Chapter 7

Network meta-analysis of different combined oral contraceptives and the risk of venous thrombosis

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Abstract

Background: Oral contraceptive use is associated with venous thrombosis risk. Although the risk of venous thrombosis has been evaluated for various estrogen doses and types of progestagen, no comprehensive comparison involving commonly used oral contraceptives is available.
Methods: A network meta-analysis was performed to assess the risk of thrombosis associated with oral contraceptive use at the level of individual types of contraceptives. Electronic databases (Pubmed, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier and ScienceDirect) were searched in November 2011 to identify potential relevant articles. We selected publications that assessed the effect of combined oral contraceptives on venous thrombosis (i.e., deep venus thrombosis and pulmonary embolism) in healthy women. Two independent reviewers extracted data from included publications. The network meta-analysis was performed using an extension of frequenist random-effects models for mixed multiple treatment comparisons and relative risks (RR) with 95% confidence intervals (CI) were reported.
Results: A total of 2011 publications were retrieved through a search strategy; 24 publications reporting on 25 studies were included. Combined oral contraceptive use increased the risk of venous thrombosis compared with non-use (RR 3.6, 95 %CI: 2.9-4.6). Oral contraceptives containing a third generation progestagen (desogestrel, gestodene or norgestimate) were associated with a higher risk of venous thrombosis than oral contraceptives with levonorgestrel (second generation) (RR 1.6, 95%CI: 1.3-1.9). Sensitivity analyses stratified by funding source, study design, or confirmed venous thrombosis did not change the findings. From the network meta-analysis at the level of individual type, the highest thrombosis risk was observed among 50 µg ethinylestradiol with levonorgestrel (RR 6.7, 95%CI: 4.0-11.2, compared with non-use), 35 µg ethinylestradiol with cyproterone acetate (RR

5.5, 95%CI: 3.9-7.7) and 30 µg ethinylestradiol with drospirenone (RR 6.0, 95%CI: 4.1-8.9), while the lowest risk was observed among 20 µg with levonorgestrel (RR 2.6, 95%CI: 1.5-4.5).
Conclusion: All combined oral contraceptives are associated with an increased risk of venous thrombosis. The effect size depends on the progestagen and the dose of ethinylestradiol.

Introduction

In 1960, shortly after the introduction of the first combined oral contraceptive, a case of venous thrombosis associated with contraceptive use was reported[1]. Since then many observational studies showed that combined oral contraceptives, containing both an estrogen and a progestagen, are associated with a two-fold to six-fold increased risk of venous thrombosis[2–5]. Despite the low incidence of venous thrombosis of about 3 per 10,000 woman-years among women of reproductive age[6], the impact of combined oral contraceptives on venous thrombosis is large because worldwide many women use oral contraceptives.

Because the estrogen compound (ethinylestradiol) in combined hormonal contraceptives was thought to cause the increased thrombosis risk, the dose of ethinylestradiol has been lowered from 150-100 µg in the earliest brands to 50 µg in the 1960s to 30-35 µg and 20 µg in the 1970s[7–9]. The reduced dose of ethinylestradiol in contraceptives was indeed associated with a reduction in the risk of venous thrombosis[10–14]. Furthermore, the currently prescribed combined oral contraceptives containing 30 µg of ethinylestradiol are associated with a higher risk of venous thrombosis than contraceptives containing 20 µg[15,16]. Besides adjustments in the dose of ethinylestradiol, the progestagen compound was also changed in an effort to reduce side-effects. After the first generation progestagens (e.g., norethisterone, lynestrol), new progestagens were developed, called second (i.e., levonorgestrel (LNG)) and third generation progestagens (i.e., gestodene (GSD), desogestrel (DSG), norgestimate (NGM))[17]. However, third generation combined oral contraceptive users have a higher risk of venous thrombosis than second generation users[15,16,18,19]. Other progestagens have been developed after the introduction of the third generation progestagens, e.g. drospirenone (introduced in 2001). The use of drospirenone in a combined oral contraceptive also increased the risk of venous thrombosis compared with non-use[15,16] and compared with than

second generation contraceptives[20,21].

The aim of the present network meta-analysis was to provide an overview of the risk of venous thrombosis per combined oral contraceptive in healthy women. Furthermore, the effect of the generation of a progestagen in combined oral contraceptive was assessed. A network meta-analysis was performed because combined oral contraceptives are mostly compared with non-use or with a contraceptive containing levonorgestrel with 30 µg ethinylestradiol resulting in gaps in direct evidence. In other words, not every combined oral contraceptive has been directly compared with all other possible combined oral contraceptives. A network meta-analysis allows evidence from direct and indirect comparisons to be summarized in a weighted average for all possible comparisons.

Methods

Search strategy and selection criteria A detailed overview of the search strategy and selection criteria can be found in the supplementary data[22]. Publications of interest were observational studies (i.e., cohort or (nested) case-control studies) that included healthy women using combined oral contraceptives. The primary outcome of interest was a fatal or non-fatal first event of venous thrombosis (deep venous thrombosis or pulmonary embolism). Publications with a minimum of 10 events in total were eligible.

The following databases were searched; Pubmed (918 articles retrieved), Embase (1198), Web of Science (298), Cochrane (57), CINAHL (111), Academic Search Premier (183) and ScienceDirect (103). Our search terms consisted of MeSH (sub)headings, text words, and word variations for "combined oral contraceptive", "estrogens", "progestagens" and "venous thromboembolism". This search strategy was amended for each database. Each database was searched from inception until 22 November 2011 (date of final search). No language restriction was applied. Beside database searches, references of potential interesting publications

were searched.

A standard form was used to select publications. Two investigators (BHS, MdB) independently assessed publications for eligibility. Titles and abstracts were screened and if deemed potentially relevant, full-texts were retrieved. Any disagreements between the investigators were discussed and if necessary, a third reviewer (OMD) was asked to resolve any disagreements. In case of multiple publications from the same study, the publication with the most updated or the most inclusive data was chosen for inclusion.

Data collection Two investigators (BHS, MdB) independently extracted data using a standard form. Data were extracted on type of combined oral contraceptive (dose and type of estrogen and progestagen), crude numbers for exposure and outcome via a 2-by-2 table, crude and adjusted risk estimates, and variables adjusted for in the analysis.

Risk of bias assessment was based on design features that could potentially bias the association between exposure and outcome. We assessed adequacy of exposure (oral contraceptive) and outcome (venous thrombosis) measurement. Specific for cohort studies, loss-to-follow-up assessment was taken into account and for case-control studies, the sampling of controls. Women are more likely to remember that they used oral contraceptives than what specific preparation they used [23,24]. Therefore, assessment of type of combined oral contraceptive through an interview or questionnaire was deemed as high risk of bias, while information from a prescription database was judged as low risk. Only 25-33% of patients presenting with clinical symptoms suggestive of venous thrombosis are diagnosed with venous thrombosis [25].Therefore, objectively confirmed venous thrombosis in all patients was judged as low risk of bias. Venous thrombosis was objectively confirmed when a deep venous thrombosis was diagnosed by plethysmography, ultrasound examination, CT, or venography; or when a pulmonary embolism was diagnosed by

ventilation-perfusion (V/Q) scanning, spiral computed tomography, or pulmonary angiography[26,27]. Less than 10% loss-to-follow-up was considered to represent a low risk of bias. For case-control studies, controls selected from a hospital population was considered to confer a high risk of bias.

For sensitivity analyses, data on funding source and first-time use were abstracted.

In case of incomplete data on dose/type of estrogen or progestagen, authors were sent an email for extra information. Emails were sent on 25 July 2012 with a reminder on 20 August 2012. In total, 80% replied to our emails.

Classification of type or combined oral contraceptives For the network meta-analysis per generation of progestagen, the following progestagens were considered first generation; lynestrenol and norethisterone. Norgestrel and levonorgestrel were categorized as second generation progestagens, whereas desogestrel, gestodene and norgestimate were classified as third generation progestagens[17]. This classification was irrespective of the ethinylestradiol dose. Publications, for which our classification could not be applied but which did provided their own classification, were included irrespective of whether this classification differed from our own. To assess the influence of combining different classifications, we repeated the analysis in studies where our own classification of generations could be applied.

Many different combined oral contraceptives are available. The most commonly used combined oral contraceptives were selected for analysis, namely 20 µg ethinylestradiol with levonorgestrel (20LNG), 30 µg ethinylestradiol with levonorgestrel (30LNG), 50 µg ethinylestradiol with levonorgestrel (50LNG), 20 µgg ethinylestradiol with gestodene (20GSD), 30 µg ethinylestradiol with gestodene (30GSD), 20 µg ethinylestradiol with desogestrel (20DSG), 30 µg ethinylestradiol with desogestrel (30DSG), 35 µg ethinylestradiol with norgestimate (35NRG), 35 µg ethinylestradiol with cyproterone acetate (35CPA), and 30

µg ethinylestradiol with drospirenone (30DRSP).

Statistical analysis A network meta-analysis was conducted per generation of progestagen in a combined oral contraceptive and per selected oral contraceptive preparation.

An extension of frequentist random-effects models for mixed multiple treatment comparisons was used. Network meta-analysis was performed with the *mvmeta* command for STATA as described by White et al[28]. Crude data (i.e., data from a 2-by-2 table) were used in the analysis. Odds ratio, risk ratio or rate ratio and appropriate variances were computed and combined in the analysis leading to an overall relative risk (RR). For publications with zero events in one group, all groups in that publication were inflated by adding 0.5.

When enough studies provided data on the same stratum (i.e., data on generations of progestagen or on specific contraceptive preparations), consistency of the results was checked through interaction analysis. An interaction term was added to the model to estimate the difference in results from direct and indirect evidence. All potential interactions were tested in an overall test to determine whether there were any inconsistencies in our network meta-analysis. Inconsistencies were only checked when there was more than one study comparing the same groups.

The following sensitivity analyses were planned: per study design, per funding source (whether industry sponsored or not), within first-time users, and according to risk of bias.

All statistical analyses were performed with STATA, version 12.0 (Statacorp LP, College Station, TX, USA).

Results

Characteristics of included studies A total of 2011 publications were retrieved through electronic and references searches. 1912 were excluded after screening of title and abstract and 75 publications were excluded after detailed assessment of the full-text.

Reasons for exclusion are shown in the flow chart (Figure 7.1, Supplementary table 7.1). Overall, 25 studies published in 24 articles were included. Two publications provided important additional information to studies included in the meta-analysis (information on first-time use); data from these publications were added to respective studies already included. Details of included studies are shown in table 7.1. Seven cohort studies, three nested case-control studies and 15 case-control studies were included.

Based on data from 14 studies that included a non-user group, combined oral contraceptive use was found to be associated with a four-fold increased risk of venous thrombosis (RR 3.6, 95%CI: 2.9-4.6).

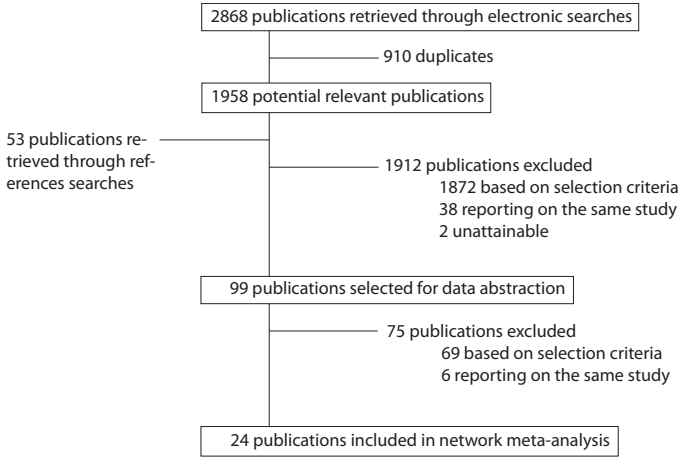

Figure 7.1: Flow chart of included and excluded publications

Table 7.1: Characteristics of included studies

Author	Year	Startdate	Enddate	Study design	No. of participants	Country
N. Gronich [29]	2011	1 Jan 2002	31 Dec 2008	Cohort	329995 women; 819749 wyrs	Israel
S.S. Jick [20]	2011	1 Jan 2002	31 Dec 2008	Case-control	186 cases; 681 controls	USA
L. Parkin [21]	2011	1 May 2002	30 Sep 2009	Case-control	61 cases; 215 controls	UK
L.A.J. Heinemann [30]	2010	Jan 2002	Feb 2006	Case-control	451 cases; 1920 controls	Austria
A. van Hylckama Vlieg [16]	2009	Mar 1999	Sep 2004	Case-control	1524 cases; 1760 controls	Netherlands
S.S. Jick [31]	2006	Jan 2000	Mar 2005	Case-control	281 cases; 1055 controls	USA
E. Samuelsson [32]	2004	1 Jan 1991	31 Dec 2000	Cohort	88 cases; 243723 wyrs	Sweden
K. Hedenmalm [33]	2004	1965	2001	Cohort	172 cases; 10016194 trtyrs	Sweden
L.A.J. Heinemann [34]	2002	Jan 1994	Jul 1999	Case-control	606 cases; 2942 controls	Germany
L. Parkin [35]	2000	Jan 1990	Aug 1998	Case-control	26 cases; 111 controls	New Zealand
R.D.T. Farmer [36]	2000	Jan 1992	Jun 1997	Cohort	287 cases; 783876 wyrs	UK
M.A. Lewis [37]	1999	Jan 1993	20 Oct 1995	Case-control	471 cases; 1702 controls	UK & Germany
R.M.C. Herings [38]	1999	1986	1995	Cohort	450000 women; 33 cases	Netherlands
J.C. Todd [39]	1999	1992	Mar 1997	Cohort	99 cases; 216356 wyrs	UK
I. Martinelli [40]	1999	Apr 1995	Apr 1998	Case-control	Unclear*	Italy
K.W.M. Bloemenkamp [41]	1999	1 Sep 1982	18 Oct 1995	Case-control	185 cases; 591 controls	Netherlands
Ø. Lidegaard [42]	1998	1994	1995	Case-control	375 cases; 1041 controls	Denmark
R.D.T. Farmer [43]	1998	Oct 1992	Sep 1995	Case-control	42 cases; 168 controls	Germany
B.S. Andersen [44]	1998	-	-	Case-control	67 cases; 134 controls	Denmark
M.A. Lewis [45]	1996	Jul 1991	Dec 1995	Case-control	505 cases; 1877 controls	UK & Germany
R. Farmer [46]	1996	-	-	Cohort	30 cases; 697000 women	UK
K.W.M. Bloemenkamp [47]	1995	1 Jan 1988	31 Dec 1995	Case-control	126 cases; 159 controls	Netherlands
WHO [48]	1995	1 Feb 1989	31 Jan 1993	Case-control	829 cases; 1979 controls	9 countries†
WHO1 [49]	1995	1 Feb 1989	3 Jan 1993	Case-control	433 cases; 1044 controls	Europe
WHO2 [49]	1995	1 Feb 1989	3 Jan 1993	Case-control	710 cases; 1954 controls	Developing

wyrs, woman-years; trtyrs, treatment-years

* Total no. of women was unclear; however, numbers were available for specific contraceptives

† Brazil, Chile, Colombia, Germany, Hong Kong, Hungary, Jamaica, Thailans, and UK

Risk of bias A total of eight studies assessed combined oral contraceptive use through an interview or questionnaire (Supplementary table 7.2). Only five studies objectively confirmed venous thrombosis in all patients, whereas eleven studies objectively confirmed venous thrombosis in a proportion of the population or subjectively confirmed venous thrombosis. Six case-control studies selected controls from a hospitalized population. Of the seven cohort studies, none reported any information about loss-to-follow-up.

Network meta-analysis comparing generations of progestagens A total of 23 studies were included for the analysis stratified per generation of progestagen in a combined oral contraceptive. Two studies reported solely on the risk of venous thrombosis in drospirenone, which is not classified as a certain generation of progestagen. Details of the number of events and total number of women or total follow-up time per group (i.e., non-use, first generation, second generation and third generation) are provided in supplementary table 7.3.

Results of the network meta-analysis according to generations of progestagen are shown in table 7.2. Users of oral contraceptives with a first generation progestagen had a 3.4-fold increased risk compared with non-users (95%CI: 2.5-4.5), for second generations the risk was 2.8-fold increased (95%CI: 2.3-3.5) and third generation users the risk was 4.5-fold increased (95%CI: 3.6-5.5). Third generation users had a higher risk of venous thrombosis than second generation users (RR 1.6, 95%CI: 1.3-1.9). Restriction to studies where our classification of generations could be applied, the results remained the same (RR_{1st} 3.6, 95%CI: 2.5-5.2; RR_{2nd} 2.9, 95%CI: 2.3-3.8; RR_{3rd} 5.2, 95%CI: 4.0-6.6 compared with non-use). A formal interaction test did not show inconsistencies in the network ($\chi^2 = 3.17$, $p = 0.67$).

Table 7.2: Overview of the results of the network meta-analysis per generation of progestagen

	Reference group			
	Non-use	**1st**	**2nd**	**3rd**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Non-use	1			
1st	3.4 (2.5-4.5)	1		
2nd	2.8 (2.3-3.5)	0.8 (0.6-1.1)	1	
3rd	4.5 (3.6-5.5)	1.3 (1.0-1.7)	1.6 (1.3-1.9)	1

Network meta-analysis comparing different combined oral contraceptives Twelve studies had data available per type of oral contraceptive preparation (Supplementary table 7.4). In all these 12 studies at least one preparation was compared with non-use or two types were compared directly. Results of the network meta-analysis per combined oral contraceptive preparation are shown in table 7.3. All selected preparations were associated with a two-fold or more increased risk of venous thrombosis compared with non-use (Figure 7.2). The relative risk estimate was the highest in 50LNG users and the lowest in 20LNG and 20GSD users. There was a dose-related effect of ethinylestradiol within gestodene and levonorgestrel users, but not in desogestrel users (Table 7.3). In other words, taking either 20DSG or 30DSG as reference did not materially alter the risk estimates for other contraceptives. The risk of venous thrombosis with the use of 35CPA and 35DRSP was approximately the same as 50LNG (RR_{30CPA} 0.8, 95%CI: 0.5-1.5 and RR_{30DRSP} 0.9, 95%CI: 0.5-1.7 compared with 50LNG). A formal interaction test could not be performed because none of the studies provided data on the same groups (Supplementary table 7.3).

Sensitivity analysis Because of the low number of included studies, sensitivity analyses were limited to analyses stratified on funding source, per study design, and objectively versus subjec-

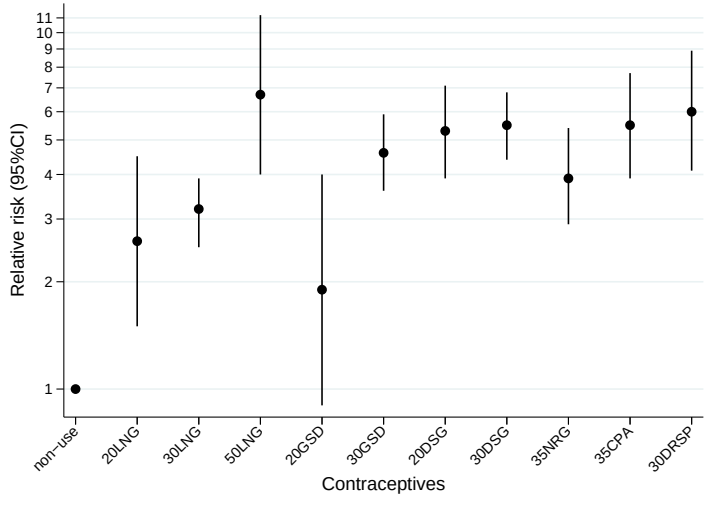

Figure 7.2: Results of the network meta-analysis per contraceptive pill on a logarithmic scale. The dots indicate the overall RR with lines representing the 95% confidence interval. Non-use was taken as the reference group

tively confirmed venous thrombosis (Table 7.4). Results from the sensitivity analysis stratified on funding source showed that the risk estimate for third generation users (compared with non-users) was lower in the industry-sponsored studies than in non-industry-sponsored studies (RR 3.3 versus RR 5.2). In cohort studies, the risk estimate for third generation users (compared with non-users) was higher than in case-control studies (RR 6.1 versus RR 4.3). All risk estimates were higher in studies with objectively confirmed venous thrombosis of which none were industry-sponsored.

Table 7.3: Overview of the results of the network meta-analysis per combined oral contraceptive pill

	Reference group Non-use RR (95%CI)	20LNG RR (95%CI)	30LNG RR (95%CI)	50LNG RR (95%CI)	20GSD RR (95%CI)	30GSD RR (95%CI)
Non-use	1					
20LNG	2.6 (1.5-4.5)	1	0.8 (0.5-1.4)	0.4 (0.2-0.8)	1.4 (0.6-3.3)	0.6 (0.3-1.0)
30LNG	3.2 (2.5-3.9)	1.2 (0.7-2.1)	1	0.5 (0.3-0.8)	1.7 (0.8-3.5)	0.7 (0.5-0.9)
50LNG	6.7 (4.0-11.2)	2.6 (1.2-5.3)	2.1 (1.2-3.6)	1	3.5 (1.5-8.4)	1.4 (0.8-2.5)
20GSD	1.9 (0.9-4.0)	0.7 (0.3-1.8)	0.6 (0.3-1.3)	0.3 (0.1-0.7)	1	0.4 (0.2-0.9)
30GSD	4.6 (3.6-5.9)	1.8 (1.0-3.1)	1.5 (1.2-1.9)	0.7 (0.4-1.2)	2.4 (1.1-5.2)	1
20DSG	5.3 (3.9-7.1)	2.0 (1.1-3.7)	1.7 (1.2-2.2)	0.8 (0.5-1.4)	2.8 (1.3-6.0)	1.1 (0.8-1.6)
30DSG	5.5 (4.4-6.8)	2.1 (1.2-3.7)	1.7 (1.4-2.1)	0.8 (0.5-1.4)	2.9 (1.4-6.1)	1.2 (0.9-1.5)
35NRG	3.9 (2.9-5.4)	1.5 (0.8-2.7)	1.2 (0.9-1.7)	0.6 (0.3-1.1)	2.1 (0.9-4.5)	0.9 (0.6-1.2)
35CPA	5.5 (3.9-7.7)	2.1 (1.2-3.9)	1.7 (1.3-2.4)	0.8 (0.5-1.5)	2.9 (1.3-6.3)	1.2 (0.8-1.7)
30DRSP	6.0 (4.1-8.9)	2.3 (1.4-3.9)	1.9 (1.4-2.7)	0.9 (0.5-1.7)	3.2 (1.4-7.1)	1.3 (0.9-2.0)

	Reference group Non-use RR (95%CI)	20DSG RR (95%CI)	30DSG RR (95%CI)	35NRG RR (95%CI)	35CPA RR (95%CI)	30DRSP RR (95%CI)
Non-use	1					
20LNG	2.6 (1.5-4.5)	0.5 (0.3-0.9)	0.5 (0.3-0.8)	0.7 (0.4-1.2)	0.5 (0.3-0.9)	0.4 (0.3-0.7)
30LNG	3.2 (2.5-3.9)	0.6 (0.5-0.8)	0.6 (0.5-0.7)	0.8 (0.6-1.1)	0.6 (0.4-0.8)	0.5 (0.4-0.7)
50LNG	6.7 (4.0-11.2)	1.3 (0.7-2.2)	1.2 (0.7-2.1)	1.7 (1.0-3.0)	1.2 (0.7-2.2)	1.1 (0.6-2.0)
20GSD	1.9 (0.9-4.0)	0.4 (0.2-0.8)	0.4 (0.2-0.7)	0.5 (0.2-1.1)	0.4 (0.2-0.8)	0.3 (0.1-0.7)
30GSD	4.6 (3.6-5.9)	0.9 (0.6-1.2)	0.8 (0.7-1.1)	1.2 (0.9-1.6)	0.8 (0.6-1.2)	0.8 (0.5-1.2)
20DSG	5.3 (3.9-7.1)	1	1.0 (0.7-1.3)	1.3 (0.9-1.9)	1.0 (0.7-1.4)	0.9 (0.6-1.4)
30DSG	5.5 (4.4-6.8)	1.0 (0.8-1.4)	1	1.4 (1.1-1.9)	1.0 (0.7-1.4)	0.9 (0.6-1.3)
35NRG	3.9 (2.9-5.4)	0.7 (0.5-1.1)	0.7 (0.5-1.0)	1	0.7 (0.5-1.1)	0.7 (0.4-1.0)
35CPA	5.5 (3.9-7.7)	1.1 (0.7-1.6)	1.0 (0.7-1.4)	1.4 (0.9-2.1)	1	0.9 (0.6-1.5)
30DRSP	6.0 (4.1-8.9)	1.1 (0.7-1.8)	1.1 (0.8-1.6)	1.5 (1.0-2.4)	1.1 (0.7-1.7)	1

Discussion

We performed a network meta-analysis based on 25 studies. Overall, combined oral contraceptive use increased the risk of venous thrombosis four-fold. We observed that all generations of progestagens were associated with an increased risk of venous thrombosis and that third generation users had an increased venous thrombosis risk compared with second generation users. All individual types of combined oral contraceptives increased thrombosis risk compared with non-use. The contraceptives 30DRSP and 35CPA increased the risk of venous thrombosis compared with any other contraceptive except for 50LNG. Users of 20LNG had the lowest risk of venous thrombosis. Whether 20GSD can be considered as safe as 20LNG remains to be determined, because only one study[16] contributed data on 32 women using 20GSD.

In this meta-analysis, bias was potentially introduced by the lack of objectively confirming venous thrombosis in all studies. Only 25-33% of patients with clinical symptoms of thrombosis are diagnosed with venous thrombosis[25]. Including cases in a study without objectively confirmed venous thrombosis would lead to overestimating the association when oral contraceptive users were more likely to be diagnosed than non-users. However, two studies showed that this bias is unlikely to depend on combined oral contraceptive use[18,19]. In studies with clinically diagnosed venous thrombosis without objective confirmation, women are misclassified irrespective of their contraceptive use leading to non-differential misclassification. Therefore, results of such studies may be an underestimation of the true association. This was confirmed by the results from our sensitivity analysis where the risk estimates were higher in studies with objectively confirmed venous thrombosis.

Strengths and limitations The internal validity of the network meta-analysis was assessed through interaction analysis modelling potential inconsistencies in the network. Our results in-

Table 7.4: Results of sensitivity analyses

	Industry N=8 RR (95%CI)	**Non-industry N=9 RR (95%CI)**	**Cohort N=7 RR (95%CI)**	**Case-control N=16 RR (95%CI)**	**Confirmed VT N=5 RR (95%CI)**	**Not confirmed VT N=10 RR (95%CI)**
Non-use	1	1	1	1	1	1
1st	3.5 (2.1-5.6)	3.3 (2.4-4.6)	3.9 (1.0-14.4)	3.5 (2.6-4.7)	4.6 (3.2-6.5)	2.8 (1.8-4.3)
2nd	2.4 (1.7-3.5)	3.1 (2.5-3.8)	3.7 (1.1-12.2)	2.8 (2.3-3.4)	3.3 (2.8-4.0)	2.6 (1.9-3.6)
3rd	3.3 (2.3-4.8)	5.2 (4.2-6.5)	6.1 (2.0-18.8)	4.3 (3.5-5.2)	6.2 (5.2-7.4)	4.3 (3.1-6.0)

dicated that potential inconsistencies are likely the results of chance. A limitation of our network meta-analysis is that the publications had to provide the number of users with number of events per type of combined oral contraceptive. A total of 16 studies provided information on combined oral contraceptive use and risk of venous thrombosis without specifying which contraceptive types were used. Therefore, the number of publications included for the meta-analysis per contraceptive is relatively low. A further limitation may be that the classification of generations of progestagen was not the same in every publication. However, no clear consensus exists on the classification into generations of progestagen. For instance, norgestimate can be categorised as a second or a third generation progestagen. However, restriction on studies where our classification could be applied did not change the results. Network meta-analysis summarizes data from direct and indirect comparisons in a weighted average. A strength of our analysis is that through a network meta-analysis the data on cimbined oral contraceptives were most effectively used. This resulted in a comprehensive overview of the risk of venous thrombosis in commonly used oral contraceptives.

Two other meta-analyses[18,50] have evaluated the risk of venous thrombosis in third generation contraceptive users versus second generation users. Both found an increased risk in third generation users (RR 1.5 95%CI: 1.2-1.8[18] and RR 1.57 95%CI: 1.24-1.98[50]) in line with our result. Although they differed in their included studies, the majority of included studies from both meta-analyses were included in our analysis. To date, no other meta-analysis summarized the data on venous thrombosis risk per combined oral contraceptive preparation.

Meaning of the study Although we observed that the risk of venous thrombosis increased with the dose of ethinylestradiol, this was dependent on the progestagen provided. There was no difference in the venous thrombosis risk between 20DSG and 30DSG, whereas oral contraceptives with other progestagens with differ-

ent doses of ethinylestradiol did show a difference in risk. It is unclear why the dose effect of ethinylestradiol might depend on the progestagen. A possibility is that there is a difference in inhibitory effects of the progestagen on the procoagulant effect of ethinylestradiol. Oral contraceptive use increases the levels of factors II, VII, VIII, protein C and decreases the levels of antithrombin and protein S. Clinical studies have showed that this effect on coagulation factors was more pronounced in desogestrel users than in levonorgestrel users, and limited to combined oral contraceptives[51,52].

The results per combined oral contraceptive preparation showed that combining different preparations into generations may not be an appropriate way to present the risk of thrombosis. The risk of venous thrombosis depended both on the dose of ethinylestradiol as well as on the progestagen provided. We suggest abstaining from any classification of contraceptives, but to compare the risk of venous thrombosis per oral contraceptive preparation.

What do these results mean for clinical practice? Prescribing combined oral contraceptives may not be a good choice with regard to the risk of venous thrombosis. However, if a woman persists in using combined oral contraceptives, only the contraceptive with the lowest risk of venous thrombosis and good compliance should be prescribed, namely levonorgestrel with 30 µg ethinylestradiol. Current practice is to increase the dose of ethinylestradiol in case of disruptions in bleeding patterns[53]. In all likelihood, our results indicate that prescribing 50LNG in case of spotting during the use of 30LNG might carry a serious adverse effect.

Conclusions Combined oral contraceptives were associated with an increased risk of venous thrombosis. The effect size may depend both on the progestagen and the dose of ethinylestradiol.

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Supplementary data

Search strategy of the review

PubMed (“Contraceptives, Oral"[mesh] OR "Contraceptives, Oral"[Pharmacological Action] OR "oral contraceptives" OR "oral contraceptive" OR "Contraceptives, Oral, Combined"[Mesh] OR "combined oral contraceptives" OR "combined oral contraceptive" OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone acetate" OR Drospirenone OR Drospirenon* OR oestrogen*[ti] OR estrogen[ti]) AND ("Ethinyl Estradiol"[mesh] OR "Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate"[Supplementary Concept] OR "estradiol valerate" OR progestogen*[ti]))) AND ("deep vein thrombosis"[ti] OR "deep venous thrombosis"[ti] OR "Venous Thrombosis"[ti] OR "Vein Thrombosis"[ti] OR "Venous Thrombosis"[mesh:noexp] OR "Thrombophlebitis"[mesh] OR "Upper Extremity Deep Vein Thrombosis"[mesh] OR Thrombophlebitis[ti] OR "pulmonary embolism"[ti] OR "pulmonary embolism"[mesh] OR "venous thromboembolism"[ti] OR "Venous Thromboembolism"[mesh] OR "venous thromboembolic disorders"[ti] OR (venous[ti] AND thromboembolic[ti] AND disorder[ti]) OR "venous thromboembolic diseases"[ti] OR "venous thromboembolic disease"[ti] OR "venous thrombotic"[ti] OR ("Thromboembolism"[mesh:noexp] AND (venous[tiab] OR vein[tiab] OR veins[tiab]))) AND (risk OR risks OR risk factor OR risk factors) AND (women OR woman OR woman* OR women* OR girl OR girls OR female) NOT (animals NOT (human AND animals))

EMBASE (exp oral contraceptive agent/ OR "oral contraceptives".mp OR "oral contraceptive".mp OR "combined oral contraceptives".mp OR "combined oral contraceptive".mp OR (((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone ac-

etate" OR Drospirenone OR Drospirenon*).mp OR oestrogen*.ti OR estrogen.ti) AND (("Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate" OR "estradiol valerate").mp OR progestogen*.ti))) AND (("deep vein thrombosis" OR "deep venous thrombosis" OR "Venous Thrombosis" OR "Vein Thrombosis").ti OR exp deep vein thrombosis/ OR Vein Thrombosis/ OR Thrombophlebitis/ OR Thrombophlebitis.ti OR "pulmonary embolism".ti OR exp lung embolism/ OR "venous thromboembolism".ti OR exp Venous Thromboembolism/ OR "venous thromboembolic disorder*".ti OR "venous thromboembolic disease*".ti OR "venous thrombotic".ti) AND (exp risk/ OR risk*.mp OR exp risk factor/) AND ((women OR woman OR woman* OR women* OR girl OR girls OR female).mp OR exp female/) AND (exp human/ OR human.ti OR patient.ti OR patients.ti)

Web of Science TS=("oral contraceptives" OR "oral contraceptive" OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone acetate" OR Drospirenone OR Drospirenon*) AND ("Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR "estradiol valerate" OR "estradiol valerate"))) AND TI=("deep vein thrombosis" OR "deep venous thrombosis" OR "Venous Thrombosis" OR "Vein Thrombosis" OR "Vein Thrombosis" OR Thrombophlebitis OR "pulmonary embolism" OR "venous thromboembolism" OR "venous thromboembolic disorder*" OR "venous thromboembolic disease*" OR "venous thrombotic") AND TS=risk* AND TS=(women OR woman OR woman* OR women* OR girl OR girls OR female) Cochrane (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME) ("oral contraceptives" OR "oral contraceptive" OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR "ethynodiol diacetate" OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR "medroxyprogesterone acetate" OR "chlormadinone acetate" OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR "Cyproterone acetate" OR Drospirenone OR Drospirenon*) AND ("Ethinyl Estradiol" OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mes-

tranol* OR "estradiol valerate" OR "estradiol valerate"))) AND ("deep vein thrombosis" OR "deep venous thrombosis" OR "Venous Thrombosis" OR "Vein Thrombosis" OR "Vein Thrombosis" OR Thrombophlebitis OR "pulmonary embolism" OR "venous thromboembolism" OR "venous thromboembolic disorder*" OR "venous thromboembolic disease*" OR "venous thrombotic") AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female)

CINAHL TITLE/ABSTRACT/KEYWORD (oral contraceptives OR oral contraceptive OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR ethynodiol diacetate OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR medroxyprogesterone acetate OR chlormadinone acetate OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR Cyproterone acetate OR Drospirenone OR Drospirenon*) AND (Ethinyl Estradiol OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR estradiol valerate OR estradiol valerate))) AND (deep vein thrombosis OR deep venous thrombosis OR Venous Thrombosis OR Vein Thrombosis OR Vein Thrombosis OR Thrombophlebitis OR pulmonary embolism OR venous thromboembolism OR venous thromboembolic disorder* OR venous thromboembolic disease* OR venous thrombotic) AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female)

Academic Search Premier (oral contraceptives OR oral contraceptive OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR ethynodiol diacetate OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR medroxyprogesterone acetate OR chlormadinone acetate OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR Cyproterone acetate OR Drospirenone OR Drospirenon*) AND (Ethinyl Estradiol OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR estradiol valerate OR estradiol valerate))) AND (deep vein thrombosis OR deep venous thrombosis OR Venous Thrombosis OR Vein Thrombosis OR Vein Thrombosis OR Thrombophlebitis OR pulmonary embolism OR venous thromboembolism OR venous thromboembolic disorder* OR venous thromboembolic disease* OR venous thrombotic) AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female)

ScienceDirect TITLE((oral contraceptives OR oral contraceptive OR combined oral contraceptive* OR ((norethisterone OR norethisteron* OR norethindrone OR norethindron* OR ethynodiol diacetate OR lynestrenol OR lynestrenol* OR norethynodrel OR norethynodrel* OR dienogest OR dienogest* OR levonorgestrel OR levonorgestrel* OR norgestrel OR norgestrel* OR dl-norgestrel OR dl-norgestrel* OR desogestrel OR desogestrel* OR norgestimate OR norgestimat* OR gestodene OR gestoden* OR medroxyprogesterone acetate OR chlormadinone acetate OR nomegestrol OR nomegestrol* OR nestorone OR nestoron* OR Cyproterone acetate OR Drospirenone OR Drospirenon*) AND (Ethinyl Estradiol OR ethinylestradiol OR ethinylestradiol* OR Mestranol OR Mestranol* OR estradiol valerate OR estradiol valerate))) AND (deep vein thrombosis OR deep venous thrombosis OR Venous Thrombosis OR Vein Thrombosis OR Vein Thrombosis OR Thrombophlebitis OR pulmonary embolism OR venous thromboembolism OR venous thromboembolic disorder* OR venous thromboembolic disease* OR venous thrombotic) AND risk* AND (women OR woman OR woman* OR women* OR girl OR girls OR female))

Criteria for considering studies for this review

Types of studies Observational studies in this review will include case-control, cohort and nested case-control designs. If available, RCT will also be evaluated and included.

Types of participants Participants will be healthy women taking combined oral contraceptives. We will exclude studies of women on hormone replacement therapy, studies of women taking non-oral or progestagen-only contraceptives and studies of women with recurrent venous thrombosis.

Types of interventions Combined oral contraceptive use will be compared to non-use or to a reference combined oral contraceptive (for example, levonorgestrel with 30 µg of ethinylestradiol). We define a woman as a non-user when either she has never been exposed to a combined oral contraceptive or she was a former/previous combined oral contraceptive user. We will categorize the combined oral contraceptive type according to the estrogen type and dose and to the progestagen type.

Types of outcome measures The outcome will be fatal or non-fatal first venous thrombosis event (deep vein thrombosis or pulmonary embolism).

Supplementary table 7.1 Characteristics of excluded studies

Author	Year	Reason for exclusion
Ø. Lidegaard	2011	Included cerebral vein thrombosis
M.K. Barsoum	2010	No data on progestagen type or ethinylestradiol dose
J.C. Dinger	2010	Included recurrent venous thrombosis
V. Tsankova	2010	Compared ever users versus never users
V. Tsankova	2010	No data on progestagen type or ethinylestradiol dose
H. Austin	2009	Other hormonal contraceptives, such as transdermal patch, vaginal ring, were included
P.G. Lindqvist	2009	No data on progestagen type or ethinylestradiol dose
P.M. Eng	2008	Compared drospirenone versus other oral contraceptive users
J.C. Dinger	2007	Included recurrent venous thrombosis
C. Huerta	2007	No data on progestagen type or ethinylestradiol dose
J.D. Seeger	2007	Included recurrent venous thrombosis
C.C. Yang	2007	Exposed consisted of hormone replacement therapy users and oral contraceptive users
K. Hedenmalm	2005	Included recurrent venous thrombosis and cerebral vein thrombosis
H.M. Pearce	2005	No comparison was included
M. Primignani	2005	Included not only venous thrombosis
C. Worralurt	2005	Included recurrent venous thrombosis and no data on progestagen type or ethinylestradiol dose
A. Girolami	2004	Included not only venous thrombosis
P. Heuser	2004	No extractable number of exposed and non-exposed women
H.E. Seaman	2004	Included recurrent venous thrombosis
S. Sidney	2004	Incomplete data on contraceptive use
H. Kieler	2003	Included recurrent venous thrombosis
I. Martinelli	2003	No data on progestagen type or ethinylestradiol dose
A. Tosetto	2003	No data on progestagen type or ethinylestradiol dose
C. Legnani	2002	Included recurrent venous thrombosis
Ø. Lidegaard	2001	Review
L. N. Meurer	2001	Review

Continued on next page

Supplementary table 7.1 – continued from previous page

Author	Year	Reason for exclusion
J.P. Vallée	2001	Review
T. Amundsen	2000	No data on progestagen type or ethinylestradiol dose
R.D. Farmer	2000	No data on progestagen type or ethinylestradiol dose
L.A. Heinemann	2000	Report on Transnational study, already included
R. Lawrenson	2000	Review
A.L. Nightingale	2000	Commentary
M.S. Burnhill	1999	Included progestagen-only contraceptives and retinal vein thrombosis
R.M. Herings	1999	Data already included
M.A. Lewis	1999	Report on Transnational study, already included
Ø. Lidegaard	1998	Review
C. Bonifacj	1997	Included recurrent venous thrombosis
R.D. Farmer	1997	Ecologic study
M.A. Lewis	1997	Report on Transnational study, already included
F.J. van der Meer	1997	Review
J.P. Realini	1997	Less than 10 venous thrombosis events
S. Suissa	1997	Duration of contraceptive use
H. Ulmer	1997	No data on progestagen type or ethinylestradiol dose
F. Grodstein	1996	No data on progestagen type or ethinylestradiol dose
M. Pini	1996	Included not only venous thrombosis and included recurrent venous thrombosis
N.R. Poulter	1996	Data already included
Y. Lis	1993	Publication of study protocol
W.O. Spitzer	1993	Publication of study protocol
D.A. Quinn	1992	No data on progestagen type or ethinylestradiol dose
M. Thorogood	1992	Included recurrent venous thrombosis and no data on progestagen type or ethinylestradiol dose
B.B. Gerstman	1991	Incomplete data on contraceptive use
E. Hirvonen	1990	No data on progestagen type or ethinylestradiol dose
WHO	1989	No data on progestagen type or ethinylestradiol dose
H. Meinel	1988	Included not only venous thrombosis and no data on progestagen type or ethinylestradiol dose
S.P. Helmrich	1987	Incomplete data on contraceptive use

Continued on next page

Supplementary table 7.1 – continued from previous page

Author	Year	Reason for exclusion
D. Bernstein	1986	No data on progestagen type or ethinylestradiol dose
R. Lambrekht	1986	No data on venous thrombosis
K. Overgaard	1986	No data on progestagen type or ethinylestradiol dose
M.P. Vessey	1986	Incomplete data on contraceptive use
J.B. Porter	1985	Less than 10 venous thrombosis events
J.B. Porter	1982	Less than 10 venous thrombosis events
L.E. Bottiger	1980	No data on ethinylestradiol dose
T.W. Meade	1980	Included not only venous thrombosis
D.B. Pettiti	1979	No data on progestagen type or ethinylestradiol dose
A.W. Diddle	1978	Less than 10 venous thrombosis cases
RCGP	1978	Included not only venous thrombosis
IPPF	1976	Communication to the editor
P.D. Stolley	1975	Included not only venous thrombosis
M. Grounds	1974	Included not only venous thrombosis
BCDS	1973	No data on progestagen type or ethinylestradiol dose
W.H. Inman	1970	No data on progestagen type or ethinylestradiol dose
H. Ludwig	1970	Unclear what is defined as high progestagen
H.A. Siegel	1969	No data on progestagen type or ethinylestradiol dose
M.P. Vessey	1969	Included recurrent venous thrombosis
W.H. Inman	1968	No data on progestagen type or ethinylestradiol dose

Supplementary table 7.2 Overview of risk of bias per study

Study	Source population*	Exposure assessment	Outcome assessment	Follow-up
N. Gronich 2011	NA	Low risk	Unclear	Unclear
S.S. Jick 2011	Low risk	Low risk	Unclear	NA
L. Parkin 2011	Low risk	Low risk	High risk	NA
L.A.J. Heinemann 2010	Low risk	High risk	High risk	NA
A. van Hylckama Vlieg 2009	Low risk	High risk	Low risk	NA
S.S. Jick 2006	Low risk	Low risk	Unclear	NA
E. Samuelsson 2004	NA	Low risk	Low risk	Unclear
K. Hedenmalm 2004	NA	Low risk	High risk	Unclear
L.A.J. Heinemann 2002	High risk	High risk	High risk	NA
L. Parkin 2000	Low risk	High risk	High risk	NA
R.D.T. Farmer 2000	NA	Low risk	High risk	Unclear
M.A. Lewis 1999	High risk	Low risk	Unclear	NA
R.M.C. Herings 1999	NA	Low risk	Unclear	Unclear
J.C. Todd 1999	NA	Low risk	High risk	Unclear
I. Martinelli 1999	Low risk	Unclear	Unclear	NA
K.W.M. Bloemenkamp 1999	Low risk	High risk	Low risk	NA
Ø. Lidegaard 1998	Low risk	High risk	High risk	NA
R.D.T. Farmer 1998	Low risk	Low risk	Unclear	NA
B.S. Andersen 1998	Low risk	Low risk	Low risk	NA
M.A. Lewis 1996	High risk	High risk	Unclear	NA
R. Farmer 1996	NA	Low risk	Unclear	Unclear
K.W.M. Bloemenkamp 1995	Low risk	Low risk	Low risk	NA
WHO 1995	High risk	Low risk	High risk	NA
WHO1 1995	High risk	Low risk	High risk	NA
WHO2 1995	High risk	Low risk	High risk	NA

NA, not applicable due to cohort design in case of source population or due to case-control design in case of follow-up

* Case-control studies: population of controls, hospitalized or community-based.

Supplementary table 7.3 Included publications with data on generation of progestagens

Design	Study	Non-use*	1st*	2nd*	3rd*
1	Hylckama 2009	421/1523	55/81	382/672	412/582
	Heinemann 2002	246/2115	45/190	131/865	28/195
	Lewis 1999	171/1268	38/97	142/562	137/401
	Bloemenkamp 1999	83/511	18/46	8/22	33/67
	Bloemenkamp 1995	46/150	8/13	20/38	37/52
	WHO1 1995	168/855	29/74	156/392	53/104
	WHO2 1995	505/2220	26/65	153/337	18/25
2	Heinemann 2010	70/1215	-	61/245	62/238
	Parkin 2000	9/95	-	3/11	12/27
	Lidegaard 1998	203/1037	-	31/85	120/244
	WHO 1995	397/1916	-	137/340	71/127
3	Samuelsson 2004	32/171206	-	-	17/14819
	Martinelli 1999	41/179	-	-	43/79
	Andersen 1998	27/133	-	-	16/23
4	Hedenmalm 2004	-	36/1898899	74/6343562	83/1739393
	Farmer 2000	-	12/39421	98/307070	161/374129
5	Gronich 2011	-	-	23/33187	384/651455
	Jick 2006	-	-	70/386	211/950
	Herrings 1999	-	-	29/121411	49/88295
	Todd 1999	-	-	32/76993	53/92052
	Farmer 1998	-	-	27/116	15/79
	Lewis 1996	-	-	96/419	156/451
	Farmer 1996	-	-	14/76600	15/65100

1st, first generation; 2nd, second generation; 3rd, third generation

* Number of cases/ total number of women in the group or total follow-up time

Supplementary table 7.4 Included publications with specific combined oral contraceptive pills

Design	Study	Non-use*	20LNG*	30LNG*	50LNG*	20GSD*	30GSD*
1	Hylckama 2009	421/1523	8/14	485/858	60/80	14/32	119/186
2	Parkin 2000	9/95	-	2/6	0/2	-	5/10
3	Lidegaard1998	203/1037	-	-	4/8	-	69/146
4	Bloemenkamp 1999	83/511	-	18/46	-	-	5/9
5	Bloemenkamp 1995	46/150	-	20/38	-	-	-
6	Farmer 2000	-	-	64/190191	-	-	63/143581
7	Todd 1999	-	-	22/49484	-	-	21/41947
8	Farmer 1996	-	-	5/35800	-	-	5/30500
9	Jick 2006	-	-	70/386	-	-	-
10	Jick 2011	-	20/151	45/282	-	-	-
11	Parkin 2011	-	-	44/233	-	-	-
12	Lewis 1996	-	-	-	-	-	-

Design	Study	20DSG*	30DSG*	35NRG*	35CPA*	30DRSP*
1	Hylckama 2009	58/85	289/397	9/13	125/187	19/33
2	Parkin 2000	4/9	3/8	-	2/3	-
3	Lidegaard1998	24/46	24/43	3/9	-	-
4	Bloemenkamp 1999	6/7	22/51	-	-	-
5	Bloemenkamp 1995	-	37/52	-	-	-
6	Farmer 2000	18/37584	65/152524	15/40440	16/25709	-
7	Todd 1999	9/10426	23/39679	-	-	-
8	Farmer 1996	-	10/34600	-	-	-
9	Jick 2006	-	87/315	124/635	-	-
10	Jick 2011	-	-	-	-	121/434
11	Parkin 2011	-	-	-	-	17/43
12	Lewis 1996	15/51	64/174	19/50	-	-

* Number of cases/ total number of women in the group or total follow-up time

General discussion