

# BMJ Open Continuation rates of oral hormonal contraceptives in a cohort of first-time users: a population-based registry study, Sweden 2005–2010

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## ABSTRACT

**Objective:** To investigate if continuation rates in first-time users of oral hormonal contraceptives differed between different formulations and to measure if the rates were related to the prescribing categories, that is, physicians and midwives.

**Design:** A longitudinal national population-based registry study.

**Setting:** The Swedish prescribed drug register.

**Participants:** All women born between 1977 and 1994 defined as first-time users of hormonal contraceptives from 2007 to 2009 (n=226 211).

**Main outcome measures:** A tendency to switch the type of hormonal contraceptive within 6 months use and repeated dispensation identical to the first were estimated as percentages and relative risks (RRs). Physicians' and midwives' prescription patterns concerning the women's continuation rates of oral hormonal contraceptive type.

**Results:** In Sweden, there were 782 375 women born between 1977 and 1994 at the time of the study. Of these, 226 211 women were identified as first-time users of hormonal contraceptives. Ethinylestradiol +levonorgestrel, desogestrel-only and ethinylestradiol +drospirenone were the hormonal contraceptives most commonly dispensed to first-time users at rates of 43.3%, 24.4% and 11.1%, respectively. The overall rate of switching contraceptive types in the first 6 months was 11.3%, which was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol+drospirenone (6.6%). The switching rate for all three products was highest in the 16-year to 19-year age group. Having a repeated dispensation identical to the initial dispensation was highest for users of ethinylestradiol either combined with levonorgestrel or drospirenone, 81.4% and 81.2%, respectively, whereas this rate for the initial desogestrel-only users was 71.5%. The RR of switching of contraceptive type within the first 6 months was 1.35 (95% CI 1.32 to 1.39) for desogestrel-only and 0.63 (0.59 to 0.66) for ethinylestradiol+drospirenone compared with ethinylestradiol+levonorgestrel as the reference category. There were no differences in the women's continuation rates depending on the prescriber categories.

**Conclusions:** Desogestrel-only users conferred the highest switcher rate to another hormonal contraceptive

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The Swedish Prescribed Drug Register covers all drugs dispensed from all Swedish pharmacies since July 2005. Since sale information is transferred directly from the cashier to the register, the data are complete and result in a high external validity for the register.
- The large amount of data gives a high precision to the point estimates.
- We have not been able to control for discontinuation due to a wish to become pregnant.

within a 6-month period. Users of ethinylestradiol +levonorgestrel were more prone to switch to another product within 6 months than women using ethinylestradiol+drospirenone. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

## INTRODUCTION

Adherence to treatment and continuation of contraceptive use is crucial in the efforts to avoid unwanted pregnancies. Oral contraceptive (OC) use is, however, generally characterised by relatively high discontinuation rates and low adherence to treatment.<sup>1</sup> The reasons for discontinuation and poor adherence have been reported to be side effects as well as the fear of side effects. The reported side effects include mood disturbances, decrease in libido, weight gain and poor bleeding control, and the fear of side effects also includes the risk of venous thromboembolism.<sup>2 3</sup> Most of these reported side effects can be attributed to the progestogen component of the pill. Consequently, new progestogens with a potential of a more beneficial profile concerning side effects

have been developed. Despite these improvements, the discontinuation rates are still high.

A huge mass of studies have been performed, but there is only sparse evidence of differences in continuation rates between different types of hormonal contraceptives. The type of progestogen<sup>4 5</sup> and the number of OC pill packages dispensed,<sup>6</sup> prescription drug or over-the-counter,<sup>7</sup> have all been proposed as determinants for continuation. Moreover, improvements of the formulations of combined hormonal contraceptives (COC) have been made in order to increase continuation rates. Such improvements include new routes of administration and different regimens, that is, monophasic, biphasic, triphasic and quadriphasic pills, patches and vaginal rings.<sup>8 9</sup> So far, there is only limited evidence that use of a specific formulation or route of administration would be a better choice concerning continuation rates.<sup>4-9</sup>

In several Cochrane reviews concerning adherence and continuation rates, the authors have concluded that most studies are hampered either by design or by involvement of pharmaceutical companies, and the results must therefore be interpreted with caution.<sup>4 5 10</sup> Actually, there is still a great need for studies emphasising continuation/discontinuation and the following risk of unintended pregnancies.

In Sweden, most contraceptives are prescribed by midwives, such as COC, progestin-only pills, implants, progestin-injectable (Depo-Provera) and hormonal-intrauterine-system (Mirena), but no combined hormonal injectables are available.

The prescription pattern in Sweden differs somewhat from that of most other countries as desogestrel-only pills have a very high market share and are the most commonly prescribed hormonal contraceptive. This is most probably an effect of media alarm and very cautious recommendations by the Swedish Medical Products Agency. Poor bleeding control is, however, more common during progestin-only-pills (POP) use and has been reported to be a common cause of discontinuation.<sup>2</sup>

We hypothesised that switching products within 6 months is more common among desogestrel-only users compared with users of ethinylestradiol+levonorgestrel and that users of ethinylestradiol+drosiprone are least prone to switching products within 6 months. The aim of the present study was to investigate if continuation rates in terms of repeated dispensed packages of the initially prescribed hormonal contraceptives differed between different formulations in a whole population. Second, the study aimed to measure if rates were related to prescribing categories, that is, physicians and midwives.

## METHODS

In this study, women identified as first-time users of hormonal contraceptives were treated as a cohort and followed for 6 months. Information on all women's prescribed and dispensed hormonal contraceptives from July 2005 to December 2010 was collected from the

Swedish Prescribed Drug Register.<sup>11</sup> The inclusion criteria for data extraction were woman born between 1977 and 1994 with at least one dispensation of hormonal contraceptives at least once during the 5.5-year period. The study population consisted of women without any dispensed hormonal contraceptive therapy in 18 months between July 2005 and December 2006 but who had received at least one dispensation between January 2007 and December 2009. This group was thus considered to be first-time users and constituted the study cohort in this study. Data from 2010 were used to identify those who had switched to a drug other than the first-dispensed drug after 2009 as well as those who had a second dispensation for the drug originally prescribed. Thus, 5.5 years data were used in this study.

The Swedish Prescribed Drug Register covers all drugs prescribed and dispensed for the entire Swedish population from June 2005 until now. From this database, we have obtained data on drugs having the Anatomical therapeutic chemical codes G03AA or G03AB (COCs) and G03AC (progestin-only), from July 2005 to December 2010. We organised data by type for the three most common drugs, here referred to by their generic names: (1) ethinylestradiol+levonorgestrel, (2) ethinylestradiol+drosiprone and (3) desogestrel-only. The remaining hormonal contraceptives were placed in two other groups. The first, 'Other oral contraceptives', included ethinylestradiol combined with lynestrenol, norgestimat or desogestrel, and the progestin-only drugs norethisterone and lynestrenol. The second, 'Other galenic forms', included intrauterine systems, transdermal patches, implants and injections. Although the correct designation for data from the Swedish Prescribed Drug Register is 'prescribed and dispensed' drugs, from now on the term used in this paper will be 'dispensed' drugs.

## Statistical analysis

The number of women who received an initial hormonal contraceptive drug during the 3-year period January 2007–December 2009 is presented by drug type and age. The population was divided into four age groups 16–19, 20–24, 25–28 and 16–28 years. The usage patterns are presented as numbers, percentages of total dispensations per product type and age group. Relative risks (RR) of either changing drug use or being prescribed the same drug were calculated together with 95% CIs for each group of OCs, with ethinylestradiol+levonorgestrel as the reference category. The CI tails were obtained using the normal distribution approximation and  $\delta$  method to derive SEs.<sup>12</sup> Those who initially used long-acting contraceptive methods (intrauterine systems, implants and injections) were not included in the risk analysis since the results would not be relevant given the length of the period of data inclusion in this study.

As the majority of hormonal contraceptives in Sweden are prescribed by midwives, the usage pattern is also described in relation to the prescribers, physician or midwife. Measures carried out divided on prescriber

categories were the prescription distribution in percentage within each prescriber category and within each product type. The percentages of first-time users who switched to a new drug within 6 months of receiving the first drug and of those who continued to use the first drug are presented in relation to the prescriber category.

## RESULTS

The Swedish census data 2010 showed that there were 782 375 women born between 1977 and 1994. The number of women who had used hormonal contraceptives at least once between July 2005 and December 2010 was 578 009 (~74%). After excluding those women who had a dispensation of OC during the first 18 months of the period, 226 211 were considered to be first-time users and were thus included in the statistical analyses.

The dispensation pattern for first-time users was: ethinylestradiol+levonorgestrel (43.3%), desogestrel-only (24.4%) and ethinylestradiol+drosiprenone (11.1%; table 1). The percentage of first-time users who switched to a different drug before 6 months had elapsed was 11.3%. The rate was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol+drosiprenone (6.6%). The group for which a different drug was most often dispensed consisted of those 16–19 years of age and this was true for all three drugs. The 25–28 years age group showed the lowest rate of change. The continuation rate, that is, having a repeated dispensation identical to the initial dispensation, was highest for ethinylestradiol+levonorgestrel (81.4%) and ethinylestradiol+drosiprenone (81.2%). The continuation rate for desogestrel-only was lower (71.5%). The rate of change decreased with age. The RR of switching to a different contraceptive within the first 6 months was 1.35 (95% CI 1.32 to 1.39) for desogestrel-only and 0.63 (0.59 to 0.66) for ethinylestradiol+drosiprenone where ethinylestradiol+levonorgestrel was used as the reference category. Hence, women using ethinylestradiol+drosiprenone had the lowest RR for changing to a different type of hormonal contraceptive while those using desogestrel-only had the highest RR. Further, comparisons between the three formulations show that desogestrel-only users not only had the highest RR for changing to a different type of hormonal contraceptive but also the lowest RR for having a second dispensation identical to the first. The RR varied neither by age group for changing the type of hormonal contraceptive during the first 6 months nor for having a repeated dispensation identical to the first.

The physicians and midwives displayed essentially the same pattern of prescribing the second prescription for first-time users and no significant differences between categories were found (table 2). It is, however, worth noting that midwives prescribed the drug ethinylestradiol+drosiprenone less often than physicians did. This drug was ranked as the fifth alternative choice for midwives and as the second alternative choice for physicians (in our five chosen groupings of hormonal contraceptives; table 2).

## DISCUSSION

In this nationwide population-based cohort study, we found that the most prescribed and dispensed hormonal contraceptives during the study period were COC-containing ethinylestradiol+levonorgestrel, desogestrel-only and COC with ethinylestradiol+drosiprenone. Women who received an initial prescription of ethinylestradiol combined with either levonorgestrel or drosiprenone were more prone to continue with the same drug. In contrast, women who received desogestrel-only as the initial prescribed and dispensed hormonal contraceptive had a 35% higher probability to choose another type of contraceptive within 6 months of use. Women who had originally received ethinylestradiol+drosiprenone were the least likely to switch contraceptive drugs during the same period of time.

The Swedish Medical Products Agency (MPA) recommends levonorgestrel-containing combined pills as the first choice when prescribing OCs. Our results show that prescribers most often follow these recommendations. But the prescription pattern in Sweden differs from most other countries as desogestrel-only pills have a high market share of approximately 25%<sup>13</sup> compared with 4.5% in Denmark and 0.3% in the USA.<sup>14 15</sup>

The clinical implications of our findings are important as the side effects or other reasons for discontinuation or switching between different contraceptives increase the risk of unwanted pregnancies. Oral desogestrel-only contraceptives have become a common choice due to fear of the increased risk of venous thromboses in women who use combined hormonal contraception and prescribers who use combined hormonal contraception. However, an irregular bleeding pattern, which is more frequent among users of progestin-only formulations, might be a reason for the higher percentage of switchers or discontinuation in this group. Therefore, when prescribing hormonal contraceptives, it is necessary to thoroughly evaluate each woman's individual risk of venous thrombosis and also provide balanced and knowledge-based information on the size of these risks.

COCs are associated with a number of positive health effects, for example, decreased menstrual blood loss and improvement in dysmenorrhoea and acne. It has been demonstrated previously that the positive health effects in addition to the contraceptive effect will most likely increase the continuation rates.<sup>16</sup> This may very well contribute to the fact that women on COCs were more prone to continue use of the initial prescribed product as compared with women using POP, although the vast majority of women are prescribed COCs for contraception and not primarily for medical reasons.

We found that among midwives, desogestrel-only was the second most commonly prescribed hormonal contraceptive. At the same time, and especially among the youngest group of women, 16–19 years old, the percentage of switchers was the highest.

Cerazette (desogestrel 75 µg) was registered in Sweden 2001 and the number of users, especially in the younger age categories, increased rapidly during the following

**Table 1** Continuation rates in first-time users of hormonal contraceptives in Sweden 2007–2009

Product type	Initial prescription and dispensation			Switching type before 6 months use				Second prescription and dispensation identical to the first			
	Age	n	Percentage of total	n	Percentage per product type	Relative risk	(95% CI)	n	Percentage per product type	Relative risk	(95% CI)
Ethinylestradiol+ levonorgestrel	16–19	73 197		8234	11.2	1 (reference)		60 945	83.3	1 (reference)	
	20–24	17 140		1613	9.4			13 158	76.8		
	25–28	7724		529	6.8			5692	73.7		
	16–28	98 061	43.3	10 376	10.6			79 795	81.4		
Ethinylestradiol+ drospirenone	16–19	11 604		952	8.2	0.73	(0.68 to 0.78)	9845	84.8	1.02	(1.01 to 1.03)
	20–24	7889		433	5.5	0.58	(0.53 to 0.65)	6261	79.4	1.03	(1.02 to 1.05)
	25–28	5655		279	4.9	0.72	(0.63 to 0.83)	4317	76.3	1.04	(1.02 to 1.06)
Desogestrel-only	16–28	25 148	11.1	1664	6.6	0.63	(0.59 to 0.66)	20 423	81.2	1.00	(0.99 to 1.00)
	16–19	29 127		4977	17.1	1.52	(1.47 to 1.57)	21 797	74.8	0.90	(0.89 to 0.91)
	20–24	14 172		1719	12.1	1.29	(1.21 to 1.37)	9657	68.1	0.89	(0.88 to 0.90)
	25–28	11 880		1206	10.2	1.48	(1.34 to 1.64)	7989	67.2	0.91	(0.90 to 0.93)
Other oral hormonal contraceptives	16–28	55 179	24.4	7902	14.3	1.35	(1.32 to 1.39)	39 443	71.5	0.88	(0.87 to 0.88)
	16–28	23 948	10.6	3016	12.6	1.19	(1.15 to 1.24)	18 179	75.9	0.93	(0.93 to 0.94)
Other galenic forms*	16–28	23 875	10.6	†							
Total	16–28	226 211	100.0	22 958‡	11.3‡			157 840‡	78.0‡		

\*Intrauterine systems, transdermal patches, implants and injections.

†Irrelevant here as the treatment has a long-term effect.

‡Excluding other galenic forms.

**Table 2** Prescription and dispensation in first-time users of hormonal contraceptives in Sweden 2007–2009 per product type and prescriber category together with continuation rates

Product type	Prescriber category	n	Distribution within prescriber category (%)	Distribution within product type (%)	Switching type before 6 months use (%)	Second prescription and dispensation identical to the first (%)
Ethinylestradiol+levonorgestrel	Midwife	83 146	45.1	84.8	10.9	82.1
	Physician	14 914	35.7	15.2	8.8	77.4
	All prescribers	98 060	40.5	100.0	10.6	81.4
Ethinylestradiol+drosiprenone	Midwife	16 461	8.9	65.5	7.0	83.3
	Physician	8686	20.8	34.5	5.8	77.2
	All prescribers	25 147	11.2	100.0	6.6	81.2
Desogestrel-only	Midwife	47 035	25.5	85.2	14.7	71.7
	Physician	8139	19.5	14.8	12.0	70.0
	All prescribers	55 174	25.6	100.0	14.3	71.5
Other oral hormonal contraceptives	Midwife	19 121	10.4	79.8	12.9	76.8
	Physician	4827	11.6	20.2	11.2	72.4
	All prescribers	23 948	10.7	100.0	12.6	75.9
All hormonal contraceptives	Midwife	184 446	100.0	81.5	11.8	78.7
	Physician	41 758	100.0	18.5	9.1	75.1
	All prescribers	226 204	100.0	100	11.3	78.0

years. During the same period, the number of teenage abortions increased<sup>17</sup> and it can be speculated that the problem with bleeding control associated with progestin-only methods have led to lower continuation rates in this group of users and, as a consequence, an increased risk of unprotected intercourse leading to unwanted pregnancies.

During the past 5 years, there has been an intense debate concerning a possible difference in the thromboembolic risk between COC-containing levonorgestrel and drospirenone. Retrospective studies have found an increased risk in women using ethinylestradiol+drospirenone compared with ethinylestradiol+levonorgestrel.<sup>18–21</sup> However, these results have been contradicted by results from prospective studies.<sup>22–25</sup> When transforming results from this kind of study into clinical recommendations, the question of continuation/discontinuation is crucial. A possibly small increase in risk may be balanced by higher continuation rates. The results from the present study indicate a more favourable profile for COC-containing drospirenone when it comes to continuation rates. To the best of our knowledge, this has not been shown previously. A possibly more favourable thromboembolic risk profile with a COC-containing ethinylestradiol+levonorgestrel may be counteracted by lower continuation rates compared with pills containing drospirenone and a possibly increased risk of unintended pregnancies. As the risk of venous thromboembolism increases rapidly during early pregnancy, this must be taken into account.

A substantial number of women had no second dispensation in 6 months of any contraceptive product (table 1). The design of the present study does not provide any information on this group and we cannot draw any conclusions. We can, however, speculate that the group is most probably a mix of women stopping contraceptive use and women switching to a non-hormonal contraceptive method. The use of copper-IUDs is widespread in Sweden and the register used in this study does not provide information on copper-IUD use as this is not a pharmaceutical product. As COC with ethinylestradiol+drospirenone is second-line treatment in Sweden, it seems reasonable that this group is bigger. The actual number of women who discontinued without switching to a non-hormonal method is unknown.

Some of the women considered as first-time users actually could have been using the same contraceptive before the period of the study. For various reasons, these women may have stopped their use and started again later on. This would most likely occur in the older age groups. If so, these women would be expected to have higher continuation rates than the younger women. As this is not the case (table 1), we do not consider this as a major source of bias.

### Strengths and limitations of the study

The Swedish Prescribed Drug Register covers all drugs dispensed from all Swedish pharmacies since July 2005.

Since sale information is transferred directly from the cashier to the register, data are complete and result in a high external validity for the register.

A further strength is that the large amount of data gives a high precision to the point estimates. These factors are the usual strengths in register research together with the avoidance of errors arising out of recall bias, which is a common problem arising when the data used have been collected from interviews and questionnaires.

We have not been able to control for a wish to become pregnant in this study. A lowered rate of 'repeated prescription and dispensation identical to the first' may to some extent be an effect of plans to become pregnant. Therefore, the percentage rates for 'repeated prescription and dispensation identical to the first' might be somewhat difficult to interpret. However, the RR estimates are useful since there is no reasonable explanation for the choice made by women to use desogestrel-only as an initial formulation to a greater extent because these women might be more prone to become pregnant.

## CONCLUSION

The three most common types of initially prescribed hormonal contraceptive in Sweden are from most to least common: ethinylestradiol+levonorgestrel (43.3%), desogestrel-only (24.4%) and ethinylestradiol+drospirenone (11.1%). Of these drugs, desogestrel-only users were most likely to switch to another drug during the first 6 months, with 14.3% changing. The RR for this type of change was 1.35, compared with ethinylestradiol+levonorgestrel. Women using drospirenone-containing COC were less likely to switch within 6 months than women using levonorgestrel-containing COC (RR 0.63; 0.59 to 0.66). Overall, the prescription pattern concerning the women's continuation rates differed only slightly between the physicians and the midwives, although there was a lowered prescription and dispensation rate of ethinylestradiol+drospirenone by midwives compared with physicians. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

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**Contributors** AJ and JB planned the study, supervised the analysis, interpreted the results and wrote the manuscript. AJ is the guarantor of the study. A-BW planned the study, prepared all data from the Swedish Prescribed Drug Register, made the statistical analyses and interpreted the

results. ML and AF interpreted the results and revised the manuscript. All authors discussed and approved the final manuscript. AJ and JB decided when and where to attempt publication.

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**Competing interests** JB has been reimbursed by Merck Sharpe & Dohme (MSD), Sweden, the manufacturer of desogestrel-containing contraceptives in Sweden, for running educational programmes and giving lectures. JB has also been paid by Bayer AB, Sweden, the manufacturer of some of the levonorgestrel-containing contraceptives and all drospirenone-containing combined oral contraceptives available in Sweden, for giving lectures.

**Ethics approval** This study was approved by the Regional Ethical Review Board, Linköping, Sweden (Dnr M125-08).

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**Data sharing statement** No additional data are available.

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