Acta Obstet Gynecol Scand 1997; 76: 252–260
Printed in Denmark – all rights reserved

Acta Obstetricia et Gynecologica Scandinavica
ISSN 0001-6349

ORIGINAL ARTICLE

The influence of thrombotic risk factors when oral contraceptives are prescribed

A control-only study

ØJVIND LIDEGAARD

From the Department of Obstetrics and Gynaecology, Herlev Hospital, University of Copenhagen, Herlev, Denmark

Acta Obstet Gynecol Scand 1997; 76: 252–260. © Acta Obstet Gynecol Scand 1997

Objectives. The aim of this study was to assess preferential prescribing of OC according to different thrombotic risk factors.
Material and methods. The control group in an ongoing Danish case-control study on stroke and OCs collected in 1994 and 1995 underwent a control-only analysis concerning the occurrence of thrombotic risk factors among users of different types of OC. Specific attention was given to differences between OCs with second and third generation progestagens. The association between specific risk factors and the pill types was assessed crude and after multivariate analysis with confounder control for age and other risk factors, in order to identify risk factors, which after these corrections still had a significant confounding influence on the prescribing of OC.
Results. Users of OCs with third generation progestagens had a significantly higher proportion of familial thrombotic disposition (23.1%) than users of OCs with second generation progestagens (7.1%) ($p=0.01$). After correction for age and other risk factors this difference was still highly significant ($p=0.002$). Among users of third generation pills the proportion of short time users (<1 year) (22.4%) was significantly higher than the per cent among users of OCs with second generation progestagens (5.5%) ($p<0.001$). This difference was still significant after correction for age and other risk factors ($p<0.001$).
Smoking, years of schooling, migraine, and body mass index did not differ significantly between the two pill groups.
Conclusion. In Denmark, women with familial thrombotic disposition are four times more likely being prescribed OCs with third versus second generation progestagens compared with women without such a disposition. At the same time users of OCs with third generation progestagens include significantly more short time users than users of OCs with second generation progestagens.
For thrombotic diseases where familial disposition or duration of use of OCs play a role for the pill-associated risk, these differences may significantly influence the thrombotic risk measures in case-control studies and non-randomized cohort studies unless confounder control is conducted for this selection.

Key words: confounder control; deep venous thrombosis; epidemiology; oral contraceptives; thrombosis; venous thromboembolism

Submitted 17 April, 1996
Accepted 25 September, 1996

During October – November 1995 steps were taken by the English and German Health Authorities to inform about a potential higher risk of venous thromboembolism (VTE) among users of oral contraceptives (OC) with the two progestagens *desogestrel* and *gestodene* compared with the risk among users of other low-dose oral contraceptives.

The 'scientific' basis of these decisions was based on information obtained from three at that time unpublished epidemiological studies. Two of the

Abbreviations:
OC: oral contraceptives; EE: ethinyl estradiol; VTE: venous thromboembolism; CL: confidence limits; BMI: body mass index.

studies, together with a fourth study from Leiden, were published in *The Lancet* on December 16, 1995 (1–4). The third 'Transnational study' was published in January 1996 (5, 6).

The four published studies all found that users of OCs containing the third generation progestagens *desogestrel* or *gestodene* have a higher risk of non-fatal VTE than users of OCs with the second generation progestagens *levonorgestrel* and *norgestrel*. The differences were significant in three of four studies. An analysis of the studies and comments from the primary investigator of the last study (7) indicate that several types of confounding bias might have influenced the results in all four studies.

Two important potential biases are the so called *'prescribing bias'* and *'length of use bias'*. The former covers the circumstance that women at a recognised increased thrombotic risk may more likely be prescribed one of the new pills than an older pill type, because the new pills have been anticipated by scientists and clinicians to be safer concerning thrombotic complications than older preparations. That circumstance would bring more thrombotic complications among users of new pills than among users of older pills if no control for this bias is realised.

The latter *'length of use bias'* covers the possibility that some pill-associated thrombotic risks may be present especially within the first year of use and that particularly users of *desogestrel* and *gestodene* containing OCs may have used OCs for a shorter period than users of other brands.

The presence of any differences between users of OCs with second and third generation progestagens respectively, could be investigated in a population of healthy Danish control women established in an ongoing case-control study on OCs and cerebral thromboembolic complications.

Objectives

The aim of this study was to investigate how different risk factors, potential confounders, age and use pattern are associated with specific types of OC, and specifically to identify any differences between users of pills with second and third generation progestagens.

Material

In October 1994 and May 1995 a total of 1,200 Danish women 15–44 years old, matched to the ages of women with cerebral thromboembolic diseases but otherwise randomly selected from the National Person Register (CPR) received a questionnaire asking for weight, height, previous thrombosis in brain, heart, legs and lungs, specified thromboembolic diseases among mother and father, years of schooling, presence of treated hypertension, diabetes (IDDM), coagulopathies, heart diseases, hyperlipidemia, migraine, present and previous smoking habits, present use of specific oral contraceptives, the length of that use, as well as the time since last use of OCs among ex-users of oral contraceptives.

The age distribution in this study is the relevant one for the evaluation of confounders for pill-associated thrombotic risks, as these events – although rare – are nearly exponentially increasing with increasing age.

Methods

The analysis was conducted as a control-only study.

Categorization of users of OC

Users of OCs were categorized according to two axes (Table I):

I: Four groups according to the estrogen content: 50 μg ethinyl estradiol (EE) pills 30–40 μg EE pills including the sequential brands, pills with 20 μg EE and progestogen only pills (mini-pills).

II: Five groups according to progestogen type: a) estrans including *norethisteron*, *lynestrenol*, and *ethynodiol*, Gonans including b) *norgestrel*, *levonorgestrel*, c) *norgestimate* d) *desogestrel* and e) *gestodene*.

The analysis was based on eight groups as illustrated in Table I.

Statistical analysis

A primary distribution of age and specific risk factors according to the eight different pill types was elaborated. Next the correlation between each risk factor and age was analysed. Comparison between second generation progestagens (*levonorgestrel*, *norgestrel* and *norgestimate*) and third generation progestagens (*desogestrel* and *gestodene*) were calculated for the 30–40 μg EE group according to each risk factor. Odds ratios indicating the proportion of women with specific risk factors among users of third generation progestagens compared with second generation preparations were calculated as an expression of the odds of being prescribed a third versus a second generation progestogen product in the presence of a specific risk factor compared with the rate among women without that

Table I. Available types of oral contraceptives in Denmark, and eight groups specifically investigated in the present analysis. Categorized according to ethinylestradiol (EE) dose and progestogen type

Progestogen types	Estrans	Norgestrel	Norgestimate	Desogestrel	Gestodene
Progestagen gen. EE dose	first generation	second generation		third generation	
50 μg EE	1				
30–40 μg EE	2	3	4	5	7
20 μg EE				6	
Progestogen only	8				

risk factor. Ninety-five percent CL were calculated.

Many of the risk factors were correlated to age. At the same time several risk factors could be mutually correlated. In order to identify the risk factors which had a significant potential confounding influence after correction for other risk factors, a multivariate analysis was conducted with confounder control for age and all other risk factors. Crude and age adjusted correlation coefficients were calculated (Table II).

Test of significance was calculated by the χ^2 and, in the case or ordinal variables, also by the partial Goodman-Kruskal gamma test. *p*-values calculated with Goodman-Kruskal gamma test were supplied with an asterisk. Level of significance was set at 5% and 95% confidence limits were calculated for the odds ratios.

In the analysis, OCs with second generation progestagens (*levonorgestrel, norgestrel and norgestimate*) are called second generation pills, and pills with third generation progestagens (*desogestrel* and *gestodene*) are called third generation pills. *Norgestimate* was included together with *levonorgestrel* as *norgestimate* is converted to *levonorgestrel.*

Results

Completed questionnaires were returned by 1,074 women, corresponding to an effective response rate of 89.5%. Of these, 207 were users of OC. All but one of these could specify the brand taken (Tables III and IV).

The use was dominated by third generation OCs (30–40 μg EE): 89.8%, and by second and third generation progestagens (85%). Surprisingly few of these relatively old users of OCs were taking progestogen only pills: 2.9%.

Age

The age distribution of the controls was primarily matched to the age distribution of women with thrombotic strokes. Generally, among young women, third generation OCs dominated, whereas

Table II. Categorization of risk factors and test for differences between users of second and third generation OCs according to specific risk factors before and after age-adjustment

Variable	Smoking cig/day	Years of schooling years	Family disposition parents	Migraine >once /month	BMI kg/m²	Length of use months
	never	7–9	yes	yes	0–22	<3
	ex-smoker	10	no	no	23–25	3–12
	1–10	11–12			26–30	12–60
	11–20				>30	>60
Categorization	>20					
χ^2	1.2	2.6	6.5	0.4	0.5	18.4
df	4	2	1	1	3	3
p-value	0.87	0.27	0.01	0.54	0.92	<0.001
Gamma	−0.10	0.22	0.59	0.24	0.03	−0.53
p-value	0.42	0.11	0.01	0.51	0.84	<0.001
Age adjusted						
χ^2	15.6	7.1	10.2	15.0	15.1	24.2
df	22	12	5	5	15	16
p-value	0.88	0.87	0.07	0.41	0.44	0.09
Gamma	−0.11	0.17	0.63	0.20	0.07	−0.53
p-value	0.38	0.26	0.002	0.58	0.63	<0.001

Table III. Characteristics of users of different types of specific oral contraceptives among 206 specified users

Type#		50 µg EE	30–40 µg EE					20 µg EE Desog.	POP
			Estrans,	Levonor.	Norgest.	Desog.	Gestodene		
Users of spec. types of OC	*n*	15	11	50	6	19	77	22	6
	%	7.3	5.3	24.3	2.9	9.2	37.4	10.7	2.9
Mean age	years	33.1	34.0	32.5	25.7	26.4	30.9	29.3	34.2
Age	15–24%	7	0	12	67	42	26	36	0
	25–34%	40	55	48	17	53	36	36	67
	35–44%	53	45	40	17	5	38	27	33
Smokers	*n*	9	7	24	0	5	32	8	3
	%	60.0	63.6	48.0	0.0	26.3	41.6	36.4	50.0
<10 years of schooling	*n*	1	3	11	1	1	14	13	1
	%	6.7	27.3	22.0	16.7	5.3	18.2	13.6	16.7
Thrombosis in 1 or 2 parents	*n*	3	4	4	0	4	17	6	1
	%	20.0	36.4	8.0	0.0	22.2	22.1	27.3	16.7
Migraine	*n*	2	3	2	0	1	5	1	0
	%	13.3	30.0	4.2	0.0	5.6	6.5	4.5	0.0
Body mass index >30	*n*	1	0	1	0	1	2	1	0
	%	6.7	0	2.0	0	5.3	2.6	4.5	0
Length of use	<1 y %	14	9	6	0	10	22	37	17
	1–5 ys %	13	9	14	83	47	33	32	0
	>5 ys %	73	82	80	17	42	45	32	83

#) Estrans: norethisterone or lynestrenol. Levnorg.=levonorgestrel or norgestrel. Norgest.=norgestimate. Desog.=desogestrel. POP=progestogen only pills.

Table IV. Characteristics of users of oral contraceptives with second and third generation progestogens. The odds ratio's express the odds of being prescribed a third versus a second generation pill in the presence of a certain risk factor compared with the same ratio among women without that risk factor

Type#		2nd gen.	3rd. gen.	OR*	All Users†	Nonusers	All
Users of specific types of OC	*n*	56	118	–	206	867	1,07 3 100
	%	27.2	57.3	–	100	100	
Mean age	years	31.7	29.9	–	31.0	36.7	35.6
Age	15–24%	17.9	30.5	1	22.8	5.9	9.1
	25–34%	44.6	39.0	0.51	42.2	24.5	27.9
	35–44%	37.5	30.5	0.48	35.0	69.7	63.0
Smokers	*n*	24	45	0.73	88	362	450
	%	42.9	38.1	0.57–0.94	43.4	42.0	42.1
<10 years of schooling	*n*	12	18	0.55	35	175	210
	%	21.4	15.3	0.37–0.81	17.0	20.3	19.6
Thrombosis in 1 or 2 parents	*n*	4	27	3.9	38	238	276
	%	7.1	23.1	2.09–7.26	18.4	27.4	25.8
Migraine	*n*	2	7	1.64	14	47	61
	%	3.7	6.0	0.44–6.11	6.8	5.6	5.8
Body mass index>30	*n*	1	4	1.97	6	51	57
	%	1.8	3.4	0.15–25.2	2.8	5.9	5.4
Length of use	<1 year %	5.5	22.4	7.07	16.3	–	–
	1–5 years %	21.8	35.3	2.79	27.6	–	–
	>5 years %	72.7	42.2	1	56.2	–	–

#) second generation OCs=OCs with levonorgestrel, norgestrel or norgestimate. Third generation OCs=OCs with desogestrel or gestodene. †) Specified users. Total users=207.

in the older age groups a relatively higher proportion of the women were taking older OCs (Fig. 1). Relatively few women in the control group, however, were young women, illustrated by the fact that, among users of third generation progestagens, the mean age was 29.9 years compared with

31.7 years among users of pills with second generation progestagens ($p=0.66$, $p^*=0.07$) (Table IV). Within the third generation group a higher proportion of users of OCs with *desogestrel*+20 μg EE or *gestodene* was found in the 35–44-year age group compared with users of OCs with *desogestrel*+30 μg EE ($p<0.05$) (Fig. 1). After correction for duration of OCs use, this association to age disappeared. None of the associations between specific risk factors and pill type were significantly changed by correction for age.

On the other hand, the majority of risk factors were correlated to age. Therefore, it was still relevant to adjust the calculated correlations for any influence from age, and to explore how correction for the other risk factors influenced the association between each risk factor and specific pill types.

In Table II the different strata included according to each variable as well as crude and age-adjusted differences between second and third generation OCs according to specific risk factors are indicated. After correction for age, significant differences was found only in relation to familial disposition and according to length of OC use.

Smoking

The percentage of smokers according to age is illustrated in Fig. 3. No significant difference in percentage of smokers between users second and third generation pills was demonstrated (Table IV, Fig. 2). When comparing thrombotic risks between users of second and third generation pills in Denmark, confounder control for smoking is not therefore expected to change the calculated odds ratios significantly.

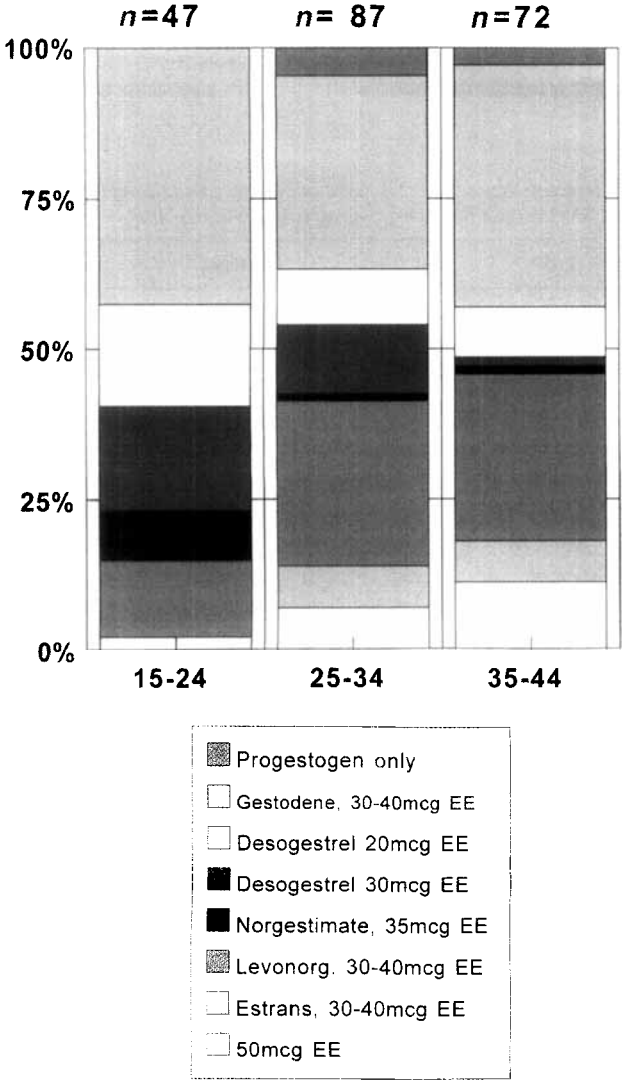

Fig. 1. OC types according to age. Women 15–44 years old, Denmark 1994/95.

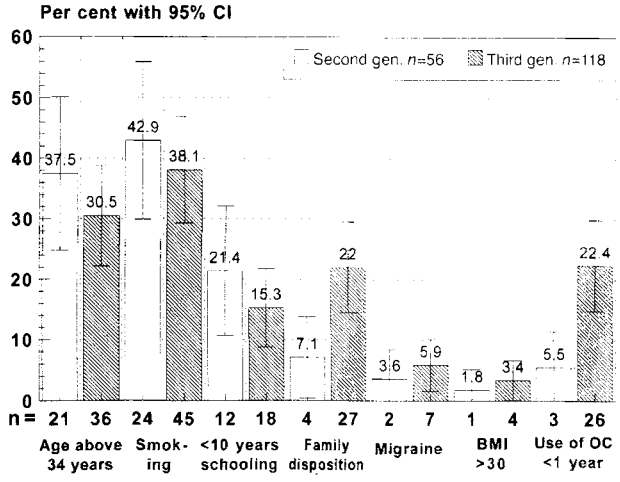

Fig. 2. Risk factors among users of oral contraceptives with second and third generation progestagens.

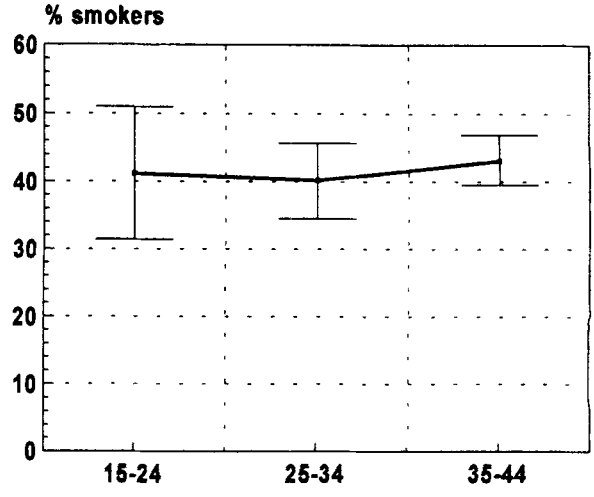

Fig. 3. Smoking habits according to age.

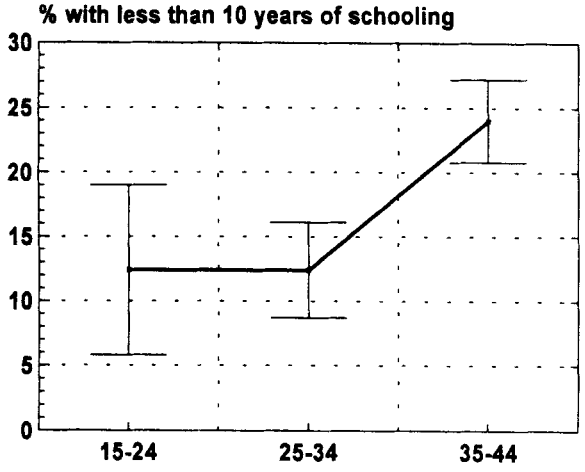

Fig. 4. Less than ten years of schooling according to age.

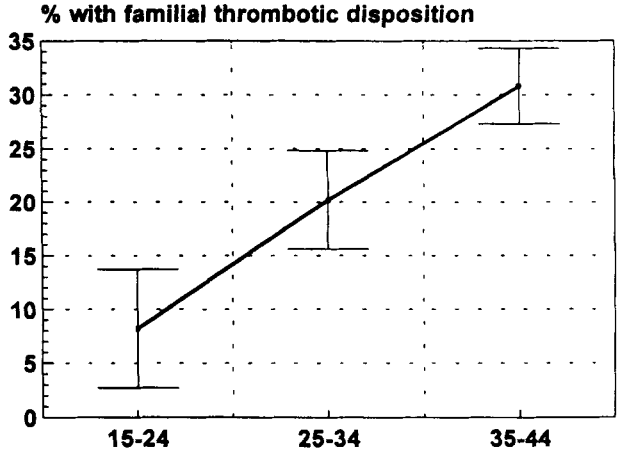

Fig. 5. Family thrombotic disposition according to age.

The crude proportion of heavy smokers among second generation users was 3.6% (2/56) and among third generation users 4.2% (5/118)(p NS).

In conclusion, in Denmark smoking habits did not significantly influence the type of OCs being prescribed. In other countries, with smoking habits different from the Danish, smoking may still be an important confounder.

Previous thrombotic events

None of the users of OCs had suffered any thromboembolic disease before. Among the non-users, four (0.5%) had experienced thrombotic events.

Predisposing medical diseases

The number of women with hypertension was four, two with diabetes (2), two with hyperlipidemia, two with coagulopathies and one with heart diseases which, together, were too few to make type specific calculations.

Years of schooling

Years of schooling was used as an operationalization of social class. Generally, women with few years of schooling have a higher incidence rate of thrombotic diseases compared with women with longer schooling. The proportion of women with few years of schooling (<10 years) according to age is illustrated in Fig. 4, and according to pill types in Tables III and IV and Fig. 2.

The proportion of women with 11–12 years of schooling decreased significantly with increasing age from 60.8% among women 15–24 years old to 30.6% among women 35–44 years old ($p^*<0.001$).

The association between years of schooling and

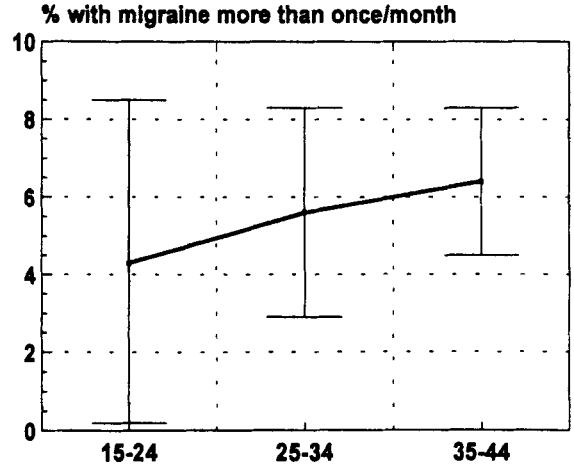

Fig. 6. Migraine among young women according to age.

OC generation was not significant ($p=0.27$, $p^*=0.11$). Twenty-one point four percent of second generation users had less than 10 years of schooling compared with 15.3% among third generation users. After adjustment for age, the association was even weaker ($p=0.87$).

In conclusion, years of schooling did not significantly influence the type of OC being prescribed.

Familial disposition

Women with one or two parents with thrombotic diseases generally have an increased risk of thrombotic diseases. Therefore, all women were asked for specific thromboembolic diseases among their parents.

The association between family disposition and age is illustrated in Fig. 5. The per cent of women with family disposition increased from 8.2% among women 15–24 years old to 30.8% among

women 35–44 years old ($p<0.001$). The difference between users and non-users of OCs disappeared after correction for age.

Among users of second generation pills, 7.1% had a familial thrombotic disposition compared with 23.1% among third generation pill users ($p=0.01$)(Fig. 2). After correction for age this difference was still highly significant ($p^*=0.002$). Correction for other risk factors did not change the significant association. The odds ratio of 3.9 indicates that women with a familial thrombotic disposition are 3.9 times more likely to be prescribed a third generation pill than a second generation pill compared with women without such a disposition.

In conclusion, familial disposition is a significant confounder, even after correction for age and other risk factors.

Migraine

Migraine predisposes for thrombotic strokes but not for AMI or DVT. The percentage of women with migraine according to age is illustrated in Fig. 6. No significant association between migraine and age could be demonstrated.

The proportion of migraine patients among users of different types of OC is illustrated in Table III and IV and Fig. 2. The difference between second generation users (3.7% with migraine) and third generation users (6.0% with migraine) was not significant before ($p=0.54$) nor after ($p=0.41$) correction for age.

In conclusion, migraine did not influence significantly the choice of pill types being prescribed.

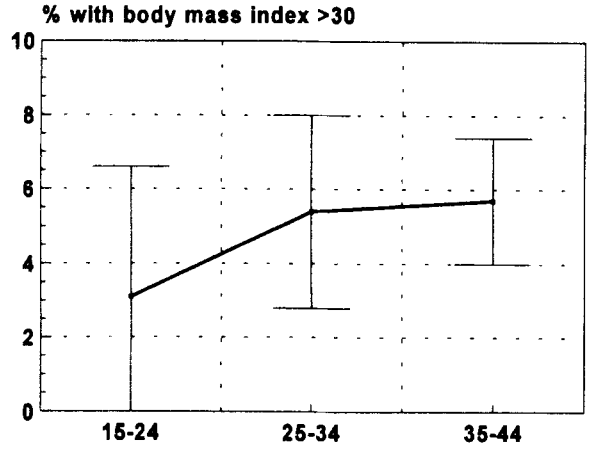

Fig. 7. High body mass index according to age.

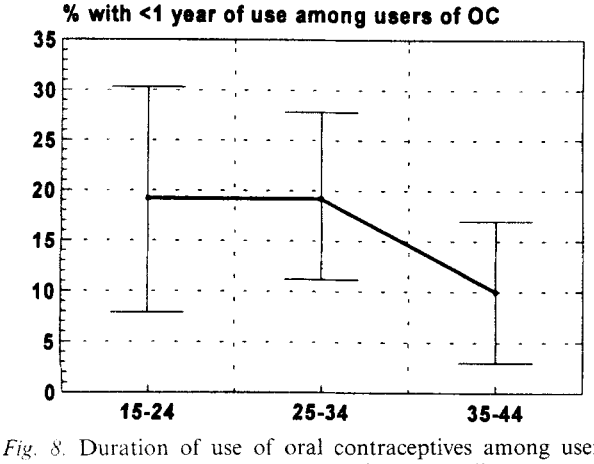

Fig. 8. Duration of use of oral contraceptives among users. Proportion with less than one year of use according to age.

Body mass index (BMI)

The average body mass indices according to age is illustrated in Fig. 7, and according to specific pill types in Table III and Fig. 2. The proportion of women with a BMI >30 increased from 3.1% among women 15–24 years old to 5.7% among women 35–44 years old ($p<0.01$).

The average BMI among second generation pill users was 22.9 kg/m^2 and among third generation pill users the same (Table IV). After correction for age the difference was still far from significant ($p^*=0.63$)(Table II). The percent of second generation users with BMI >30 was 1.8% and 3.4% among third generation users. The corresponding odds ratio of 1.97 had wide confidence limits: 0.15–25.2.

In conclusion, BMI did not significantly influence the odds of being prescribed a third versus a second generation product.

Length of use

Some studies have indicated that women are especially susceptible to thrombotic complications within their first months of pill use.

Fig. 8 illustrates that the proportion of short time users (less than 1 year) decreases significantly with increasing age.

Among second generation users of OC, 5.5% of the users had used the pill for less than one year, compared with 22.4% of users of third generation pills ($p<0.001$, $p^*<0.001$)(Fig. 2). These differences were still highly significant after correction for age ($p^*<0.001$) and other risk factors. In the group of users of *desogestrel*+20 μg EE, 37% had used the pill for less than one year, compared with 10% among users of *desogestrel*+30 μg EE.

In conclusion, women with less than 1 year of OC use are about seven times more likely to be third than second generation users compared with women with >5 years use.

Discussion

OC-categorization

Where do OCs with *norgestimate* belong? The chemical substance is converted to *levonorgestrel* when metabolized. That was the reason for regarding them as second generation progestagens. As the *levonorgestrel* level in *norgestimate* users is lower than in other second generation pills, and as they came on the market at about the same time as third generation progestagens, a categorization together with third generation pills would also have been appropriate. The low number of users of this pill type implies that the findings in the present analysis would not be changed much if they, alternatively, were included in the third generation group.

Age

It was a little surprising not to find large age difference between users of different types of OCs. The explanation is two opposite trends: Young women are generally prescribed new types of oral contraceptives, while older women continue with types they have already taken for years. That trend has been demonstrated clearly in Denmark in 1983 and 1990 (8, 9) and in Britain during the period 1972–1987 (10).

On the other hand, older women and women at risk may increasingly have been prescribed the new types of OCs, anticipating that these products are safer concerning thrombotic risks than the older brands. The first trend is probably stronger than the latter. In this study, however, with women mostly more than 30 years old, the age distribution was different from the normal distribution of OC users, who are primarily women younger than 30 years old. Thereby the latter trend seems to have a relatively high influence in the present data sample.

It is important to remember that the age distribution of the control group analysed in the present study is relevant according to thrombotic risks, as thrombotic diseases increase nearly exponentially with increasing age; ischemic strokes and AMI more than VTE.

Smoking

Twelve years ago we found a higher proportion of smokers among women on the pill than among non-users of OCs (11). Today, the proportion of smokers among users and non-users of OCs is the same in Denmark (9) but still higher among users in e.g. United Kingdom (12). Therefore, today smoking is not as important a confounder concerning thrombotic risks as it was years ago in Denmark, but may still be important in other countries with a stronger association between OC use and smoking.

It is remarkable that none of the *norgestimate* users were smokers. That may, however, be due to chance, as only six (2.9%) of the OC-users were *norgestimate* users.

Previous thrombotic events

It is encouraging that none of the users of OCs had any previous thrombotic events, as it suggests a general awareness among the prescribing general practitioners.

Years of schooling

Generally, in Denmark the use of OCs has been weakly correlated to length of schooling (9, 11). Schooling does not seem to influence significantly the type of OCs being prescribed.

Familial disposition

The results from the present analysis suggest that general practitioners are asking women about thrombotic disposition before prescribing OC, and that the information about this disposition influences whether OCs are being prescribed and, if so, the OC type according to progestogen type.

As up to 30% of women with the highest thrombotic risk (the oldest) have a familial thrombotic disposition, the confounding influence from family disposition may be of quantitative importance.

If women with a familial thrombotic disposition have a relative risk of thrombotic diseases (without pill use) of 2, and 7.1% and 23.1% of second and third generation users respectively have such a disposition, then that difference would bring 15% more thrombotic events among third compared with second generation users. With higher relative risks, a higher proportion of disposed, or with synergism between disposition and OC use concerning thrombotic risks, the difference (bias) will be correspondingly higher.

Migraine and body mass index

The presence of migraine may influence whether OCs are prescribed, but hardly which types are chosen in case of ordination. A women's weight does not seem to influence the OC-type being prescribed. The number of women with a high body mass index was, however, low, and the statistical power of the calculations was therefore weak.

Length of use

Several studies have indicated that length of use of OCs is of significance for the pill-associated thromboembolic risk (13–15). Although this association has not been found by all investigators (16), the higher proportion of short time users among third generation pill users may overestimate the risk of venous thromboembolism of these pills compared with second generation pills, unless correction for this difference is realized. For other thrombotic complications such as ischemic stroke, no association to length of use has been documented (17).

Significance as confounders

The result from the present analysis demonstrates that the mutual relationship between the different risk factors was in fact less than expected. Correction for risk factors such as smoking, age, years of schooling, body mass index and migraine does not ensure an adequate control for familial disposition nor for duration of OC use.

The present results indicate that familial thrombotic disposition and length of OC use are significant confounders when comparing second and third generation OCs. Other significant confounders (risk factors) might have been documented, however, if the analyzed population had been larger.

Correction for the two significant confounders in this study is crucial in order not to over-estimate a difference in thrombotic risk between second and third generations products. No correction was made for familial disposition in three of four recently published studies (1, 2, 4, 5).

Conclusion

Women with family thrombosis disposition are about four times more likely to be prescribed third than second generation OCs compared with women without family disposition. Users of OCs who have taken the pill for less than one year are seven times more likely to be a third than a second generation user compared with women who have used OCs for more than five years.

As both thrombotic disposition and length of use of OCs may influence the risk of thrombotic diseases, it is important to control for these potential confounders in epidemiological analyses on OC-associated thromboembolic events.

Acknowledgments

The author would like to express appreciation to Svend Kreiner for his statistical analyses. The costs of the study were covered by a grant from Organon International.

References

1. World Health Organization Collaborative Study on cardiovascular disease and steroid hormone contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. Lancet 1995; 346: 1575–82.
2. World Health Organization Collaborative Study on cardiovascular disease and steroid hormone contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. Lancet 1995; 346: 1582–8.
3. Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Büller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995; 346: 1593–6.
4. Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of ideopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 1995; 346: 1589–93.
5. Spitzer WO, Lewis MA, Heinemann LAJ, Thorogood M, MacRae KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. BMJ 1996; 312: 83–7.
6. Lewis MA, Spitzer WO, Heinemann LAJ, MacRae KD, Bruppacher R, Thorogood M. Third generations oral contraceptives and risk of myocardial infarction: an international case-control study. BMJ 1996; 312: 88–90.
7. Lewis MA, Heinemann LAJ, MacRae KD, Bruppacher R, Spitzer WO. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. Contraception 1996; 54: 5–13.
8. Lidegaard Ø. Oral contraception in Denmark in 1983. (Da). Ugeskr Laeger 1984; 146: 1172–4.
9. Lidegaard Ø. Use of oral contraceptives in Denmark from 1980–1990 and smoking habits among fertile women in 1990. (da). Ugeskr Laeger 1993; 155: 3550–8.
10. Thorogood M, Vessey MP. Trends in use of oral contraceptives in Britain. Br J Fam Plann 1990; 16: 41–56.
11. Lidegaard Ø, Overgaard K, Hauch O. The oral contraceptive user. Acta Obstet Gynecol Scand 1988; 67: 27–31.
12. Thorogood M, Vessey M. Oral contraceptive prescribing in the presence of risk factors. Br J Fam Plann 1991; 17: 2–3.
13. Sartwell PE, Masi AT, Arthes FG, Greene GR, Smith HE. Thromboembolism and oral contraceptives: An epidemiologic case-control study. Am J Epidemiol 1969; 90: 365–80.
14. Böttiger LE, Boman G, Eklund G, Westerholm B. Oral contraceptives and thromboembolic disease: Effects of lowering oestrogen content. Lancet 1980; i: 1097–1101.
15. Böttiger LE, Westerholm B. Oral contraceptives and thromboembolic disease. Acta Med Scand 1991; 190: 455–63.
16. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J 1969; 2: 651–7.
17. Lidegaard Ø. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. BMJ 1993; 306: 956–63.

Address for correspondence:
Dr Øjvind Lidegaard
Olgasvej 23
DK-2950 Vedbæk
Denmark