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ORIGINAL ARTICLE

Oral contraceptives and thrombosis

From risk estimates to health impact

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Objective. The scientific debate on oral contraceptives (OCs) and thrombotic diseases continues unabated. The aim of this survey was to evaluate available scientific data on OCs and thrombotic diseases and to make tentative prescription recommendations of OCs to women with and without various thrombotic risk factors.

Consensus. In women 15–29 years old, venous thromboembolism is about twice as common as arterial complications. In women between 30 and 44 years, the number of arterial complications exceeds venous diseases by about 50%. The mortality from arterial diseases is 3.5 times higher than the number of deaths from venous diseases in women below 30 years, and 8.5 times higher in women 30–44 years old. A significant disability is more frequent in women suffering and surviving an arterial complication than in women with venous thromboembolism.

Although many important scientific issues still have to be addressed, the available scientific data suggests a differential influence of OCs with second and third generation progestagens on the risk of venous and arterial diseases. OCs with second generation progestagens seem to confer a smaller increase in the risk of venous diseases and a higher increase in risk of arterial complications, compared with OCs containing third generation progestagens. The possible difference on the venous side seems to be smaller than primarily anticipated.

Results. Young women without any known risk factor for thrombotic diseases may use any low-dose OC. If OCs are prescribed to women with known risk factors for arterial thrombotic disease; e.g. smoking, diabetes, controlled hypertension, migraine without aura, family disposition of acute myocardial infarction (AMI) or thrombotic stroke, a low-dose pill with a third generation progestagen may have an advantage. If OCs are considered for women with risk factors for venous disease such as severe obesity, varicose veins, family history of VTE or with factor V Leiden mutation, a low-dose combined pill with a second generation progestagen may be preferable.

In women above 30 years, OCs with third generation progestagens generally seem to confer less overall thrombotic morbidity, mortality and disability than OCs with second generation progestagens. These women should reconsider, however, the indication of combined OCs in the presence of significant risk factors of thrombotic diseases.

Key words: cerebral thrombosis; disability; mortality; myocardial infarction; oral contraceptives; second generation progestagens; third generation progestagens; venous thromboembolism

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In late 1995 and early 1996, four independent epidemiological studies demonstrated an increased risk of venous thromboembolism (VTE) among current users of combined oral contraceptives

Abbreviations:
OCs: oral contraceptives; VTE: venous thromboembolism; AMI: acute myocardial infarction; CTA: cerebral thromboembolic attacks.

(OCs). These studies also demonstrated a differential risk between users of OCs with so-called second generation progestagens (*levonorgestrel ±norgestimate*) and users of OCs with third generation progestagens (*desogestrel* or *gestodene*) in favor of the former (1–7). Warnings against OCs with third generation progestagens had previously been sent out by the English health authorities already in October 1995, before any of these new studies were published. Soon thereafter warnings were also issued by the German and Norwegian authorities.

The first consequences were a decline in use of OCs in England (8), concern among millions of OC-users, and confusion among professionals concerning how to advise their clients. The next consequence was increasing abortion rates, especially in England. Small increases were seen also in Norway, Sweden and Finland (9–12).

During the two years that followed, the scientific debate continued, new studies were published, and professionals asked: what is the scientific evidence for a real difference between different types of OCs concerning the risk of VTE; are there also differences on the arterial side; what is the health impact of these figures; and how should we advise our patients? The aim of this survey is an attempt to answer these questions based on current knowledge.

The debate

Unfortunately, the debate soon became polarized and rather emotional. On the one hand, researchers in many countries were concerned about potential confounding bias in the conducted studies (7, 13–17), and were of the opinion that the warnings from the health authorities were premature. On the other hand, some of the authors of the original studies not only denied the possibility of any bias (18–20) but also accused other health authorities for not having reacted appropriately (19). It is apparent that consensus has not as yet been reached.

New studies and evaluation of bias and confounding

A summary of the original studies on OCs and VTE was briefly presented in this journal in 1996 (13). With further studies subsequently published, we have new possibilities of evaluating each of the potential confounding factors relevant for the primarily conducted studies.

Bias from length of OC use

It is now generally accepted that the risk of VTE in users of OCs decreases with length of use. Women who are genetically predisposed for VTE (e.g. women with resistance to activated protein C) and who develop VTE when using OCs stop taking the pill leaving a healthier group of users of OCs ('healthy user effect'). As users of OCs with the newer third generation progestagens generally have taken OCs for a shorter period compared with users of OCs with the older second generation progestagens (21), it is crucial to control for this bias in observational studies. In the primary report from the WHO study, it was stated that 'Duration of current episode of use and lifetime duration of use did not affect the risk estimates of VTE' (1). In a letter published two months later, the results were stratified in new current users and women who had previously used OCs according to length of current use (3). A clear decrease in risk of VTE by length of use was demonstrated in new users of OCs with second as well as third generation progestagens. The results from the stratified analysis, however, did not change the risk ratio between second and third generation OCs.

In one of the original four studies, no information on duration of OC use was present (4), and in another study the statistical power to adjust for length of OC use was too weak (5). In the primary publication from the Transnational study group, adjustment was made for 'duration of use of OCs before the current episode' (6). In a later analysis (7), the risk was associated with time in a similar way; the risk of specific product groups increased linearly by year of market introduction, suggesting the same kind of 'attrition of susceptibles' by length of use.

In an ongoing five-year Danish case-control study, a significant difference in the risk ratio of VTE between users of OCs with third vs. second generation progestagens, decreased by 20% and was no longer significant, after controlling for duration of OC use (22).

Duration of current use thus still seems to be an important effect modifier. The inadequate control for duration of use in the primarily published studies indicates that the risk estimates of third versus second generation pills most likely are overestimated in at least two of these studies. On the other hand, the new analyses demonstrate that this single confounding factor can hardly explain the whole difference demonstrated between OCs with second and third generation progestagens.

Prescribing bias

It has been empirically confirmed that new OCs with third generation progestagens are prescribed to women at an increased thrombotic risk more often than OCs with second generation progesta-

gens (21, 23). Women at an increased risk of VTE include women with APC-resistance, obesity, superficial varicose veins, and family history of VTE. In as far as all these potential confounders are adjusted for, prescribing bias is unlikely to play any important role. The problem is that none of the conducted studies did control for all these confounders at the same time. Another problem is that a sufficient confounder control demands a certain sample size in order to be statistically valid. The group of Vandenbroucke argues that as the four original studies together analyzed all these confounders, and did not find any significant confounding influence, 'the four studies overlap in their capacity to meet the criticisms' (20). This is, in our opinion, a simplification of the problem. The fact that one study does not find a *significant* influence from a potential confounder may, firstly, be due to a low statistical power, and secondly, it does not exclude an influence from that confounder in other studies. Duration of OC use is a good illustration of this fact.

Vandenbroucke et al. have argued that as knowledge of APC-resistance is of a much more recent date than the collection of the patients from the four studies, this predisposition could not have had any confounding influence (20). However, as women with APC-resistance will have a higher chance of having family members with VTE, a bias according to APC-resistance could easily be introduced without any knowledge about APC-resistance.

Only one of the four studies controlled for family history of VTE (4). Thus, in three of the four initial studies, this missing control may, and we repeat may, have overestimated the risk ratio between OCs with third and second generation progestagens. In the ongoing Danish study, this confounder was included, and the risk ratio (3rd versus 2nd) was lower than in the primarily published studies.

Thus prescribing bias is still an issue, and family VTE is not the only but probably the most important factor to control for in this respect.

Inverse dose-response relationship

In three studies, the highest risk of VTE was found for products with the lowest dose of ethinylestradiol (EE) (2, 7, 24). In the latter study by Farmer et al. (24), the risk of VTE among users of OCs with desogestrel+30 μg EE was identical with that of users of OCs with levonorgestrel. In this study, the increased risk among users of OCs with third generation progestagens relative to users of OCs with second generation progestagens was due solely to an increased risk among users of OCs with desogestrel+20 μg EE. So far, these paradoxical findings have not been explained satisfactorily, but they suggest some kind of selection bias, perhaps a combination of starter effect and prescribing bias.

Incidence studies

If OCs with third generation progestagens do imply a higher risk for VTE than use of OCs with second generation progestagens, a significant increase in the incidence rate of VTE among young non-pregnant women should have been expected with the introduction of the new pills. On the other hand, the dramatic reduction in use of OCs with third generation progestagens in the UK, Norway and Germany in late 1995 and early 1996, should have resulted in a significant decrease in VTE in the same age segment of women compared to 1994 and 1995 in these countries, even if the overall number of OC-users has been stable. Thus, trend analyses of incidence and mortality data during the period in which OCs with third generation progestagens came on the market may be useful in evaluating selection bias against a causal influence on VTE from different types of OCs.

No trend data on the incidence of VTE in young non-pregnant women has been published, and no data on the trend in England, Norway or Germany after the dramatic fall in use of OCs with third generation progestagens, have been published. In Norway, however, where nearly 50,000 women stopped taking third generation OCs during the last quarter of 1995, there was no major change in the incidence of VTE among non-pregnant women over the years 1994, 1995, and 1996 (National hospital discharge data, Skjeldestad, personal communication). In Denmark, no decrease in use of OCs with third generation progestagens has taken place during the last four years, and the incidence of VTE in young women there has also been stable (Lidegaard, personal communication).

Two analyses on VTE-mortality trends have been published. In The Netherlands, VTE mortality statistics in women and men 15–49 years old during the period 1980–1994 demonstrated a significant increase in VTE deaths in women, but not in men (25). However, the per cent increase among men was exactly as large as in women, but due to an absolute lower number of VTE deaths in men, their increase was not significant. Furthermore, no age stratification was performed, and pregnant women were not excluded. As oral contraceptives are used primarily by young women (below 30 years) and as VTE deaths in non-pregnant women 15–30 years account for only about 10% all VTE deaths in women 15–49 years, such an unstratified

analysis does not bring much information as to the influence of specific OC exposures in young women.

A more qualified analysis was done in England and Wales, in which the trend in VTE deaths during the period 1984–1992 among specifically young women 15–29 years old was analyzed (26). Pregnant women were not excluded. A significant increase in VTE deaths among young women but not among women 30–44 years or among men was demonstrated, suggesting an influence from the new third generation products.

A possible confounding aspect in trend analyses on the incidence and mortality data is the rather dramatic increase in age at first full term pregnancy and birth in women all over the industrialized world. As pregnancy accounts for about one third of all VTE in young women, and as the incidence rate of VTE increases with increasing age, statistics without exclusion of pregnant women are expected to demonstrate an increase in VTE in young women by time even without any influence from OCs. Such an increase of 150% in VTE among pregnant women was actually demonstrated in Denmark during the period 1984–1994 (27). Therefore, any trend analysis on the influence of OCs has to exclude pregnant women in order to exclude the increase in VTE among pregnant women.

In conclusion, no incidence data on VTE among young non-pregnant women have been published, and the sparse data on trends in VTE deaths are too unspecific to provide any support or repute a causal difference in risk of VTE between OCs with second and third generation progestagens, respectively.

Biological plausibility

In early 1997, Rosing et al. (28) published a metabolic study which demonstrated a different influence on the sensitivity to activated protein C in women using OCs with second and third generation progestagens. Although no molecular mechanism was suggested for these findings, this is the first of many metabolic studies, indicating not only a different influence from these two products, but also suggesting a possible explanation for some of the epidemiological findings. According to this study, the decrease in sensitivity to activated protein C in women heterozygote for a factor V mutation corresponded to the decrease in women with no mutation during the use of a third generation pill.

We find this new insight into the coagulation mechanisms interesting, but we have to await confirmation from other studies before any decisive conclusion can be drawn. Future studies should include more specifications concerning the precise methodological and laboratory circumstances applied to achieve these results. We are far from a full biochemical understanding of the course of events in women developing VTE, but the new results encourage further analyses of possible biological mechanisms.

Conclusion on OCs and VTE

At present (May 1998), the majority of epidemiological studies have demonstrated differences in risk for VTE between OCs with second and third generation progestagens. None of the studies have been able to fully control or adjust for bias, but the difference is smaller in the new studies compared to the primary reports, probably due to residual confounding in the latter (29). A real difference in the risk of VTE between users of OCs with third versus second generation progestagens is with the available data, nevertheless, possible, perhaps even probable. The absolute risk of VTE in young women is low (about 1/10,000 women years), and the VTE risk estimates of OCs in general are not higher than previously reported.

Arterial thrombosis

In evaluating specific types of OCs, it is obviously not sufficient to look only at a single rare side effect such as VTE. For Health authorities, and doctors concerned with prescribing OCs, it is crucial to include other relevant risks and benefits.

Oral contraceptives and myocardial infarction

Four independent studies have now suggested a differential risk of myocardial infarction (AMI) in users of OCs with second and third generation progestagens, respectively (30–34). In the Transnational study, the risk was four times higher in users of OCs with second compared with third generation progestagens (30). The same tendency was found in the other three studies (32-34), but the difference was not statistically significant in contrast to the findings in the Transnational study.

Although selection bias may be in effect in these studies, the primary problem is the small sample size and risk of type 2 error in three of the four studies (32–34). It is important to realise that any residual confounding in these studies tends to overestimate the risk of OCs with third generation progestagens and underestimate the risk of second generation products due to the same preferential prescribing as described for VTE. In other words,

the difference in favor of OCs with third generation OCs might be even higher than suggested in the available studies.

Oral contraceptives and thrombotic stroke

Six recent studies have been published with data on the influence of low-dose OCs on the risk of thrombotic strokes (35–39).

In the WHO-study (35), in Europe, second and third generation OCs implied odds ratio's (ORs) of thrombotic strokes of 1.5 (0.7–3.4) and 1.8 (0.3–9.4) respectively. In the developing countries, third generation OCs had an OR of 1.2 (0.2–5.9) compared with an OR of 3.4 (2.2–5.1) for second generation products when compared with non-users of OCs. These differences were not statistically significant. The statistical power of the WHO-study to detect any difference between second and third generation products was, however, low.

With 45 current users of OCs with third generation progestagens among cases, the statistical power in the Transnational study (36) was higher. The risk estimates were, however, about twice as high with hospital controls than with community controls 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 controls as reference was close to the results from an ongoing Danish study which found a risk estimate of 2.4 (1.4–4.2) (37). 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). The higher risk of thrombotic stroke among users of OCs with second as compared with third generation progestagens in the Danish study was significant.

In the studies of Petitti et al. (38) and Schwartz et al. (39) none had taken third generation OCs. Thus the overall risk estimate of ischemic stroke of 1.2 (0.5–2.6) and 1.4 (0.5–3.8), respectively, primarily reflects the risk among users of OCs with first and second generation progestagens.

Further data are necessary to clarify whether there is a difference in risk of thrombotic stroke between users of OCs with second and third generation progestagens. However, the results on AMI and thrombotic stroke together indicate that a real difference concerning arterial thrombotic complications in general may exist between these two types of progestagens.

Health impact

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

* age specific incidence rates of each disease,
* age specific mortality rates of each disease,
* the proportion of disabled women for each disease,
* the relative risk of each disease among users of specific types of OCs as compared with that of non-users of OCs.

Incidence and mortality rates of thrombotic diseases in young women

In 1977, a National Patient Register (NPR) was established in Denmark. Since then, this register has recorded all discharges at all Danish hospitals including information about specific discharge diagnoses coded according to the WHO interna-

Table I. Thrombotic diseases in young women in Denmark 1980–1993[40]. CTA=cerebral thromboembolic attacks, AMI=myocardial infarction, VTE=venous thromboembolism

Denmark 1980–93	CTA[1] All	AMI All	VTE[2] All	VTE non-preg	Ratio[3] arterial/venous
15–29 years					
Incidence per million years	46[4]	6.2	170	108	0.5
Mortality per million years	1.0	1.1	1.1	0.6[5]	3.5
Case fatality rate	2.2%	18%	0.6%	0.6%	–
30–44 years					
Incidence per million years	222[4]	114	270	231	1.5
Mortality per million years	5.1	28.7	4.4	4.0[5]	8.5
Case fatality rate	2.3%	25%	1.7%	1.7%	–

[1] CTA=thrombotic strokes+transitory cerebral ischemic attacks (TIA).
[2] VTE=deep venous thrombosis+pulmonary embolism.
[3] Ratio among non-pregnant women.
[4] Incidence figures for CTA 1987–1993.
[5] In the calculation of the death rates of VTE in non-pregnant women, it was anticipated that the proportion of pregnant women among the VTE-deaths corresponded to the proportion of pregnant women in women with non-fatal VTE.

tional classification of diseases. During the period 1980–1993, the WHO ICD-8 was used in Denmark, and from January 1, 1994 the ICD-10 replaced the ICD-8 codes.

An analysis was made on data from the NPR covering the period 1980–1993 including the relevant diagnoses (40). The age-specific incidence rates of cerebral thromboembolic attacks (CTA), AMI and VTE are indicated in Table I. As a significant proportion of young women with VTE were pregnant, the figures for non-pregnant women with VTE are indicated as well. Among women with AMI and CTA, the proportion of pregnant women was less than 1% and about 5%, respectively.

From the Danish Death Statistics (published annually by the Danish National Board of Health), we also obtained age-specific death rates of these diseases, also indicated in Table I. In the calculation of the death rates of VTE in non-pregnant women, it was anticipated that the proportion of pregnant women among the VTE-deaths was 36.5% in women below 30 years, and 14.5% in women 30–44 years old, corresponding the proportion of pregnancy in women with non-fatal VTE.

It appears from Table I that all three diseases increase by increasing age, the arterial diseases more than the venous diseases. Furthermore, the morbidity among women below 30 years is very low for all the considered diseases. The number of venous complications are about twice as common as the arterial diseases in women 15–29 years, whereas the number of arterial complications exceeds the venous diseases in women 30–44 years by about 50%.

The mortality is generally low among women with CTA (2–2.5%) and VTE (0.6–1.7%), compared with a significant case-fatality rate among women with AMI (18–25%). The mortality from arterial diseases was 3.5 times higher than the number of deaths from venous diseases in women below 30 years, and 8.5 times higher in women 30–44 years old.

The proportion of disabled women who survive a thrombotic disease is generally higher and more severe after arterial thrombosis than after venous thromboembolism. Although venous diseases are more frequent in young women, the health impact of the arterial diseases is generally higher than the clinical consequences after venous diseases.

The influence of OCs on incidence and mortality of thrombotic diseases

The WHO has recently published a report assessing the (at Oct. 1997) available epidemiological data on the influence of different types of OCs on different thrombotic diseases (41). The report concludes that the incidence of all thrombotic diseases in young women is low, that OCs in general increase the risk of VTE, and that OCs with third generation progestagens probably carry a small risk of VTE beyond that attributable to OCs with second generation progestagens. For AMI that the suggestion that users of OCs with third generation progestagens may have a lower risk than users of OCs with second generation progestagens remains to be substantiated, and for thrombotic stroke that further data on thrombotic stroke are necessary to make any firm conclusion as to the influence of different types of OCs on this disease.

For women below 30 years, we find empirical support for the conclusion that use of OCs with third generation progestagens may imply a higher risk of VTE but a lower risk of thrombotic deaths and thrombotic disability than use of OCs with second generation OCs. For women between 30 and 45 years in general, thrombotic morbidity, mortality and disability seem all to be lower in users of third generation OCs than in users of second generation OCs.

Clinical guidelines

Prescribing OCs should generally be based upon an integrated evaluation of need, wish from client, individual risk factors including age, as well as non contraceptive benefits and risks for the woman. Therefore general guidelines often do not make much sense. Looking only on thrombotic diseases and combined OCs, our tentative advice is as follows:

* Women without any known risk factor for thrombotic diseases may take any low-dose OCs. In women above 30 years, however, OCs with third generation progestagens seem to confer less overall thrombotic morbidity, mortality and disability than OCs with second generation progestagens.
* If OCs are prescribed to women with a risk factor for arterial thrombotic diseases (smoking, diabetes, controlled hypertension, migraine without aura, family disposition for AMI or thrombotic stroke) a low-dose pill with a third generation progestagen seems to be preferable. The woman should be informed about the relative and absolute risk of thrombosis by taking OCs.
* If OCs are decided for women with a risk factor for venous diseases (severe obesity, varicose veins, family history of VTE or with factor V Leiden mutation) a low-dose pill with a second generation progestagen seems to be preferable in

women below 30 years, whereas in women above 30 years any low-dose pill may be chosen. The woman should be informed about the relative and absolute risk of thrombosis by taking OCs.

* Women with severe hypertension, migraine with aura, antithrombin III deficiencies, who are homozygote for Leiden factor V mutation, who have had previous thrombotic diseases, or with combined risk factors should not take combined OCs.
* Women with family history of VTE (parents or siblings) should be screened for factor V mutations before OCs are prescribed.

What did we learn

From the primary and secondary published epidemiological data, the actions taken from health authorities, the scientific debate that followed, the public reaction, and the increasing abortion rates, we have learnt:

* That a single aspect in the evaluation of drugs with many metabolic and clinical benefits and risks is scientifically insufficient for general clinical recommendations.
* General recommendations have to be based on fully elaborated scientific data, and should include an overall consideration of benefits and risks. For OCs such an evaluation usually demands a coordinated work by epidemiologists and gynecologists.
* Relative risks have to be considered together with absolute risks.
* Epidemiological studies are crucial in the continuous evaluation of drug safety aspects, but in the interpretation of the results, a careful evaluation of the effect of bias and confounding is important.

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