Third generation oral contraceptives and risk of venous thrombosis: meta-analysis

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Abstract

Objective To evaluate quantitatively articles that compared effects of second and third generation oral contraceptives on risk of venous thrombosis.
Design Meta-analysis.
Studies Cohort and case-control studies assessing risk of venous thromboembolism among women using oral contraceptives before October 1995.
Main outcome measures Pooled adjusted odds ratios calculated by a general variance based random effects method. When possible, two by two tables were extracted and combined by the Mantel-Haenszel method.
Results The overall adjusted odds ratio for third versus second generation oral contraceptives was 1.7 (95% confidence interval 1.4 to 2.0; seven studies). Similar risks were found when oral contraceptives containing desogestrel or gestodene were compared with those containing levonorgestrel. Among first time users, the odds ratio for third versus second generation preparations was 3.1 (2.0 to 4.6; four studies). The odds ratio was 2.5 (1.6 to 4.1; five studies) for short term users compared with 2.0 (1.4 to 2.7; five studies) for longer term users. The odds ratio was 1.3 (1.0 to 1.7) in studies funded by the pharmaceutical industry and 2.3 (1.7 to 3.2) in other studies. Differences in age and certainty of diagnosis of venous thrombosis did not affect the results.
Conclusions This meta-analysis supports the view that third generation oral contraceptives are associated with an increased risk of venous thrombosis compared with second generation oral contraceptives. The increase cannot be explained by several potential biases.

Introduction

In 1995-6 increased risks of venous thrombosis were reported among women using so called third generation oral contraceptives compared with second generation products, with odds ratios ranging from 1.5 to 2.2.[1–4] Other investigators suggested that confounding, bias, or both, accounted for the findings.[5–8] In 1999, Farley et al reported a meta-analysis and found an increased risk of 1.9 (95% confidence interval 1.5 to 2.2).[9] However, their aim was to review qualitatively the arguments claiming that the difference in risk for different oral contraceptives is not real. They did not formally consider characteristics of the included studies that might affect their results. In the present meta-analysis we quantified these aspects.

Methods

We searched Medline for articles published from October 1995 to December 2000 using the terms third generation oral contraceptives, desogestrel, and gestodene combined with thromboembolism and venous thrombosis. We retrieved additional references from reviews, other articles of interest, and experts in the field. We reviewed all English language articles containing original data on third generation oral contraceptives and venous thrombosis. Inclusion criteria were (*a*) cohort or case-control design, (*b*) cases defined as women with venous thrombosis or thromboembolism, (*c*) sufficient data provided to reconstruct two by two tables or determine relative risk and confidence intervals, (*d*) data collected before November 1995, and (*e*) data collected in Western countries. We chose October 1995 as the end date because at that time four studies were published relating third generation oral contraceptives to venous thrombosis.[1–4] Consequently, changes in prescription of oral contraceptives may have potentially affected the results of later studies. To avoid heterogeneity, we included studies in only Western countries.

Cases were considered confirmed when venous thrombosis was objectively diagnosed (by ultrasound examination, plethysmography, or venography). A study was included only once if there were multiple publications.

We performed an overall analysis based on the adjusted odds ratios and on the two by two tables separately. We calculated adjusted odds ratios by pooling adjusted odds ratios from individual studies using a general variance based random effects method, weighting individual study results by the inverse of their variance.[10] Results were considered heterogeneous when homogeneity was unlikely ($P < 0.10$). To determine the stability of the overall risk estimate, we did a sensitivity analysis in which each study was successively eliminated.

If possible we also extracted or recalculated two by two tables. We combined the odds ratios from the individual studies using the Mantel-Haenszel method,[10] providing a crude odds ratio. For subgroup analyses, we pooled adjusted and unadjusted results because of

Editorial by Drife

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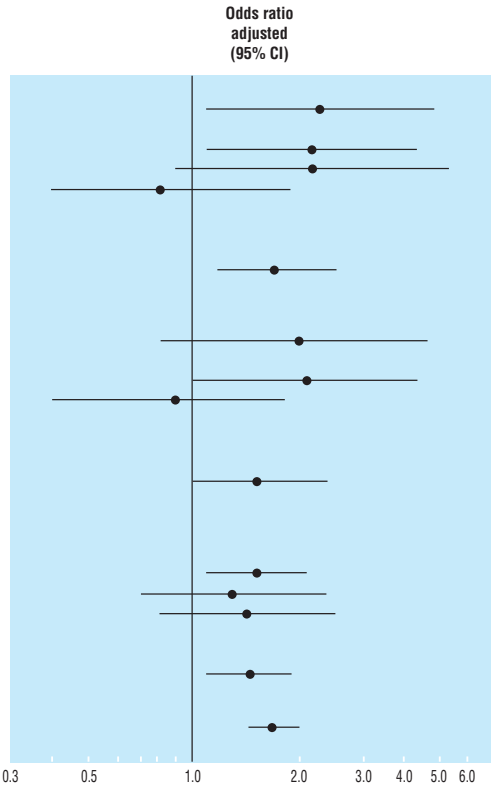
BMJ 2001;323:131–4

Study	Cases n	Controls n	Odds ratio unadjusted (95% CI)	Odds ratio adjusted (95% CI)
Desogestrel *v* levonorgestrel				
WHO[12]	31/80	26/129	1.9*	2.3†
Spitzer[4]	72/89	137/311	1.8	-
Jick[2]	30/23	91/141	2.0	2.2
Bloemenkamp[3]	37/20	15/18	2.2	2.2
Farmer[5]	-	-	-	0.8
Lidegaard[7]	48/31	41/54	2.0	-
Bloemenkamp[11]	28/26	30/42	1.5	-
Total	246/269	340/695	1.9 (1.5 to 2.3)	1.7 (1.2 to 2.6)
Gestodene *v* levonorgestrel				
WHO[12]	22/80	23/129	1.5*	2.0†
Spitzer[4]	55/89	112/311	1.7	-
Jick[2]	22/23	68/141	2.0	2.1
Farmer[5]	-	-	-	0.9
Lidegaard[7]	69/31	77/54	1.6	-
Bloemenkamp[11]	5/26	4/42	2.0	-
Total	173/249	284/677	1.7 (1.3 to 2.2)	1.5 (1.2 to 2.4)
Third *v* second generation (type of progestagen unspecified)				
WHO[1]	53/156	51/236	1.6	-
Spitzer[4]	127/132	249/402	1.6	1.5
Farmer[5]	-	-	-	1.3
Lidegaard[7]	117/34	118/60	1.7	1.4
Farmer[13]	15/27	64/89	0.8	-
Total	312/349	482/787	1.5 (1.2 to 1.8)	1.4 (1.1 to 1.9)
Overall			1.6 (1.3 to 1.9)	1.7 (1.4 to 2.0)



* Women from Western countries (Germany and Oxford region)
† Women from Oxford region only

Fig 1 Overall odds ratios and 95% confidence intervals for venous thrombosis with different categories of oral contraceptives

the limited number of studies with subgroup data, resulting in a pooled odds ratio.

Results

Of 114 studies identified, nine case-control[1–5 7 11–13] and three cohort studies[2 5 14] examined use of oral contraceptives and risk of venous thrombosis. Three studies provided additional analyses on earlier reported results,[6 15 16] and were included in our stratified analysis.

Overall analysis

The overall adjusted odds ratio for third versus second generation oral contraceptives for the risk of venous thrombosis was 1.7 (95% confidence interval 1.4 to 2.0), with no heterogeneity (P = 0.78). In a sensitivity analysis, the adjusted odds ratio varied between 1.6 and 1.8, and the 95% confidence interval never included 1. The crude odds ratio was similar to the adjusted odds ratio (crude odds ratio = 1.6, 95% confidence interval 1.3 to 1.9). The overall results were not materially dependent on definitions of oral contraceptives (fig 1). For all subgroups, crude odds ratios, based on the two by two tables were similar to adjusted odds ratios.

Stratified analyses

Figure 2 shows that the pooled odds ratios for third versus second generation preparations were always increased between 1.7 and 3.1. Source of funding modified the estimates: the odds ratio was 1.3 (1.0 to 1.7) in studies directly financed by pharmaceutical industries and 2.3 (1.7 to 3.2) in other studies. Differences in age and certainty of diagnosis of venous thrombosis did not affect the results, nor did excluding the cohort study by Herings et al.[14]

Extended studies

The odds ratio remained essentially the same when the original studies[2 5] were replaced by reports updated after October 1995.[17–20]

Discussion

Our meta-analysis shows that third generation oral contraceptives are associated with a 1.7-fold increased risk of venous thrombosis compared with second generation oral contraceptives. After stratifying by various factors and examining selected subgroups, the increased risk remained.

A meta-analysis depends on the quality of the studies included. Observational studies are susceptible to bias because other risk factors of venous thrombosis may be unbalanced across users of second and third generation oral contraceptives. We did not give quality scores to included studies because of their inherent subjectivity and potential to result in diverging summary estimates.[21] However, the key elements affecting internal validity (ascertainment, diagnostic and inclusion criteria, exposure assessment, matching, and control factors),[22] were listed in the tables (see *BMJ*'s website) and investigated in the stratified and sensitivity analyses.

Quality issues

We believe three issues are important for the quality of our meta-analysis. Firstly, we assessed reliability of outcome by subgroup analysis with confirmed cases only. Secondly, we assessed appropriate adjustment for confounding by comparing adjusted and unadjusted odds ratios and by presenting stratified analyses. The presence of confounding is unlikely because the pooled crude odds ratios were almost equal to the pooled adjusted odds ratios. Source of funding modified the estimates. Some studies provided stratified data only for specific subgroups of women (for example, age in first time users).[6 14] Nevertheless, these studies were included. In addition, the sensitivity analysis showed that the overall risk estimates were stable.

Thirdly, we evaluated the quality of assessment of exposure. The definition of second and third generation oral contraceptives was not fully consistent across reports.[1 4–7 13] However, different definitions did not affect the results materially (fig 1). Differential recall of second versus third generation contraceptives is unlikely because most studies collected data before October 1995 or used information from medical records.

Our pooled odds ratios may be underestimates because publication bias can never be excluded. For example, the Dutch press recently reported that a drug company kept results secret that confirmed an increased risk of venous thrombosis with third generation oral contraceptives.[23]

Another cause of underestimation is that relative risks estimated from the original data are in general lower than those derived from matched regression analysis. However, this cannot be addressed with published data. Over the past years, the discussion about the findings has concentrated on several potential biases,[8 9 24 25] including healthy user bias, recency of introduction bias, duration of use of oral contraceptives, diagnostic suspicion and referral bias, and prescribing and switching bias. These are discussed further on the *BMJ*'s website.

Source of funding

The pooled odds ratio of studies without explicitly mentioned industry sponsoring was higher than that of studies without such support, although the increased risk was significant in both groups. Different results for industry and non-industry sponsored studies have also been reported for calcium channel antagonists and non-steroidal anti-inflammatory drugs.[26 27]

Absolute risks

To appreciate the importance of increases in relative risk, knowledge of absolute risks is required. We estimated that the excess risk for users of third generation oral contraceptives over second generation preparations was 1.5 per 10 000 woman years. This may be an underestimation, because the estimate from the study by Jick et al was confined to cases that met a very strict definition.[2] Among new users the incidence is much higher (6.6 per 10 000 woman years).

Death rates from venous thrombosis are low (about 3%),[28] although non-fatal events can also have serious effects. We crudely calculated that four deaths per 1 000 000 woman years could be prevented by switching from third to second generation products. Although the risks are small, they should be considered when deciding which oral contraceptive to use.

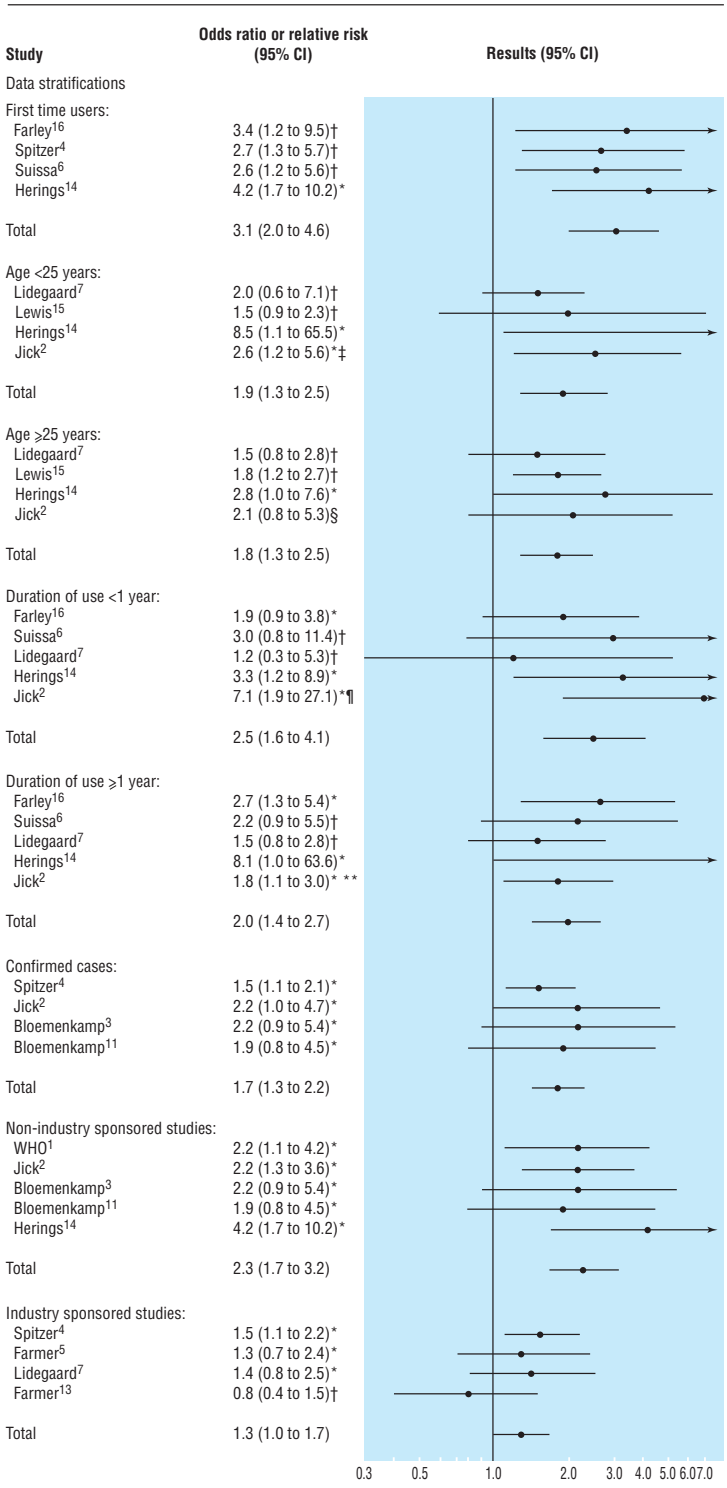


Fig 2 Effect of patient characteristics on odds ratios or relative risks of third versus second generation oral contraceptives for venous thrombosis

What is already known on this topic

Third generation oral contraceptives have been reported to increase the risk of venous thrombosis compared with second generation oral contraceptives

The findings have been vigorously debated, with suggestions that the results can be explained by confounding or bias, or both.

What this study adds

Women taking third generation oral contraceptives have a 1.7-fold increased risk of venous thrombosis compared with those taking second generation oral contraceptives

Risk is highest in first time users

The biases were not large enough to account for the observed results

Conclusion

Our meta-analysis supports the view that third generation oral contraceptives are associated with a 1.7-fold increased risk of venous thrombosis compared with second generation oral contraceptives. The risk is highest in first time users. Although confounding can never be excluded with certainty in observational studies, it seems that the biases that have been suggested and examined are not sufficient to account for the results.

Contributors: JMK participated in the design, execution, and analysis of the study and writing the paper. AA and DEG initiated the study, participated in designing, analysing, and reporting the study, and supervised all aspects of the study. DEG is the guarantor

Funding: None.

Competing interests: JMK has worked on a study into second and third generation contraceptives sponsored by the Netherlands Thrombosis Foundation.

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(Accepted 7 June 2001)

One hundred years ago

The doctor in politics

The medical profession is treated by politicians as a negligible quantity, but this is partly because it does not know, and partly because it does not care to use, its power. What doctors could do if they chose to use the legitimate influence which they have, is shown by an incident in a recent electoral campaign in America. The defeat of Governor Charles S. Thomas, of Colorado, for a seat in the United States Senate was, according to the *Maryland Medical Journal*, due to the influence of the medical profession, who determined to punish him for an insulting veto message. The doctors all over the State worked for democratic and fusion candidates who would pledge themselves to oppose Governor Thomas. The Governor was perfectly sure of his nomination until the Legislature assembled, when he found that he lacked four votes. The bitterness of his defeat was doubtless increased by the fact that it was due to the action of the despised doctors.

(*BMJ* 1901;i:1038)