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The pill

The controversy continues

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Oral contraceptives (OC) are, or perhaps more correctly, were, until recently, being taken by approximately 65 million women worldwide, which corresponds to approximately 6% of all women of reproductive age. OCs have been available since the early 1960s and there is substantial evidence to suggest that no single medication has had such a profound impact on our reproduction and social life as the pill. In the Scandinavian countries, 30–50% of young women have been reported to be using OCs. Its widespread use here and elsewhere throughout the world for several decades indicates that women and their doctors have considered that the benefits of OCs outweigh potential side-effects.

On October 18th, 1995, the Committee on Safety of Medicines in the United Kingdom sent a warning to all British doctors and pharmacists about OCs containing desogestrel (Marvelon®/Desolett® and Mercilon®) or gestodene (Gynera®, Milvane®, Minulet® and Tri-minulet®). A similar warning was subsequently distributed by the German and Norwegian health authorities. As these OC types dominate the market in Northern Europe, many gynecologists, general practitioners, women of reproductive age, different national bodies on drug safety, and people in general have been asking:

- What was the background for these actions?
- How do we interpret the new studies?
- What do we do now concerning the prescription of OCs?
- What is the moral of this story?

Background

The decision to distribute the 'Dear doctor letter' was based on information obtained from three as yet unpublished epidemiological studies. Two of the studies, together with a fourth study from Leiden were published in The Lancet on December 16th, 1995 (1–4). The third study, the so-called 'Transnational study' by Spitzer et al. is still (December 1995) unpublished.

All four studies:

- are epidemiological studies;
- have investigated the influence of different types of OC on the risk of developing deep venous thrombosis (DVT) and pulmonary embolism (PE). (DVT and PE are collectively called *v*enous *t*hrombo*e*mbolism or VTE);
- have found that users of OC containing the third generation progestagens *desogestrel, gestodene* (and in one study *norgestimate*) have a higher risk of non-fatal VTE than users of OC with the second generation progestagen *levonorgestrel* and *norgestrel.*

Other epidemiological key points on the three published studies are given in Table I and are summarized briefly below.

WHO-study[1,2]

This is a multinational case-control study and the majority of cases were collected in third world countries. OCs with third generation progestagens

Table I. Three published studies on DVT/PE and oral contraceptives. Design, material and main results

Study Primary investigator[ref]	WHO-study Farley[1,2]	Leiden study Bloemenkamp[3]	GPR database Jick[4]
Design	Case-control	Case-control	Cohort
Data sampling	1989–1993	1988–1992	1991–1994
Centres involved	21	1	365 practice
Countries involved	17, Global	Netherlands	England
Results			
DVT/PE† Cases total	1,143	126	80‡
Cases/contr.§ (n)	174/235	126/159	75/300
OR all OC	4.2¶	–	–
85% CI	3.1–5.6	–	–
OR second generation*	3.6¶	3.8¶	1* ref
95% CI	2.5–5.1	1.7–8.4	–
OR third generation□	7.4¶	8.7¶	2.2*
95% CI	4.2–12.9	3.9–19.3	1.1–4.4
Confounder control''			
Age	+	+	+
Previous thrombosis	+	+	+
Familial disposition	–	+	–
Body mass index	(+)	–	+
Varicose veins	(+)	–	–
Referral bias	–	–	–
Diagnostic bias	(+)	–	–
Prescribing bias	–	–	–
Switching bias	–	–	–
Length of use biasß	+	–	–

† DVT = deep venous thrombosis, PE = pulmonary embolism
‡ Case-control design in the cohort (nested case-control analysis)
§ Cases and controls involved in the actual analysis
* Second generation OC: OC with levonorgestrel/norgestrel
□ Third generation OC: OC with desogestrel, gestodene or norgestimate
¶ Odds ratio compared with non-users (never users + ex-users of OC)
ß In this study users of OC with third generation progestagens are compared with users of OC with second generation progestagens.
'' – indicates control, (+) indicates insufficient control-indicates no control

were only used in a minority of the centers. The overall odds ratio (OR) (which is a good approximation to relative risk for rare diseases) for VTE among users of OC compared with non-users was 4.2 (95% CI 3.1–5.6). That figure is a little less than previously published figures on the OC-associated risks of VTE. This study did not find any consistent relation between VTE risk and the dose of ethinylestradiol (EE). However, OCs with second generation progestagens generated an OR of 3.6 (2.5–5.1) compared with non-users of OC while the OR for third generation progestagens was 7.4 (4.2–12.9).

Body mass index above 30 kg/m^2 (OR 2.7), previous hypertension during pregnancy (OR = 1.7) and varicose veins (OR = 2.7) were all significant risk factors. Adjustment in some centers for some of these risk factors did not significantly change the calculated odds ratios for different OC groups. No control was made concerning family disposition of VTE as no information about that disease was available. Family AMI or stroke were not risk factors of VTE. Correction for family AMI or stroke was without significance for the OC-associated VTE risk.

The Leiden study[3]

The new study, which was not available to the English, German and Norwegian health authorities at the time the warning letters were distributed, is a case-control study from The Netherlands. The study was conducted during 1988–1992 and includes 126 verified cases of DVT and 159 age-matched 'healthy' controls. OC with gestodene or norgestimate were used by so few women that they were excluded from the analysis. Compared with non-users of OC, women on second generation progestagens (levonorgestrel) had an odds ratio for DVT of 3.8 (1.7–8.4) and users of desogestrel an odds ratio of 8.7 (3.9–19.3), when combined (in both groups) with 30 μg EE. The investigators found a family history of *DVT* to be a significant risk factor of DVT (OR 2.9 (1.6–5.1)). Control for that risk factor, however, did not change the calculated odds ratios for second and third generation products. No control was performed concerning body mass index, varicose veins or duration of use.

The GPRD study[4]

This study is based on reports from 365 general practices in England and is a non-randomized cohort study. Jick et al. performed a specific analysis on all non-fatal VTE cases associated with the use of OCs containing levonorgestrel, desogestrel, or gestodene during the period January 1991 – November 1994. A total of 80 cases of DVT were reported, corresponding to an absolute risk of DVT among users of levonorgestrel of 1.6/10,000/year, of 2.9/10,000/year among users of desogestrel and of 2.8/10,000/year for users of OC with gestodene. These absolute risks are generally lower than previously reported. In order to control for age, smoking and body mass index, 75 of these cases were matched with 300 healthy OC-users from the same database. Compared with users of levonorgestrel, users of desogestrel and gestodene containing OC had an odds ratio for VTE of 2.2 (1.1–4.4) and 2.1 (1.0–4.4) respectively. No control was made for family disposition, varicose veins, or length of OC use.

They also analyzed 15 fatal thromboembolic complications (eight after levonorgestrel use, two after desogestrel use and five after gestodene use). Relative risk compared with levonorgestrel was found to be 0.4 (0.1–2.1) for OC with desogestrel and 1.4 (0.5–4.5) for OC with gestodene. These differences were not statistically significant.

Interpretation of the new results

All three (four including the unpublished transnational study) are independent studies of acceptable size and consequently provide reasonable statistical power for crude analysis. As all three studies appear to provide valid diagnoses and valid information about specific OC exposition, there is no sound reason to doubt that VTE occurs more often among users of third generation progestagens compared with users of second generation progestagens. However, as has been emphasized many times before, such a significant association is not the same as a proven causal relationship. It is therefore extremely important to discuss the interpretation and implications of these new findings and in particular how to interpret the differences between users of second and third generation progestagens.

In principle two explanations of these findings are possible. They may indicate a true causal relationship or they may be a consequence of some kind of selection bias. Before evaluating these two explanations we have to consider the documented risk factors of VTE.

Risk factors for VTE

Documented risk factors are a body mass index above 30kg/m^2, parents or siblings with VTE, hypertension in pregnancy and varicose veins. Some, but not all, have found an increased risk among short-time users of OC (5–7). Generally, some other well-established risk factors for arterial thrombosis such as smoking, hypertension, diabetes, family AMI or stroke and migraine do not seem to play any significant role on the venous side.

Circumstances supporting a causal relationship:

- The correlations were statistically significant in all three studies, and the results are very similar. However, this similarity could also indicate the presence of the same confounding factors in all three studies.
- Confounder control was performed to some extent, according to some known risk factors (Table I), and these adjustments had only little influence on the calculated odds ratios.

Circumstances which raise doubts concerning a causal relationship:

- In many, if not all, countries the new pills with third generation progestagens have been marketed as safer than the older pills, specifically concerning thrombotic events. Therefore, many gynecologists and general practitioners have prescribed these new pills to women at an anticipated increased thrombotic risk. This type of selection in prescribing OC implies a potential bias in non-randomized epidemiological studies, and is called '*prescribing bias*' or '*preferential prescribing*'.

  The following factors should be taken into account when considering confounder control for OCs and VTE; body mass index, family disposition of specifically VTE, varicose veins and if possible also for hypertension during pregnancy and duration of OC use. None of the three published studies performed an adequate control for the majority of these confounders (Table I). In fact, only few of these confounders were considered in each study.
- A large proportion of women with VTE in England (more than two thirds!) are treated outside hospitals (as opposed to the situation in Scandinavia). If women on the pill are more likely referred to hospital than non-users (*referral bias*), this would not only incur an overestimation of the OC-associated risk in general, but may also influence the difference between second and third generation users if third generation users are more likely to be referred to hospital than second generation users. Users of third generation OC have generally used OC for a shorter period than users of second generation pills. If DVT occurring shortly after start of OC have a higher probability of being referred to hospital than DVT attacks after several years of OC use, that circumstance could artifically increase the risk of third compared to second generation products.
- Women taking OC may have been more prone to being subjected to diagnostic investigations when presenting with symptoms of DVT so that '*diagnosis bias*' may have had the same consequence as '*referral bias*'. None of the studies evaluated that possibility, although no significant differences were found between different categories of validity concerning the VTE diagnoses in the WHO study.
- If women who have experienced different kinds of side-effects associated with OC use, such as headache, weight gain, dizziness, have systematically been shifted to newer OC with third generation progestagens (which has probably been the case), then this selection would also bring about a potential bias, as such women probably are more prone to thrombotic complications than other women (*switching bias*).
- The new results demonstrate a decreased risk of VTE for a product which has not been changed (levonorgestrel with 30 μg EE) rather than an increased risk for the desogestrel/gestodene

products. This circumstance supports an alternative selection of users of second generation products. It should be noted that the relative risk of VTE for the desogestrel-containing products were generally in line with risk indications for second generation products 10–15 years ago when they were new (8).

- We have *no plausible biological explanation* for a higher risk of VTE for third compared with second generation progestagens. On the contrary, metabolic studies have suggested a lower risk for third generation progestagens compared with older products.
- *No increase in the occurrence of VTE* among young women has been demonstrated during the period in which the majority of OC users shifted from second to third generation progestagens. Such an increase would be expected if third generation progestagen pills imply twice the risk of VTE than second generation pills.

Conclusion concerning a causal relationship versus selection bias

Until further epidemiological data is available, it is reasonable to conclude that some of the difference, and possibly the whole difference, between second and third generation progestagens found in these three published studies may be explained by selection bias, in particular prescribing bias. The basic problem is, however, whether new studies will be able to control for prescribing bias. One problem is the identification of risk factors for VTE and another practical problem is the fact that some women, for some not very conscious reasons, are recommended a new pill 'just for safety'. All clinically working physicians know that such intuition may play an important role in the choice of the type of OC being prescribed.

On the other hand at present, we cannot prove that the new results are due primarily to bias and we therefore have to accept the possibility of a causal influence of third versus second generation pills on VTE risk.

What do we do now concerning prescribing of OC?

When recommending specific types of oral contraceptives it is necessary to consider other (more important) risks as well as benefits. Concerning thrombotic risks, the priority according to severity among the affected women and according to frequency should be: cerebral thrombosis, myocardial infarction, pulmonary embolism and DVT. We have so far some unpublished evidence that no difference exists between the different progestagen types concerning stroke risk, which is primarily influenced by the EE dose (9, 10). We have also indications of a decreased risk of AMI (although not significantly so) among users of third compared with second generation progestagens. These preliminary reports have to be published and evaluated, in order to permit an empirical and balanced support for general recommendations.

Those who are convinced that the new studies reflect a causal influence of third versus second generation pills may consider recommending women who are at an increased risk of specifically VTE (body mass index >30 kg/m^2, varicose veins or family with specifically VTE) a second generation product.

On the other hand, women with arterial thrombotic dispositions (smokers, family AMI or stroke) probably should still be advised to take a low estrogen OC containing a third generation progestagen product. Thus, the majority of women will be able to continue with the product they are already using.

Moral for future actions

- General recommendations have to be based on published scientific data, knowledge about the clinical reality, and include an overall consideration of benefits and risks. Such an evaluation usually demands a coordinated effort by epidemiologists and gynecologists.
- Relative risks have to be considered together with absolute risks.
- Intensified epidemiological research is necessary in order to clarify the impact of type-specific OC and of user characteristics on the risk of different types of cardiovascular diseases.
- Premature actions from health authorities may not only damage the possibility of performing a reasonable choice of OC type among our contraceptive users, but may also destroy the possibility of obtaining the scientific data we still need in order to ensure empirical support for our professional statements.

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