

AOGS MAIN RESEARCH ARTICLE

# Oral contraception in Denmark 1998–2010

NADIA M. WILSON<sup>1</sup>, MAJA LAURSEN<sup>2</sup> & ØJVIND LIDEGAARD<sup>1</sup>

<sup>1</sup>Gynecological Clinic, Rigshospitalet University Hospital, University of Copenhagen, Copenhagen, and <sup>2</sup>Danish Medicines Agency, Copenhagen, Denmark

## Key words

Combined oral contraceptives, estrogen dose, oral contraceptives, progestins, progestogens

## Correspondence

Nadia M. Wilson, Rigshospitalet University Hospital, Gynecological Clinic, University of Copenhagen, 2100 Copenhagen, Denmark.  
E-mail: nadia.mynster.wilson@gmail.com

## Conflict of interest

All authors have completed the Unified Competing Interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf), and declare that: Øjvind Lidegaard has within the last three years received honoraria for speeches in pharmacoepidemiological issues, including fees from Bayer Schering Pharma Denmark and Novo Nordisk. The primary investigator will be an expert witness in a legal US case in 2011–2012. Nadia M. Wilson and Maja Laursen had nothing to declare.

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## Introduction

The pill is still the most popular contraception in Europe, and Denmark is no exception (1,2). Its popularity reflects an overall positive benefit–risk ratio. Among the non-contraceptive benefits are a regular bleeding pattern, less menstrual bleeding and reduced dysmenorrhea. The most important risk is a several-fold increased risk of venous thromboembolism.

The traditional pill consists of the synthetic estrogen ethinylestradiol (EE) and a synthetic progesterone-acting

## Abstract

**Background.** Oral contraceptives (OC) are the most popular contraception in Denmark. Overall figures on use are well described, but more detailed use patterns according to type and age need to be updated. **Objectives.** To assess trends in the use of OC including progestogen-only pills among Danish women in 1998–2010 and to describe in detail use patterns in 2010. **Design.** Annual cross-sectional prescription statistics. **Setting.** Denmark. **Population.** Danish women 10–49 years old. **Material and methods.** Analysis of prescription data from the National Registry of Medicinal Products Statistics from 1 January 1998 through 31 December 2010. **Results.** Combined OC (COC) with 50 µg estrogen decreased their market share from 3% in 1998 to zero in 2010, and COC with 30–40 µg estrogen decreased to 50% in 2010, in contrast, COC with 20 µg estrogen increased to 46% in 2010. Progestogen-only pills accounted for 4%. COC with levonorgestrel decreased, while the use of pills with desogestrel and gestodene among two-thirds of current users was constant. **Conclusion.** Low-dose COCs gradually replaced middle-dose pills. Pills with newer progestogens are used primarily by young women, and 85% of users in 2010 were on products with desogestrel, gestodene, drospirenone or cyproteroneacetate. We still need low-dose pills with 1<sup>st</sup> and 2<sup>nd</sup> generation progestogens on the Scandinavian market.

**Abbreviations:** COC, combined oral contraceptives; DDD, defined daily dose; EE, ethinylestradiol; OC, oral contraceptives; POP, progestogen-only pills.

hormone called progestogen. A new pill introduced in 2009 contains the natural estrogen estradiolvalerate and the old progestogen dienogest (3). Estrogen dose varies from 50 to 20 µg EE. Pills without estrogen are the so-called progestogen-only pills (POP) (4). Along with a reduction in the estrogen dose, new types of progestogens have been developed. Although a classification into different generations is widely used, it is not quite consistent. Most frequently, the term first generation (1<sup>st</sup>) combined oral contraceptives (COC) pertains to older high-dose pills with 50 µg EE. As

**Table 1.** Categorization of different types of oral contraceptives according to estrogen type and dose and progestogen type. White areas indicate that the combination was available in Denmark in 1998–2010.

Groups	Progestogen type						
	Norethis- terone	Levo- norgestrel	Norges- timate	Deso- gestrel	Gesto- dene	Dros- pirenon	Cypro- terone
50ug EE	High dose		Patch	Vg. Ring			
30-40ug EE	1st	2nd	2nd	3rd	3rd	4th	
15-20ug EE							
0ug EE (POP)	POP			a)			
E2V-dienogest	b)						

<sup>a)</sup>Cerazette<sup>®</sup>; <sup>b)</sup>E2V-dienogest = estradiol valerate-dienogest = Qlaira<sup>®</sup>. Vg. Ring, vaginal ring or NuvaRing<sup>®</sup>; Patch, Evra<sup>®</sup>; EE, ethinylestradiol; POP, progestogen only pills; 1<sup>st</sup> = first generation oral contraceptives (OC); 2<sup>nd</sup>, second generation OC; 3<sup>rd</sup>, third generation OC; 4<sup>th</sup>, fourth generation OC.

these products are no longer on the market in Denmark, we restrict the term 1<sup>st</sup> generation to COCs with norethisterone. Second generation (2<sup>nd</sup>) pills include COCs with norgestrel, levonorgestrel or norgestimate, and third generation (3<sup>rd</sup>) pills include those with desogestrel or gestodene (4). A fourth generation (4<sup>th</sup>) pill can be added, describing the more recently synthesized progestogen drospirenone, which in addition to a progesterone effect also has an anti-mineralocorticoid effect (5). A COC with cyproterone acetate has not been classified in terms of the generation concept.

A nuanced discussion of the risk profile of different oral contraceptives (OC) implies knowledge of the use of different OCs among women according to age and calendar year. The objective of this article was to analyse trends in the use of OC among Danish women in 1998–2010, and to assess the distribution of different types of OC by age. Parenteral hormonal contraceptive products such as contraceptive patches, the vaginal ring and the levonorgestrel intrauterine system (LNG-IUS) have in recent years been introduced on the market, but will not be dealt with in this study, which focuses on oral contraceptives.

## Material and methods

This study is based on data from the National Registry of Medicinal Products (statistics), where sales data from pharmacies in the primary health care sector have been collected since 1994. This national registry records all redeemed prescriptions for Danish citizens according to Anatomical Therapeutic Chemical (ATC) codes, including the amount prescribed in defined daily doses (DDD). Included in this

review is the sale of combined OCs and POPs among Danish women 10–49 years old from 1 January 1998 to 31 December 2010. The different types were categorized according to estrogen dose and progestogen type, as indicated in Table 1.

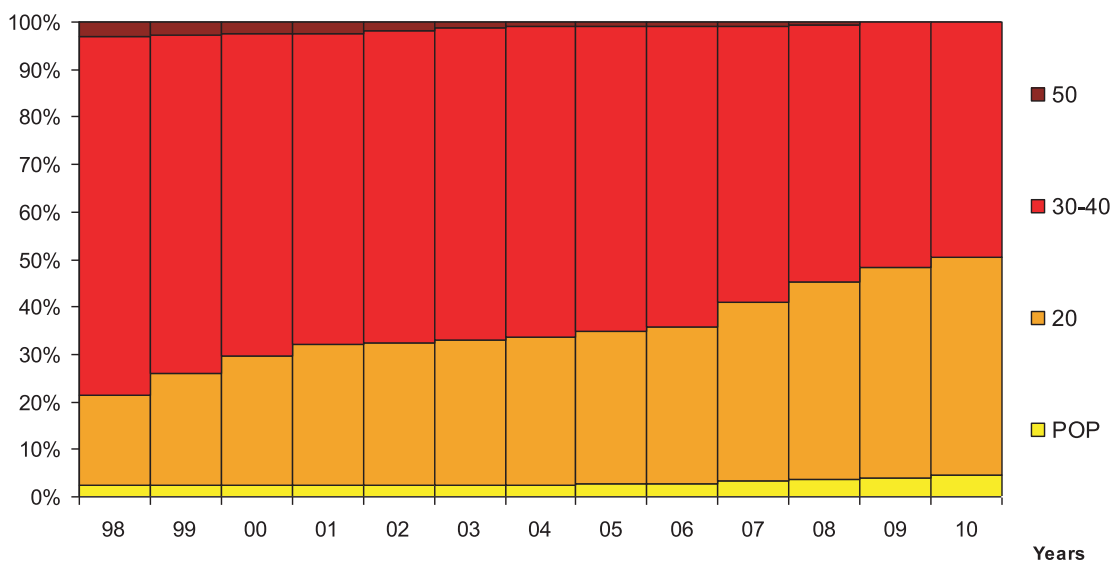
The study was approved by the Danish Data Protection Agency (J.no: 2010–41-4778). Ethical approval is not requested for registry-based studies in Denmark.

## Results

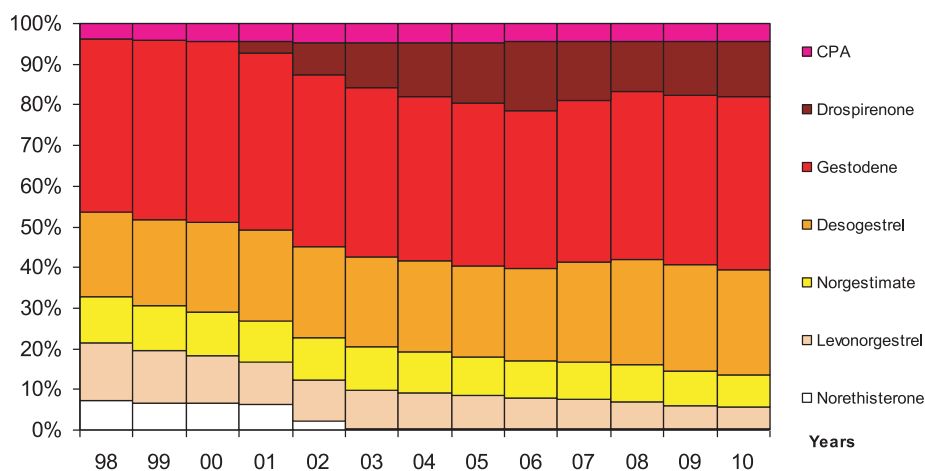
From 1998 to 2010 there was an overall increase in sales of OCs from 331 477 to 352 062 DDD per day, corresponding to an increase from 28.5 DDD per 100 women 15–49 years old in 1998 to 32.6 DDD per 100 women in 2010.

The changes through the study period according to estrogen dose are illustrated in Figure 1. The sale of COCs containing 50 and 30–50  $\mu\text{g}$  EE decreased gradually in favor of low estrogen COCs with 20  $\mu\text{g}$  EE. The use of POP demonstrated a slight increase from 2.5% in 1998 to 4.5% in 2010. COCs with 30–40  $\mu\text{g}$  EE still make up the greatest share of the market despite a decrease from 75.7% in 1998 to 49.6% in 2010. In 1998, COCs containing 50  $\mu\text{g}$  EE already accounted for a limited 3% of the sale, which in 2004 had decreased to 0.95% and in 2010 to 0%. In contrast, the sale of COCs with 20  $\mu\text{g}$  EE increased from 18.8% in 1998 to over 31.1% in 2004 and 45.8% in 2010.

Figure 2 shows the sale of COCs, POPs excluded, in the period by progestogen type. In that time, COCs with desogestrel and gestodene had a stable and dominating two-thirds share of the market. From 2001, the new COC with drospirenone



**Figure 1.** Development of distribution of different oral contraceptives including progestogen-only pills (POP) according to estrogen dose (50, 30–40, 20 µg ethinylestradiol (EE)) in 1998–2010 in Denmark.



**Figure 2.** Development of distribution of different combined oral contraceptives according to progestogen type through the period 1998–2010. CPA, cyproteroneacetate.

increased its market share to 16.9% of the COC market in 2006, followed by a decrease the next two years, stabilizing at 13.6% in 2010. At the same time the market share of COCs with levonorgestrel decreased from 14.3% in 1998 to 5.4% in 2010. Use of a COC with norgestimate decreased from 11.2% in 1998 to 8.0% in 2010 and use of a COC with norethisterone fell from a market share of 7.3% in 1998 to virtually no sale (0.2%) in 2010. The COC with cyproteroneacetate had a stable market share of 3.9–4.9%.

Details of the market shares of the different combinations of estrogen dose and progestogen type in 2010 and 1998 are given in Table 2. In 1998, 3<sup>rd</sup> generation COCs

(desogestrel and gestodene) with 30 µg EE had a share of 42.9% and 20 µg EE 18.8%, a total of 61.7%. COCs with norethisterone and levonorgestrel accounted for 7.1 and 13.9%, respectively. COCs with norgestimate had an 11% share of the market and cyproteroneacetate 3.8%. A POP with norethisterone accounted for 2.2% and a POP with levonorgestrel 0.3%, making a total of 2.5%. In 2010, 3<sup>rd</sup> generation COCs with 20 µg EE accounted for 40.8%, and those with 30 µg EE for 24.3% of the market, or 65.1% in total. In 2010, the COC with drospirenone represented 12.9% of the market, and norgestimate 7.6%. COCs with levonorgestrel had 5.1% of the market and COCs with

**Table 2.** Use of different oral contraception as a percent of total use by specific combinations of estrogen type and dose and progestogen type in Denmark in 1998 and 2010.

		1998					
Groups	Estrogen dose	Progestogen type					
		Norethis-terone	Levo-norgestrel	Norges-timate	Deso-gestrel	Gesto-dene	Dros-pirenone
	50ug EE	1.6	1.4	-			
	30-40ug EE	5.5	12.5	11	7.8	35.1	3.8
	15-20ug EE				12.5	6.3	
	0 ug EE (POP)	2.2	0.3		0		

		2010					
Groups	Estrogen dose	Progestogen type					
		Norethis-terone	Levo-norgestrel	Norges-timate	Deso-gestrel	Gesto-dene	Dros-pirenone
	50ug EE	0	0	-			
	30-40ug EE	0.2	5.1	7.6	4.9	19.4	4.1
	15-20ug EE				19.6	21.2	4.8
	0 ug EE (POP)	1.6	0		2.9		
	E2V-dienogest	0.4					

EE, ethinylestradiol; POP, progestogen-only pills; E2V-dienogest, estradiol valerate-dienogest = Qlaira®.

cyproteroneacetate 4.1%. A POP with norethisterone accounted for 1.6% and a POP with desogestrel 2.9%, or 4.5% in total.

Figure 3 shows the distribution of COCs according to progestogen type in different age groups. The newer products have had a relatively higher market share in younger age groups as compared with older products. In women below 30 years, only a few used COCs with levonorgestrel and up to more than 90% were users of 3<sup>rd</sup> or 4<sup>th</sup> generation COCs or a COC with cyproteroneacetate.

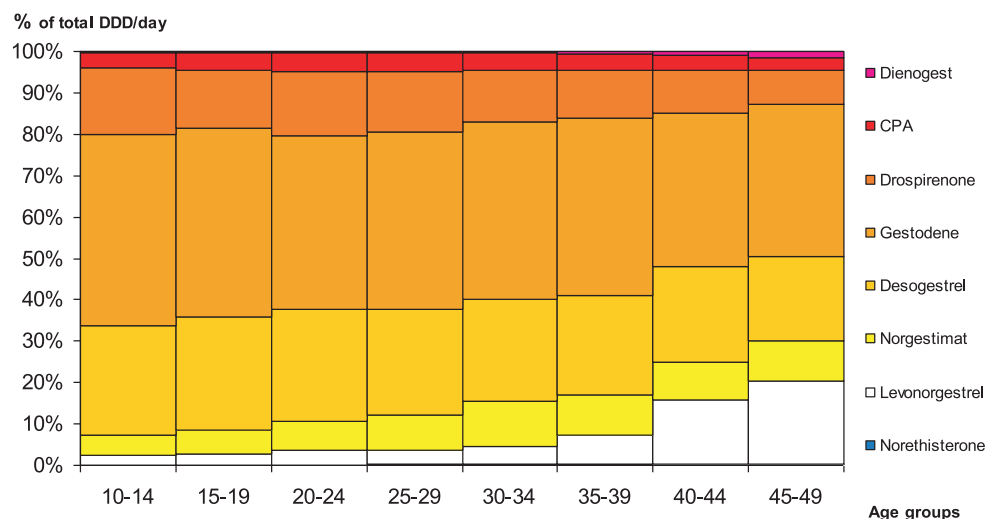
In Figure 4 we have displayed the age distribution for selected types of COCs according to progestogen type. This demonstrates more clearly the very different age profiles that the different COC types are associated with. The most left-shifted curve shows the COCs with desogestrel. The curves for COC with gestodene, cyproteroneacetate and drospirenone had a similar course (not shown). COCs with norgestimate are still predominant with young women. COCs with lev-

onorgestrel had a biphasic course with maximum in the age groups 20–24 years and 40–44 years. Finally, a COC with dienogest (Qlaira®· Bayer Pharmaceuticals, Berlin, Germany) had the most right-shifted curve, with a predominance among women >30 years.

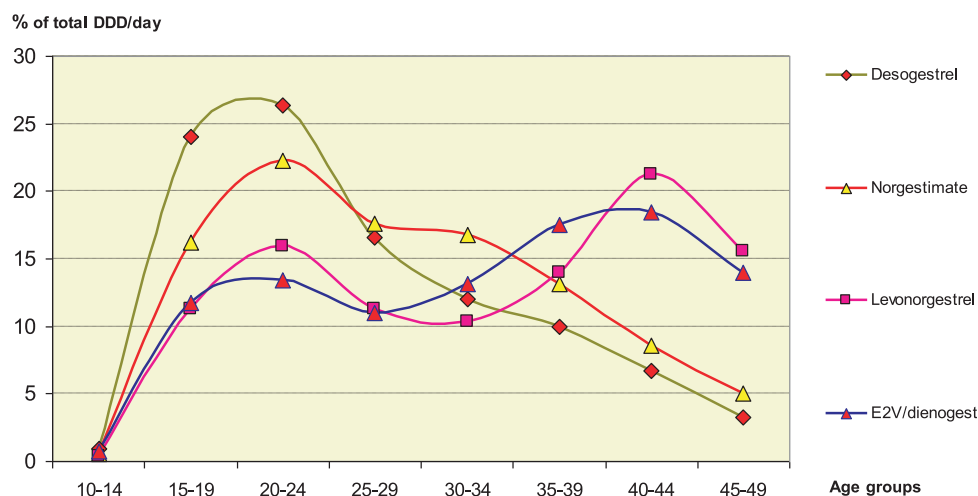
## Discussion

Oral contraceptives are still increasing their contraceptive market share in Denmark, where a third of the women of reproductive age is on the pill. The move toward pills with lower doses of estrogen is seen all over the world, and use of pills with the lowest dose of estrogen (20 ug EE) approaches half of the market.

In contrast, Denmark is a European exception concerning the high proportion of women being on OCs with 3<sup>rd</sup> generation progestogens. In the Netherlands, for example, the use of 2<sup>nd</sup> generation levonorgestrel accounted for the largest



**Figure 3.** Use of different combined oral contraceptives in Denmark 2010 according to progestogen type in percentages of the total defined daily dose/day sold in each age group. DDD, defined daily dose; CPA, cyproteroneacetate.



**Figure 4.** Age distribution of selected combined oral contraceptive users according to progestogen type in Denmark 2010. DDD, defined daily dose; E2V/dienogest, estradiol valerate-dienogest = Qlaira®.

proportion (21%) in a recent study control group, and the second largest proportion were 3<sup>rd</sup> generation desogestrel (6%) and gestodene (4%) (6). Unlike Denmark, pills with 30  $\mu\text{g}$  were the most commonly used dose of estrogen in the control group (84%) compared with 20  $\mu\text{g}$  (11%) and 50  $\mu\text{g}$  (4%). One reason for the low use of the older 1<sup>st</sup> and 2<sup>nd</sup> generation pills could be better compliance associated with the newer progestogens (5). Another reason could be the request for low-dose pills, which are not available for 1<sup>st</sup> and 2<sup>nd</sup> generation COCs. As these older progestogens might imply a lower risk of thromboembolic complications compared with the newer progestogens (7), COCs with 20  $\mu\text{g}$  EE combined

with 1<sup>st</sup> and 2<sup>nd</sup> generation progestogens are needed in the Scandinavian countries.

The findings according to age confirm first that newer products (except Qlaira®) are still taken more often by younger women of reproductive age, whereas women of older reproductive age continue to use the pills they have used for years and have been satisfied with.

Although a COC with drospirenone has continued to increase in its market share since it was introduced in 2001, in Denmark high media attention on isolated cases of venous thromboembolism in 2007 caused a decreased sale the following three years.

OCs are widely used in other Scandinavian countries. In Norway and Sweden the prevalence of OC use is also increasing. In Norway, among married women aged 15–49 years, OC use increased from 20.6% in 1998 to 31.0% in 2005. In Sweden, older data show an increase from 23% in 1981 to 27.4% in 1996. Presumably, the prevalence is even higher today. This pattern applies for other European countries, such as the UK, where the prevalence has increased from 22.0% in 1998 to 28.0% in 2008/2009. Thus Denmark has one of the highest percentages of OC use in Europe (8). In the USA, low-dose COCs with 1<sup>st</sup> and 2<sup>nd</sup> generation progestogens have a large share of the market (9), although COCs with drospirenone recently became the market leaders.

The National Registry of Medicinal Products statistics are based on transfer of a sale electronically by bar codes, which makes these statistics rather reliable. They also include parallel imports and re-imports. The use among citizens buying medicine on-line from foreign countries is, however, not included. This proportion is still quite low, but could increase in the years to come. Medicine that is sold is not necessarily taken. However, the vast majority of women get new prescriptions every three months. It is difficult to imagine such a practice prevailing if the women did not take the bought medicine. As for those few women with only one prescription, some might have terminated their use before expiry of the prescription.

This study did not include the newer parenteral products such as patches, implants, vaginal rings, the levonorgestrel intrauterine system and subcutaneous depot injections. Although these products are important alternatives to OCs they still have a limited market share and have therefore only influenced the use of oral contraceptives to a minor extent.

## Conclusions

Over a decade, low-dose COCs have gradually replaced middle-dose pills. In Denmark, OCs with the newer progestogens desogestrel, gestodene and drospirenone have dominated the market throughout the last decade, whereas OCs with levonorgestrel, norgestimate and POPs each account for about a 5% market share. Pills with newer progestogens are used primarily by young women. Recent studies suggesting a

differential risk of venous thrombosis associated with the use of COC containing different progestogens warrant attention and a reconsideration of the use of COCs with older progestogens over the coming years. Low-dose pills with 1<sup>st</sup> and 2<sup>nd</sup> generation progestogens also need to be introduced in the Scandinavian countries.

## Funding

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