Oral contraceptives and venous thromboembolism: a quantitative discussion of the uncertainties

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Objectives. The majority of post-thrombotic women are barred from using oral contraceptives. We evaluated this policy for its clinical relevance.


Setting. A Medline computer search, from 1966 to 1993, in multiple languages, with the following index terms: thrombosis, thrombophlebitis, vein, venous, pulmonary embolism, contraceptives, oestrogen, oral.

Study selection. A total of 588 articles or abstracts were reviewed for controlled studies, in which an index group was compared with a control group. Included were one randomized trial, six follow-up studies and eight case-control studies.

Main outcome measures. Summary thrombosis risk for oral contraceptive users, number needed to discontinue oral contraceptives to prevent one (recurrent) thrombosis, comparison of additional unwanted pregnancies and postpartum thrombosis between alternative birth-control methods.

Results. The studies proved highly heterogeneous with regard to size and direction of the risk estimate. The summary relative risk of first thrombosis during oral contraceptive use was 2.9 (95% CI, 0.5-17). Since the risk of thrombosis recurrence is not well known, we estimated alternatives, making various hypothetical assumptions, wherein women would continue to take oral contraceptives after a first episode of thrombosis, or stop and switch to use of an intra-uterine device, condom or the progestogen-only pill. Depending on the assumptions with regard to recurrence risk and the existence of possible subgroups with genetic coagulation defects, the cost-benefit ratio of advising against the use of oral contraceptives after a first thrombosis varied tremendously.

Conclusions. Our analysis shows that we lack the necessary data for recurrence risk of venous thrombosis during continuing use of oral contraceptives, or after switching to other modes of contraception. This reflects the clinical uncertainties that result in highly contradictory advice to young women who have experienced a first thrombosis. Only follow-up studies on recurrence risk will settle the issue.

Keywords: benefit-risk ratio, meta-analysis, oral contraceptives, venous thrombosis.

Introduction

Since the first report on the occurrence of pulmonary embolism in a young woman who used a combined oral contraceptive (the oestrogen mestranol and the progestogen norethynodrel) was published in 1961 [1], many studies on the relationship between oral contraceptive use and venous thromboembolism have been reported. Concern about recurrent venous thrombosis caused many physicians to advise women to cease use of oral contraceptives after a first thrombotic episode. This implies that the woman involved is forever barred from using oral contraceptives. This policy has major consequences, and should be evaluated for its clinical relevance, i.e. its absolute effect and benefit-risk ratio. Two issues will
be considered here. First, the size of the absolute risk and the effect of advice against the use of oral contraceptives: how many women should discontinue oral contraceptive use in order to prevent one thrombosis? Secondly, since oral contraceptives are the most reliable, easily reversible method of contraception, the risk of alternative methods should be taken into account. These alternative methods will result in more pregnancies and undoubtedly more pregnancy terminations, as well as puerperia, which in itself increases the risk of deep vein thrombosis. Therefore, the cure may be worse than the ailment. In this meta-analysis we have attempted to quantify all these aspects, in order to reach conclusions that may assist the clinician in rational decision-making. Given that the recurrence risk of thrombosis is not well known, we must rely on a sensitivity analysis that tests various hypothetical risks.

Methods

Data collection and definitions

We searched for studies, published in English, French or German, in which the risk of venous thrombosis for women who used oral contraceptives as a method of birth control had been estimated. The studies were identified by using a computerized literature search (Medline (1 January 1966 to 31 December 1993), with the following index terms: thrombosis, thrombophlebitis, vein, venous, pulmonary embolism, contraceptives, oestrogen, oral), and by cross-referencing. A first selection was made on the basis of the abstracts, after which the entire manuscripts were reviewed. The analysis in this report is limited to controlled studies, in which an index group is compared to a control group. Excluded were case series and studies controlled by general population data, and reports in which data for venous thrombosis could not be differentiated from data for arterial thrombosis. In some reports, parts of the data were published more than once. From these articles we selected only those reporting the original or final results. Overall data on venous thrombotic events which also included figures for rarely occurring (neurological, ophthalmic or mesenteric) thromboses were included.

Study characteristics, such as type of study, oestrogen dose, and use of objective methods to diagnose venous thromboembolism, were independently scored by two authors. In the event of disagreement, the other two authors were consulted, and a consensus could be reached in all cases.

Number needed to discontinue oral contraceptive use

Whereas a relative risk (RR) is useful for establishing a causal association, it provides little information about the clinical relevance, which is dependent on the absolute risk, i.e. the probability for an individual patient. From the absolute risk one may, by simple calculation, estimate the number of women that should discontinue the use of oral contraceptives in order to avoid one thromboembolic event [2]. Obviously, if a drug increases the risk from 1/1000 to 10/1000 (risk difference 9/1000), a total of 10000/9 (1/risk difference) = 111 women should discontinue this drug in order to avoid one thromboembolic event.

To perform this analysis, we need to estimate the incidence of thrombosis in those women who use oral contraceptives, and in those who do not use them. First, we estimated the overall incidence (I) of venous thrombosis in women of child-bearing age, by dividing the number of first, objectively confirmed episodes of deep vein thrombosis in 15- to 44-year-old women over a 5-year period (data from the Leiden Thrombophilia Study (LETS) [3]) by the total number of women-years of this age group in the same well-defined greater Leiden area. The incidence of thrombosis among oral contraceptive users (I_e) and non-users (I_0) can be estimated from this overall incidence (I) by the following equation:

\[
I_e = (\text{proportion of pill-users} \times \text{pooled relative risk} \times I_0) + (\text{proportion non-users} \times I_0) = I.
\]

I_e can be determined by multiplying I_0 by the pooled risk estimate. Age-specific data for oral contraceptive use for women aged 15 to 44 years were obtained from the Dutch Central Bureau of Statistics [4].

In order to obtain more information about the risk-benefit ratio with regard to unwanted pregnancies or post-partum thrombosis, we hypothetically compared the number of expected birth control failures and recurrent thrombotic episodes in three cohorts of 100000 post-thrombotic women, each using oral contraceptives or alternative birth-control methods for 1 year. The thrombosis frequency during pregnancy or during the post-partum period was esti-
A total of 588 papers and abstracts were examined for possible inclusion in the study. We reviewed 206 studies in detail and identified 18 controlled studies.

Results

During the 5-year period (1988–1992) of the LETS study we observed 101 female patients between 15 and 44 years of age with a first, objectively confirmed venous thrombotic event. Therefore, the overall incidence (I) was 2/10000. In total, 41 708 (42%) women aged 15–44 years may be expected to use oral contraceptives. Substituting these values into the
equation, we obtain \((0.42 \times 2.9 \times 1_0) + (0.58 \times 1_0) = 2/10000\). Therefore, the incidence for non-oral contraceptive users was calculated to be 1.1 per 10000, and the incidence for oral contraceptive users was calculated to be 3.3 per 10000. If oral contraceptive use increases the risk of venous thrombosis from 1.1 to 3.3 per 10000 (risk difference 2.2/10000), a total of 4545 asymptomatic women should refrain from using oral contraceptives in order to prevent a first episode of deep vein thrombosis within 1 year. At present, the recurrent risk of venous thrombosis, after a woman has stopped using oral contraceptives because of this thrombosis, is not known. It might be higher than the baseline risk, since these women might have other risk factors, but it must be lower than the primary risk during oral contraceptive use, since an important risk factor has been removed. Therefore, we have tentatively used a relative risk of two for recurrent thrombosis in women who have stopped taking oral contraceptives after their thrombotic episode. It will be at least as high as the primary risk, and may be higher if there are women who are particularly sensitive to the thrombogenic effect of oral contraceptives. By way of sensitivity analysis we have set absolute risks of thrombosis recurrence at 4.4/10000 (primary risk for oral contraceptive users (3.3/10000) + additional recurrence risk of 1.1/10000), 9.9/10000 and 33/10000 (representing relative risks of 3 and 10, i.e. complementary to the risk of other factors). The latter risks may appear to be high. However, they approach the risks that are observed in subgroups with genetic coagulation deficiencies [27, 28]. On the basis of these absolute risks, 4545, 1299 or 325 women, respectively, should discontinue the use of oral contraceptives in order to avoid one second thrombotic episode per year.

Table 1 lists the outcome with regard to pregnancies and thrombosis in five hypothetical cohorts of 100000 post-thrombotic women monitored for 1 year. The results are highly variable, not only with regard to assumptions about recurrence rate, but also with regard to assumptions about contraceptive failures. Under all but the highest assumption for
Table 1 Comparison of thrombosis outcome in three cohorts of post-thrombotic women

<table>
<thead>
<tr>
<th></th>
<th>Oral contraceptive (100000 py)</th>
<th>Intra-uterine device (100000 py)</th>
<th>Condom (100000 py)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of recurrent VT‡</td>
<td>4.4/10000</td>
<td>9.9/10000</td>
<td>33/10000</td>
</tr>
<tr>
<td>Cases of VT</td>
<td>44</td>
<td>99</td>
<td>330</td>
</tr>
<tr>
<td>Failure rate</td>
<td>0.03 (0.001*)</td>
<td>0.03 (0.001*)</td>
<td>0.03 (0.008*)</td>
</tr>
<tr>
<td>Unwanted pregnancies</td>
<td>3000 (100*)</td>
<td>3000 (100*)</td>
<td>3000 (800*)</td>
</tr>
<tr>
<td>Frequency of VT during pregnancy and puerperum</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Additional cases of VT§</td>
<td>30 (1*)</td>
<td>30 (1*)</td>
<td>30 (8*)</td>
</tr>
<tr>
<td>Total number of VT</td>
<td>74 (45*)</td>
<td>129 (100)</td>
<td>360 (331*)</td>
</tr>
</tbody>
</table>

*Data when the lowest expected failure rates were applied
‡py, person years
§VT, venous thrombosis.
§§Calculated by: (number of pregnancies) x (thrombosis risk, pregnancy and puerperum)

Discussion

The results of this overview suggest that oral contraceptives are associated with an almost three-fold increase in risk of venous thrombosis. Given the low absolute thrombosis risk in 15- to 44-year-old women, the effort that must be made to prevent recurrent thrombosis is highly dependent on assumptions about recurrence risk and contraceptive failure rates.

The selected studies were not homogeneous, i.e. the results showed more variation around the summary estimate than could be explained by chance alone. The studies are therefore difficult to interpret as a whole. The pooled summary estimate of case-control studies (RR 4.2) was higher than the pooled summary estimate of follow-up studies (RR 2.1). In both study designs, biases may explain at least some of the results, as was nicely illustrated by Katerndahl et al. [29]. Interestingly, in the only randomized controlled trial, which will not have suffered from the biases described above, no difference was found in thrombosis risk between 4965 oral contraceptive users (aged 15 to 40 years) and a group of 4933 control women who were using vaginal barrier methods (RR 1.1; 95% CI, 0.4-2.9) [26].

Publication bias, caused by under-reporting smaller studies with no significant effect, must always be considered as a possible explanation of the outcome in a critical review. However, 'funnel plot' analysis of the distribution of the various study outcomes ranked by their standard errors did not suggest that such a bias was present (Fig. 1) [30].

The 'true' underlying thrombotic risk also varies according to the type of oral contraceptive used. The overall results of the 15 studies were dealing with higher-dose oestrogen-containing pills, which appear to be associated with a higher thrombosis risk than currently marketed 'sub-fifty' formulations [31-34]. Furthermore, women with leg symptoms who are using oral contraceptives are more likely to be diagnosed as having venous thrombosis than women with the same leg symptoms who are not current users of oral contraceptives. This detection and referral bias will result in an overestimation of the relative risk, the more so since, in the studies selected, for many patients the diagnosis was not confirmed by means of an objective test, which will without doubt have resulted in numerous false-positive diagnoses [35, 36], especially for women using oral contraceptives [37].
The use of condoms of intra-uterine devices as an alternative to oral contraceptives will lead to more unwanted pregnancies. Under the lowest assumptions for thrombosis risk among typical couples this might give an increase in the occurrence of venous thrombosis (Table 1). The decision of whether to continue using oral contraceptives after a thrombotic event or to switch to an intra-uterine device or progestagen-only pills is a more difficult one. The risk of thrombosis is decreased, but the risk of unwanted pregnancies can be increased considerably compared to that associated with oral contraceptive use, depending on which efficacy criterion is used.

The data are based on the total number of women with a first thrombosis. For specific subgroups, i.e. those with genetic coagulation disorders, the risk will be higher. Evidence supporting this view is already available for deficiencies of protein C, protein S and antithrombin [38]. However, these genetic risk factors have a very low prevalence in the general population, and hitherto played only a minor role in considerations when advising women who had experienced a first thrombosis during oral contraceptive use. However, this situation might change completely with the recent discovery of genetic resistance to activated protein C, which is present in 3% of the general population and in 20% of unselected consecutive thrombosis patients [39]. It leads to a sevenfold increase in thrombosis risk, which might be further enhanced by oral contraceptive use [27-28]. For these women, who represent a significant proportion of young women with deep venous thrombosis, future follow-up studies will describe the magnitude of the recurrent risk. Even so, in all of these women with genetic coagulation disorders, the consequences of prescribing less reliable birth-control methods should be carefully considered, given the additionally increased percentages of pregnancy- and post-partum thrombosis [40].

Our attempt to quantify the difficult clinical decision of whether or not to discontinue the use of oral contraceptives after a first thrombosis has led to the startling realization that we lack the necessary data. Depending on the assumptions made, one can arrive at totally opposite conclusions. This appears to be a reflection of the uncertainties that exist in current clinical practice, where highly contradictory advice is given to young women. In the end, the relative subjective fears of either thrombosis or pregnancy, and the relative acceptability of different forms of contraception for a woman and her partner, might be the decisive factors.

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