last number is then summed across the six age groups to give the estimated total number of deaths that would be "saved" by switching. The calculation was for deaths from venous thromboembolism saved by switching from third generation oral contraceptives to second generation products. We based our calculations both on the Office of Population Censuses and Surveys' 1993 total of 103 deaths and on its 1992 total of 43 deaths.

For each exposure group (third generation, second generation, and first generation contraceptives and non-use), the proportion of total deaths in each age group is a function of the odds ratio for that exposure category and the prevalence of use for that exposure category.[12] The estimates are based on the assumptions that (*a*) odds ratios from a study comprising mainly non-fatal cases can be generalised to fatal cases, (*b*) the odds ratios apply equally to all age groups, (*c*) assumption (*a*) applies equally to all age groups, and (*d*) the prevalence of use of the various oral contraceptive categories in the relevant population is reflected by the prevalence in the controls.

Results

We report results for 471 cases and 1772 controls (789 from hospital and 983 from the community) in the United Kingdom and Germany (table 2). There were 183 cases of pulmonary embolism (with four fatal events) and 288 cases of deep vein thrombosis without report of pulmonary embolism.

Table 3 shows the key results. Overall, there was a fourfold higher relative risk of venous thromboembo-

Table 3—*Odds ratios of venous thromboembolism for current use of different groups of oral contraceptives*

Comparison	United Kingdom			Germany			Total		
	No of cases exposed (n=282)	No of controls exposed (n=1048)	Odds ratio (95% confidence interval)*	No of cases exposed (n=189)	No of controls exposed (n=724)	Odds ratio (95% confidence interval)*	No of cases exposed (n=471)	No of controls exposed (n=1772)	Odds ratio (95% confidence interval)*
All oral contraceptives† *v* no current use	167	411	3·4 (2·4 to 4·9)	146	333	5·5 (3·5 to 8·7)	313	744	4·0 (3·1 to 5·3)
First generation products‡ *v* no current use	1	3	2·0 (0·2 to 20·8)	38	56	8·3 (4·5 to 15·2)	37	59	5·7 (3·4 to 9·4)
Second generation products‡ *v* no current use	64	189	3·0 (1·9 to 4·5)	68	213	3·7 (2·2 to 6·2)	132	402	3·2 (2·3 to 4·3)
Third generation products‡ *v* no current use	98	197	4·4 (3·0 to 6·6)	29	52	6·7 (3·4 to 13·0)	127	249	4·8 (3·4 to 6·7)
Products containing levonorgestrel *v* no current use	37	131	2·5 (1·5 to 4·0)	52	180	3·4 (2·0 to 5·7)	89	311	3·0 (2·0 to 3·9)
Third generation products *v* second generation products‡	98	197	1·5 (1·0 to 2·2)	29	52	1·8 (1·0 to 3·3)	127	249	1·5 (1·1 to 2·1)
Products containing gestodene *v* second generation products‡	45	101	1·4 (0·9 to 2·3)	10	11	2·6 (1·0 to 7·2)	55	112	1·5 (1·0 to 2·2)
Products containing desogestrel *v* second generation products‡	53	96	1·6 (1·0 to 2·5)	12	25	1·5 (0·8 to 3·1)	72	137	1·5 (1·1 to 2·2)

*Adjusted for linear age, smoking, alcohol use, study centre, body mass index, and duration of exposure to oral contraceptives used before current oral contraceptive.
†Including progesterone only oral contraceptives.
‡Users of progesterone only oral contraceptives (17 cases and 34 controls) were not classified as users of first, second, or third generation products. Thus rows and columns do not necessarily add up. Including them as third or second generation products makes no meaningful difference to odds ratios.

lism associated with current use of any oral contraceptive versus no current use. For any oral contraceptive, we included brands not fulfilling criteria for the three generations as defined. In the same comparison the odds ratio for the United Kingdom was 3·4 (2·4 to 4·9) and for Germany was 5·5 (3·5 to 8·7). For third generation contraceptives versus second generation products in both countries, the odds ratio was 1·5 (1·1 to 2·1). The odds ratios for second generation and third generation products versus no current use were 3·2 (2·3 to 4·3) and 4·8 (3·4 to 6·7) respectively. Compared with no current use, the lowest point estimate we found for use of an oral contraceptive was for second generation products containing levonorgestrel. The odds ratios for third generation products containing gestodene and for those containing desogestrel were similar. The point estimates for all comparisons were higher in the German data than the British data.

Table 4 shows the distribution of use of types of oral contraceptive by selected variables among 1772 controls in the United Kingdom and Germany. These variables were the predefined subset of cardinal data, which are listed in table 1.

Results for all five countries—The odds ratio of venous thromboembolism associated with current use of any oral contraceptive versus no current was 4·5 (3·5 to 5·9), with 340 cases and 783 controls exposed to such products. For third generation products versus second generation products, the odds ratio was 1·7 (1·3 to 2·4), with 149 cases and 262 controls exposed. All other odds ratios were slightly higher than for the United Kingdom in Germany. The odds ratios for third generation products containing gestodene and for those containing desogestrel were similar, being 1·7 (1·2 to 2·5) and 1·8 (1·2 to 2·6) respectively.

POTENTIAL BIAS

We considered a number of effects that might have biased our results, including differential prescription of the newer preparations and higher alertness leading to diagnostic or referral biases. To examine these possibilities we undertook additional analyses by diagnostic category and by whether women were using an oral contraceptive for the first time. The odds ratios of both categories of venous thromboembolism associated with use of third generation products versus use of second generation products were 2·0 (1·2 to 3·4) for pulmonary embolism and 1·2 (0·8 to 1·9) for deep vein thrombosis. In an analysis restricted to first time users of any oral contraceptive the odds ratio for use of third generation products versus second generation products was 2·7 (1·3 to 5·7); when the same analysis was restricted to women who had previously used an oral contraceptive the odds ratio was 1·4 (1·0 to 2·1).

The matched analysis (British and German data combined) for third generation versus second generation products resulted in an odds ratio of 1·6 (1·2 to 2·2). For second generation products versus no current use, it was 3·0 (2·2 to 4·0), and for third generation products versus no current use, it was 4·9 (3·6 to 6·7). When we compared third generation versus second generation products using community controls only, the odds ratio was 1·4 (1·0 to 2·0); with hospital controls only, it was 1·7 (1·2 to 2·5). For second generation products versus no current use, we found an odds ratio of 3·4 (2·4 to 4·9) with community controls and 3·5 (2·4 to 5·0) with hospital controls. For third generation products versus no current use, we found an odds ratio of 4·7 (3·3 to 6·8) with community controls and 6·0 (4·0 to 8·9) with hospital controls.

ESTIMATES FOR POPULATIONS

The population aetiological fraction for current use of all third generation oral contraceptives in comparison with use of second generation products was 9% in the United Kingdom and 11% in Germany. Given the prevalence of use of third and second generation preparations in the controls in this study and the observed odds ratio of 1·5 (1·1 to 2·1) for third compared with second generation products, the point estimate is consistent with an excess of five deaths based on the Office of Population Censuses and Surveys' 1992 total and 10 deaths based on the 1993 total. The confidence interval for the odds ratio and the change in coding of deaths from venous thromboembolism in England and Wales between 1992 and 1993 gives a range of one to 19 excess deaths from this cause per year. In Germany the range is from two to 15 additional deaths and the point estimate is consistent with seven excess deaths.

Table 4—*Distribution of use of oral contraceptives by selected variables from the cardinal data set among 1772 controls in the United Kingdom and Germany. Values are numbers (percentages) of subjects*

		Users of oral contraceptives*		
	Non-users (n=1028)	1st Generation (n=59)	2nd Generation (n=402)	3rd Generation (n=249)
Age (years):				
16-24	206 (20·0)	11 (18·6)	147 (36·6)	128 (51·4)
25-34	372 (36·2)	23 (39·0)	177 (44·0)	99 (39·8)
35-44	450 (43·8)	25 (42·4)	78 (19·4)	22 (8·8)
Body mass index ≥30	127 (1·4)	5 (8·5)	26 (6·5)	12 (4·8)
Alcohol intake (No of drinks):				
>1 monthly and <1 weekly	365 (35·5)	11 (18·6)	160 (39·8)	104 (41·8)
>1 weekly	204 (19·8)	11 (18·6)	73 (18·2)	62 (24·9)
Smoking				
Current smoker	379 (36·9)	28 (47·5)	169 (42·0)	97 (38·9)
Medical history:				
Hypertension	71 (5·1)	3 (5·1)	18 (4·5)	9 (3·6)
Diabetes	16 (1·7)	1 (1·7)	1 (0·3)	2 (0·8)
Pre-eclampsia	57 (1·7)	1 (1·7)	9 (2·2)	4 (1·8)
Year of accession:				
1993	111 (10·8)	13 (22·0)	50 (12·4)	18 (7·2)
1994	604 (58·8)	32 (54·3)	249 (61·9)	147 (59·0)
1995	313 (30·4)	14 (23·7)	103 (25·6)	84 (33·7)

*Users of progesterone only pills (17 cases, 34 controls) not classified as users of first, second, or third generation oral contraceptives.

Discussion

We have found a weak association, with an odds ratio of 1·5, between increased risk of venous thromboembolism and use of third generation oral contraceptives as opposed to second generation products. Before evaluating the clinical and public health significance of this observation, we must consider the effects of potential biases that might have distorted the risk estimates.

POTENTIAL BIAS

Diagnostic bias might have occurred if doctors had been more likely to investigate and hence to diagnose venous thromboembolism in women taking the newer oral contraceptives. However, the observed elevated odds ratio in cases with the more serious diagnosis of pulmonary embolism, which is likely to be investigated carefully in all women, militates against diagnostic bias.

Referral bias could have played a part if women receiving the newer oral contraceptives were more likely to be admitted to hospital. Almost all of our cases of venous thromboembolism were identified in hospitals. It is not possible to test for this bias in this data set.

Prescribing bias would have occurred if doctors had recommended newer products, advertised as safer, for patients with higher risk profiles. We adjusted for the presence of the risk factors for which we had data—that is, age, obesity and smoking—and found no change in our point estimates. We did not have any

data on family history of venous thromboembolism. The existence of prescribing bias is not corroborated in our data.

A further potential bias might have occurred with attrition of susceptible subjects—meaning that the longer that one extends the window of observation, the fewer the adverse events noted per unit of time. That is because those patients susceptible to side effects tend to drop out of the corresponding user group at an early stage or are switched by their doctor to another product. In contrast, if a product is well tolerated prudent doctors and safety conscious patients tend to continue to use it, so that patients who will have been taking a product for a long time would be expected to be at lower risk than first time users of any brand.

If first time users of oral contraceptives were selectively prescribed preparations containing the newer progestogens a bias will have been introduced. First time users would include women at an unidentified higher risk of thrombosis due to genetic factors, while long term users are "survivors," who have remained free of events. Thus, our main reference group (second generation product users) may have comprised women at the lowest risk possible. When we adjusted for duration of lifetime use of oral contraceptives preceding the current use of oral contraceptive and for length of use of the most recent oral contraceptive, the point estimate did in fact decline by 12% to 1·4. We also confirmed that first time users were at appreciably higher risk than subsequent users. Also, as shown in table 3, users of second generation products containing levonorgestrel, which has been on the market for about 20 years, exhibited the lowest odds ratios we found when compared with no current use.

The matched conditional regression analyses strongly suggest that no overmatching occurred. Using community controls rather than hospital controls as reference groups made little difference in the estimates and in the resulting conclusions.

ASSESSMENT OF RISK

All the odds ratios reported are low, the point estimates ranging from 1·4 to 1·9 and the best adjusted estimate being 1·5. Venous thromboembolism is rare in young women, and the importance of the weak association observed in this study is better judged by the attributable risk. Given the prevalence of use of third generation oral contraceptives in the controls in this study, the observed odds ratio of 1·5 for preparations containing third generation as opposed to second generation progestogens might result in one to 19 excess deaths from venous thromboembolism annually in England and Wales. Given the various assumptions used in the calculations of deaths, we can only give a range of estimates for lives saved by switching from third generation oral contraceptives to second generation products.

Translating the results of epidemiological case-control studies to routine clinical practice is difficult, particularly when the associations found are not strong or are ambiguous. We have found a weak association between third generation oral contraceptives and venous thromboembolism when second generation oral contraceptives are the reference group. The modest increase in risk must be taken seriously even if it is not certain that the relation is causal. A woman using an oral contraceptive containing a third generation rather than a second generation progestogen may have an increased risk of death from venous thromboembolism of six per million per year in the United Kingdom. These excess events must be interpreted in the context of differences in mortality from myocardial infarction and stroke for users of oral contraceptives. The increased risk of venous thromboembolism alone is equivalent to the increased risk of death from cancer and heart disease if a woman smoked 10 cigarettes a year.[26] Our data justify clinical prudence but allow doctors and women seeking contraception to exercise informed choice.

Key messages

- Concern has recently been raised that third generation oral contraceptives, which contain gonane progestogens (desogestrel, gestodene, and norgestimate), increase the risk of thromboembolism
- This case-control study examined risk of venous thromboembolism associated with different types of oral contraceptive
- Overall, there was a fourfold higher relative risk of thromboembolism associated with current use of any oral contraceptive versus no current use
- The risk of thromboembolism was 1·5 times higher for third generation contraceptives compared with second generation products
- Our data indicate the need for clinical prudence but allow doctors and women seeking contraception to exercise informed choice

This article is available on the Internet (home page: http://www.bmj.com/bmj/) with additional tables giving distribution of cardinal variables in all five countries, classification list of oral contraceptives, inclusion criteria for cases, and definitions for hospital controls.

The investigators were accountable only to the scientific reference board (members listed below), which approved the protocol, received periodic reports, and conducted audits on the field and of the data before submission. This board was advised by the statistical advisory group (members listed below) on statistical issues. The board was also advised by an ad hoc peer review task force (members listed below). Data were processed in the Data Management Centre of the Potsdam Institute of Pharmacoepidemiology and Technology Assessment under the oversight of the statistical advisory group.

Funding: Unconditional grant from Schering AG Berlin.

Conflict of interest: Study was funded by Schering AG Berlin.

Appendix

The Transnational Research Group on Oral Contraceptives and the Health of Young Women consisted of:

OVERSEEING BOARD AND ADVISORY GROUPS

Scientific reference board—U Bergman (Karolinska Institute); M Breckwoldt (University of Freiburg); J Collins, S MacLeod (chair) (McMaster University); F Kemper (University of Munster); J Le Lorier (University of Montreal); 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 Bergman; J Daling (Fred Hutchinson Cancer Research Centre, University of Washington); M Elstein (St Mary's Hospital, Manchester); J Hanley; S Lock (chair) (Wellcome Trust); S MacLeod; W Ray; L Rosenberg (Boston University); S Suissa (McGill University).

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Third generation oral contraceptives and risk of myocardial infarction: an international case-control study

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See p 83 and editorial by McPherson

Abstract

***Objective*—To test whether use of combined oral contraceptives containing third generation progestogens is associated with altered risk of myocardial infarction.**

***Design*—Matched case-control study.**

***Setting*—16 centres in Austria, France, Germany, Switzerland, and the United Kingdom.**

***Subjects*—Cases were 153 women aged 16-44 with a myocardial infarction event. Controls were 498 women (at least 3 controls per case) unaffected by myocardial infarction who were matched with their corresponding case for age and for hospital or community setting within four months of the index infarction.**

***Main outcome measures*—Odds ratios derived with stratified analyses and unconditional logistic regression to adjust for potential confounding variables.**

***Results*—The estimated odds ratio for myocardial infarction of third compared with second generation oral contraceptives among all 651 study subjects was 0·36 (95% confidence interval 0·1 to 1·2) (P=0·11). The odds ratio for the United Kingdom and Germany alone was 0·45 (0·1 to 1·8) (P=0·26). Other odds ratios for the five countries were 3·1 (1·5 to 6·3) (P=0·003) for use of second generation products *v* no current use and 1·1 (0·4 to 3·4) (P=0·9) for use of third generation products *v* no current use. Among the confounding variables the independent contribution of smoking (for which adjustment was made in the above estimates) proved to be important (10·1 (5·7 to 17·9), P < 0·001).**

***Conclusion*—An odds ratio of 0·45 with wide confidence intervals shows that third generation oral contraceptives compared with second generation products are associated with a reduced risk of myocardial infarction or with no difference. This finding from an interim analysis should be interpreted with extreme caution. However, the excess risk of venous thromboembolism associated with the use of third generation products may be balanced by the reduced risk of myocardial infarction associated with the same products.**

Introduction

The aim of the transnational project was to examine the safety of the third generation combined oral contraceptives, which contain the progestogens gestodene and desogestrel. At the outset gestodene was of special interest because of concerns in the European

The full list of members of the group is given at the end of the accompanying article (p 83)

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