Thrombotic diseases in young women and the influence of oral contraceptives

Øjvind Lidegaard, Associate Professor, DrMedSci
Herlev, Denmark

OBJECTIVE: In the evaluation of the clinical impact of thrombotic diseases in young women, age-specific incidence rates must be calculated for both arterial and venous thrombotic diseases, but also the case-fatality rate and figures for the clinical consequences among those who survive thrombosis must be included. The aim of this analysis was to quantify the clinical impacts of both arterial and venous thrombotic diseases among young, nonpregnant women and thereafter to assess the influences of oral contraceptives on these measures.
STUDY DESIGN: Nationwide register data on the morbidity and mortality of venous thromboembolism, myocardial infarction, and thrombotic stroke in Denmark, 1980-1993, and 3 ongoing case-control studies to assess the influence of oral contraceptives on the risk for development of these thrombotic diseases.
RESULTS: In women 15-29 years old venous thromboembolism is about twice as common as arterial complications, whereas in women 30-44 years old the number of arterial complications exceeds that of venous diseases by about 50%. The mortality rate from arterial diseases is 3.5 times higher than that from venous diseases among women <30 years old and 8.5 times higher than that from venous diseases in women 30-44 years old. The proportion of women with a significant disability among women who had an arterial complication was about 30%; the proportion was about 5% among women with venous thromboembolism.
CONCLUSION: Anticipating a differential influence on venous and arterial diseases from oral contraceptives with second- and third-generation progestogens, it was calculated that users of oral contraceptives with second-generation progestogens had 30% greater increased risk of thrombotic diseases, 260% greater increased risk of thrombotic deaths, and 220% greater increased risk of thrombotic disability than users of oral contraceptives with third-generation progestogens. (Am J Obstet Gynecol 1998;179:S62-7.)

Key words: Cerebral thrombosis, disability, mortality, myocardial infarction, oral contraceptives, venous thromboembolism

In the current discussion on oral contraceptives (OCs) and thrombotic diseases, much attention has been given to the relative risk estimates of thrombotic disease among current users of OCs compared with the risk among nonusers. This is, however, only a part of the necessary database that must be included to achieve a complete picture of the health impact of OCs on thrombotic diseases.

The aims of this article are as follows:

- To establish age-specific incidence and mortality rates of different thrombotic diseases in young women
- To present relative risk estimates of development of different types of thrombotic diseases among users of different types of OCs derived from 3 ongoing Danish case-control studies on OCs and (1) cerebral thromboembolic attacks, (2) acute myocardial infarction, and (3) venous thromboembolism
- To make a quantitative assessment of the impact of OCs on these 3 main thrombotic diseases in young women

The scope is thus not to establish an overall risk-benefit calculation for OCs but only to quantify their impact on thrombotic diseases.

In considering thrombotic diseases in young women, 3 diseases and 3 disease measures have clinical relevance. The 3 major thrombotic diseases that affect women are cerebral thromboembolic attack (including thrombotic strokes and transient ischemic attacks), acute myocardial infarction, and venous thromboembolism (including deep venous thrombosis and pulmonary embolism). Initially, it is important to realize that venous and arterial diseases have quite different etiologies, clinical manifestations, clinical consequences, and treatments. It is therefore not unlikely that sex hormones have differential effects on the venous and the arterial circulations.

The clinical impact of a thrombotic disease is deter-

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Reprint requests: Øjvind Lidegaard, Associate Professor, DrMedSci, Department of Obstetrics and Gynaecology, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

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Table I. Diagnostic codes included in the incidence and mortality figures for venous thromboembolism, myocardial infarction, and cerebral thromboembolism in Denmark through the period 1980-1993

ICD-8 codes	*Clinical condition*
451.00*	Deep venous thrombosis in nonpregnant women
450.99*	Pulmonary embolism in nonpregnant women
410.09 / 99†	Acute myocardial infarction
432‡	Occlusion of precerebral artery
433‡	Cerebral thrombosis
434‡	Cerebral embolism
435‡	Transient cerebral ischemic attack
436‡	Cerebral apoplexy§
634.99‖	Deep venous thrombosis or pulmonary embolism in pregnancy
671.01‖	Deep venous thrombosis in puerperium
673.09, 673.19, 673.99‖	Pulmonary embolism in puerperium

*Venous thromboembolism is 451.00 and 450.99.
†Acute myocardial infarction is 410.09 and 410.99.
‡Cerebral thromboembolic attacks are 432 through 436.
§Thrombotic cases constitute between 80% and 90%.
‖Pregnancy-related venous thromboembolism is 634.99, 671.01, 673.09, 673.19, and 673.99.

mined by the incidence of the disease, its mortality rate (the case-fatality rate), and the clinical consequences that this disease has for those who survive it. Because age is the primary risk factor for all thrombotic diseases, age should be clearly specified for all figures under discussion. The first condition for doing this is to establish exact age-specific incidence and mortality rates of the 3 main events among young women. Because pregnancy is significantly related to the venous diseases and at the same time excludes the use of OCs, statistics on venous thromboembolism should as far as possible exclude pregnant women.

In 1977 a National Patient Register was established in Denmark. Since that time this register has recorded all discharges from all Danish hospitals, including information about specific discharge diagnoses coded according to the World Health Organization international classification of diseases (ICD) as well as a personal identification number, patient age, and patient residence. During the period 1980-1993, the World Health Organization ICD-8 codes were in use in Denmark. By January 1, 1994, the ICD-10 codes had replaced the ICD-8 codes.

Material and methods

We made an analysis of data from National Patient Register covering the period 1980-1993 and including the relevant diagnoses (Table I). The period of analysis was restricted to these 14 years because of important code differences between ICD-8 and ICD-10. From the Danish Death Statistics (published annually by the Danish National Board of Health), we also obtained age-specific death rates for these diseases.[1]

The results from the first 2 study-years (1994-1995) of 3 ongoing case-control studies provided relative risk estimates for specific thrombotic diseases among women who were using different types of OCs compared with nonusers of OCs.[2,3] The design was 3 nationwide case-control studies including all Danish hospitals. All women 15-44 years old who for the first time had a venous thromboembolism, an acute myocardial infarction, or a cerebral thromboembolic attack diagnosed during the period 1994-1995 were included, as were 1200 control subjects matched to the age of the cerebral thromboembolic attack case patients.[2,3]

Results

Thrombotic diseases in young women. The age-specific incidences of cerebral thromboembolic attack, acute myocardial infarction, and venous thromboembolism are indicated in Table II and Figs. 1 through 3. Because a significant proportion of young women with venous thromboembolism were pregnant, the figures for nonpregnant women with venous thromboembolism are given as well. The proportion of pregnant women with acute myocardial infarction is <1% and that among women with cerebral thromboembolic attack is about 5%.[4]

The age-specific mortality rates are also indicated in Table II and Figs. 1 through 3. In the calculation of the death rates from venous thromboembolism among nonpregnant women, it was anticipated that the proportion of pregnant women among the deaths from venous thromboembolism would correspond to the proportion of pregnant women among women with nonfatal venous thromboembolism: 36.5% among women <30 years old and 14.5% among women 30-44 years old. It appears from Table II and Figs. 1 through 3 that all 3 diseases increase rapidly with increasing age, with the arterial diseases increasing almost exponentially and the venous diseases increasing more linearly. Furthermore, the morbidity rates and especially the mortality rate among women <30 years old are extremely low for all the considered diseases. The number of venous complications is

Table II. Thrombotic diseases among young women in Denmark, 1980-1993

	CTA (all)[*]	*AMI (all)*	*VTE (all)*[†]	*VTE (nonpregnant)*	*Ratio (arterial/venous)*[‡]
15-29 y					
Incidence (cases/million women/y)	46[§]	6.2	170	108	0.5
Mortality (deaths/million women/y)	1.0	1.1	1.1	0.6[‖]	3.5
Case fatality rate (%)	2.2	18	0.6	0.6	—
30-44 y					
Incidence (cases/million women/y)	222[§]	114	270	231	1.5
Mortality (deaths/million women/y)	5.1	28.7	4.4	4.0[‖]	8.5
Case fatality rate (%)	2.3	25	1.7	1.7	—

CTA, Cerebral thromboembolic attack; *AMI,* myocardial infarction; *VTE,* venous thromboembolism.
[*]Cerebral thromboembolic attack includes thrombotic strokes and transient cerebral ischemic attacks.
[†]Venous thromboembolism includes deep venous thrombosis and pulmonary embolism.
[‡]Ratio among nonpregnant women.
[§]Incidence figures for cerebral thromboembolic attack are for 1987-1993.
[‖]In calculation of death rates for venous thromboembolism among nonpregnant women, it was anticipated that the proportion of pregnant women among the venous thromboembolism deaths would correspond to the proportion of pregnant women among women with nonfatal venous thromboembolism.

Table III. Risk of cerebral thromboembolism, acute myocardial infarction, and venous thromboembolism according to different types of oral OCs in 3 ongoing Danish case-control studies

	CTA		*AMI*		*VTE**	
OC generation	*Odds ratio*	*95% CI*	*Odds ratio*	*95% CI*	*Odds ratio*	*95% CI*
First generation	1.9	0.9-3.9	4.8	2.1-11	1.8	0.9-3.6
Second generation	2.4	1.4-4.2	1.8	0.8-4.3	1.6	1.0-2.5
Third generation	1.3	0.8-2.2	1.1	0.5-2.5	2.3	1.6-3.2

Results from first 2 study-years. Definitions: *First generation,* OCs with 50 μg ethinyl estradiol or estrans; *second generation,* OCs with 30 to 40 μg ethinyl estradiol and levonorgestrel or norgestimate; *third generation,* OCs with 20-40 μg ethinyl estradiol and desogestrel or gestodene. *CTA,* Cerebral thromboembolic attack; *AMI,* myocardial infarction; *VTE,* venous thromboembolism.
[*]Risk estimates corrected for differences in duration of OC use.

about twice as great as that of arterial diseases among women 15-29 years old, whereas the number of arterial complications exceeds that of venous diseases among women 30-44 years old by about 50%.

The mortality rate was generally low among women with cerebral thromboembolic attack (2%-2.5%) and venous thromboembolism (0.6%-1.7%), compared with a significant case-fatality rate among women with acute myocardial infarction (18%-25%). The mortality from arterial diseases was 3.5 times higher than that from venous diseases among women <30 years old and 8.5 times higher among women 30-44 years old (Table II).

Three ongoing Danish case-control studies. Of questionnaires sent out, 309 for cerebral thromboembolic attack, 113 for acute myocardial infarction, 586 for venous thromboembolism, and 1200 for control subjects, 90%, 91%, 89%, and 90%, respectively, responded. After exclusion of women with previous thrombosis, pregnancy, or an uncertain diagnosis, 219 valid cerebral thromboembolic attack case patients, 94 women with acute myocardial infarction, 375 women with venous thromboembolism, and 1041 control subjects were available for analysis.

After multivariate analysis, odds ratios for each disease were calculated for specific OC types, with nonusers of OCs as reference. Analyses were made according to estrogen dose and progestogen type. First-generation OCs were defined as OCs with 50 μg ethinyl estradiol or with estrans, second-generation OCs were defined as OCs with between 30 and 40 μg ethinyl estradiol combined with levonorgestrel or norgestimate, and third-generation OCs were defined as OCs with between 20 and 40 μg ethinyl estradiol combined with desogestrel or gestodene. The results are indicated in Table III.

First-generation OCs increased the risk of acute myocardial infarction significantly, second-generation OCs increased the risk of cerebral thromboembolic attack and venous thromboembolism significantly, and third-generation OCs increased the risk of venous thromboembolism significantly. The risk of venous thromboembolism was primarily influenced by duration of current use. For all OCs together, the risk of venous thromboembolism was 2.2 (1.2-4.0) times higher during the first year of use and 1.1 (0.6-1.9) times higher during the next 4 years compared with the risk among long-term (>5 years) users. The average risk estimates of venous thromboembolism shown in Table III were recalculated after a standardization in length of use corresponding to

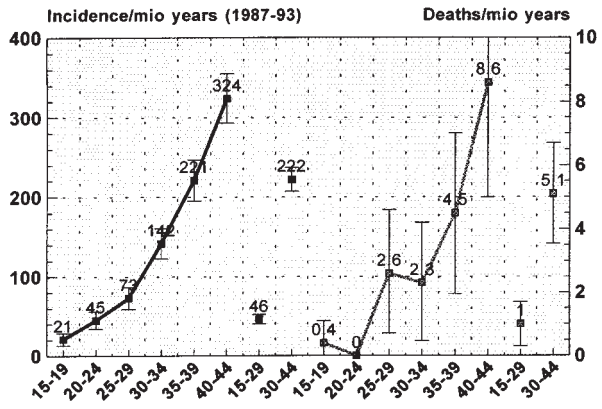

Fig. 1. Cerebral thromboembolic attacks *(filled squares)* and cerebral thromboembolic attack deaths *(open squares)* among young women in Denmark. Morbidity (for 1987-1993) was 1071 and mortality (for 1980-1993) was 48. *Error bars*, 95% confidence intervals; *mio years*, million women / y.

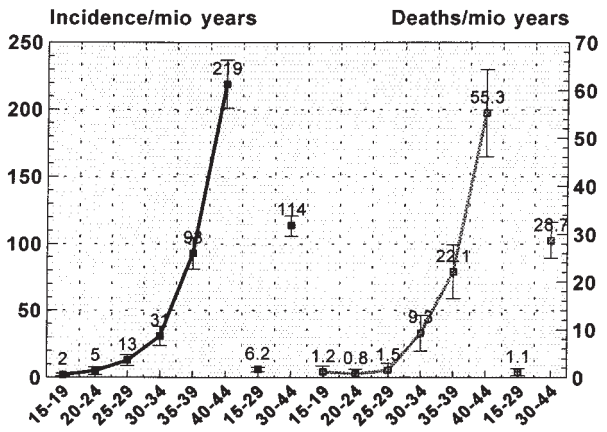

Fig. 2. Myocardial infarction incidence *(filled squares)* and deaths *(open squares)* among young women in Denmark (for 1980-1993). Morbidity was 937 and mortality was 233. *Error bars*, 95% confidence intervals; *mio years*, million women / y.

the distribution among users of OCs with first-generation progestogens so that the length-of-use distributions were identical for the different product groups. After adjustment for differences in duration of current use among users of OCs with second- and third-generation progestogens, respectively, no significant difference in risk of venous thromboembolism was found between users of these 2 product groups.

The odds ratios shown in Table III were applied in the calculations in the next section.

Clinical consequences among women who survive thrombotic disease. The degree of disability among women surviving the thrombotic event is also an important clinical issue. In the 3 ongoing Danish case-control studies, all women were asked for clinical symptoms after and as a consequence of the thrombotic disease. The proportions of women with a significant disability were about 30% for cerebral thromboembolic attack, about 30% for acute myocardial infarction and about 5% for venous thromboembolism. These figures are used in the calculations performed later in this article.

Impact of OCs on thrombotic diseases. To assess the impact of different types of OCs on thrombotic diseases in young women, it is necessary to have figures for the following:

- The incidence rate of each diagnosis
- The mortality rate for each diagnosis
- The proportion of disabled women for each diagnosis
- The relative risk of each disease among users of specific types of OCs, compared with that of nonusers of OCs

An impact calculation was made on 1 million women 15-44 years old who were taking OCs with second-and

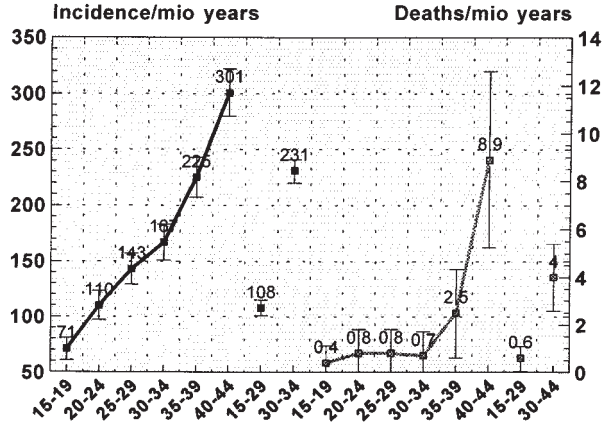

Fig. 3. Venous thromboembolism incidence (filled squares) and deaths (open squares) among young women in Denmark (for 1980-1993). Pregnant and puerperal women are excluded. Morbidity was 2653 and mortality was 42. *Error bars*, 95% confidence intervals; *mio years*, million women / y.

third-generation progestogens (Tables IV and V). Pregnant women with cerebral thromboembolic attack and venous thromboembolism were excluded from these calculations. The odds ratios from the 3 Danish case-control studies were applied (Table III).

From Table V it appears that, with users of OCs with third-generation progestogens used as reference, current users of OCs with second-generation progestogens had overall a 30% greater increase in thrombotic morbidity rate, corresponding to 88 thrombotic cases / million users / y, a 260% higher increase in thrombotic mortality rate, corresponding to 13 excess thrombotic deaths / million women / y, and a 220% higher increase in thrombotic disability, corresponding to 56 cases of disabled women / million users / y.

The same calculation restricted to women <30 years

Table IV. Impact of OCs on thrombotic diseases

	Nonusers of OCs	*Users of second-generation progestogens*	*Users of third-generation progestogens*
CTA*			
Relative risk	1	2.4	1.3
Incidence	150‡	+210	+45
Mortality	3‡	+4	+1
Disability	45‡	+63	+14
AMI			
Relative risk	1	1.8	1.1
Incidence	60	+48	+6
Mortality	15	+12	+1
Disability	18	+14	+2
VTE†			
Relative risk	1	1.6	2.3
Incidence	170‡	+102	+221
Mortality	2‡	+2	+3
Disability	8‡	+5	+10

Incidence, mortality, and disability values are given as events/million women of reproductive age (15-44 years old).
*Cerebral thromboembolic attack includes thrombotic strokes and transient cerebral ischemic attacks
†Venous thromboembolism includes deep venous thrombosis and pulmonary embolism.
‡Pregnant women excluded.

Table V. Venous and arterial complications among women using second- and third-generation progestogens

	Users of second-generation progestogens	*Users of third-generation progestogens*	*Ratio of second- to third-generation*
Morbidity			
Arterial	+258	+51	5.1
Venous	+102	+221	0.5
Total	+360	+272	1.3
Mortality			
Arterial	+16	+2	8.0
Venous	+2	+3	0.7
Total	+18	+5	3.6
Disability			
Arterial	+77	+16	4.8
Venous	+5	+10	0.5
Total	+82	+26	3.2

Incidence, mortality, and disability values are given as events/million women/y.

old gave a 10% lower increase in thrombotic morbidity rate, corresponding to 20 thrombotic cases/million users/y, a 120% higher increase in thrombotic mortality rate, corresponding to 1.3 thrombotic deaths/million women/y, and a 160% higher increase in thrombotic disability, corresponding to 17 excess cases of disabled women/million users/y for users of OCs with second- versus third-generation progestogens.

Comment

Incidence and mortality data. From the ongoing Danish case-control studies in which all the diagnoses are validated, we know that the validity of the diagnoses in the National Patient Register is not 100%. Generally, the acute myocardial infarction and cerebral thromboembolic attack diagnoses are more reliable than diagnoses of venous thromboembolism because of better diagnostic equipment for the former. The technical misclassification of thrombotic diseases among young women in the National Patient Register is <5%. For venous thromboembolism, a further 5% to 15% of the diagnoses are clinically uncertain. This uncertainty, however, does not substantially influence the overall calculations performed. The absolute incidence rates are in good accordance with corresponding estimates from England and the United States.[5-8]

The mortality codes are generally reasonably valid because autopsies are performed on nearly all young women dying in Denmark. The only important uncertainty is the proportion of women dying of venous thromboembolism who are pregnant, because a significant proportion of pregnant women with venous thromboembolism unfortunately are coded with the codes for nonpregnant women. Furthermore, sometimes the thrombotic event is considered as the main cause of death, whereas in other instances the pregnancy is coded as the main cause of death. This uncertainty could at most have underestimated the venous thromboembolism deaths by about a third.

Risk estimates from case-control studies. The risk estimates of venous thromboembolism are comparable with the estimates found in an English case-control study[9] but lower than those found in the World Health Organization multicenter study[10,11] and the Transnational Study.[12] The risk estimates of acute myocardial infarction among users of different types of OCs are very close to the estimates found in 3 independent recent epidemiologic studies.[13-15] This circumstance probably also reflects the relatively high validity of this diagnosis compared with that of venous thromboembolism.

Concerning the risk estimates of thrombotic strokes among users of first-, second-, and third-generation OCs, there is more controversy. The World Health Organization found estimates in line with ours in developing countries, whereas in the European centers there was no difference in risk between users of second- and third-generation OCs.[16] Relatively few women had taken third-generation OCs in this World Health Organization study; the statistical power was therefore correspondingly low.

With 45 current users of OCs with third-generation progestogens among stroke cases, the statistical power in the Transnational study was higher.[17] The risk estimates in that study were, however, about twice as high with hospital control subjects than with community control subjects as reference. The risk estimate of ischemic stroke of

2.6 (1.5-4.6) among current users of second generation OCs and with community control subjects as the reference was close to our results. On the other hand, the risk estimate for current use of third-generation OCs of 3.4 (1.8-6.3) was higher than the Danish estimate of 1.3 (0.8-2.2). Two recent American studies[18,19] assessing the risks of ischemic stroke among users of first- and second-generation OCs found risk estimates that were in the lower end of the confidence limits of our estimates. Thus the Danish risk estimate of thrombotic stroke among users of second-generation OCs was in the middle of the estimates indicated in other studies, whereas the estimate for third-generation OCs was in the lower end of those indicated in other studies.

Impact of OCs on thrombotic diseases. This study confirms that the incidence and mortality rates of thrombotic diseases among young women are generally low, and the health impact of OCs is correspondingly small. According to the presented data from a well-defined and systematically recorded population, women >30 years old who are taking OCs with third-generation progestogens may have less risk of thrombotic morbidity, mortality, and disability than users of OCs with second-generation progestogens. For women <30 years old, 20 thrombotic cases should be balanced against 1.3 thrombotic deaths and 17 women with significant thrombotic disability to allow recommendation of third- rather than second-generation progestogens or vice versa. Thus a weighted analysis such as the one presented here does not emerge in any consistent recommendation of a particular progestogen type.

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