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Case-control study of oral contraceptives and risk of thromboembolic stroke: results from international study on oral contraceptives and health of young women

Lothar A J Heinemann, Michael A Lewis, Margaret Thorogood, Walter O Spitzer, Irene Guggenmoos-Holzmann, Rudolf Bruppacher, and the Transnational Research Group on Oral Contraceptives and the Health of Young Women

ZEG-Centre for Epidemiology and Health Research Berlin, D-16341 Zepernick, Germany
Lothar A J Heinemann, *director and professor*
EPES Epidemiology Pharmaco-epidemiology and Systems Research, D-12165 Berlin, Germany
Michael A Lewis, *director*
Health Promotion Sciences Unit, London School of Hygiene and Tropical Medicine, London WC1E 7HT
Margaret Thorogood, *reader*

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Abstract

Objective: To determine the influence of oral contraceptives (particularly those containing modern progestins) on the risk for ischaemic stroke in women aged 16-44 years.
Design: Matched case-control study.
Setting: 16 centres in the United Kingdom, Germany, France, Switzerland, and Austria.
Subjects: Cases were 220 women aged 16-44 who had an incident ischaemic stroke. Controls were 775 women (at least one hospital and one community control per case) unaffected by stroke who were matched with the corresponding case for 5 year age band and for hospital or community setting. Information on exposure and confounding variables were collected in a face to face interview.
Main outcome measures: Odds ratios derived with stratified analyses and unconditional logistic regression to adjust for potential confounding.
Results: Adjusted odds ratios (95% confidence intervals) for ischaemic stroke (unmatched analysis) were 4.4 (2.0 to 9.9), 3.4 (2.1 to 5.5), and 3.9 (2.3 to 6.6) for current use of first, second, and third generation oral contraceptives, respectively. The risk ratio for third versus second generation was 1.1 (0.7 to 2.0) and was similar in the United Kingdom and other European countries. The risk estimates were lower if blood pressure was checked before prescription.
Conclusion: Although there is a small relative risk of occlusive stroke for women of reproductive age who currently use oral contraceptives, the attributable risk is very small because the incidence in this age range is very low. There is no difference between the risk of oral contraceptives of the third and second generation; only first generation oral contraceptives seem to be associated with a higher risk. This small increase in risk may be further reduced by efforts to control cardiovascular risk factors, particularly high blood pressure.

Introduction

The transnational case-control study on oral contraceptives and the health of young women was launched in 1991. There were three substudies for cardiovascular events (venous thromboembolism, myocardial infarction, and thromboembolic stroke). The results for venous thromboembolism[1] and myocardial infarction[2] have been reported. We report the results of the

evaluation of the relation between the use of three generations of oral contraceptives and the occurrence of ischaemic (thromboembolic) stroke.

Subjects and methods

The detailed description of the methods used has been published elsewhere[3]; the methods were similar to those of the recently published World Health Organisation study.[4] In summary, women aged 16-45 years were enrolled in 16 centres in five countries (Austria, France, Germany, Switzerland, and the United Kingdom) between July 1993 and February 1996. At least one hospital and one community control in the same 5 year age band as the case was matched to each incident case with an average of three controls per case. The procedure for control selection with exclusion criteria was defined in the protocol.[3] Cases were accepted as ischaemic stroke if the symptoms lasted longer than 24 hours and if there was evidence of (pre)cerebral arterial stenosis or occlusion, cerebral thrombosis, or embolism.[3] The diagnosis of thromboembolic stroke was based on computed tomography, magnetic resonance imaging, or angiography within 3 weeks of the event.[3] Current use of oral contraceptives was defined as use within 3 months before the diagnosis of the case or the admission date of the hospital control or the interview date of the community control. Oral contraceptives were divided into three categories: first generation (high dose: $\geq$50 g ethinyloestradiol), second generation (low dose: $<$50 µg with other gestagens), and third generation (low dose with either gestodene or desogestrel). We report unmatched odds ratios with 95% confidence intervals adjusted for potential confounders and matched odds ratios (matched by age and centre) as a sensitivity verification (with STATA software[5]). To be consistent with the WHO study[6] we classified norgestimate as second generation in our analysis but report it in both ways in the table.

Results

In total 220 women with thromboembolic stroke (cases) and 336 hospital and 439 community controls were recruited. Of these, 67 cases were enrolled in the United Kingdom, 82 in Germany, 37 in France, 19 in Switzerland, and 15 in Austria. The table shows the adjusted unmatched odds ratios for occlusive stroke in women currently using oral contraceptives: 4.4 (2.0 to 9.9) for first generation, 3.4 (2.1 to 5.5) for oral contraceptives with second generation progestins, and for 3.9 (2.3 to 6.6) third generation. The point estimates derived from the matched analysis were slightly lower. The risk ratio for third versus second generation in the unmatched analysis was 1.1 (0.7 to 2.0) and similar in the matched analysis (table). Stratified by region, the fully adjusted odds ratios in the United Kingdom for second generation oral contraceptives versus no current use were 5.0 (1.5 to 17.1) and 6.2 (2.1 to 18.8) for third versus no use. The figures were 3.9 (2.2 to 7.0) and 3.7 (1.9 to 7.1), respectively, for the same comparisons in continental Europe. The adjusted odds ratios of second generation versus no use were 7.0 (3.8 to 12.8) for hospital controls and 2.6 (1.5 to 4.6) for community controls; and the estimates for third generation versus no use were 5.8 (3.0 to 11.3) for hospital controls and 3.4 (1.8 to 6.3) for community controls. The odds ratios for stroke were lower if the blood pressure was checked before prescription (odds ratios for checked versus not checked were 1.8 (1.0 to 3.0) versus 4.5 (2.1; 9.6) for second generation use versus non-current use and 2.5 (1.4; 4.4) versus 4.6 (2.0; 10.6) for third generation use, respectively).

Oral contraceptive uses and risk of ischaemic stroke. Use refers to current use. Norgestimate coded as second generation oral contraceptive

	Exposed		Odds ratio (95% CI)	
Comparison	Cases	Controls	Unmatched*	Matched†
Any use *v* no use	124	276	3.6 (2.4 to 5.4)	2.9 (2.0 to 4.0)
First generation use *v* no use	15	27	4.4 (2.0 to 9.9)	3.5 (1.8 to 7.4)
Second generation *v* no use‡	58	144	3.4 (2.1 to 5.5)	2.6 (1.7 to 3.9)
Levonorgestrel *v* no use	38	105	2.9 (1.7 to 5.0)	3.1 (1.9 to 5.0)
Third generation use *v* no use§	45	92	3.9 (2.3 to 6.6)	3.1 (1.9 to 5.0)
Third *v* second generation use¶	45	92	1.1 (0.7 to 2.0)	1.2 (0.7 to 2.0)
Third generation *v* levonorgestrel use	45	92	1.4 (0.7 to 2.5)	1.4 (0.8 to 2.4)

*Adjusted for linear age, centre, smoking, hypertension, hypercholesterolaemia, parity, alcohol use, body mass index, family history of stroke, duration of use of current oral contraceptive.
†Adjusted for hypertension, smoking, number of births.
‡With norgestimate classified as third generation 3.1 (1.9 to 5.0).
§With norgestimate classified as third generation 4.3 (2.6 to 7.3).
¶With norgestimate classified as third generation 1.4 (0.8 to 2.4).

Discussion

Our study confirms the well established, increased relative risk for thromboembolic stroke in women who use oral contraceptives; the median value of the published relative risk estimates is between 2 and 4.[7] The risk estimates for high dose oestrogen oral contraceptives (first generation) are higher than those for the low dose pills, but there was no difference between those containing second or third generation progestagens. The recently published WHO study, which used almost identical methods and classifications, found an adjusted odds ratio (conditional analysis) for ischaemic stroke of 2.99 (1.65 to 5.40) associated with current use of any oral contraceptive in Europe.[6] With the same analytic approach our data resulted in an odds ratio of 2.9 (2.0 to 4.0). Our results agree with the findings of the WHO study (Europe) with respect to the odds ratios for first generation progestins but yield slightly higher estimates for second and third generation progestins. There was no significant difference between the

Key messages

- This study shows a slightly increased relative risk of thromboembolic stroke in women currently using oral contraceptives compared with women not using them. The high dose oestrogen pills carry a higher risk than the low dose formulations, irrespective of the type of progestin
- The absolute risk of occlusive stroke for women who currently use modern oral contraceptives is very small—that is, the incidence in this age range is very low and not different between second and third generation oral contraceptives
- This small increase in risk can be controlled by avoiding prescription of oral contraceptives to women who have evidence of cardiovascular disease, in particular high blood pressure

Department of Epidemiology and Biostatistics, McGill University Montreal, QC, Canada H3A 1A2
Walter O Spitzer, *professor emeritus*

Institute of Medical Statistics, Epidemiology and Informatics, Free University Berlin, D-12200 Berlin, Germany
Irene Guggenmoos-Holzmann, *director and professor*

University Basle, CH-4310 Rheinfelden, Switzerland
Rudolf Bruppacher, *professor*

Correspondence to: Professor Heinemann

estimated risk of thrombotic stroke in users of second versus third generation pills. The United Kingdom and the continental countries had similar findings. These odds ratios should be assessed against the backdrop of the small absolute risk they entail and in the context of the clear benefits of use of oral contraceptives for women of reproductive age. The annual event rate is between 1-1.6 stroke events per 10 000 women aged 25-44—that is, 1 stroke per 12 000 women. Three strokes per 100 000 women per year may be attributable to the use of oral contraceptives. This risk could be controlled by avoiding prescription of the pill in women who have important cardiovascular risk factors such as high blood pressure and might be lessened by appropriate management of these risk factors.

The investigators were accountable only to the Scientific Reference Board (members listed in reference 1).

Transnational case-control study. Principal investigators: WO Spitzer (Montreal, 1993-5), LAJ Heinemann (Berlin, 1996 to date). Scientific review board: U Bergman (Stockholm), M Breckwoldt (Freiburg), J Collins (Toronto), F Kemper (Munster), J LeLorier (Montreal), S MacLeod (Toronto), K MacRae (London, until May 1995), W Ray (Nashville), J Schlesselman (Pittsburgh). Centre directors: Austria—H Concin (Bregenz), G Stark (Graz), K Pfeiffer (Innsbruck), R Weitgasser (Salzburg); France—B Begaud (Bordeaux), B Boissel (Lyons). Germany—J Haerting, F Lautenschlaeger (Halle), K Püschel (Hamburg), F Hoffmann (Jena), BP Robra (Magdeburg), M Lustermann (Nordhausen), I Schulzki (Schwerin), S Boethig (Zwickau). Switzerland—F Gutzwiller (Zurich). United Kingdom—L de Caestecker (Glasgow), C McCollum (till August 1995), P Hannaford (from August 1995) (Manchester), R Mann (Southampton). Publication committee: I Guggenmoos-Holzmann (Berlin); R Bruppacher (Basle); M Lewis (Berlin); M Thorogood (London), LAJ Heinemann (Berlin). Data management centre: M Lewis, D Kühl-Habich, C Klindworth, A Assmann (Potsdam) (for more extensive list of collaborators see reference 1).

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Underreporting of mortality from RhD haemolytic disease in Scotland and its implications: retrospective review

Charles R Whitfield, Alaeddin Raafat, Stanislaw J Urbaniak

See editorial by van Dijk

Department of Obstetrics and Gynaecology, the Queen Mother's Maternity Hospital, University of Glasgow, Glasgow G3 8SH
Charles R Whitfield, *emeritus regius professor of midwifery*
Academic Transfusion Medicine Unit, Department of Medicine and Therapeutics, University of Aberdeen, Regional Transfusion Centre, Foresterhill, Aberdeen AB9 2ZW
Alaeddin Raafat, *honorary lecturer in transfusion medicine*
Stanislaw J Urbaniak, *honorary reader in transfusion medicine*
Correspondence to: Professor Whitfield

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Clarke et al surveyed the decline in RhD haemolytic disease in England and Wales from 1977-92 by reviewing the statistics of the Office of Population Censuses and Surveys; during that time deaths attributable to RhD haemolytic disease had fallen from 18.4 to 1.3 per 100 000 live births.[1] We surveyed RhD alloimmunisation in mothers resident in Scotland between 1987 and 91 and confirmed that fetal loss from RhD haemolytic disease was greater than that listed by the General Register Office in Scotland. Underreporting has serious implications for recognising, understanding, and preventing this potentially lethal disease.

Subjects, methods, and results

Data on deaths attributable to RhD haemolytic disease during 1987-91 were obtained from: death certificates; details of pregnancies in Scottish residents who had antibody to RhD antigen and were managed at the Queen Mother's Hospital; and a retrospective study identifying women in whom RhD antibodies were detected for the first time during 1987-91 (table). The definition of mortality from RhD haemolytic disease included all abortions after fetal death, stillbirths, and neonatal deaths attributed to RhD incompatibility or its treatment and deaths after 28 days of life in which RhD haemolytic disease or its treatment was the primary cause.[2]

Only four deaths were listed by the General Register Office in Scotland; all were neonatal deaths occurring in women immunised against RhD before 1987. Four deaths occurred in the cohort but none were listed through the General Register Office in Scotland. Twelve other pregnancies managed at the Queen Mother's Hospital during this time (mothers alloimmunised before 1987) resulted in deaths related to RhD haemolytic disease. Ten of the pregnancies ended with abortions after fetal death, and two resulted in liveborn infants treated in utero by repeated blood transfusions. These two infants were delivered electively more than two months preterm but died from complications on the first and 95th days of life.

Thirteen of the 20 deaths resulted from alloimmunisation against RhD antigen during a first pregnancy. In four cases maternal RhD antibodies were first detected within two days of delivery, and in the remaining nine during gestation. There was also good documentation of antepartum immunisation in relation to at least two of the deaths from second pregnancies.

Comment

A review of the case notes of deaths recorded as Rh haemolytic disease in England and Wales showed that disease was often caused by antibodies other than RhD antibody or was wrongly coded. Our data show that