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Decline in Cerebral Thromboembolism Among Young Women After Introduction of Low-Dose Oral Contraceptives: An Incidence Study for the Period 1980–1993

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The aim of this study was to analyze age-specific incidence rates (IRs) of cerebral thromboembolic attacks (CTA) among women and men 15–44 years of age in Denmark from 1980 through 1993 and to quantify possible influences from oral contraceptives (OC) on the incidence figures. The discharge diagnoses ICD 432–436 from all Danish neurological, neurosurgical and medical departments during the period 1980–1993 were identified in a central diagnosis register. The use of OC was achieved from complete sale statistics during the study period and cross-sectional studies assessing the type-specific use of OC at different ages. During the 14-year study period, 2,100 female and 2,552 male attacks were registered. Men had an exponentially increasing IR with increasing age. Compared with men in the period 1980–86, women had more attacks in the 20–35-year age group and fewer attacks above the age of 35. After 1987 the sex differences below the age of 35 were not significant. From the first half (1980–86) to the last half (1987–1993) of the study period, women below 30 years had a significantly falling CTA IR of −20.4%, compared with a non-significant fall of −9.5% among men below 30 years. In the age group above 30 years, women experienced a not significant increase of 4.2%, men a significant increase of 11.4%. Assuming that use of OC implied an average relative risk of CTA of 2.5 and pregnancy a relative risk of 4, a correction was made for the contribution of incident cases among women. The corrected IRs had a close co-variation with the IRs of men up to the age of 35. Thereafter, men had higher IR as is the case for older age groups. It is concluded that women's pregnancies and use of OC may explain the higher IRs of CTA in young fertile age compared to those of men. The more pronounced fall in IRs among young women compared with young men through the last 14 years may be a consequence of the reduced hormonal content of OC. CONTRACEPTION 1995; 85–92

KEY WORDS: cerebral thrombosis, cerebral embolism, cerebrovascular disease, cerebrovascular disorders, epidemiology, oral contraceptives, Denmark

Introduction

Several epidemiological studies have demonstrated a statistical association between use of oral contraceptives (OC) and the risk of developing cerebral thromboembolism.[1–14] Three recent studies found an estrogen dose-dependent association.[12–14] A Danish study demonstrated that pills with 50 g estrogen implied a relative risk (RR) of cerebral thromboembolism of 2.9, OC with 30–40 g estrogen a RR of 1.8, whereas pure progestogen pills did not confer any increased risk (RR = 0.9).[13]

It is still a matter of concern whether this statistical association represents a causal relationship or reflects some kind of selection phenomenon. If women somehow predisposed for cerebral thromboembolic attacks (CTA) are more inclined to take OC than non-predisposed women, a statistical association would be present between use of OC and the risk of CTA, but there would be no expected excess of CTA among fertile women compared with the incidence among age-matched men.

If, on the other hand, the documented associations are causal, we would expect: after appropriate confounder control, that the incidence rates (IRs) of thrombotic diseases among women in fertile age would exceed those of men of the same ages, especially in the age groups with a high percentage use of OC, as well as a reduction in the female IRs with the reduced hormonal content in purchased OC.

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Incidence studies of CTA in fertile age are complicated by the fact that very few women experience these events. Moreover, several different factors influence the thrombotic risk in fertile age. Nevertheless, incidence studies may be a useful instrument in the evaluation of a possible causal influence of specific exposures, including OC.

In Denmark, a central database of discharge diagnoses permits calculation of age-specific IRs of even very rare diseases. The incidence of CTA among women and men 15–44 years old is about 150 per year for each sex. A nearly exponentially increasing IR with increasing age has previously been demonstrated.[15]

The influence of oral contraceptives on the risk of cerebral thromboembolism is principally determined by three circumstances:

(1) The percentage of women at a specific age that use OC;
(2) The types of OC used at that specific age; and
(3) The increase in risk of cerebral thromboembolism among users of a specific type of OC compared with that of non-users (the relative risk). This risk is restricted to present users of OC.

The aim of this study was to explore how the IRs of cerebral thromboembolism among young women and men have changed in Denmark during the period 1980 through 1993, and how these changes were associated with the use of OC according to age and with the secular changes in the types of OC prescribed during the study period.

Material and Methods

The use of oral contraceptives has been rather stable in Denmark throughout the last 15 years, with an average percent of users in the age group 15–44 years of 23–25%.[13,16–19] They are primarily used by young fertile women (Tables 1 and 2). During the last 14 years, the use of preparations with 50g estrogen has decreased and the use of 30–40g preparations has increased (Table 1 and Fig. 1).[13,16,17]

In Denmark, all hospitalized patients are coded with a discharge diagnosis according to the International Classification of Diseases (ICD). Since 1977, these discharge diagnoses have been centrally recorded together with a personal identification number in the National Patient Register.

This study was based on an analysis of this database covering the 14-year period 1980–1993. Cerebral thromboembolic attacks (CTA) include the ICD diagnoses 432 (occlusion of pre-cerebral artery), 433 (cerebral thrombosis), 434 (cerebral embolism), 435 (transitory cerebral ischaemic attack (TIA)), and 436 (cerebral apoplexy), as thrombotic cases have been found to constitute 80–90% of these unspecified cases.[20,21]

Information about the sale of specific types of oral contraceptives during the study period was provided by the Danish Drug Statistics. The use of oral contraceptives at specific ages was analyzed in two cross-sectional studies during the study period, the first from 1983,[16,22] the second in connection with a case-control study conducted in 1990.[13] The control-data from this study included information on the use of specific types of oral contraceptives at specific ages in 1990.

Population statistics were provided by Danmarks Statistik.[23] Only "first ever" strokes were included in this study. If a woman was discharged more than once under one of the diagnoses 432–434 or 436 during the study period, the first discharge diagnosis from a neu-

Table 1. Use of different types of oral contraceptives (OC) in Denmark in 1983 and 1990 and average relative risk of cerebral thromboembolism among users at specific ages

Year/Age	OC Use (%)	Distribution Among Users			Average Relative Risk Among Users of OC†
		50 μg e* (%)	30/40 μg e (%)	Mini-pills (%)	
1983 (n = 788‡)					
15–24	40	37	56	7	2.3
25–34	18	59	32	9	2.5
35–44	12	62	27	11	2.5
1990 (n = 1316§)					
15–24	50	6	87	7	1.99
25–34	20	8	82	10	1.98
35–44	8	21	54	25	1.96

*e = estrogen content.
†Assuming that 50 μg, 30/40 μg and mini pills imply RRs of 3, 2, and 1, respectively.
‡Figures from Ref. 16.
§Figures from Refs. 13 and 17.

Table 2. Use of oral contraceptives (OC) in 1983 and 1990, percentage of pregnant women in 1983, incidence rates (IRs) of cerebral thromboembolism (1980–86), and IRs adjusted for use of OC and pregnancies (1980–86)

Age	OC Use* 1983 (95% CL) (%)	OC Use† 1990 (95% CL) (%)	Pregnant Women (%)	Crude IR 1980–86 /100,000	Adjusted‡ IR 1980–86 /100,000	IR Men 1980–86 /100,000
15–19	32 (25–39)	50 (30–70)	0.8	1.90	1.28	2.56
20–24	48 (40–57)	51 (40–62)	6.0	5.31	3.22	3.37
25–29	22 (15–29)	24 (17–31)	8.4	10.3	7.74	5.44
30–34	13 (7–19)	17 (12–22)	4.2	13.3	11.1	10.4
35–39	15 (9–21)	11 (8–15)	1.1	17.3	14.1	22.7
40–44	9 (4–14)	6 (4–8)	0.1	33.4	32.3	45.9

*Figures from Ref. 16. The age distribution in this study differed slightly in using the age groups 15–20, 21–25, 26–30, 31–35, 36–40 and 41–45 (n = 788).
†Figures from Ref. 13 (n = 1316).
‡Assuming that pregnancy implies a relative risk for CTA of 4.0. The pregnancy corrected figures $\times'$ were calculated as $\times' = \times/[(1 - p) + p \times 4]$, where p is 3/4× the prevalence of pregnant women at a specific age, and × the observed incidence.

rological department was chosen, in order to achieve as specific a diagnosis as possible. On the other hand, the diagnosis 435 (TIA) was not restricted because new events of that diagnosis (in contrast to the other diagnoses) represent new attacks.

After establishing age-specific mean annual IRs for women and men during 1980–1986 and 1987–93, the overall trend in the incidence rates of CTA from 1980–86 to 1987–1993 was calculated for the two 15-year age groups 15–29 and 30–44 years. Finally, age-specific incidence rate ratios (IRR) were calculated.

A theoretical calculation was performed of the expected changes in the female IRs as a consequence of the diminished hormonal content of OC and the trend among men, and these expected trends were compared with the observed female trends.

Level of significance was set at 0.05; 95% confidence limits were calculated for the incidence rate figures.

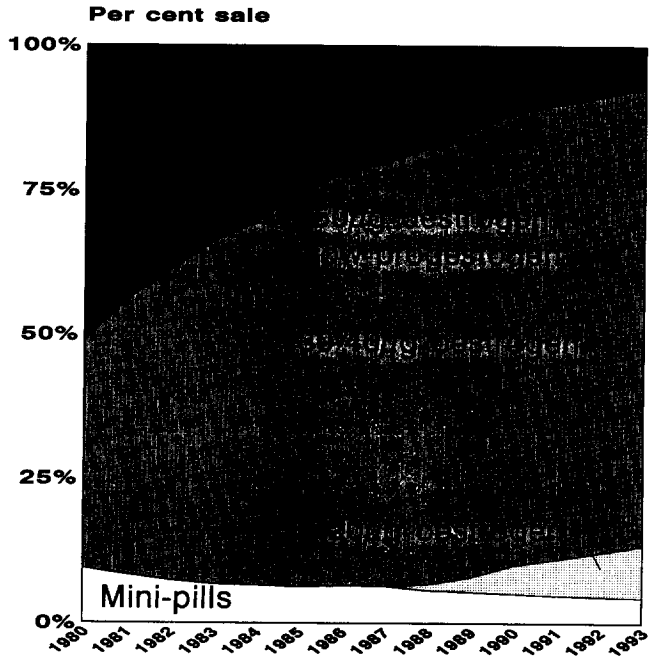

Figure 1. Change in types of oral contraceptives sold in Denmark 1980–1993 according to hormonal content.

Assumptions

The calculations performed in this study were made basically on three assumptions:

- That the data in the two cross-sectional studies from 1983 and 1990 were representative for the Danish female population during 1980–86 and 1987–93, respectively.
- That the relative risk of CTA implied by using oral contraceptives with 50 g, 30–40 g, and 0 g estrogen is 3, 2, and 1, respectively.
- That these dose-specific relative risks are constant throughout fertile age.

These assumptions are evaluated in the *Discussion* section.

Results

During the 14-year study period, a total of 2,100 female and 2,552 male CTA diagnoses were registered (after restriction for re-admissions). The distribution among women and men on the five included diagnoses was identical and without significant changes during the study period (Table 3).

Age-Specific IRs Among Women and Men 1980–1986 and 1987–1993

The five-year age-specific mean annual IRs during 1980–1986 and 1987–1993 are illustrated in Figures 2 and 3. The IRs among men increased nearly exponentially with increasing age. Men 15–29 years old experienced a 9.5% non-significant decrease in the IRs

Table 3. Cerebral thromboembolism among women and men 15–44 years of age in Denmark, 1980–1993

	Women		Men	
Diagnosis (ICD)	**N**	**(%)**	**N**	**(%)**
Occlusion of pre-cerebral artery (432)	127	6.0	128	5.0
Cerebral thrombosis (433)	590	28.1	723	28.3
Cerebral embolism (434)	130	6.2	137	5.4
Transitory ischemic attack (TIA, 435)	664	31.6	791	31.0
Cerebral apoplexy (436)	589	28.0	773	30.3
Total	2,100	99.9	2,552	100.0

from the first to the latter period. In the age group 30–44 a significant increase of 11.4% was observed (Figure 4).

Women also had a rapidly increasing IR with increasing age. In 1980–86 this increase was approximately linear from the age of 15 to 40 years (Figure 2). In the period 1987–93 the IRs in the age group 20–34 years were lower, in the age group 35–39 higher, and between 15–19 and 40–44 unchanged compared with the IRs in 1980–86 (Figure 3).

Overall, the IRs among women 15–29 years old fell 20.4% from 1980–86 to 1987–93, a trend that was significantly different from the increase of 4.2% among women 30–49 years old (Fig. 4).

Compared with men in the period 1980–86, women had *higher* IRs from 20 to 34 years (significantly different only between 25 and 29 years) and significantly *lower* IRs in the 35–44-year age group. For 1987–93,

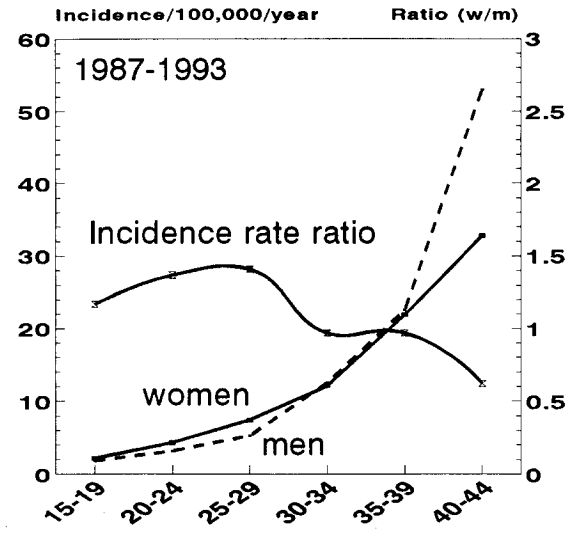

Figure 3. Mean annual incidence rates and incidence rate ratios of cerebral thromboembolic attacks (CTA) among women and men in Denmark 1987–93 according to age.

significant differences between women and men were found only in the 40–44 year age group.

Incidence Rate Ratios

In order to clarify the differences between women and men, incidence rate ratios were calculated for the two periods according to five-year age groups (Figures 2 and 3). During both periods, this ratio crossed the level of equality in the age group 30–34 years. (The number of women with CTA below 20 years was

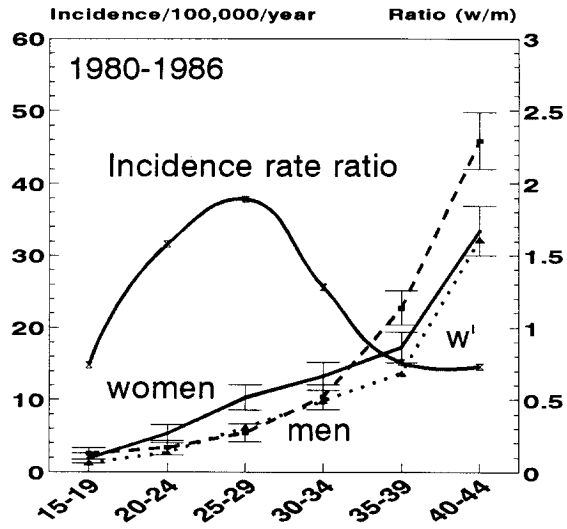

Figure 2. Mean annual incidence rates of cerebral thromboembolic attacks (CTA) among women and men in Denmark 1980–86 according to age (95% CL are indicated), incidence rates corrected for use of oral contraceptives and pregnancy (w'), and incidence rate ratios through 1980–86.

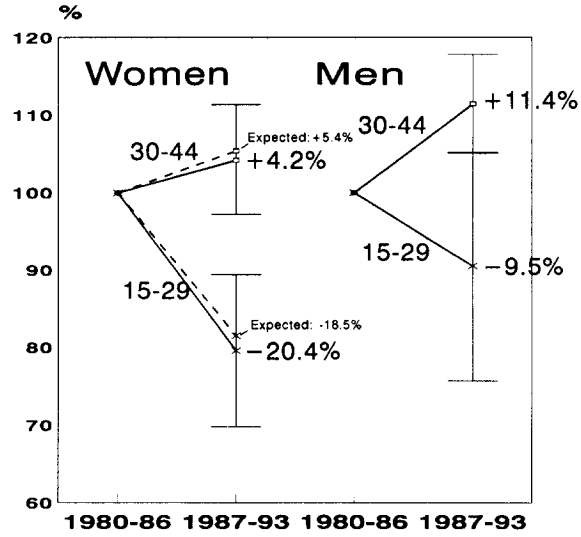

Figure 4. Change in incidence rates of cerebral thromboembolism from 1980–86 to 1987–93 among women and men aged 15–29 and 30–44 years. Expected trend for women due to changes in the hormonal content of OC is indicated; 95% CL indicated.

small; the differences in this age group, therefore, were not significant). An excess of attacked women and a reduction from 1980–86 to 1987–93 in the difference between the two sexes was demonstrated in those age groups with a high percentage use of OC.

Contribution From Oral Contraceptives and Pregnancy

Assuming a causal relationship between use of oral contraceptives/pregnancy and CTA, it was possible to correct the female incidence rates for the contribution of the OC- and pregnancy-induced attacks (Table 2). For the period 1980–86, the use of OC was anticipated to imply a relative risk of CTA of 2.5 according to the actual distribution of different types of OC at different ages in the cross-sectional study from 1983 (Table 1). Pregnancy was assumed to confer a relative risk of CTA of 4.[24] The corrected IRs had a close co-variation with the incidence figures of men until the age of 35 (Table 2 and Figure 2). Thereafter, the IRs of men exceeded those of women, as is the case for all older age groups. Similar corrections were made for the female IRs during 1987–1993, with the same result (not included in the figures).

Expected Influence From the Changing Pattern in OC Types

In order to explain the fall in the female IRs, consideration was given to the expected consequences of the altered pattern in OC types (change against lower dosed pills) concerning the female IRs.

First, an incidence rate weighted percent of users of OC was calculated for the two age groups 15–29 and 30–45 years. For the period 1980–1986, this percent was 31 for women 15–29 years old, and 11% for women 30–44 years. For the period 1987–93, the corresponding percentages were 34 and 9.7 for women at 15–29 and 30–44 years, respectively. It was now possible to calculate the expected percent change in the female IRs due to the changes in the hormonal content of OC from the first to the second period. If the IR of the first period is set to 100, then the influence from OC on the IR for the second period may be calculated as $100\times(p_2 \times RR_2 + (1-p_2))/(p_1 \times RR_1 + (1-p_1))$ where p_1 is the percentage use of OC in the first period, p_2 is the percentage use of OC in the second period, RR_1 and RR_2 are the average relative risk of CTA among users of OC in the first and the second period, respectively. These average relative risks were calculated in Table 1 to be 2.5 during 1980–86 and 2.0 in 1987–93. The calculated OC-responsible change for the 15–29-year age group was −9% and for the 30–45-year age group −6%. In order to achieve the expected number in the second period, an addition was made between these calculated OC-responsible trends and the percentage change in the respective male incidence rates, anticipating that other potential exposures influencing the IRs among men also influence those of women.

The calculated expected trends are plotted in Figure 4. If the applied relative risks and use-pattern of OC are true, and all other influences were similar with those on men, the expected development in the female IRs from 1980–86 to 1987–93 would be −9% −9.5% = −18.5% for the 15–29 year age group and −6% + 11.4% = +5.4% for the 30–44 year age group.

For the 15–29-year age group, the observed fall was 20.4%, whereas the 30–44-year age group had an increase of 4.2%.

Discussion

This study represents an observation of about 2 million women and men over a period of 14 years. It is primarily important to realize that several environmental conditions have changed during this historical follow-up period of 14 years, some of which may have influenced one sex more than the other. Therefore, any change in IRs during the study period or any difference between the two sexes may be due to several different factors, some of which were not included in this study.

The Validity of the CTA Diagnoses

In 1982, Lidegaard analyzed case records of 109 female CTA patients aged 15–40 years, procured via local diagnosis registers at Danish neurological departments.[7] He found two cases of mis-classification. The previously mentioned case-control study from 1990 included 746 women 15–44 years of age suffering from a CTA, identified in the National Patient Register during the period 1985–1989.[13] Among these primarily collected patients, 66 (8.8%) were excluded because of "wrong diagnosis." Wrong diagnoses included first of all patients who later were diagnosed as having multiple sclerosis or were said to have had a vascular spasm or a severe migrainous attack. The latter circumstances concerned primarily the TIA diagnosis (ICD 435). A few cases were later revised as brain tumours. Only about 2% were technical misclassifications. This low percent reflects the fact that young CTA patients are usually extensively examined including CT and/or MR scanning.

For the actual study, that magnitude of misclassification could not have influenced the results significantly. Moreover, these errors are expected to have an equal effect on the two sexes and the two sub-periods during the 14-year study period.

Validity of the OC Percentages and Applied Relative Risks

Women have been found to bring valid information on use/non-use of OC.[25,26] Two other Danish cross-sectional studies from 1987 (n=949)[18] and 1988 (n=692)[19] generally found percentages of use of OC according to age which were within the confidence limits of the estimated percentages used in this analysis.[17] It has to be admitted, however, that the figures for the sub-types of OC used at specific ages were based on information from few persons, and that the calculated expected trends therefore imply some statistical uncertainty. Nevertheless, the type-distribution in the two spot tests from 1983 and 1990 agree very well with the sale statistics on specific types of OC during the study period.

The 95% confidence limits around the applied relative risks on 3, 2 and 1 were 1.6–5.4, 1.1–2.9 and 0.4–2.4, respectively.[13] Some statistical uncertainty therefore also applies to these figures. The case-control study from which the applied relative risks originate found no sign of changing relative risk with increasing age. Therefore, the assumption of stable relative risks during the fertile period was empirically supported. The relative risk of 4 among pregnant women, is possibly too high.[24] However, the contribution from pregnancy to the corrected IRs for women during 1980–86 is small, due to the low percentages of pregnant women. Therefore, these corrections would not be much influenced by an alternative anticipation of a relative risk of, e.g., 2.

Differences Between Women and Men

The association between use of OC and the risk of CTA documented in case-control and cohort studies may principally be a consequence of one or more of the following three circumstances:

1) A statistical coincidence (error of first order).
2) A selection phenomenon, users of OC being predisposed for CTA by other means than their use of OC.
3) A causal relationship between OC and the risk of developing CTA.

A statistical coincidence is unlikely as several studies have all found a positive association, although of different sizes. No studies have found a protecting influence of OC, which was to be expected if the associations found in other studies only represent coincidence.

Several studies have reported age-specific IRs of stroke and/or CTA in young people[15,20,21,27–36] (Table 4). Of 13 studies, eight did not discriminate between hemorrhages and ischemic strokes,[20,28,30–33,35,36] and one did not subdivide the 15–44-year age group.[28] Nevertheless, four of these eight studies demonstrated higher incidence rates of strokes among young women compared with young men.[20,30,32,33] The remaining five studies specifically analyzed ischemic strokes among young women and men, and four found higher incidence rates among women than men.[15,21,29,34] One study included only 22 patients and demonstrated higher incidence rates among women only in the 35–44 year age group.[27]

These sex differences did not reach the level of significance in the majority of the studies (due primarily to low numbers). In Denmark, a significant difference in stroke incidence between women and men found in the 1970's and the first half of the 1980's disappeared at the same time as low-dose OC came into more common use, so that today (1987–93), even in a sample of 2,436 young cases, no significant sex difference is demonstrable in the age groups with a high percent use of OC.

Trends in Female Incidence Rates and Oral Contraceptives

If the use of OC is responsible for the higher IRs among young women compared with those of men, we would expect some relationship between the changes in the pill doses used and the female IRs.

The main methodological problem is the few thrombotic cases in those age groups in which the use of OC is most prevalent, and on the other hand, the few users of OC in older fertile age groups where the IRs of CTA are relatively high.

In the age group 15–29 years, the expected fall of −18.5% was very close to the observed trend of −20.4%. About one-half of this decrease was anticipated to be a consequence of factors influencing both sexes. This study design does not permit any conclusions as concerns these potential causes. The important message from this study is that the shift from middle estrogen pills (50g) to mini-(30–40g) and micro-estrogen (20g) pills can explain the whole difference in the trends in CTA IRs between women and men during the study period; in other words, the theoretically calculated changes anticipating a causal relationship are supported by the development observed.

In the 30–44-year age group, the expected influence from OC was less pronounced, due to the low percent of OC use in these age groups. But again, the expected and observed trend were very close to one another.

The Influence From Other Factors

Except for a fall among the youngest women (15–19 years), the percent of smokers among fertile women

Table 4. Studies assessing the incidence rate of cerebrovascular diseases (CeVD) among young women and men, listed according to year of publication

First Author	Nationality	Period of Data Sample	CeVD Entities	No. of Cases	Age Group	Incidence Rate Men 100,000/year	Incidence Rate Women 100,000/year	Rate Ratio ♀ > ♂
Abu-Zeid (Ref. 27)	CN	1970–71	occlusive strokes	22	20–34	4.3	3.2	no
					35–44	11.1	15.3	yes
Harmsen (Ref. 28)	S	1970–75	stroke	91	15–44	13.0	9.0	no
Robins (Ref. 20)	USA	1975–76	stroke	22	<35	2.5	4.1	yes
					35–44	41.5	25.7	no
Arbuckle (Ref. 29)	UK	1975–76	occlusive strokes	10	<35	0.7	1.7	yes
				14	35–44	9.8	8.7	no
Kramer (Ref. 30)	USA	1974–76	stroke	11	20–34	4.0	8.0	yes
					35–44	39.7	22.8	no
Mettinger (Ref. 21)	S	1973–77	occlusive strokes	321	25–34	1.8	3.2	yes
					35–44	5.2	2.8	no
Bonita (Ref. 31)	NZ	1981–82	stroke	31	15–24	7.6	2.6	no
					25–34	15.5	2.9	no
					35–44	53.2	31.7	no
Lidegaard (Ref. 15)	DK	1977–82	occlusive strokes	176	15–24	1.5	3.3	yes
				519	25–34	6.2	8.1	yes
				1,276	35–44	25.8	22.2	no
Marini (Ref. 32)	I	1984–89	stroke and TIA	33	15–24	?	?	yes
				92	25–34	?	?	yes
				183	35–44	?	?	no
Guidetti (Ref. 33)	I	1987–89	stroke	1	15–24	0	2.9	no
				10	25–34	11.1	17.0	yes
				18	35–44	31.4	19.6	no
Kittner (Ref. 34)	USA	1988	cerebral infarction	55	15–39	8.6	10.6	yes
				45	40–44	58.9	62.5	no
Leno (Ref. 35)	E	1986–88	stroke	8	16–25	5.9	3.7	no
				14	26–35	10.0	7.7	no
				32	36–45	26.6	23.3	no
Bonita (Ref. 36)	NZ	1991	stroke	4	15–24	5	4	no
				11	25–34	14	7	no
				46	35–44	44	37	no
Lidegaard (this study)	DK	1980–93	occlusive strokes and TIA	331	15–24	2.8	3.4	yes
				1,018	25–34	8.5	10.7	yes
				3,303	35–44	36.1	26.3	no

has been stable through the eighties.[16,17,37] The percentage of smokers among Danish women is approximately the same as that among men. Therefore, smoking habits cannot be the explanation of either the differences between women and men or of the female trends during the study period.

During the 1980's, a gradually higher proportion of women received an education and entered the employment market. If occupational circumstances are responsible for some strokes, this trend is expected to increase rather than decrease the female IRs. Therefore, occupational circumstances are unlikely to be the explanation of the decline in the female trends below 35 years, but may be of significance for the significant increase in the female IRs in the age group 35–39 years and for the increase in the IRs among men 30–34 and 40–44 years old.

As long as no other influence can explain the specific reduction in the female IRs below the age of 35 years, the reduction in the hormonal content of OC is likely to be a major factor for the declining occurrence of CTA among young women.

Conclusion

The IRs of cerebral thromboembolism in the 15–34-year age group were significantly higher among women than among men in the early 1980s in contrast to all older age groups. The IR among women below 30 years of age has decreased by 20% during the period 1980–1993 compared with a fall of 9.5% among men. In the age group 30–44 years, men had a significant increase of 11%, women a not significant increase of 4.2%.

The excess of CTA among young women before 1987 could be explained alone by the use of OC and pregnancies in these age groups, and the significant fall in the young female IR during the last 14 years

may be a consequence of the reduced hormonal content of OC. At present, no other exposures explain these trends in CTA among young women and men in Denmark.

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