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Do Norwegian health personnel comply with guidelines when prescribing COCs to starters?

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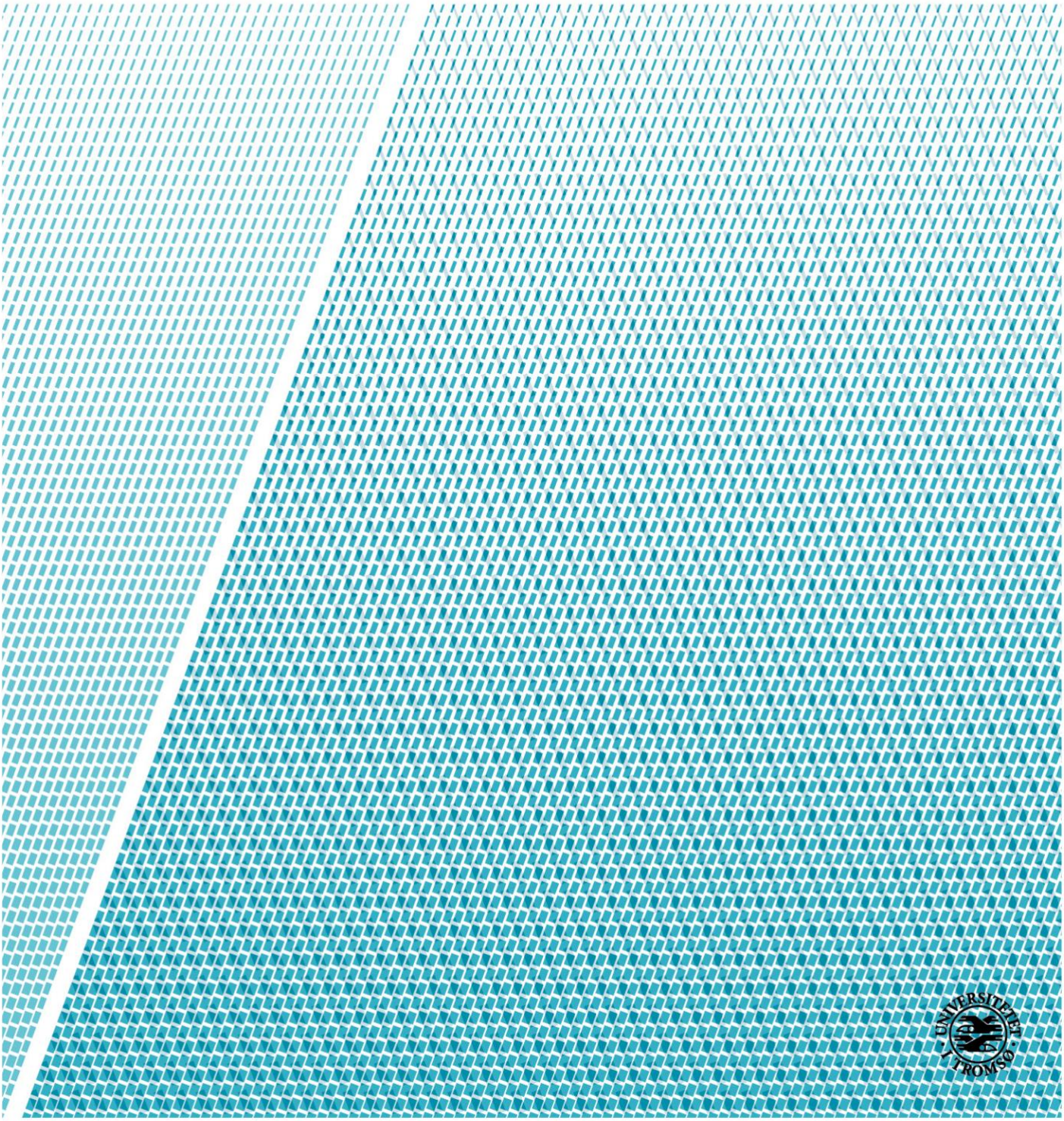

Preface

In this master thesis I have focused on combined oral contraceptives (COCs) and venous thromboembolism (VTE). Although this topic has received a lot of attention ever since the first pill was launched in the 1960s, it is still of current interest because of recent studies reporting a higher risk of VTE for users of the newer COCs. Only few years ago the Norwegian prescribing guidelines for COCs to starters were updated based on this recent knowledge. Therefore, in this study I wanted to assess the latest changes in prescription pattern of COCs to starters by changes in national recommendations.

Thank you very much my supervisor, professor at the university, Finn Egil Skjeldestad, who had the idea for the thesis and who has taken responsibility for applications and collecting and sorting of data. A very engaging supervisor who has spent countless hours helping me with my thesis. Thanks for excellent guidance, helpful advices and for being a fantastic facilitator. I have learned so much in this process and I couldn´t do this without you!

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Table of contents

Abstract

Introduction: Combined oral contraceptives (COCs) containing levonorgestrel are associated with the lowest risk of venous thromboembolism (VTE). The Norwegian Medicines Agency (NOMA) updated the guidelines in 2011 and recommends the low risk products to starters.

Aim: The purpose of this study is to assess changes in prescription pattern of COCs to starters between 2008 and 2016 by provider in line with changes in national recommendations for use.

Material and methods: In a case series design, we have analyzed types of COCs prescribed to starters between 2008 and 2016 in the Norwegian Prescription Database (NorPD). All analyses were done in SPSS version 22.0 with Chi-square test for categorical variables.

Results: The total prescription rate of COCs with levonorgestrel to starters increased from 41% in 2008 to 80% in 2016, with the greatest increase from 2011 to 2012. The rate has increased among starters in all age groups, but it decreased by increasing age of starters. Public health nurses and midwifes, who had highest compliance to guidelines, prescribed COCs with levonorgestrel to 96% of the starters < 20 years in 2016, compared with 75% and 86% among the other main prescribers general practitioners and doctors with no specialty. All professions prescribed recommended COCs in a smaller proportion to older starters.

Conclusion: All professions have increased their prescription rate of COCs with levonorgestrel to starters, public health nurses and midwifes to the greatest extent. General practitioners, who are one of the main prescribers, may prescribe a larger proportion of the recommended COCs to starters to further increase the population of users with the lowest risk of VTE.

Key words: Contraceptives, hormonal contraception, combined oral contraceptives, venous thromboembolism, gestagens, physician prescription pattern, women health.

Abbreviations:

E	Estradiol
EE	Ethinyl estradiol
EV	Estradiol valerate
COCs	Combined oral contraceptives
NOMA	Norwegian Medicines Agency
NorPD	Norwegian Prescription Database
VTE	Venous thromboembolism

1 Introduction

1.1 Combined oral contraceptives and venous thromboembolism

Combined oral contraceptives (COCs) have been on the market since the 1960s (1), and it´s now estimated that about 100 millions of women use this kind of contraception worldwide (2). COCs may potentially have multiple serious complications, and venous thromboembolism (VTE) is the most frequent and important one (3).

COCs have great impact on several mediators in both the fibrinolytic and the coagulation system with a net prothrombotic effect (4-7). Numerous epidemiological studies have demonstrated that the increased risk of VTE depends on both the dose of estrogen (8-11) and the type of gestagen in the pills (8-10, 12-20). The absolute risk of VTE is low even for users of COCs, but since the usage is widespread, a large proportion of VTEs will be associated with COCs among young, non-pregnant women.

1.2 The history of the pill in the light of VTE

The first COCs developed contained high doses of estrogen (> 50 μg) and different types of gestagens (1). Cases of VTE among users were reported shortly after the introduction of the first pill in the early 60´s (21, 22). The first observational study that showed an association between COCs and VTE was published in 1967 (23). In 1970 Inman and colleagues reported that the risk of VTE increases with increasing estrogen dose (11). Only a few years later pills with 50 μg estrogen replaced COCs with higher dosages of estrogen. Later, the estrogen dose was further reduced to 30 μg and 20 μg. The replacement of the high-estrogen preparations has proven to be highly effective in reducing the risk of VTE (24).

Newer gestagens have been developed over time, and COCs with the gestagens levonorgestrel and norethisterone became dominant on the market in the 80´s. Pills with the gestagens desogestrel and gestodene (not on the Norwegian marked) were developed the following years, and then, after the year 2000, pills with the gestagen drospirenone were

launched. Later, pills with the gestagens nomegestrol and dienogest became available on the market (25).

In 1995 three independent studies showed an increased risk of VTE associated with the use of COCs containing desogestrel or gestodene compared with pills containing levonorgestrel, despite the same dose of estrogen (12, 14, 18). Later, additional studies have confirmed these results (8-10, 13, 15, 17, 20), and more recent studies have shown the same association for COCs with drospirenone (8, 9, 16, 17, 19, 20). A major Danish study published in 2011 showed that users of COCs containing desogestrel, gestodene or drospirenone were at least at twice the risk of VTE compared to users of COCs with levonorgestrel (17). A few studies found no difference in risk of VTE between the various gestagens in COCs (26-29). Dragoman et al performed a meta-analysis on studies assessing the risk of VTE among women using COCs before 2016, and found a significant increased risk of VTE for newer COCs compared with levonorgestrel containing products (30).

1.3 Mechanisms of different risk of thrombosis

What we know today is that the prothrombotic effect of COCs is mainly related to the dose of estrogen, while the gestagens seem to reverse this effect (31). The risk of VTE when using low-dose COCs (< 50 μg) is small (32), and evidence of a further decrease in risk associated with a reduction from 30 to 20 μg ethinyl estradiol (EE) is lacking (8, 9, 17). The differences in risk thus depend on the type of gestagen in the pill. The theory is that the various gestagens have different ability to reverse the prothrombotic effect of the estrogen, and that levonorgestrel has greater ability to reverse this effect than the newer gestagens (31). One theory is that gestagens reduce the level of sex hormone binding globulin (SHBG), which reflects the level of ´´estrogenisity´´ in the blood, and that levonorgestrel reduces the level to a greater extent than newer labelled gestagens (33-35). Use of COCs is also associated with acquired resistance to activated protein C, an important inhibitor of the coagulation, and another theory is based on that levonorgestrel causes less APC-resistance than gestagens like desogestrel and drospirenone (36, 37).

1.4 Prescribing guidelines for COCs to starters

In 2006 we had no Norwegian prescribing guidelines for COCs to starters, but Regional Drug Information Centers recommended, based on Swedish and Danish guidelines, COCs with levonorgestrel (38). At this time The Norwegian Medicines Agency (NOMA) only advised against prescribing desogestrel containing products because of studies showing that COCs with this gestagen are associated with a higher risk of VTE compared with pills containing levonorgestrel (39). Since studies published the following years showed that pills with drospirenone are associated with the same risk of VTE as pills with desogestrel, NOMA recommended COCs with levonorgestrel to starters in the minutes from a meeting in the Committee on Side Effects of Drugs in January 2009 (40). Based on studies published between 2007 and 2011, showing that COCs with levonorgestrel are associated with the lowest risk of VTE, NOMA updated the Norwegian guidelines in 2011. COCs with levonorgestrel were recommended for starters, and switching to another type of COCs was an alternative if the women was not satisfied with the levonorgestrel containing pills (41). In the autumn of 2013 The European Medicines Agency (EMA) published a report on COCs and risk of thrombosis that supported the updated recommendations in Norway (32). Thus, the strength of the recommendations to prescribe COCs with levonorgestrel to starters has gradually increased during the study period. The recommendations were identical in 2016 (42).

COCs with norethisterone have the same risk of VTE as levonorgestrel containing products. This gestagen only exists in biphasic pills and is not the recommended first choice to starters because of less control of bleeding pattern (43). The risk of VTE for nomegestrol and dienogest is not yet known, and COCs with these gestagens are thus not recommended as first choice. Table 1 presents gestagen and estrogen content in COCs on the market in the study period. Table 2 shows the knowledge we have today about the different gestagens and the associated risk of VTE (32).

1.5 Changes in prescription pattern?

Although the relation between the different types of gestagens in COCs and the risk of VTE has been known for some years, there is limited data to support substantial changes in prescription patterns of hormonal contraception, including COCs. We know minimal to what extent the publications on COC type and VTE since 1995 have led to increased prescription rate of COCs with levonorgestrel to starters, and how different providers practice new information on risk of VTE when prescribing COCs.

The purposes of this study is to assess changes in prescription pattern of COCs to starters between 2008 and 2016 by provider in line with changes in national recommendations for use.

2 Material and methods

2.1 Study design and data material

In a case series design we have analyzed data from Norwegian Prescription Database (NorPD). NordPD was established 1st of January 2004 and registers drugs delivered by pharmacies to users (44). For every drug a pseudonym is given to the user and the prescriber as a replacement for their personal identification number. User information comprises month and year of birth, gender and home municipality. Detailed information about the prescribed drug is also registered, in addition to date for delivery and which pharmacy that has delivered it. For prescribers, the NorPD includes information on gender, year of birth and profession.

2.2 Selection of the study population

We assessed types of COC that has been prescribed to first-ever COC users, ´´starters´´, between 1st of January 2008 and 30th of June 2016. By starting our study in 2008 we include more real starters because we exclude women who have used COCs between January 1st 2004 until they entered the study after January 1st 2008.

A total of 939 469 women were registered in NorPD between 1st of January 2004 and 30th of June 2016. We excluded women who did not use COCs in the period (n=282 104) and women who used COC before 2008 (n=370 517). In addition, we excluded prescriptions from pharmacist/veterinarian (n=65), women with age ≥ 50 years (n=519) and prescriptions with missing user age (n=313) and without/with missing prescriber ID (n=895/n=47). We identified 285 009 women who were eligible for analysis.

2.3 Variables

COCs are categorized as pills with levonorgestrel, norethisterone, desogestrel/drospirenone and dienogest/nomegestrol. The year and age for first prescription of COC is categorized into five groups (2008, 2009-2010, 2011-2012, 2013-2014 and 2015-2016/10-14, 15-19, 20-24, 25-29, 30-34 and ≥ 35 years). Health region (Northern, Central, Western and Southern/Eastern) determined residence of users. Information about prescribers comprised gender (male, female), age (≤ 29, 30-39, 40-49, 50-59 and ≥ 60 years) and profession of provider (doctor with no specialty, general practitioner, gynecologist, doctor with other specialty and public health nurse/midwife). Public health nurses and midwifes only had requisition rights for COCs to women between 16 and 19 years old. Doctors with no specialty includes doctors in specialization, postgraduate student from medical school doing their internship and medical students who has a valid license issued in the fifth year of medical school. Doctors with more than one specialty were denoted with the most recent specialty.

2.4 Analyses

All analyses were done in Statistical Package for Social Sciences (SPSS) version 22.0 with Chi-square test for categorical variables at a significance level $p < 0.05$.

When estimating the annual proportion of starters, we applied data for starters from NorPD, while the denominator comprised data for the entire female population 15-49 years from Statistics Norway after adjustment were made for starters in previous years.

3 Results

3.1 Characteristics of starters and prescribers

Over the study years the proportion of starters among women at reproductive age (15-49 years) has been stable at 3.2-3.3%. Most starters are below 20 years, and there has been a relative increase in the proportion of starters among the youngest women (table 3, upper panel).

The proportion of prescriptions to starters in the different health regions has been very stable over time (table 3, central panel).

While general practitioners were the main prescribers the first study years, doctors with no specialty had the highest proportion of prescriptions to starters the last study years (table 3, lower panel). Public health nurses and midwifes prescribed approximately 25% of the COCs. Prescriptions to starters by gynecologists have been low and slightly decreasing over time. Doctors with other specialties had the lowest proportion of prescriptions to starters (table 3, lower panel).

The age of providers has gradually increased during the study period for all professions, except for doctors with no specialty. Among the main prescribers of COCs to starters there has been minimal differences in gender (except for public health nurses and midwifes who are nearly 100% women).

3.2 Prescriptions of different types of COCs 2008-2016

Levonorgestrel has been the most prescribed gestagen in COCs throughout the whole study period. The total prescription rate of COCs with levonorgestrel to starters has increased from 41% in 2008 to 80% in 2016 (table 4, upper panel and figure 1) (X^2-trend; $p < 0{,}000$). The greatest increase is seen from 2011 to 2012, and in 2012 the number of prescriptions of COCs with levonorgestrel to starters became greater than the number of COCs with desogestrel and drospirenone together. After 2012 the prescription rate of COCs with levonorgestrel increased gradually, but the increase was small the last years of the study (figure 1). Pills with dienogest and nomegestrol had a volume of prescriptions to starters

below 1% for each during the whole study period. The prescription rate of COCs with norethisterone have been low and descending (table 4, upper panel and figure 1).

The proportion of starters who have obtained COCs with the lowest dose of estrogen has not changed during the study period (table 4, lower panel). The prescription rate of COCs with levonorgestrel has increased in similar terms for pills with both 20 and 30 μg estrogen, while the prescription rate of COCs with other gestagens, independent of estrogen dose, has decreased.

3.3 Prescriptions and user age

The prescription rate of COCs with levonorgestrel has increased among starters in all age groups (figure 2) (X^2-trend; $p < 0{,}000$; age stratified analyses). The differences between the various age groups were small before 2012, but from then a larger increase is seen among the youngest starters (< 20 years and 20-24 years). The prescription rate of levonorgestrel containing products decreased by increasing age of starters. In 2016, the prescription rate of the recommended COCs ranged from 64.5% among starters aged ≥ 35 to 85% among starters < 20 years (figure 2).

3.4 Prescriptions by profession

All professions increased their prescription rate of COCs with levonorgestrel to starters over the study years (figure 3 and 4) (X^2-trend; $p < 0{,}000$; age and profession stratified analyses). The greatest differences between the various professions are mainly seen after 2011. Public health nurses and midwifes, who only had rights to prescribe to women in this age group, increased their prescription rate of levonorgestrel containing products to the greatest extent, to 96% in 2016 (figure 3). The other main prescribers, general practitioners and doctors with no specialty, increased their prescription rate of COCs with levonorgestrel to 75% and 86% among starters < 20 years. Gynecologists, the providers with the lowest number of prescriptions in this age group, have followed the same pattern as general practitioners. Doctors with other specialty have had the lowest prescription rate of levonorgestrel containing COCs to starters < 20 years throughout the study period, and the rate was 59% in 2016 (figure 3).

The increase in prescription rate of COCs with levonorgestrel seen among starters < 20 years has been less among starters aged > 20 for all provider groups (figure 4). The last study years, the various professions prescribed levonorgestrel containing products in a rate approximately 10% lower to starters aged 25-49 compared with starters < 20 years. Among starters 20-24 years this prescription rate was somewhere in between. The greatest difference in prescription rate of COCs with levonorgestrel between starters below and above 20 years is seen among gynecologists. They have had the lowest prescription rate of levonorgestrel containing products, together with doctors with other specialties, throughout the study period among starters > 20 years (60% in 2016) (figure 4). The majority of prescriptions among gynecologists have been to starters aged 25-49, while general practitioners and doctors with no and other specialties have had a more even distribution of starters in the age groups 20-24 and 25-49 years.

4 Discussion

The total prescription rate of COCs with levonorgestrel to starters has, independent of estrogen dose, increased from 41% in 2008 to 80% in 2016. The greatest increase is seen from 2011 to 2012. This may be related to the updated recommendations by NOMA in 2011, which stated that COCs with levonorgestrel should be the first choice to starters because of the lower risk of VTE. The fact that 4 out of 5 starters obtained the recommended COCs in the first half of 2016, underline high compliance to recommendations.

The greatest increase in prescription rate of recommended COCs is seen among the youngest starters (< 20 years and 20-24 years), and the prescription rate of levonorgestrel containing products decreased by increasing age of starters. Some women included in the study, mainly in the oldest age groups, have used COCs before 2004 and may be ´´restarters´´. The risk of VTE is highest the first few months of use, and restarters who have had a pill-free break of more than one month have the same risk of thrombosis as real starters (45). The restarters in this study have had a break of at least 4 years, and pills with levonorgestrel should be the first choice based on the risk of VTE. Nevertheless, restarters have experiences that may affect what type of COC they want, and this may explain the differences in prescription pattern among women in the different age groups. The

proportion of restarters have decreased during the study period, and the decrease has been greatest among the oldest women. This explains why the proportion of young starters increased during the study years.

Public health nurses and midwifes, who only had requisition rights for COCs to women < 20 years, have increased their prescription rate of COCs with levonorgestrel to starters to the greatest extent, to 96% in 2016. Why this proportion is much higher than for the other professions among starters in the same age group, may be explained by midwifes and public health nurses possibly being more aware of and have higher compliance in general to best practice recommendations. The other main prescribers, doctors with no specialty and general practitioners, prescribed the recommended COCs to 86% and 75% of the starters aged < 20 in 2016. Especially general practitioners may increase their prescription rate of COCs with levonorgestrel to further increase the total proportion of starters obtaining COCs with the lowest risk of VTE. Although gynecologists and doctors with other specialties have had the lowest prescription rate of COCs with levonorgestrel to starters, they have contributed to a small number of prescriptions and thus the influence on the total proportion of starters getting the recommended COCs will be less important for overall use.

All professions prescribed recommended COCs in a smaller proportion to older starters. The greatest difference between starters below and above 20 years is seen among gynecologists, but they probably have a larger amount of prescriptions to restarters compared with the other professions since gynecologists have a higher volume of prescriptions to older women.

The strength of this study is the large dataset with reliable information about prescriptions and providers, and with all prescriptions in the country included based on compulsory electronic reporting from all pharmacies to the NordPD. There are only few excluded cases in the study because of missing information.

The Medical product agency in Sweden and Denmark also updated their recommendations based on the increasing scientific evidence regarding a differential risk of VTE with COC with different gestagens, but Finland and Iceland still have no national guidelines (46). Compared with Norway, where COCs with levonorgestrel constituted a larger proportion from before, the share of the recommended products increased in a larger proportion in Denmark, from 13% in total in 2010 to 50% in 2013. The Danish studies showing a relation between gestagens and VTE (9, 17) received a lot of attention in Denmark, and this may explain the great increase in this country. In Iceland the total proportion of COCs with levonorgestrel increased, in Finland it remained below 1 % contrasting with a slight decrease in Sweden (46). Compared with the other Nordic countries, the changes in the prescription pattern of COCs in Norway, due to the updated recommendations, have been satisfying.

Probably the increased prescription rate of COCs with levonorgestrel in Norway has led to a decreased incidence of VTE among young women in the same period of time. The effect of the changed prescription pattern has to be assessed in future studies.

5 Conclusion

The total proportion of starters who obtained COCs with levonorgestrel increased from 41% in 2008 to 80% in 2016, with the greatest increase from 2011 to 2012. All professions have increased their prescription rate of recommended COCs, mainly among the youngest starters, with the greatest increase among public health nurses and midwifes. Norwegian health personnel do comply relatively well with the new guidelines, but general practitioners may prescribe a larger proportion of the recommended COCs to starters to further increase the population of users with the lowest risk of VTE.

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7 Tables

Table 1. Gestagen and estrogen content in COCs on the Norwegian market 2008-2016.

Gestagen	**Estrogen – type and dosage**
Levonorgestrel	20 μG EE 30 μG EE
Norethisterone	35 μG EE
Desogestrel	20 μG EE 30 μG EE
Drospirenone	20 μG EE 30 μG EE
Dienogest	3+2+2+1 mg estradiol valerate (EV)
Nomegestrol	1,5 mg estradiol (E)

Table 2. The different gestagens in COCs and the associated risk of VTE.

Risk of developing VTE over a year	
Not using COCs and are not pregnant	2 per 10 000 women
COCs with levonorgestrel or norethisterone	5-7 per 10 000 women
COCs with desogestrel or drospirenone	9-12 per 10 000 women
COCs with dienogest or nomegestrol	Not yet known

Table 3. Characteristics of starters of COCs and prescribers 2008-2016 (%).

	2008	**2009-10**	**2011-12**	**2013-14**	**2015-16***
	N=38 128	*N=70 244*	*N=65 796*	*N=64 640*	*N=46 192*
	%	%	%	%	%
USER AGE (YEARS)					
< 20	58,4	62,5	63,2	64,2	65,4
20-24	12,8	12,3	14,0	14,7	14,9
25-29	11,0	9,1	8,3	7,8	7,5
30-34	9,0	7,6	6,6	5,9	5,6
≥ 35	8,7	8,5	8,0	7,4	6,7
HEALTH REGION					
SOUTHERN/EASTERN	53,4	53,2	53,5	53,4	53,1
WESTERN	22,5	23,0	22,8	22,8	23,3
CENTRAL	14,4	14,3	14,2	14,4	14,4
NORTHERN	9,6	9,5	9,5	9,5	9,3
PRESCRIBER					
DOCTORS WITH NO SPECIALTY	21,9	23,7	27,7	31,9	33,5
GENERAL PRACTITIONERS	42,1	37,3	35,1	32,7	31,1
GYNECOLOGISTS	8,9	7,9	7,5	7,0	6,9
DOCTORS WITH OTHER SPECIALTIES	6,7	4,8	3,9	3,6	3,6
PUBLIC HEALTH NURSES/MIDWIFES	20,4	26,3	25,8	24,9	24,9

**Until 30th of June, 2016*

Table 4. Prescription rate of different types of COCs to starters 2008-2016 (%).

	2008	**2009-10**	**2011-12**	**2013-14**	**2015-16***
	N=38 128	*N=70 244*	*N=65 796*	*N=64 640*	*N=46 192*
	%	%	%	%	%
TYPE OF GESTAGEN					
LEVONORGESTREL	41,4	37,3	55,2	73,3	79,3
NORETHISTERONE	6,5	3,4	2,2	1,7	1,4
DESOGESTREL	28,6	37,1	25,9	11,9	7,5
DROSPIRENONE	23,5	21,6	15,5	12,0	11,1
DIENOGEST		0,7	0,9	0,6	0,5
NOMEGESTROL			0,3	0,4	0,3
GESTAGEN/ESTROGEN CONTENT					
LEVONORGESTREL/20 µG EE	25,1	22,3	31,0	42,0	46,4
DESOGESTREL/20 µG EE	27,0	35,5	24,7	11,0	6,8
DROSPIRENONE/20 µG EE	6,9	8,5	6,0	5,8	5,3
LEVONORGESTREL/30 µG EE	16,3	15,0	24,2	31,3	32,9
DESOGESTREL/30 µG EE	1,7	1,6	1,1	0,9	0,7
DROSPIRENONE/30 µG EE	16,6	13,1	8,6	6,3	5,8
NORETHISTERONE/35 µG EE	6,5	3,4	2,2	1,7	1,4
DIENOGEST/3+2+2+1 MG EV		0,7	0,9	0,6	0,5
NOMEGESTROL/1,5 MG E			0,3	0,4	0,3

**Until 30th of June, 2016*

8 Figures

Figure 1. Prescription rate of COCs to starters by gestagen content 2008-2016.

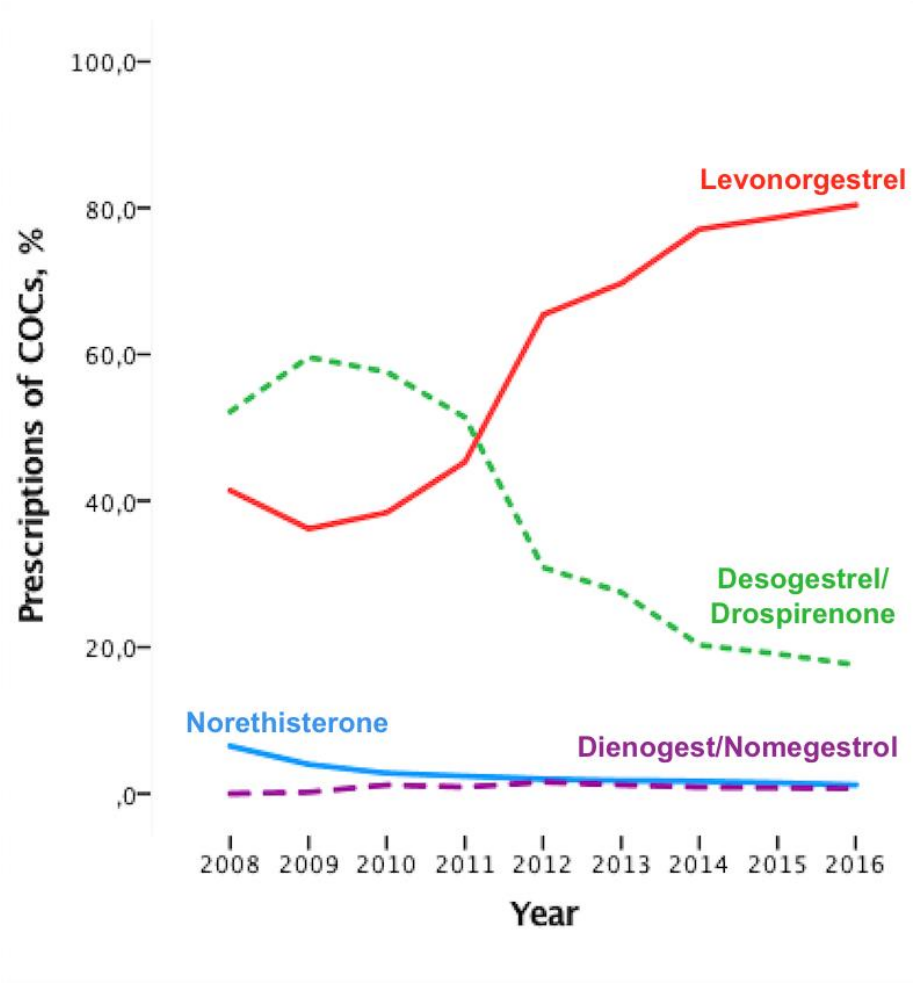


Figure 2. Prescription rate of levonorgestrel COCs to starters by age 2008-2016.

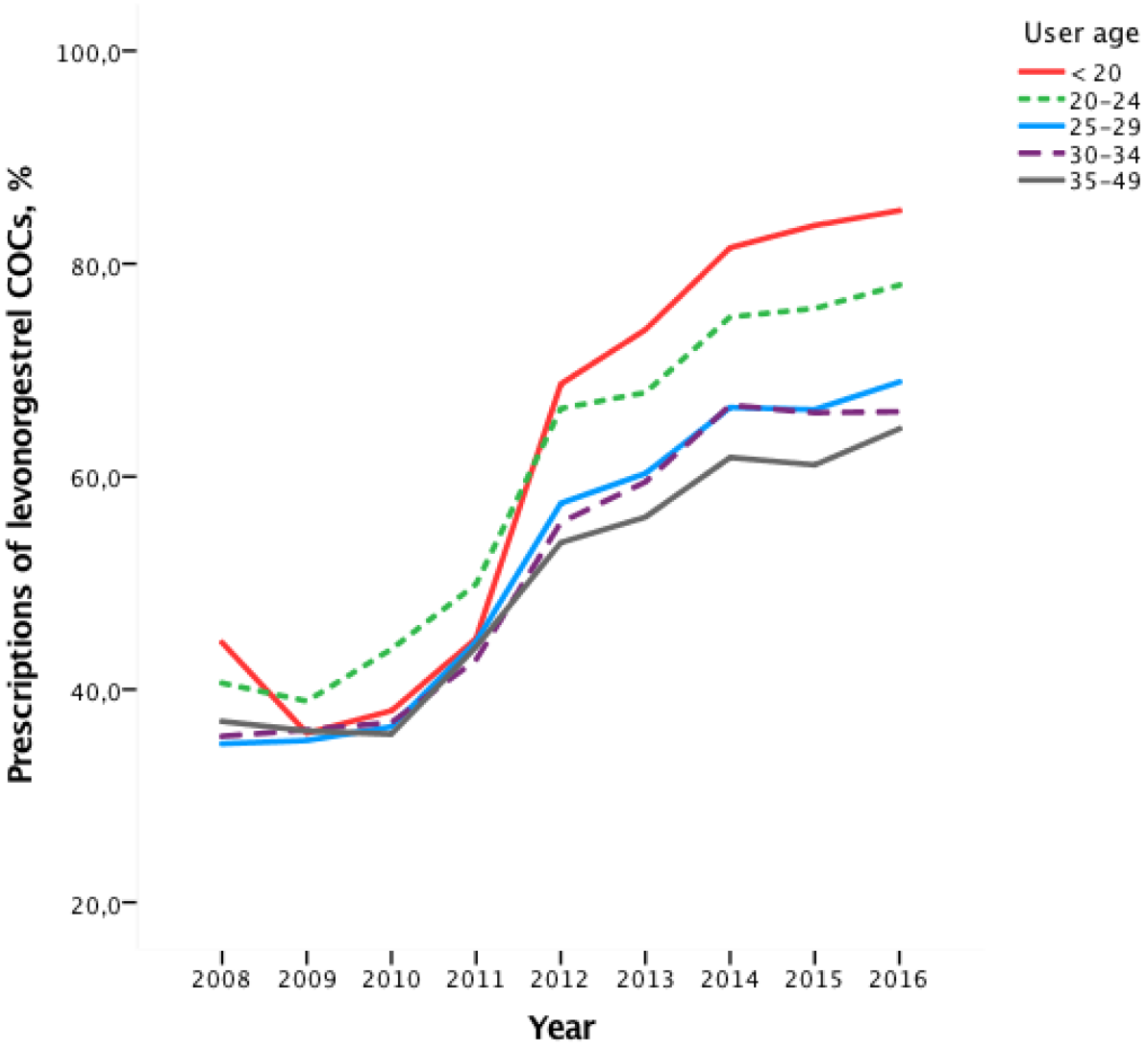


Figure 3. Prescription rate of levonorgestrel COCs to starters < 20 years by profession 2008-2016.

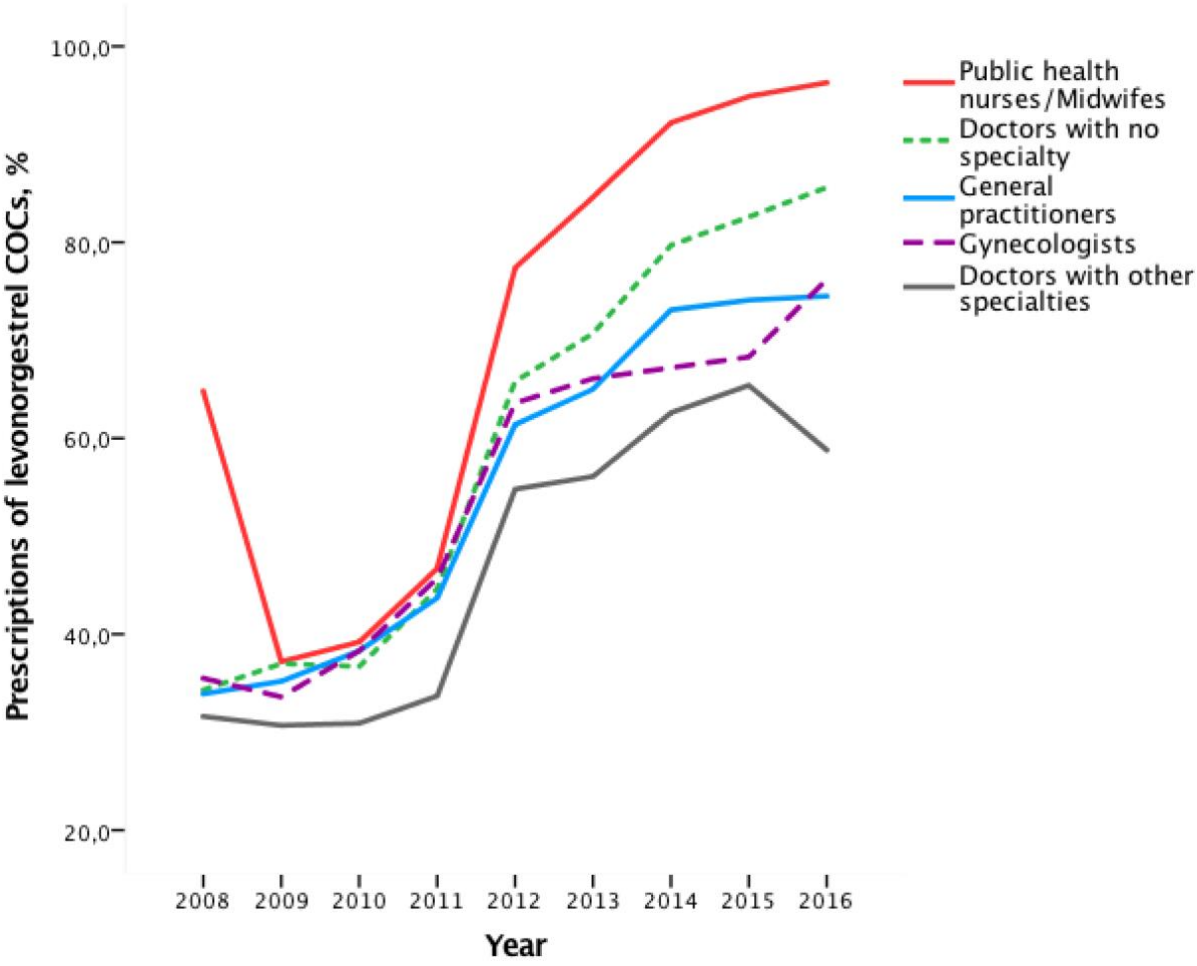
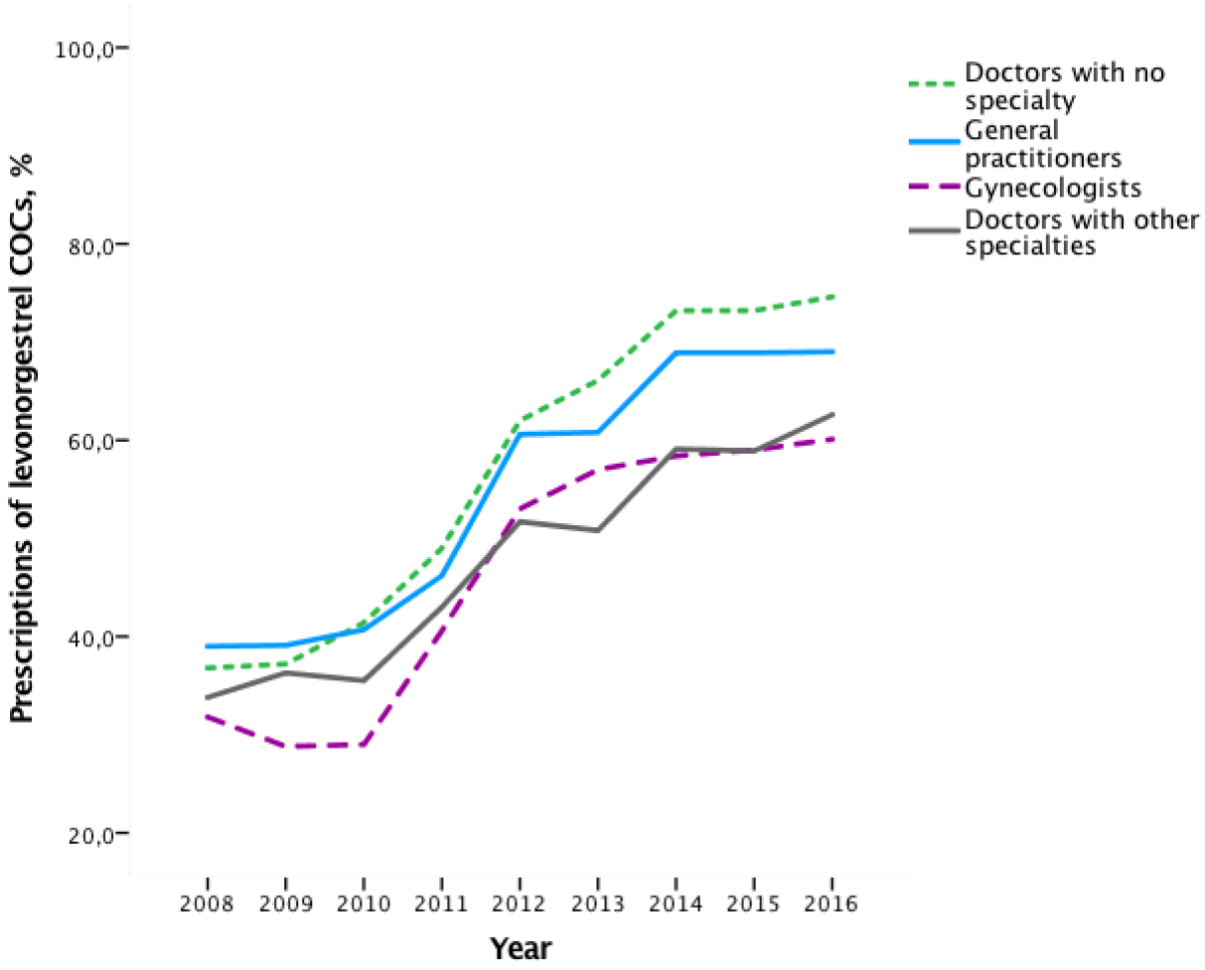


Figure 4. Prescription rate of levonorgestrel COCs to starters ≥20 years by profession 2008-2016.



9 GRADE assessment of main articles

<table>
<tr><td colspan="3">Reference:
Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Büller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995;346:1593-6</td><td>Design: Case-control study
Level of scientific evidence: IIb
Grade: 1-2</td></tr>
<tr><td>Objective
We compared the risk of deep-vein thrombosis (DVT) during use of the newest OCs, containing a third-generation progestagen, with the risk of ''older'' products.
Conclusion
Use of low-dose OCs with a third-generation progestagen carries a higher risk of DVT than the previous generation of OCs.
Country
Netherlands.
Years Data Collection
1988-1992.</td><td>Data source/base population:
Cases selected from the files of three anticoagulation clinics in the Netherlands, which monitor anticoagulant treatment in all patients within a well-defined geographical area. Invited 474 patients (both sexes) with a first episode of proven DVT between Jan 1, 1988 and Dec 31, 1992, who were aged less than 70 and who were not known to have malignant disorders.

Cases (n=126):.
Women aged 15-49 from the population described above.
Excluded: Not pregnant, nor in the puerperium, hat not had a recent miscarriage and hat not used injectable progestagens at the time of their thrombosis.

Controls (n=159):
Each thrombosis patient was asked to find his or her own health control subject according to the following criteria: same sex, the same age (+/- 5 years), no biological relationship, no history of VTE, no use of coumarins for at least 3 months and no known malignant disorder.

Collection of information:
Cases and controls were met for an interview between 1990 and 1993 (6-19 months after the DVT-episode) about risk factors, OC-use and for a blood sample (to determine factor V Leiden gene). Information on the type of OCs used at the time of the thrombosis (or index date in the control) was obtained from the interview supplemented with data from the hospital discharge letter.

Exposure:
• Type of OC (OCs with desogestrel vs. older products)
• Factor V-Leiden mutation or not
• Family history (positive if a first degree relative with VTE/negative)
• Previous pregnancy (ever/never)

Confounding: Age.

Statistical analyses: Logistic regression.</td><td>Users of desogestrel containing OC had a 2.5-fold higher risk (95% CI 1.2-5.2) than users of all other OC types combined.

Family history and previous pregnancy could not explain the excess risk.

Carriers of factor V Leiden mutation has a 8-fold increased risk of DVT with the use of desogestrel containing OC compared with non-carriers.</td><td>Checklist:

1) Were the casus-control groups recruited from comparable sections of the population? Probably, but selection of controls uncertain.
2) Are the groups comparable in relation to important background factors? Not presented.
3) Is the case group condition sufficiently described/the diagnose validated? Not adequately described, but all cases selected from anticoagulation clinics.
4) Is the control group without the actual condition/diseases? Yes (but based on the information from the controls)
5) Has the author considered important confounding factors in design/analyses? Not sufficiently (not BMI/duration of use)
6) Is the exposure for danger/injury/action measured and graded equally in the groups? Not relevant.
7) Was the person who measured the exposure blinded with regard to who was case/control? No.
8) Was the response rate sufficient in both groups? Not presented.

Limitations
- Small number of cases/controls (wide confidence intervals)
- Important backgrounds factor not presented
- Confounding: BMI? Duration of use?
- Recruitment of the controls
- Self-reported exposure (uncertain exposure, recall bias?)</td></tr>
</table>

Reference:	Design: Case-control study	
Dinger J, Assmann A, Möner S, Minh TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care 2010;36:123-29	Level of scientific evidence	IIb
	Grade:	1-2

Objective	Material and methods	Results	Discussion
The primary objective of the study was to clarify whether the use of the oral contraceptive 2 mg dienogest/30 µg ethinyl-estradiol (DNG/EE) is associated with a higher risk of venous thromboembolism (VTE) than the use of other combined oral low-dose contraceptives (i.e. containing ≤ 30 µg EE), particulary oral contraceptives containing levonorgestrel (LNG). The secondary objective was to investigate the VTE risk associated with drospirenone/ethinyl-estradiol (DRSP/EE) in comparison to low-dose LNG/EE. **Conclusion** The study confirms that COC use is associated with an increased risk of VTE. The VTE ORs that compared DNG/EE and DRSP/EE with other low-dose COCs (including LNG/EE) were close to unity and do not indicate a higher risk for users of DNG/EE or DRSP/EE. **Country** Germany. **Years Data Collection** 2002-2008.	**Data source:** Study centres included outpatient offices from primary care sector and specilised diagnostic centres from all federal states of Germany. All women provided written informed consent. **Cases** (n=681): A randomly selected sample of 250 primary care physicians, internists, gynaecologists and radiologists from all federal states of Germany were contacted by mail regarding whether they had seen any cases of VTE between January 2002 and Februar 2008. Eligible cases were women, aged 15-49 years, with a clinical diagnosis of VTE. *Validation of the diagnosis:* Medical records were abstracted by the reporting physican. The diagnosis of VTE had to be confirmed by imaging procedures or clinical examination plus a positive result from a less specific diagnostic test and/or specific anticoagulatory treatment. Missing/illegible information requested from the cases or physicians by telephone interviews. Classification: Definite, probable, no VTE. Eligible cases were asked by their physicians to participate in the study, and completed a questionnaire on personal characteristics, symptoms and signs of VTE, and potential risk factors for VTE. **Controls** (n=2720): Each VTE matched with four community-based controls (i.e. without confirmed or potential VTE) from randomly selected households within the same town as the respective case, matched by age and area of residence. Contacted at their homes by trained interviwers, asked to complete a similar questionnaire. **Exposure:** • COC-use: Never use, ever use (current use/past use) • Type of COC: DNG/EE, low-dose LNG/EE, DRSP/EE, other low-dose COC. **Confounding:** Personal history of VTE, family history of VTE, BMI, duration of COC use, parity, education level, chronic disease, concomitant medication and smoking. **Statistical analyses:** Conditional logistic regression.	Current COC use was associated with about a two-fold increased risk of VTE compared with no use. The VTE ORs that compared DNG/EE and DRSP/EE with other low-dose COCs (including LNG/EE) were close to unity and do not indicate a higher risk for users of DNG/EE or DRSP/EE.	**Checklist:** ***1)*** *Were the casus-control groups recruited from comparable sections of the population?* **Yes**. ***2)*** *Are the groups comparable in relation to important background factors?* **No**, current and ever-use of COCs, obesity, family and personal history of VTE were more prevalent among the cases. ***3)*** *Is the case group condition sufficiently described/the diagnose validated?* **Uncertain** - some insecurity because of missing/illegible information in medical records (n?), and included probable cases. ***4)*** *Is the control group without the actual condition/diseases?* **Uncertain** (only based on what the controls said?) ***5)*** *Has the author considered important confounding factors in design/analyses?* **Yes**, **but** not acute risk factors for VTE (surgery, immobilisation etc.), thus have done sub-analysis of idiopathic VTE. ***6)*** *Is the exposure for danger/injury/action measured and graded equally in the groups?* Not relevant. ***7)*** *Was the person who measured the exposure blinded with regard to who was case/control?* **Uncertain**. ***8)*** *Was the response rate sufficient in both groups?* **No**, 13.1% among cases did not participate. **Limitations** - Limited selection of the total population (based on what the 250 the health workers remember)/Selection of controls/high non-response rate among cases - Self reported exposure/BMI/other risk factors (recall bias?) - Validation of the diagnosis/included propable cases - Not excluded cases with personal/family history of VTE/acute risk factors for VTE (Included non-idiopathic cases? Confounding?) - Industry sponsored

Reference:	**Design: Case-control study**	
Organization WHO. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1995;346:1582-8	Level of scientific evidence:	IIb
	Grade:	2(-3)

Objective	Material and methods	Results	Discussion
A multinational hospital-based case-control study of the risk of venous thromboembolic disease associated with combined oral contraceptives (OCs) done in 1989-93 prompted a separate inquiry comparing the risk of venous thromboembolism (VTE) associated with low oestrogen (<35 µg ethinyl-estradiol) OCs containing levonorgestrel with risks in low oestrogen preparations containing the third-generation progestagens desogestrel or gestodene.	**Base population:** Participating centres where there were any cases or controls who were current users of COCs containing third-generation progestogens (10 of the 21 centres in nine countries). *Excluded*: Died within 24 h of admission, history of stroke/DVT/PE/acute myocardial infarction, natural/surgical menopause, recent history (6 weeks) of pregnancy, major illness causing prolonged bed rest og surgery. **Cases** (n=829): Women admitted to hospital wih idiopathic VTE in the participating centers. *Validation of the diagnosis*: Published data and opinions of four senior clinicians in each centre identified all eligible cases. ValidationBased on medical history, examination and inverstigations: Definite, probable, possible or other cases of DVT/PE. **Hospital controls** (n=2135): 3 female controls for each case matched by hospital, date of admission and age, with one of 27 diagnoses considered to have no association with OC use. **Community controls** (n=506): In the Oxford-region: Up to 2 community controls were randomly selected for each case by referring to the records of the GP with which the case was registered. Contacted by letter/phone call if no answar. No GP-bases controls were interwied for 18 cases. **Interviews:** All cases and controls interwied in standard way, by the same people. The GP-controls were interviewed at home within 4 months of the date of case´s admission to hospital. 11 cases not interwied because of illness/dead, closest available relative or friend interwied. **Exposure:** • Current users: - Third generation progestogens (desogestrel and gestodene) - Levonorgestrel/< 35µg ethinyl estradiol and OCs with norgestimate - Others • Non-users (past and never users) **Confounding:** BMI, live births, alcohol consumption, smoking, hypertension, hypertension in pregnancy, diabetes and varicose veins. **Statistical analyses:** Conditional logistic regression.	OR for current use of OCs containing desogestrel og gestodene was 2,6 compared with current use of OCs containing levonorgestrel.	**Checklist:** ***1)*** *Were the casus-control groups recruited from comprable sections of the population?* **Yes**, cases/controls from the same place. ***2)*** *Are the groups comparable in relation to importan background factors?* **Some differences**, but adjusted for in the analyses. ***3)*** *Is the case group condition sufficiently described/the diagnose validated?* **Yes**, but varying degrees of certainty (taken into accunt in the analyses). ***4)*** *Is the control group without the actual conditon/disease?* **Yes**. ***5)*** *Has the author considered important confounding factors in design/analyses?* **Yes**. ***6)*** *Is the exposure for danger/injury/action measured and graded equally in the groups?* Not relevant. ***7)*** *Was the person who measured the exposure blinded with regard to who was case/control?* **No**. ***8)*** *Was the response rate sufficient in both groups?* **No**, low response rate among GP-controls. **Strengths** - Adjustment for important confounders **Limitations** - Self reported and uncertain exposure/BMI/other risk factors (information bias?) - Varying resultats among GP- and hospital controls (selection bias?) - High non-respons rate among GP-controls
Conclusion Current users of low oestrogen dose combined OCs containing desogestrel or gestodene appear to be at higher risk of VTE than users of combined OCs containing levonorgestrel.			
Countries Colombia, UK (Oxford region), Jamaica, Tyskland, Ungarn, Chile, Brasil, Hong Kong and Thailand.			
Years Data Collection 1989-93.			

Reference: Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenon or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ 2011;340:d2139.			**Design: Case-control study** Level of scientific evidence: IIb Grade: 3
Objective	**Material and methods**	**Results**	**Discussion**
To examine the risk of non-fatal idiopathic venous thromboembolism in current users of a combined oral contraceptive containing drospirenon, relative to current users of preparations containing levonorgestrel. **Conclusion** These findings contribute to emerging evidence that the combined oral contraceptive containing drospirenone carries a higher risk of venous thromboembolism than do formulations containing levonorgestrel. **Country** UK. **Years Data Collection** 2002-2009.	**Data source:** UK General Practice Research Database. **Base population:** Starters of a new episode of oral contraceptives (received from GP) containing 30µg oestrogen in combination with either drospirenone or levonorgestrel in the age group 15-44 years after 1st of May 2002. The date of the first new prescription for a study OC as the date of entry into the study cohort. *Excluded:* History of VTE, cancer, chronic renal failure, myocardial infarction, stroke, other cardiovascular disease, treated hypertension, treated hyperlipidaemia, type 1 diabetes, colitis, SLE, RA, spondylopahies, psoriatic arthritis, cystic fibrosis, injecting drug use and coagulation defects. **Cases** (n=61)**:** Women who had a recorded diagnosis of non-fatal idiopathic venous thromboembolism after their entry into the cohort (index date) and were current users of a sturdy oral contraceptive (a prescription that would have extended to the index date or to within 30 days of the date). The case had to have at least one year of recorded medical information before the index date. *Excluded*: Women with important clinical risk factors for VTE within the 3 months before the index date: Pregnancy, surgery, major injury, or prolonged immobility. *Validation of the diagnosis:* Treated with an anticoagulant and not receiving prescriptions for OC after the index date. Received hospital discharge/outpatient clinic letters for 31 cases, four cases considered non-idiopathic. **Controls** (n=215)**:** Up to four controls matched by age, number of years of recorded data and general practice. Had to be current users of a study OC and to have hat at least one year of recorded medical information before index date. Same exclusion criteria as cases. **Exposure:** COCs with 30µg estrogen and either drospirenone or levonorgestrel. **Confounding:** BMI, history of varicose veins, smoking status, antidepressant use and duration of use. **Statistical analyses:** Logistic regression.	Current use of the drospirenone contraceptive was associated with a threefold higher risk of non-fatal idiopathic venous thromboembolism compared with levonorgestrel use. OR, adjusted for BMI, 3.3 (95% CI 1.4-7.6).	**Checklist:** ***1)*** *Were the casus-control groups recruited from comparable sections of the population?* **Yes** (data from the entire population/country) ***2)*** *Are the groups comparable in relation to important background factors?* **Some differences** adjusted for in the analyzes. ***3)*** *Is the case group condition sufficiently described/the diagnose validated?* **Yes**, with hospital discharge/outpatient clinic letters for 31 of the 61 cases. ***4)*** *Is the control group without the actual condition/disease?* **Yes**. ***5)*** *Has the author considered important confounding factors in design/analyses?* **Yes**. ***6)*** *Is the exposure for danger/injury/action measured and graded equally in the groups?* Not relevant. ***7)*** *Was the person who measured the exposure blinded with regard to who was case/control?* **Uncertain**. ***8)*** *Was the response rate sufficient in both groups?* Not relevant. **Strengths** - Reliable data on contraceptive use (no recall bias) - An entire population (but only women who have obtained their contraceptives from GPs) **Limitations** - Small number of cases (wide confidence intervals) - Validation: Not specified treatment time with anticoagulant. Did not obtain copies of hospital discharge/outpatient clinic letters for all cases, possibly some non-idiopathic cases included?

Reference: Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ 2011;340:d2151.			**Design: Case-control study** Level of scientific evidence: IIa Grade: 3
Objective	**Material and methods**	**Results**	**Discussion**
To compare the risk of non-fatal venous thromboembolism in women receiving oral contraceptives containing drospirenone with that in women receiving oral contraceptives containing levonorgestrel. **Conclusion** The risk of non-fatal venous thromboembolism among users of oral contraceptives containing drospirenone seems to be around twice that of users of oral contraceptives containing levonorgestrel, after the effects f potential confounders and prescribing biases have been taken into account. **Country** US. **Year Data collection** 2002-2008.	**Data source:** PharMetrics database. **Base population:** Users of COCs with 30 µg ethinyl estradiol and either drospirenone or levonorgestrel in the age group 15-44 years from 1st f January 2002 until the end of December 2008. *Excluded*: Women with risk factors for VTE, as any history of cancer, renal failure, chronic cardiovascular disease or inflammatory or autoimmune conditions. **Cases** (n=186): Women aged 15 to 44 years who were current users of COCs with drospirenone or levonorgestrel and who had a first-time recorded claim for a clinically diagnosed VTE in 2002 or later (index date). Cases had to have at least 6 months of medical history before the index date. Current user defined as having a recorded claim for a prescription of a study contraceptive whose filled use extended to within 30 days before the index date or beyond the index date. *Validation of the diagnosis*: Long term anticoagulation must have been started promptly, and no contraceptive containing estrogen could be prescribed after index date. No validation through review of primary records. *Excluded*: Women with important clinical risk factors for VTE within the 90 days before the index date: Severe lower limb injury, major surgery, severe trauma or pregnancy. **Controls** (n=681): 4 controls to each case, matched by year of birth and the index date of the case, who was current users of one of the study contraceptives after 1st of January 2002. All had to have at least six months of enrolment in their health plan before index date. The same exclusion criteria to controls as to cases. **Exposure:** COCs with 30 µg EE and either drospirenone or levonorgestrel. **Confounding:** Duration of use, switching from a different hormonal contraceptive, obesity, other comorbidities and number of visits to a physician or emergency room in the six months before the index date. **Statistical analyses:** Conditional logistic regression.	Conditional OR for VTE for COCs with drospirenone compared to levonorgestrel was 2.3. None of the included confounders was significant (minimum 10 % change in OR).	**Checklist** ***1)*** *Were the casus-control groups recruited from comparable sections of the population?* **Yes**, all recruited from the British population by the PharMetrics database. ***2)*** *Are the groups comparable in relation to important background factors?* **Yes**. Some differences that are adjusted for in the analyzes. ***3)*** *Is the case group condition sufficiently described/the diagnosis validated?* **Yes**, but not through review of primary records. ***4)*** *Is the control group without the disease?* **Yes**. ***5)*** *Has the author considered important confounding factors in design/analyses?* **Yes**, **but** family disposal and BMI not included. ***6)*** *Is the exposure for danger/injury/action measured and graded equally in the groups?* Not relevant. ***7)*** *Was the person who measured the exposure blinded with regard to who was case/control?* **No**. ***8)*** *Was the response rate sufficient in both groups?* Not relevant. **Strengths** - An entire population - Comparable groups - Exclusion criteria **Limitations** - Missing informastion about BMI and family history, but has probably little impact because these women will not get a COC - Validation: May have included some false cases/non-idiopathic cases or missed cases

Reference: Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423.			**Design: Cohort study** Level of scientific evidence: IIa Grade: 3(-4)
Objective	**Material and method**	**Results**	**Discussion**
To assess the risk of venous thromboembolism from use of combined oral contraceptives according to progestogen type and oestrogen dose. **Conclusion** After adjustment for length of use, users of oral contraceptives with desogestrel, gestodene, or drospirenone were at least at twice the risk of venous thromboembolism compared with users of oral contraceptives with levonorgestrel. **Country** Denmark. **Years Data collection** 2001-2009	**Data source:** - Statistics of Denmark, identification of the women and level of education. - National register of medical products (tilsv. NorPD), use of hormonal contraception. - National Registry of Patients (tilsv. NPR) ICD-10. - National cause of death registry **Included** (n=1 436 130): Women 15-49 years from 1 January 1995 to 31 December 2009. **Excluded** (n=140 010): Women with a history of any type of venous or arterial thrombotic events, with malignancy, undergone gynecological surgery, pregnancy, ovarian stimulation and women with coagulation disturbances (n=140 010) **Outcome** (n=4307): First event VTE. **Validation of the diagnosis:** Anticoagulation therapy for at least four weeks (67,1%). Validated hospital charts of 200 randomly selected women (76%). **Main exsposure:** • Use of COC: Current user (starting/new/restarted/switched use) and non-user (never/former use). • Type of gestagen: Norethisterone, levonorgestrel, norgestimate, desogestrel, gestodene, drospirenone, cyproterone. • Estrogen dose: 50 µg, 30-40 µg, 20 µg. • Duration of use: Duration of actual use. Categorization: < 3 months, 3-12 months, >12 months ≤4 years, >4 years. • Type of hormonal contraception: COC, POP, hormonal IUD. **Confounding:** Age, calendar year (to deal with potential long-term confounding by body mass index) and education. **Statistical analyses:** Poisson regression.	The RR of VTE decreased with decreasing estrogen dose, no differences was apparent between COCs with drospirenone and 30 and 20 µg estrogen. Compared to non-users, RR of VTE in current users of COCs with levonorgestrel was 2.19, with desogestrel 4.21, with gestodene 4.23 and with drospirenone 4.47. Use of COCs with new gestagens gives twice as high risk of VTE compared to COCs with levonorgestrel (unchanged when adjusted for length of use). The risk of VTE was not increased with use of POP and IUD. RR for VTE increased with increasing age and was reduced with increasing length of education.	**Checklist:** ***1)*** *Are the groups comparable in relation to important background factors?* **Yes**, those included in the study are all women with registered exposure and outcome (the whole country). ***2)*** *Are the groups recruited from the same section of the population?* **Yes**. ***3)*** *Were the exposed individuals representative for a defined section of the population?* **Yes**, all ethnical groups in Denmark included. ***4)*** *Was the study prospective?* **Yes**. ***5)*** *Were exposure and outcome measured equal and reliable in the two groups?* **Yes**. ***6)*** *Were sufficient number of persons in the cohort followed up?* **Yes**, all women in Denmark. ***7)*** *Is it performed drop out analyses?* Of less importance. ***8)*** *Was the follow up time lengthy enough to prove positive and/or negative outcomes?* **Yes**. ***9)*** *Are important confounding factors in design/implementation considered?* **Uncertain**. Age, calendar year and education included. Comorbidity? ***10)*** *Was the person who evalueted the results (end points) blinded group identification?* Unlikely to matter because of the large database, but those validated hospital charts were blinded. **Strengths** - Reliable data on contraceptive use - An entire population/great number of person-years - Good validation of the diagnosis **Limitations** - Confounders: Comorbidity?