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Third-generation oral contraceptive and deep venous thrombosis: From epidemiologic controversy to new insight in coagulation

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Four epidemiologic studies showed a twofold increase in risk of deep venous thrombosis with the use of oral contraceptives containing third-generation progestins, relative to second-generation products. These findings have been strongly debated ever since, and new studies have been added. In the current article we examine whether the findings can be explained by potential biases or other shortcomings of the epidemiologic studies. We conclude that complete certainty cannot exist but that the most rational conclusion from the epidemiologic findings and their discussion is that an increased risk of deep venous thrombosis with third generation contraceptives is likely, especially in first time and young users. The controversy has recently led to new insights in coagulation. Women who use third-generation contraceptives acquire a resistance to the blood's own anticoagulation system, similar to the activated protein C resistance that is seen in persons who carry the factor V Leiden mutation but different from that in women using second-generation contraceptives. (*Am J Obstet Gynecol* 1997,177:887-91)

Key words: Oral contraceptives, venous thromboembolism, thrombosis, gestodene, desogestrel, norgestimate, levonorgestrel, epidemiology, bias, factor V Leiden, activated protein C resistance (APC resistance)

In December 1995 and January 1996, four epidemiologic studies were published, showing that the risk of deep venous thrombosis with "third generation contraceptives" is two times higher than with second generation pills.¹⁻⁴ The major third-generation contraceptives contain 30 µg ethinyl estradiol, in combination with desogestrel or gestodene. The latter formulations are derivatives of levonorgestrel, the main second-generation progestin. Another derivative, norgestimate, is difficult to classify because it is partially metabolized to levonorgestrel and partially to other intermediates. Very low-dose pills containing a third generation progestin in combination with 20 µg ethinyl estradiol were also introduced. In the United States third-generation contraceptives contain desogestrel or norgestimate, in Europe they also contain gestodene.

The studies

The original finding of an elevated venous thrombosis risk with third generation contraceptives was in a worldwide case control study on the side effects of oral contraceptives by the World Health Organization (WHO)⁵, the evidence on third- versus second-generation contraceptives was found in the analysis of the European subset of the study and was based on 769 cases, 1979 hospital controls, and 246 community controls. The relative risk for venous thrombosis among users of third generation contraceptives in comparison with second-generation users was 2.6, in comparison with nonusers the relative risk was 9.1. These unexpected findings were confirmed by a cohort analysis and a nested case-control study in the United Kingdom General Practice Research Data-base (UK-GPRD), based on 80 cases of nonfatal venous thrombosis among 238,130 otherwise healthy women. The relative risks of the third-generation products relative to those of second generation ones were 1.8 and 1.9 in the cohort analysis and 2.2 and 2.1 in the nested case-control analysis. A second confirmation came from the reanalysis of a Dutch case-control study, originally set up to study hereditary risk factors in venous thrombosis. 126 women with venous thrombosis and 159 controls yielded a relative risk of 2.5 for the desogestrel-containing third-generation contraceptive relative to the second-genera-

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tion one and an overall relative risk of 8.7 relative to nonusers. A third confirmation came from an industry-sponsored case-control study across Europe, the Transnational study, with a protocol that was very close to that of the WHO study, in which 471 cases and 1772 controls yielded a relative risk of 1.5 for third-generation products in comparison with a mix of other products.

The risks

The baseline incidence of deep venous thrombosis among young women who do not use oral contraception is between 0.5 and 1 per 10,000 per year¹⁻³; this is increased threefold to fourfold by second-generation contraceptives⁵ and, according to the four studies, another two times by third-generation contraception. In comparison with that of nonusers, the overall risk of third-generation contraceptive users might be increased eightfold. The case fatality rate of venous thrombosis is between 1% and 2% in young persons.⁶ The absolute risks are small. However, the first question is whether the observation that third-generation contraceptives increase the risk of venous thrombosis more than second-generation products is valid.

The biases

The publications were followed by a large correspondence and a series of other publications pointing at possible biases in the four studies (see our acknowledgment at the end of the article). The central argument was that the size of the relative risk of third- versus second-generation contraceptives, a twofold increase of venous thrombosis, is in a range that makes it susceptible to bias. Similarly, it was argued that the remarkable consistency of four studies across Europe, with different protocols and different funding arrangements, all finding an elevated risk of third-generation contraceptives, has little meaning in itself: They all might have been biased in the same way. When such arguments are used, however, it is necessary to specify the biases—to examine whether they can in effect be operating and what evidence we need to answer them.

“Starter” and “healthy user” bias. The first objection is that venous thrombosis associated with third-generation contraception would occur mainly in young first-time users who have started contraception with the newer pills. Among these new users are women who are susceptible to the thrombogenic effects of contraceptives because they have never been “challenged.” In contrast, second-generation pill users are represented mainly by women who have already used oral contraceptives for a long time and who have never had thrombosis; therefore they have stayed with their trusted brand. They are the “healthy users.”

If this theory is true, the difference between third- and second-generation products should disappear when we

look separately at first venous thrombosis in new users. This was possible in three studies; the effect did not disappear. In the Transnational study a separate analysis for first-time users yielded a relative risk of third- versus second-generation pills of 2.7; for continued use the relative risk was 1.4.⁴ In the UK-GPRD the relative risk of thrombosis for third-generation versus second-generation products during the first 6 months of use was 9.2 for desogestrel and 5.6 for gestodene; after that time it became 1.8.² In the WHO study the overall relative risk in first-time users of third- versus second-generation pills was 5.4, which lowered to 2.4 thereafter.¹ Similarly elevated risks in new users were found in two new studies: a case-control study from Denmark and a pharmacoepidemiologic linkage study in The Netherlands.^{7,8}

The WHO investigators provided an additional cross tabulation for type of oral contraceptive, for the first year of use, and for new users separately.⁹ Whereas the risk was always higher in the first year of use among new users, the relative distance between third- and second-generation products remained about twofold. (Relative to nonusers the risk among new users during the first year of use was twentyfold for third-generation contraceptives, which lowered to tenfold afterward. For second-generation contraceptives the relative risk was ninefold for first year of use among new users, which lowered to twofold to threefold afterward.) This shows that there might indeed be a “starter” effect but also that this effect is stronger for third-generation contraceptives. Because the analysis is now separate for new and recent users, “likes” are compared with “likes,” and there is no more room for this bias.

The “recency of introduction” bias. A reanalysis of a subset of the Transnational study showed that the relative risks of deep venous thrombosis are higher for recently introduced contraceptives.¹⁰ The authors called this phenomenon the “attrition of susceptibles.” It is the same as the “starter” and “healthy user” bias, and the problem was solved in the above-described analyses. In addition, this finding in the Transnational study only held for one age category (containing only about half of the cases in the study); close examination of the published data in subsequent correspondence has shown that the trend with recency of introduction did not exist among the youngest users (see our acknowledgment at the end of the article).

“Prescribing” bias. The second objection is that third-generation products were preferentially prescribed to women at high risk for venous thrombosis. When examining this argument, we should specify what could make a physician predict that a young woman who has never had a venous thrombosis previously has a higher risk for venous thrombosis.

Textbooks on venous thrombosis offer very few clinical risk factors that predict the occurrence of a first venous

thrombosis in healthy young persons (see our acknowledgment at the end of the article) The status of superficial varicose veins as a risk factor for deep venous thrombosis is debated¹¹, they lead mainly to superficial thrombosis Superficial varicose veins may result from an earlier venous thrombosis, but women with an earlier thrombosis were excluded from all studies Obesity is a weak risk factor, except for gross obesity (which is infrequent in young first-time users) Contrary to widespread belief, smoking is not a risk factor for venous thrombosis (in contrast to arterial thrombosis) A clear risk factor for venous thrombosis is family history, in particular, when coupled with the factor V Leiden mutation³ Knowledge about this genetic risk is of a much more recent date than the collection of the patients for the studies All risk factors that are likely to have been screened for at first prescription of the oral contraceptive, such as smoking, hypertension, alcohol use, serum cholesterol, familial cardiovascular disease, diabetes, and others, are risk factors for arterial, not venous, thrombosis

A Dutch pharmacoepidemiologic linkage study showed that women who use other cardiovascular medication, for example, oral anticoagulation, use third-generation contraceptives more often⁸ Third-generation contraceptives would have been prescribed to women who had been barred from second-generation pills in the past, because the newer pills were perceived as safer This putative extension of prescription to women with contraindications concerns risk factors for arterial thrombosis and not for venous thrombosis In the case of oral anticoagulation this medication will have been started because of an episode of venous thrombosis or another medical indication This could never have biased any of the four studies, because all studies were limited to first thrombosis and women who were on a regimen of anticoagulation would have been excluded

In the WHO study, as well as the Transnational study, which adhered to the same protocol, and in the UK-GPRD study all women with major disease leading to prolonged immobilization were excluded Whereas there might have been women in these studies whose prescription of third-generation contraceptives was one of the recent extensions, at maximum, this might have included some with mild hypertension, hypercholesterolemia, or mild diabetes, which in the early uncomplicated stages are not risk factors for venous thrombosis Risk factors that were not excluded, such as venous thrombosis after trauma or elective surgery in a young women, are unpredictable at the time of prescribing oral contraceptives

There are also "utilization studies" in which doctors have been asked what pill they would consider in different risk circumstances (see our acknowledgment at the end of the article) Doctors have answered that in known risk situations they would prescribe the pill that is perceived to be safest When a comparison was made with their actual practice, they adhered less to their ideal

behavior,¹² which is a common finding in studies about the quality of actual medical care The studies showed that doctors are very often "blanket prescribers"

Although the "selective prescription" argument seems tenuous, because it is unlikely that a routinely prescribing physician can predict whether a first venous thrombosis will develop in a healthy young woman, the influence of several risk factors was assessed in the four studies Analyses were published with and without stratification for age and for all putative risk factors, alone or in several combinations—obesity, family history of venous thrombosis, factor V Leiden mutation, superficial varicose veins, previous pregnancies, hypertension during pregnancy, smoking, and alcohol use The relative risk of third- versus second-generation products always remained increased¹⁴ The four studies overlap in their capacity to meet the criticisms All known biases and confounders, except family history of thrombosis, have been addressed by the WHO study Family history was addressed in the Leiden study

The 20 µg and the norgestimate objection. In several studies the highest risk was found for the most recently introduced third-generation contraceptive containing only 20 µg ethinyl estradiol^{1 10 13} Although the numbers are small, this has been brought as evidence for selective prescribing, because it is illogical to find the highest risk with the lowest-dose pills A study based on the MediPlus database in Britain, on 83 cases and a total of 202,517 woman years, found an overall relative risk of third-generation versus second-generation contraceptives of 1.7¹³ On subgroup analysis in a nested case-control study with close age matching, only the relative risk of the 20 µg product remained elevated It was argued that the age pattern for prescription of this contraceptive was different The study was criticized in subsequent correspondence for including unverified cases and because the original studies retained their original relative risks also after reanalysis with closer age matching (see our acknowledgment at the end of the article) A possible explanation of the unexpected finding of the highest risk with the 20 µg product is a combination of a "starter effect" with a third-generation effect The very high relative risks associated with this contraceptive correspond with the risk in the first year of use among new and recent users of third-generation contraceptives in the WHO study⁹

A similar objection has been made about the norgestimate-containing contraceptive that is difficult to classify as second or third generation The extent to which it is metabolized to the second-generation levonorgestrel is reported differently (see our acknowledgment at the end of the article) It has metabolic effects (on high-density lipoprotein and anticoagulation) that are similar to the other third-generation products It has also been introduced recently

“Diagnostic” and “referral” bias. A third objection is that all studies might have overestimated the risk of contraceptives because of a bias toward the diagnosis of venous thrombosis in women who use oral contraceptives.¹⁴ If the association between oral contraceptives and venous thrombosis would largely be a matter of diagnostic bias, then we would expect that the association would disappear, or be much diminished, among those cases in which the diagnosis is so obvious that one does not need the clue of oral contraceptive use to make the diagnosis. Inversely, the association would be stronger in cases in which the diagnosis is uncertain, because the additional information on oral contraceptive use might have led to the diagnosis. This has never been shown true.^{15, 16} In two of the recent studies a separate analysis was made for cases with definite and probable diagnoses. The increased risk of third- versus second-generation contraceptives remained at 2.6 and 2.8 for the WHO study and at 2.2 and 2.2 for the UK-GPRD study.^{1, 2}

The incidence problem. Another argument is that the newer studies have shown only a lower frequency of thrombosis among second-generation users, instead of a higher one among third-generation users.¹⁴ Comparisons are made with older studies that showed higher frequencies of thrombosis. This disregards the diagnostic problems of venous thrombosis. The best comparisons remain those within the same study, because the same diagnostic criteria have been used, all studies are internally consistent in showing the increased risk.

Time trends. It was argued that an increase in the overall incidence of venous thromboembolism has never been demonstrated among young women, whereas such an increase would have been expected if third-generation contraceptives really carried twice the risk.¹⁴ This contradiction does not exist, because there has been an increase in venous thrombosis-related mortality among young women in the United Kingdom and in The Netherlands.^{17, 18} Moreover, it was found that among younger women the risk of fatal venous thrombosis is higher than the risk of death from myocardial infarction. This information, which was debated in subsequent correspondence (see our acknowledgment at the end of the article), is important as a guide in prescribing to younger women.

“Switching” bias. A new bias has been proposed, the “switching bias,” which would occur when women switch from second- to third-generation products, for example, because of “headaches and dizziness.” It is said that this might indicate an increased risk for venous thrombosis.¹⁴ The lack of a medical basis for this argument makes it impossible to address it meaningfully. It has also been argued that switching of brand of contraceptive pill was in the past most often from second to third generation.¹⁹ No reason for switching that is associated with the risk of venous thrombosis has been demonstrated.

Biologic plausibility: New coagulation findings

It has been argued that there is no biologic plausibility for an increase in venous thrombosis risk of third- over second-generation contraceptives.¹⁴ However, the exact mechanism by which oral contraceptives cause deep venous thrombosis was never understood.

Very recently, researchers²⁰ from Maastricht, The Netherlands, have shown that women who use third-generation contraceptives acquire a degree of resistance to the blood's own anticoagulation system, the protein C/S system, that is close to the degree of activated protein C resistance that is witnessed in persons who carry the factor V Leiden mutation. In contrast, women using second-generation contraceptives show only about half of this effect, a difference that was highly statistically significant. The “Leiden mutation” is a mutation in coagulation factor V that renders it less sensitive to inactivation by activated protein C.²¹ Persons who carry this mutation have about an eightfold risk for venous thrombosis, which is indeed similar to the overall risk of third-generation contraceptives. In earlier epidemiologic studies it was found that carriership of the mutation strongly interacts with oral contraceptive use. Women who both carry the mutation and use oral contraceptives have a risk of thrombosis that is increased more than thirtyfold.²² This increase in risk is of the order of magnitude for the increase in homozygotes for the mutation, whose risk increase is fiftyfold or more.²³ Interestingly, in the new test system from Maastricht, heterozygote carriers of the mutation who use oral contraceptives have coagulation results that are similar to those of homozygotes, again corroborating the epidemiologic estimates.

Comment

When we examine the arguments that studies showing a higher risk of venous thrombosis for third-generation contraceptives are biased, the arguments are found to have been largely dismissed by the data. From an epidemiologic point of view this does not yet lead to complete certainty. Unknown biases that are therefore unmeasured and uncontrolled always remain possible. They remain a matter of belief. Nevertheless, the collective evidence that we have at present is difficult to refute. Therefore the most rational epidemiologic point of view is that a greater risk of deep venous thrombosis among users of third-generation contraceptives is likely. The epidemiologic evidence has very recently been corroborated by new coagulation findings. These findings have importance beyond the third- and second-generation controversy, because they shed new light on the mechanisms of venous thrombosis with oral contraceptive use and confirm earlier epidemiologic findings of a synergy between oral contraceptive use and carriership of the factor V Leiden mutation in the causation of venous thrombosis.

Because the controversy on third-generation oral contraceptives and deep venous thrombosis has generated a large volume of correspondence in several journals, we have cited only references that give an overview of several lines of argument or make specific points

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