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Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users who are carriers of hereditary prothrombotic conditions

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Abstract

Objective: To investigate whether users of oral contraceptives who are carriers of a hereditary prothrombotic condition (factor V Leiden mutation, protein C, S, or antithrombin deficiency) have an increased risk of cerebral sinus thrombosis.

Design: Comparison of a prospective series of cases of cerebral sinus thrombosis with population data.

Setting: Neurological teaching hospitals from different regions in the Netherlands (cases) and a representative sample of the non-institutionalised Dutch population (controls).

Subjects: 40 women aged 18-54 years with cerebral sinus thrombosis (cases) and 2248 women aged 18-49 years (controls).

Main outcome measure: Current use of oral contraceptives at the time of the thrombosis (cases) or at the time of the questionnaire (controls). Prevalences of a hereditary prothrombotic condition in patients and in the population with odds ratios.

Results: 34 of 40 (85%) women with cerebral sinus thrombosis used oral contraceptives, versus 1007 of 2248 (45%) of the control women; the age adjusted odds ratio was 13 (95% confidence interval 5 to 37). Seven of 36 patients (19%) had a prothrombotic deficiency, versus 7% expected in the population; this corresponds to a threefold to fourfold increase in risk. In women who used oral contraceptives and also carried a prothrombotic defect, the odds ratio for cerebral sinus thrombosis was about 30 relative to women who had neither risk factor.

Conclusion: The use of oral contraceptives and being a carrier of a hereditary prothrombotic condition increase the risk of and interact in a multiplicative way in the development of cerebral sinus thrombosis.

Introduction

Epidemiological studies have shown that oral contraceptives carry a small but increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism).¹ Furthermore, women who use oral contraceptives and carry the factor V Leiden mutation have a higher risk of venous thromboembolism than expected from the mere addition of these risks.² Although the association between oral contraceptives and venous thromboembolism is generally accepted, there remains discussion about possible sources of bias that might influence the magnitude of the risk.

Cerebral venous sinus thrombosis is a relatively rare disease, often with cerebral infarcts, which may lead to seizures, other neurological symptoms, or death. Patients with sinus thrombosis, however, may recover completely.³ Oral contraceptives and hereditary prothrombotic conditions, such as protein C, S, and antithrombin deficiency and factor V Leiden mutation, have been reported as possible causes of cerebral sinus thrombosis.⁴

We compared a series of patients with cerebral venous sinus thrombosis from a prospective treatment trial with population data from the Netherlands to investigate the risk of oral contraceptive use and prothrombotic conditions for cerebral sinus thrombosis.

Patients and methods

Cases

Cases were patients with cerebral sinus thrombosis (newly diagnosed) who participated in a treatment trial from July 1992 to November 1996 that compared low molecular weight heparin in a therapeutic dose with placebo in a randomised double blind design. Patients

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younger than 18 years and pregnant women were excluded. The trial was conducted in neurological teaching hospitals in different regions in the Netherlands and the United Kingdom. Cerebral sinus thrombosis was confirmed by conventional angiography or magnetic resonance imaging and angiography. For the present analysis we selected all women aged 18-54 from the Dutch part of the trial population who were not in the puerperium (within 30 days post partum).

Information on use of oral contraceptives at the time of the initial symptoms of sinus thrombosis was obtained from the patient or nearest relative and supplemented with hospital discharge letters.

Blood samples were collected and analysed in the participating hospitals. Antithrombin activity and protein C activity were measured with chromogenic assays.⁵ Protein C antigen, and total and free protein S were determined by enzyme linked immunosorbent assay (ELISA) as described elsewhere.^{6,7} Values were defined as abnormal if they were below the 5th centiles of the values determined in a group of healthy subjects. Resistance to activated protein C was assessed by the activated protein C dependent prolongation of the activated partial thromboplastin time.⁸ An activated protein C ratio below 2.0 or a normalised ratio lower than 0.80 was considered abnormal. The mutation at position Arg 506 in factor V was determined with polymerase chain reaction techniques as described previously.⁹

Controls

The controls comprised a random sample of 2248 women aged 18-49 years from different regions in the Netherlands who were interviewed in 1994 about their current use of contraceptives (continuous health interview survey of the Central Department of Statistics of the Netherlands¹⁰; the methodology of the questionnaire has been described previously¹¹).

Statistics

We calculated odds ratios as approximations of relative risks on the basis of the crude numbers or the percentage distribution; confidence intervals, when appropriate, were calculated by the methods of Woolf or Robins.¹² When observed odds were compared with estimated population frequencies we omitted the calculation of the confidence intervals.

Use of oral contraceptives and prothrombotic disorders in cases (women with cerebral venous sinus thrombosis aged 18-54 years, puerperium excluded) and use of oral contraceptives in controls

Age (years)	Cases			Proportion (%) of controls taking contraceptives
	Proportion (%) taking contraceptives	No with factor V Leiden	No with C, S, or antithrombin deficiency	
18-19	3/3 (100)	1	0	60/107 (56)
20-24	7/7 (100)	0	0	271/336 (81)
25-29	4/4 (100)	1	1	255/400 (64)
30-34	7/7 (100)	2	0	176/392 (45)
35-39	5/6 (83)	0	1	105/342 (31)
40-44	3/5 (60)	0	0	79/336 (24)
45-49	4/5 (80)	0	0	61/335 (18)
50-54	1/3 (33)	1	0	No data
Total	34/40 (85)	5*	2†	1007/2248 (45)

*Data missing for four women. †Data missing for three women.

Results

Forty women with cerebral sinus thrombosis who met the inclusion criteria were studied. The age related use of oral contraceptives in cases and controls and the prevalence of hereditary coagulation abnormalities in the cases are given in the table.

Use of oral contraceptives

Of the 40 cases, 34 (85%) were using oral contraceptives at the time of the sinus thrombosis. In the control group 1007 of 2248 women (45%) aged 18-49 years were using oral contraceptives. The age adjusted odds ratio for all ages (with the control data for the age group 45-49 also covering ages 50-54) was 13 (95% confidence interval 5 to 37). The age adjusted odds ratio restricted to the ages 18-49 was 18 (5 to 59).

Coagulation abnormalities

In 34 of the 40 women factor V Leiden mutation status was determined by DNA analysis and was present in four (12%). Activated protein C resistance was measured in two women in whom no DNA was obtained, indicating the presence of the factor V Leiden mutation in one. Thus five of 36 women had factor V Leiden mutation (14%; 5% to 30%). In the population the prevalence of factor V Leiden mutation is estimated to be 4-5%.¹³ Protein C, S, and antithrombin activity were assessed in 37 women; two (5%) were deficient for protein C.

Hence, a prothrombotic disorder was present in seven out of 36 patients with cerebral sinus thrombosis (19%; 8% to 36%). The estimated prevalence of protein C or S deficiency, or antithrombin deficiency, or of both, in the general population is 2-3%.^{14,15} Thus, the prevalence of any hereditary prothrombotic disorder, including factor V Leiden, in the population is approximately 7% (6-8%). In carriers of hereditary prothrombotic conditions the odds ratio for developing sinus thrombosis is therefore 3.2.

Interaction between oral contraceptives and hereditary prothrombotic conditions—In the population the use of oral contraceptives and being a carrier of a hitherto unknown hereditary prothrombotic condition are probably independent, at least in women who have never had venous thrombosis. If the prevalence of hereditary prothrombotic conditions is 7% and 45% of women aged 15-49 in the population use oral contraceptives we may expect that 3% of women in the population both use contraceptives and carry a prothrombotic abnormality, 42% use contraceptives only, 4% carry the prothrombotic abnormality only, and 51% have neither risk factor. In the 36 patients for whom we had complete data these percentages were 17%, 72%, 3%, and 8%, respectively. There is a clear excess of women with both risk factors in the patient series (17% v 3%). If the estimated population percentages are used as reference the odds ratio for development of sinus thrombosis in women with both risk factors versus women with neither would be 34. The odds ratios we found for the use of oral contraceptives (about 10) and for hereditary prothrombotic disorders (three to four) imply that oral contraceptives and being a carrier of a hereditary prothrombotic condition interact multiplicatively in their association with sinus thrombosis.

Outcome of sinus thrombosis—Most patients recovered from their sinus thrombosis, but six (15%) had a poor outcome after 3 months' follow up (four died, two were handicapped). Use of contraceptives was not associated with a worse outcome. Four of the 34 women (12%) who used contraceptives had a poor outcome after 3 months (three died and one was disabled by a severe paralysis of her right arm and cognitive impairment) compared with two out of six women (33%) not taking contraceptives.

Discussion

We have found an increased risk of cerebral venous sinus thrombosis in women who use oral contraceptives and are carriers of a hereditary prothrombotic disorder. In addition, we found that the use of contraceptives multiplies the risk of hereditary prothrombotic conditions.

Sources of bias

Before evaluating the clinical significance of our findings we must consider potential sources of bias. Because the cases were obtained in a treatment trial and the controls were a representative sample of the population, can the cases really be regarded as originating from the general population base? As all major neurological centres in the Netherlands, to which patients with sinus thrombosis are referred, participated in the trial the patients in the trial are representative of all patients with sinus thrombosis in the Netherlands. As there was no selection as to use of oral contraceptives or any other characteristic that might be related to use of contraception, the use of contraceptives in these patients can be validly compared with population data.

Pregnant women were excluded from the trial, and women in the puerperium or with a recent miscarriage were excluded from the analysis but not from the controls. Therefore oral contraceptive use in the controls might be slightly underestimated. The estimated percentage of premenopausal women who were pregnant or in the puerperium in the Netherlands was 5% in 1994,¹⁰ which is too small to affect our results.

As sinus thrombosis is a rare condition the chance that women with this disease were present in the control group is fairly small. According to the British registrar general the average mortality during the period 1952-61 from sinus thrombosis was $0.4/10^6$ /year.¹⁶ If we assume a mortality of 10%, the incidence would be $4/10^6$ /year.

Diagnostic suspicion and referral bias might occur if doctors were more likely to diagnose sinus thrombosis in women taking oral contraceptives. Women taking contraceptives might be under better medical supervision, and contraceptive use is known to increase the risk of venous thromboembolism. This type of bias has been suggested for deep vein thrombosis.¹⁷ For sinus thrombosis this bias seems unlikely. Sinus thrombosis is a rare and alarming disease, often with severe neurological symptoms.³ It seems reasonable to assume that all patients with sinus thrombosis are referred to a hospital, irrespective of oral contraceptive use. Misdiagnosis in our patients is unlikely because conventional angiography or magnetic resonance

imaging, which are regarded as reliable diagnostic procedures for sinus thrombosis,¹⁸ were used in all cases.

Known risk factors

In various case series oral contraceptive use alone¹⁹ or superimposed on a hereditary prothrombotic disorder has been suggested as an aetiological factor for sinus thrombosis. A recent Italian case-control study in patients with sinus thrombosis found an odds ratio for oral contraceptive use of 4.2, after exclusion of pregnant and puerperal women. The presence of the factor V Leiden mutation in itself increased the risk for sinus thrombosis about ninefold.^{20 21}

Other probable risk factors for sinus thrombosis are pregnancy and puerperium.³ In our treatment trial seven women in the puerperium were included. Many other risk factors for sinus thrombosis have been reported in retrospective series, including the known risk factors for deep vein thrombosis, but a significant association with sinus thrombosis has not been demonstrated. The influence of smoking—if any—is unknown.

There is ample evidence that oral contraception predisposes to venous thromboembolism,^{1 17} especially when the factor V Leiden mutation is present.² The risk of leg vein thrombosis in women with the mutation who use oral contraceptives compared with women without the mutation who do not, increases more than 30-fold.² The tentative analysis of the interaction between oral contraceptive use and hereditary prothrombotic conditions in our study points in the same direction.

Recently, a biological explanation of the increased risk for venous thrombosis in oral contraceptive users was reported.²² In this study the effects of activated protein C on thrombin generation in the plasma of women using oral contraceptives were compared with the response in women not using oral contraceptives and in women heterozygotic or homozygotic for the factor V Leiden mutation. Oral contraceptives induced a degree of activated protein C resistance comparable with the resistance caused by a factor V Leiden mutation. In women heterozygotic for factor V Leiden mutation who used contraceptives the activated protein C resistance was as high as that among women homozygotic for the mutation.²² These results fit with the epidemiological data, including those from our series of patients with cerebral venous thrombosis, and are an additional argument against objections that the epidemiological findings are merely explained by prescription bias or other sources of confounding.

That sinus thrombosis is predominantly a disease of women was already clear from recent retrospective series.²³ A comparison with sex distribution in larger series in the past, which showed no or a much less marked predominance of women in sinus thrombosis,²⁴ suggests a shift in the epidemiology and aetiology of the disease in recent years. Possibly the widespread use of oral contraceptives has caused this increasing relative number of women with sinus thrombosis.

Conclusion

We conclude that the major risk factors for deep vein thrombosis and cerebral venous sinus thrombosis in women are the same. As the absolute risk for sinus thrombosis in premenopausal women is low, with an

Key messages

- The use of oral contraceptives is associated with an increased risk of cerebral venous sinus thrombosis
- This risk of cerebral venous sinus thrombosis in women who use oral contraceptives is larger if there is an additional hereditary prothrombotic factor (protein C, S, or antithrombin deficiency, factor V Leiden mutation)
- The association between oral contraceptives, thrombophilia, and deep vein thrombosis is also valid for cerebral sinus thrombosis
- Women do not need to stop using oral contraceptives as the absolute risk of cerebral sinus thrombosis is very small

estimated incidence of $4/10^6$ /year, our findings should not be used to advise against oral contraceptive use in all women. In women who have a history of venous thrombotic disease, including sinus thrombosis, however, advice against use of oral contraceptives should be considered, especially in women with a hereditary prothrombotic disorder.

The Cerebral Venous Sinus Thrombosis Study Group comprised S F T M de Bruijn, J Stam, A W A Lensing, J G P Tijssen, P M Bossuyt, L J Kappelle, J Van Gijn, D W J Dippel, P J Koudstaal, J J Van Hilten, R A C Roos, J L A Eekhof, J J Van der Sande, H L Hamburger, J Lodder, C C Tijssen, F W Bertelsman, J C Koetsier, P Sandercock, P Humphrey, G N Mallo, P Verlooy, H K Van Walbeek, J W Snoek, and C L Franke.

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Contributors: SFTMdeB, JS, and JPV formulated the research hypothesis, designed the study, analysed the data, and wrote the paper. MMWK analysed the data on prothrombotic disorders and helped to write the paper. SFTMdeB collected and checked all data on use of contraceptives and prothrombotic disorders, assisted by M Budde. SFTMdeB, JS, and JPV are guarantors for the paper.

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Fifty years ago

The new NHS: The press and the profession

Speaking at the opening of the East Glamorgan County Hospital on Saturday, Mr. Aneurin Bevan, the Minister of Health, gave this advice to doctors: "Do not allow your minds to be inflamed or your judgment to be distorted by slogans which are addressed to your emotions and not to your intelligence." This sound piece of advice is perhaps hardly necessary for members of a profession used to making a differential diagnosis. The doctor uses the methods of science, and the politician the technique of the hustings. At this moment the medical profession is being subjected to abuse, misrepresentation, and malicious innuendo from the highly emotional press which supports Mr. Bevan. This

campaign was started by the *Tribune*, of which Mr. Bevan was a director and editor until he took office in the present Government in 1945. The *Tribune* suggested that "the BMA may still try to fight the battle of the Tory Party against the development of a socialist service," and it went on to state: "Politically, the Minister's firmness has been most important. If he had been weak in face of this reactionary profession . . . it would have increased doubts as to the intention to carry out a socialist programme." (Editorial, 24 January 1948, p 155. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)