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Patterns of adherence to 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. To measure if rates were related to prescribing categories, i.e. physicians and midwives.

Design A longitudinal national population-based registry study

Setting The Swedish prescribed drug register

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

Main outcome measures Tendency to switch type of hormonal contraceptive within 6 months use and repeated dispensation identical to the first, Physicians' and midwives' prescription patterns. **Results** In Sweden, 782 375 women were born 1977-1994 at the time of the study. 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 for first-time users, 43.3 %, 24.4 % and 11.1 %, respectively. The overall rate of switching contraceptive type in the first six months was 11.3%, highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). group. Having a repeated dispensation identical to the initial 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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone compared to ethinylestradiol + levonorgestrel. The physicians' and midwives' prescription patterns concerning the women's continuation rates differed only slightly.

Conclusion Desogestrel-only users conferred the highest switcher rate to another hormonal contraceptive within a 6-months period. Users of ethinylestradiol + levonorgestrel were more prone to switch to another product within six months than women using ethinylestradiol + drospirenone. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

ARTICLE SUMMARY

Article focus

- Compliance and adherence to contraceptives is of outmost importance to avoid unintended pregnancies
- In Sweden, a change in prescription pattern has been observed, from combined oral contraceptives to progestin-only-pills, most probably due to media alarm
- Do adherence to treatment differ between POPs and different formulations of combined oral contraceptives?

Key messages

- Users of progestin-only pills more frequently choose another hormonal contraceptive method, or discontinue use within six months, than users of combined oral contraceptives
- Users of drospirenone containing combined oral contraceptives were the least likely to switch method

Strengts 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, data is complete and results 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.

INTRODUCTION

Compliance and continuation of contraceptive use is crucial in the efforts to avoid unwanted pregnancies. Oral contraceptive (OC) use is however; generally characterized by poor compliance, low adherence and relatively high discontinuation rates (1). Reasons for poor adherence and discontinuation have been reported to be side effects but also the fear of side effects. Reported side effects include mood disturbances, decrease in libido, weight gain and poor bleeding control and the fear also includes the risk of venous thromboembolism (2, 3). 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, discontinuation rates are still high.

A huge mass of studies has been performed, but there is only sparse evidence of differences in continuation rates between different types of hormonal contraceptives. Type of progestogen (4, 5), number of oral contraceptive pill packages dispensed (6), prescription drug or over the counter (7) 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 adherence. Such improvements include new routes of administration and different regimens, i.e. mono-, bi-, tri-, and four -phasic pills, patches and vaginal rings (8, 9). 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 (4-9).

In several Cochrane reviews 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 (4,5,10). Actually, there is still a great need for studies emphasizing continuation/discontinuation and risks of poor compliance and as a consequence a risk of unintended pregnancies.

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

The prescription pattern in Sweden somewhat differs from most other countries as desogestrel-only pills have a very high market share and is 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 POP-use and has been reported to be a common cause of discontinuation (2).

We hypothesised that switching product within six months is more common among desogestrel-only users compared to users of etinylestradiol + levonorgestrel and that users of ethinylestradiol + drospirenonone are least prone to switch product within six 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. Secondly to measure if rates were related to prescribing categories, i.e. physicians and midwives.

METHODS

In this study, women identified as first-time users of hormonal contraceptives were treated as a cohort and followed for six 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 (11). The inclusion criteria for data extraction were: female born 1977-1994 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 the 18 months between July 2005 - December 2006 but who had received at least one dispensation between January 2007-December 2009. This group was thus considered to be first-time users and constituted the study cohort in this study. Data from 2010 was 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 was used in this study.

The Swedish Prescribed Drug Register covers all drugs prescribed and dispensed for the entire Swedish population from June 2005 to the present. From this database we have obtained data on drugs having the Anatomical therapeutic chemical codes G03AA or G033AB (combined hormonal contraceptives) and G03AC (progestin only), from July 2005 to December 2010. We organized data by type for the three most common drugs, here referred to by their generic names: 1) ethinylestradiol + levonorgestrel, 2) ethinylestradiol + drospirenone and 3) desogestrel-only. The remaining hormonal contraceptives were placed in two other groups. The first, "Other oral contraceptives", included ethinylestradiol combined with either 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 three-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% confidence intervals for each group of oral contraceptives, with

ethinylestradiol + levonorgestrel as the reference category. The CI tails were obtained using the normal distribution approximation and delta method to derive standard errors (12). 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 prescribers, physician or midwife. Measures carried out divided on prescriber categories were the prescription distribution in percent 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 and of those who continued to use the first drug are presented in relation to 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 + drospirenone (11.1%) (Table 1). The perecentage of first-time users who switched to a different drug before six months had elapsed was 11.3%. The rate was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The group for whom 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 of age group showed the lowest rate of change. The continuation rate, i.e. having a repeated dispensation identical to the initial, was highest for ethinylestradiol + levonorgestrel (81.4%) and ethinylestradiol + drospirenone (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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone where ethinylestradiol + levonorgestrel was used as the reference category. Hence, women using ethinylestradiol + drospirenone had the lowest RR for changing to a different type of hormonal contraceptive while those using desogestrel-only had the highest. 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 did neither vary by age group for changing the type of hormonal contraceptive during the first 6 months nor for having a repeated dispensation identical to first.

The physicians and midwives displayed essentially the same pattern of prescribing the second prescription for first-time users. It is, however, worth noting that midwives prescribed the drug ethinylestradiol + drospirenone 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).

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 first			
	Age	n	% of total	n	% per product type	Relative risk	(95% CI)	n	% per product type	Relative risk	(95% CI)
Ethinylestradiol + Levonorgestrel	16-19	73197		8234	11.2	1 (reference)		60945	83.3	1 (reference)	
	20-24	17140		1613	9.4			13158	76.8		
	25-28	7724		529	6.8			5692	73.7		
	16-28	98061	43.3	10376	10.6			79795	81.4		
Ethinylestradiol + Drospirenone	16-19	11604		952	8.2	0.73	(0.68-0.78)	9845	84.8	1.02	(1.01-1.03)
	20-24	7889		433	5.5	0.58	(0.53-0.65)	6261	79.4	1.03	(1.02-1.05)
	25-28	5655		279	4.9	0.72	(0.63-0.83)	4317	76.3	1.04	(1.02-1.06)
	16-28	25148	11.1	1664	6.6	0.63	(0.59-0.66)	20423	81.2	1.00	(0.99-1.00)
Desogestrel only	16-19	29127		4977	17.1	1.52	(1.47-1.57)	21797	74.8	0.90	(0.89-0.91)
	20-24	14172		1719	12.1	1.29	(1.21-1.37)	9657	68.1	0.89	(0.88-0.90)
	25-28	11880		1206	10.2	1.48	(1.34-1.64)	7989	67.2	0.91	(0.90-0.93)
	16-28	55179	24.4	7902	14.3	1.35	(1.32-1.39)	39443	71.5	0.88	(0.87-0.88)
Other oral hormonal contraceptives	16-28	23948	10.6	3016	12.6	1.19	(1.15-1.24)	18179	75.9	0.93	(0.93-0.94)
Other galenic forms[a]	16-28	23875	10.6								
Total	16-28	226211	100.0	22958c	11.3c			157840[c]	78.0[c]		

[a] intrauterine systems, transdermal patches, implants and injections
[b] irrelevant here as the treatment has long term effect
[c] 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 first %
Ethinylestradiol + levonorgestrel	Midwife	83146	45.1	84.8	10.9	82.1
	Physician	14914	35.7	15.2	8.8	77.4
	All prescribers	98060	40.5	100.0	10.6	81.4
Ethinylestradiol + drospirenone	Midwife	16461	8.9	65.5	7.0	83.3
	Physician	8686	20.8	34.5	5.8	77.2
	All prescribers	25147	11.2	100.0	6.6	81.2
Desogestrel only	Midwife	47035	25.5	85.2	14.7	71.7
	Physician	8139	19.5	14.8	12.0	70.0
	All prescribers	55174	25.6	100.0	14.3	71.5
Other oral hormonal contraceptives	Midwife	19121	10.4	79.8	12.9	76.8
	Physician	4827	11.6	20.2	11.2	72.4
	All prescribers	23948	10.7	100.0	12.6	75.9
All hormonal contraceptives	Midwife	184446	100.0	81.5	11.8	78.7
	Physician	41758	100.0	18.5	9.1	75.1
	All prescribers	226204	100.0	100	11.3	78.0

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 + drospirenone. Women who received an initial prescription of ethinylestradiol combined with either levonorgestrel or drospirenone were more prone to continue with the same drug. On the contrary, women who received desogestrel-only as the initial prescribed and dispensed hormonal contraceptive had 35 % higher probability to choose another type of contraceptive within 6 months of use. Women who originally had received ethinylestradiol + drospirenone were the least likely to switch contraceptive drug during the same period of time.

The Swedish Medical Products Agency (MPA) recommends levonorgestrel containing combined pills as the first choice when prescribing oral contraceptives. 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% (13) compared to 4,5% in Denmark and 0.3% in the United States (14, 15).

The clinical implications of our findings are important as side effects or other reasons for discontinuation or switching between different contraceptives increase the risk for unwanted pregnancies. Oral desogestrel-only contraceptives have become a common choice due to fear of the increased risk for venous thromboses in both 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 for venous thrombosis and also provide a balanced and knowledge based information on the size of these risks. We found that among midwives desogestrel-only was the second most common prescribed hormonal contraceptive. At the same time and especially among the youngest group of women, 16 – 19 years, the percentage of switchers was the highest.

Cerazette® (desogestrel 75µg) was registered in Sweden 2001 and the number of users, especially in the younger age categories increased rapidly during the following years. During the same time, the number of teenage abortions increased (16) and it can be speculated that the problem with bleeding control associated with progestin–only methods have lead to poorer compliance in this group of users and as a consequence an increased risk of unprotected intercourse leading to unwanted pregnancies.

During the past five 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 (17-20). However these results have been contradicted by results from prospective studies (21-24). When transforming results from this kind of studies into clinical recommendations, the question of adherence and compliance is crucial. A possible small increase in risk may be balanced by a better adherence to treatment. The results from the present study indicate a more favourable profile for COC containing drospirenone when it comes to adherence and compliance. To our best knowledge this has not previously been shown. A possible more favourable thromboembolic risk profile with a COC containing ethinylestradiol + levonorgestrel may be counteracted by a poorer adherence compared with pills containing drospirenone and a possible increased risk of unintended pregnancies. As the risk of venous thromboembolism increases rapidly already during early pregnancy this must be taken into account.

A substantial number of women had no second dispensation in six 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 most probably the group is 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.

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 is complete and results 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 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 of 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 six months with 14.3% changing. The RR for this type of change was 1.35, compared to ethinylestradiol + levonorgestrel. Women using drospirenone-containing COC were less likely to switch within six months than women using levonorgestrel-containing COC (RR 0.63; 0.59-0.66). The prescription pattern concerning the women's continuation rates differed overall only slightly between the physicians' and the midwives', although there was a lowered prescription and dispensation rate of ethinylestradiol + drospirenone by midwives compared to 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 guarantor of the study.

ABW 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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JB report financial relations to MSD Sweden and Bayer AB, Sweden (see attached declaration). The other investigators declared no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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

Data sharing: No additional data available.

What is already known on this topic

Compliance and adherence to contraceptive use is almost always overestimated in clinical trials. Data on difference in compliance and adherence between different formulations of oral contraception is lacking or of poor quality. Knowledge of adherence and compliance is essential when it comes to avoid unintended pregnancies.

What this study adds

Users of progestin-only pills more frequently choose another hormonal contraceptive method or discontinue use within six months. Users of drospirenone containing combined oral contraceptives were the least likely to switch method. The results indicate a more favourable profile concerning adherence to treatment for drospirenone containing combined oral contraceptives. This may be of clinical interest when it comes to a decision of what type of oral contraceptives the individual woman should be recommended.

STROBE Statement – checklist of items that should be included in reports of observational studies.

1a	Done
1b	Done
2	Done
3	*Intoduction*, last paragraph
4	*Method*, first sentence
5	*Method*, first and second paragraph
6a	*Method*, first and second paragraph
6b	We consider this as not relevant
7	In *Statistical analysis,* there are descriptions of the variables: “age groups”, “changing type” and “using same drug after 6 months”
8	Not relevant – all information is from the Swedish Prescribed Drug Register
9	In this study with an intention to solely describe the switching/ continuation rate and not to explain its underlying causes, the risk of presenting biased results is not an immediate problem. Especially not since we consider the external validity in this study as very high.
10	We consider this as not relevant
11	*Statistical analyses*
12a	Relative risks together with 95% CIs are used for the analyses, and its composition in terms of risk outcome and reference category in the ratio as well as CI interval calculations are presented in *Statistical analysis*.
12b	We consider this as not relevant
12c	We have used register data with a most probable complete registration (see *Strengths and limitations of the study*)
12d	Please see item 12c
12e	We have previously calculated the proportions for switching product within 12 months and found the pattern quite similar.
13a	See table 1 and table 2
13b	We consider this as not relevant
13c	We believe that the description of inclusion is rather uncomplicated and that the description in *Method*, first and paragraph is easy to follow.
14a	We have not included data on such information in this study
14b	There are no missing data in our chosen variables
14c	The follow-up time is exactly six months for each woman in the study.
15	Please see table 1 and table 2
16a	Please see table 1
16b	Please see *Statistical analyses*
16c	Please see table 1
17	We consider this as not relevant
18	*Discussion*, first paragraph
19	Please see *Strengths and limitations of the study*
20	*Conclusion*
21	Very high external validity (see *Strengths and limitations of the study*)
22	No funding

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Competing interests:
Jan Brynhildsen (JB) has been reimbursed by Merck Sharpe & Dohme (MSD), Sweden, the manufacturer of desogestrel-containing contraceptives I 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.
JB has also been the member of the Swedish medical advisory board of MSD between 2008 and 2012.

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16th January 2013

Dear Dr. Josefsson

BMJ.2013.010282 entitled "Patterns of adherence to oral hormonal contraceptives in a cohort of first time users: a population based registry study, Sweden 2005-2010"

Thank you for sending us your paper. We read it with interest but I regret to say that we have decided not to publish it in the BMJ.

We enjoyed reading the study and were impressed by the comprehensive nature of your dataset. However we also noted the limitations and particularly that the nature of the study makes it difficult to know why people started particular preparations and also why people switched (or discontinued). The study may be appropriate for a specialist journal and hopefully lead to further research into the adverse effects of the different preparations.

We receive over 8000 submissions a year and accept less than 10%. We do therefore have to make hard decisions on just how interesting an article will be to our general clinical readers, how much it adds, and how much practical value it will be.

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Yours sincerely

Krishna Chinthapalli
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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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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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Key words: Hormonal contraceptives; Oral contraceptives; Patient adherence; Registries ; Follow-up studies

Word count:

ABSTRACT

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

Design A longitudinal national population-based registry study

Setting The Swedish prescribed drug register

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

Main outcome measures Tendency to switch type of hormonal contraceptive within 6 months use and repeated dispensation identical to first were estimated as percentages and relative risks. 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 1977-1994 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 for first-time users, 43.3 %, 24.4 % and 11.1 %, respectively. The overall rate of switching contraceptive type in the first six months was 11.3%, highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The switching rate for all three products was highest in 16-19 year age group. Having a repeated dispensation identical to the initial 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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone compared to ethinylestradiol + levonorgestrel as reference category. The physicians' and midwives' prescription patterns concerning the women's continuation rates differed only slightly.

Conclusion Desogestrel-only users conferred the highest switcher rate to another hormonal contraceptive within a 6-months period. Users of ethinylestradiol + levonorgestrel were more prone to switch to another product within six months than women using ethinylestradiol + drospirenone. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

ARTICLE SUMMARY

Article focus

- Continuation of contraceptive use is of outmost importance to avoid unintended pregnancies
- In Sweden, a change in prescription pattern has been observed, from combined oral contraceptives to progestin-only-pills, most probably due to media alarm
- Do continuation rates differ between different formulations of combined oral contraceptives?

Key messages

- Users of progestin-only pills more frequently choose another hormonal contraceptive method, or discontinue use within six months, than users of combined oral contraceptives
- Users of drospirenone containing combined oral contraceptives were the least likely to switch method

Strengts 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, data is complete and results 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.

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 characterized by relatively high discontinuation rates and low adherence to treatment(1). Reasons for discontinuation and poor adherence have been reported to be side effects but also the fear of side effects. Reported side effects include mood disturbances, decrease in libido, weight gain and poor bleeding control and the fear also includes the risk of venous thromboembolism (2, 3). 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, discontinuation rates are still high.

A huge mass of studies has been performed, but there is only sparse evidence of differences in continuation rates between different types of hormonal contraceptives. Type of progestogen (4, 5), number of oral contraceptive pill packages dispensed (6), prescription drug or over the counter (7) 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, i.e. mono-, bi-, tri-, and four -phasic pills, patches and vaginal rings (8, 9). 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 (4-9).

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 (4,5,10). Actually, there is still a great need for studies emphasizing continuation/discontinuation and the following risk of unintended pregnancies.

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

The prescription pattern in Sweden somewhat differs from most other countries as desogestrel-only pills have a very high market share and is 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 POP-use and has been reported to be a common cause of discontinuation (2).

We hypothesised that switching product within six months is more common among desogestrel-only users compared to users of etinylestradiol + levonorgestrel and that users of ethinylestradiol + drospirenonone are least prone to switch product within six 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. Secondly to measure if rates were related to prescribing categories, i.e. physicians and midwives.

METHODS

In this study, women identified as first-time users of hormonal contraceptives were treated as a cohort and followed for six 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 (11). The inclusion criteria for data extraction were: female born 1977-1994 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 the 18 months between July 2005 - December 2006 but who had received at least one dispensation between January 2007-December 2009. This group was thus considered to be first-time users and constituted the study cohort in this study. Data from 2010 was 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 was used in this study.

The Swedish Prescribed Drug Register covers all drugs prescribed and dispensed for the entire Swedish population from June 2005 to the present. From this database we have obtained data on drugs having the Anatomical therapeutic chemical codes G03AA or G033AB (combined hormonal contraceptives) and G03AC (progestin only), from July 2005 to December 2010. We organized data by type for the three most common drugs, here referred to by their generic names: 1) ethinylestradiol + levonorgestrel, 2) ethinylestradiol + drospirenone and 3) desogestrel-only. The remaining hormonal contraceptives were placed in two other groups. The first, "Other oral contraceptives", included ethinylestradiol combined with either 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 three-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% confidence intervals for each group of oral contraceptives, with

ethinylestradiol + levonorgestrel as the reference category. The CI tails were obtained using the normal distribution approximation and delta method to derive standard errors (12). 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 prescribers, physician or midwife. Measures carried out divided on prescriber categories were the prescription distribution in percent 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 and of those who continued to use the first drug are presented in relation to 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 + drospirenone (11.1%) (Table 1). The perecentage of first-time users who switched to a different drug before six months had elapsed was 11.3%. The rate was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The group for whom 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 of age group showed the lowest rate of change. The continuation rate, i.e. having a repeated dispensation identical to the initial, was highest for ethinylestradiol + levonorgestrel (81.4%) and ethinylestradiol + drospirenone (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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone where ethinylestradiol + levonorgestrel was used as the reference category. Hence, women using ethinylestradiol + drospirenone had the lowest RR for changing to a different type of hormonal contraceptive while those using desogestrel-only had the highest. 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 did neither vary by age group for changing the type of hormonal contraceptive during the first 6 months nor for having a repeated dispensation identical to first.

The physicians and midwives displayed essentially the same pattern of prescribing the second prescription for first-time users. It is, however, worth noting that midwives prescribed the drug ethinylestradiol + drospirenone 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).

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 first			
	Age	n	% of total	n	% per product type	Relative risk	(95% CI)	n	% per product type	Relative risk	(95% CI)
Ethinylestradiol + Levonorgestrel	16-19	73197		8234	11.2	1 (reference)		60945	83.3	1 (reference)	
	20-24	17140		1613	9.4			13158	76.8		
	25-28	7724		529	6.8			5692	73.7		
	16-28	98061	43.3	10376	10.6			79795	81.4		
Ethinylestradiol + Drospirenone	16-19	11604		952	8.2	0.73	(0.68-0.78)	9845	84.8	1.02	(1.01-1.03)
	20-24	7889		433	5.5	0.58	(0.53-0.65)	6261	79.4	1.03	(1.02-1.05)
	25-28	5655		279	4.9	0.72	(0.63-0.83)	4317	76.3	1.04	(1.02-1.06)
	16-28	25148	11.1	1664	6.6	0.63	(0.59-0.66)	20423	81.2	1.00	(0.99-1.00)
Desogestrel only	16-19	29127		4977	17.1	1.52	(1.47-1.57)	21797	74.8	0.90	(0.89-0.91)
	20-24	14172		1719	12.1	1.29	(1.21-1.37)	9657	68.1	0.89	(0.88-0.90)
	25-28	11880		1206	10.2	1.48	(1.34-1.64)	7989	67.2	0.91	(0.90-0.93)
	16-28	55179	24.4	7902	14.3	1.35	(1.32-1.39)	39443	71.5	0.88	(0.87-0.88)
Other oral hormonal contraceptives	16-28	23948	10.6	3016	12.6	1.19	(1.15-1.24)	18179	75.9	0.93	(0.93-0.94)
Other galenic forms[a]	16-28	23875	10.6			[b]					
Total	16-28	226211	100.0	22958c	11.3c			157840[c]	78.0[c]		

[a] intrauterine systems, transdermal patches, implants and injections
[b] irrelevant here as the treatment has long term effect
[c] 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 first %
Ethinylestradiol + levonorgestrel	Midwife	83146	45.1	84.8	10.9	82.1
	Physician	14914	35.7	15.2	8.8	77.4
	All prescribers	98060	40.5	100.0	10.6	81.4
Ethinylestradiol + drospirenone	Midwife	16461	8.9	65.5	7.0	83.3
	Physician	8686	20.8	34.5	5.8	77.2
	All prescribers	25147	11.2	100.0	6.6	81.2
Desogestrel only	Midwife	47035	25.5	85.2	14.7	71.7
	Physician	8139	19.5	14.8	12.0	70.0
	All prescribers	55174	25.6	100.0	14.3	71.5
Other oral hormonal contraceptives	Midwife	19121	10.4	79.8	12.9	76.8
	Physician	4827	11.6	20.2	11.2	72.4
	All prescribers	23948	10.7	100.0	12.6	75.9
All hormonal contraceptives	Midwife	184446	100.0	81.5	11.8	78.7
	Physician	41758	100.0	18.5	9.1	75.1
	All prescribers	226204	100.0	100	11.3	78.0

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 + drospirenone. Women who received an initial prescription of ethinylestradiol combined with either levonorgestrel or drospirenone were more prone to continue with the same drug. On the contrary, women who received desogestrel-only as the initial prescribed and dispensed hormonal contraceptive had 35 % higher probability to choose another type of contraceptive within 6 months of use. Women who originally had received ethinylestradiol + drospirenone were the least likely to switch contraceptive drug during the same period of time.

The Swedish Medical Products Agency (MPA) recommends levonorgestrel containing combined pills as the first choice when prescribing oral contraceptives. 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% (13) compared to 4,5% in Denmark and 0.3% in the United States (14, 15).

The clinical implications of our findings are important as side effects or other reasons for discontinuation or switching between different contraceptives increase the risk for unwanted pregnancies. Oral desogestrel-only contraceptives have become a common choice due to fear of the increased risk for venous thromboses in both 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 for venous thrombosis and also provide a 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 previously been demonstrated that positive health effects in addition to the contraceptive effect most likely will increase continuation rates (16). 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 common prescribed hormonal contraceptive. At the same time and especially among the youngest group of women, 16 – 19 years, the percentage of switchers was the highest.

Cerazette® (desogestrel 75µg) was registered in Sweden 2001 and the number of users, especially in the younger age categories increased rapidly during the following years. During the same time, the number of teenage abortions increased (17) 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 five 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 (18-21). However these results have been contradicted by results from prospective studies (2225). When transforming results from this kind of studies into clinical recommendations, the question of continuation/discontinuation is crucial. A possible 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 our best knowledge this has not previously been shown. A possible 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 possible increased risk of unintended pregnancies. As the risk of venous thromboembolism increases rapidly already during early pregnancy this must be taken into account.

A substantial number of women had no second dispensation in six 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 most probably the group is 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 later on started again. 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 is complete and results 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 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 of 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 six months with 14.3% changing. The RR for this type of change was 1.35, compared to ethinylestradiol + levonorgestrel. Women using drospirenone-containing COC were less likely to switch within six months than women using levonorgestrel-containing COC (RR 0.63; 0.59-0.66). The prescription pattern concerning the women's continuation rates differed overall only slightly between the physicians' and the midwives', although there was a lowered prescription and dispensation rate of ethinylestradiol + drospirenone by midwives compared to 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 guarantor of the study.

ABW 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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JB report financial relations to MSD Sweden and Bayer AB, Sweden (see attached declaration). The other investigators declared no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing: No additional data available.

What is already known on this topic

Compliance and adherence to contraceptive use is almost always overestimated in clinical trials. Data on difference in compliance and adherence between different formulations of oral contraception is lacking or of poor quality. Knowledge of adherence and compliance is essential when it comes to avoid unintended pregnancies.

What this study adds

Users of progestin-only pills more frequently choose another hormonal contraceptive method or discontinue use within six months. Users of drospirenone containing combined oral contraceptives were the least likely to switch method. The results indicate a more favourable profile concerning adherence to treatment for drospirenone containing combined oral contraceptives. This may be of clinical interest when it comes to a decision of what type of oral contraceptives the individual woman should be recommended.

Continuation rates of ~~Patterns of adherence to~~ oral hormonal contraceptives in a cohort of first time users: a population based registry study, Sweden 2005-2010

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Key words: Hormonal contraceptives; Oral contraceptives; Patient adherence; Registries ; Follow-up studies

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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 rates were related to prescribing categories, i.e. physicians and midwives.

Design A longitudinal national population-based registry study

Setting The Swedish prescribed drug register

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

Main outcome measures Tendency to switch type of hormonal contraceptive within 6 months use and repeated dispensation identical to first were estimated as percentages and relative risks. 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 1977-1994 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 for first-time users, 43.3 %, 24.4 % and 11.1 %, respectively. The overall rate of switching contraceptive type in the first six months was 11.3%, highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The switching rate for all three products was highest in 16-19 year age group. Having a repeated dispensation identical to the initial 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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone compared to ethinylestradiol + levonorgestrel as reference category. The physicians' and midwives' prescription patterns concerning the women's continuation rates differed only slightly.

Conclusion Desogestrel-only users conferred the highest switcher rate to another hormonal contraceptive within a 6-months period. Users of ethinylestradiol + levonorgestrel were more prone to switch to another product within six months than women using ethinylestradiol + drospirenone. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

ARTICLE SUMMARY

Article focus

- Continuation of ~~Compliance and adherence to~~ contraceptive use~~s~~ is of outmost importance to avoid unintended pregnancies
- In Sweden, a change in prescription pattern has been observed, from combined oral contraceptives to progestin-only-pills, most probably due to media alarm
- Do continuation rates ~~adherence to treatment~~ differ between different formulations of combined oral contraceptives?

Key messages

- Users of progestin-only pills more frequently choose another hormonal contraceptive method, or discontinue use within six months, than users of combined oral contraceptives
- Users of drospirenone containing combined oral contraceptives were the least likely to switch method

Strengts 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, data is complete and results 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.

INTRODUCTION

Adherence to treatment ~~Compliance~~ and continuation of contraceptive use is crucial in the efforts to avoid unwanted pregnancies. Oral contraceptive (OC) use is however; generally characterized by ~~poor compliance,~~ relatively high discontinuation rates and low adherence to treatment~~and relatively high discontinuation rates~~ (1). Reasons for discontinuation and poor adherence ~~and discontinuation~~ have been reported to be side effects but also the fear of side effects. Reported side effects include mood disturbances, decrease in libido, weight gain and poor bleeding control and the fear also includes the risk of venous thromboembolism (2, 3). 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, discontinuation rates are still high.

A huge mass of studies has been performed, but there is only sparse evidence of differences in continuation rates between different types of -hormonal contraceptives. Type of progestogen (4, 5), number of oral contraceptive pill packages dispensed (6), prescription drug or over the counter (7) 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 ~~adherence~~. Such improvements include new routes of administration and different regimens, i.e. mono-, bi-, tri-, and four -phasic pills, patches and vaginal rings (8, 9). 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 (4-9).

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 (4,5,10). Actually, there is still a great need for studies emphasizing continuation/discontinuation ~~and risks of poor compliance~~ and the following ~~as a consequence a~~ risk of unintended pregnancies.

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

The prescription pattern in Sweden somewhat differs from most other countries as desogestrel-only pills have a very high market share and is the most commonly prescribed hormonal contraceptive. This is most probably an effect of media alarm and very cautious

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recommendations by the Swedish Medical Products Agency. Poor bleeding control is, however, more common during POP-use and has been reported to be a common cause of discontinuation (2).

We hypothesised that switching product within six months is more common among desogestrel-only users compared to users of etinylestradiol + levonorgestrel and that users of ethinylestradiol + drospirenonone are least prone to switch product within six 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. Secondly to measure if rates were related to prescribing categories, i.e. physicians and midwives.

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METHODS

In this study, women identified as first-time users of hormonal contraceptives were treated as a cohort and followed for six 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 (11). The inclusion criteria for data extraction were: female born 1977-1994 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 the 18 months between July 2005 - December 2006 but who had received at least one dispensation between January 2007-December 2009. This group was thus considered to be first-time users and constituted the study cohort in this study. Data from 2010 was 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 was used in this study.

The Swedish Prescribed Drug Register covers all drugs prescribed and dispensed for the entire Swedish population from June 2005 to the present. From this database we have obtained data on drugs having the Anatomical therapeutic chemical codes G03AA or G033AB (combined hormonal contraceptives) and G03AC (progestin only), from July 2005 to December 2010. We organized data by type for the three most common drugs, here referred to by their generic names: 1) ethinylestradiol + levonorgestrel, 2) ethinylestradiol + drospirenone and 3) desogestrel-only. The remaining hormonal contraceptives were placed in two other groups. The first, "Other oral contraceptives", included ethinylestradiol combined with either 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 three-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% confidence intervals for each group of oral contraceptives, with ethinylestradiol + levonorgestrel as the reference category. The CI tails were obtained using the normal distribution approximation and delta method to derive standard errors (12). 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 prescribers, physician or midwife. Measures carried out divided on prescriber categories were the prescription distribution in percent 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 and of those who continued to use the first drug are presented in relation to 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 + drospirenone (11.1%) (Table 1). The perecentage of first-time users who switched to a different drug before six months had elapsed was 11.3%. The rate was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The group for whom 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 of age group showed the lowest rate of change. The continuation rate, i.e. having a repeated dispensation identical to the initial, was highest for ethinylestradiol + levonorgestrel (81.4%) and ethinylestradiol + drospirenone (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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone where ethinylestradiol + levonorgestrel was used as the reference category. Hence, women using ethinylestradiol + drospirenone had the lowest RR for changing to a different type of hormonal contraceptive while those using desogestrel-only had the highest. 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 did neither vary by age group for changing the type of hormonal contraceptive during the first 6 months nor for having a repeated dispensation identical to first.

The physicians and midwives displayed essentially the same pattern of prescribing the second prescription for first-time users. It is, however, worth noting that midwives prescribed the drug ethinylestradiol + drospirenone 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).

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 first			
	Age	n	% of total	n	% per product type	Relative risk	(95% CI)	n	% per product type	Relative risk	(95% CI)
Ethinylestradiol + Levonorgestrel	16-19	73197		8234	11.2	1 (reference)		60945	83.3	1 (reference)	
	20-24	17140		1613	9.4			13158	76.8		
	25-28	7724		529	6.8			5692	73.7		
	16-28	98061	43.3	10376	10.6			79795	81.4		
Ethinylestradiol + Drospirenone	16-19	11604		952	8.2	0.73	(0.68-0.78)	9845	84.8	1.02	(1.01-1.03)
	20-24	7889		433	5.5	0.58	(0.53-0.65)	6261	79.4	1.03	(1.02-1.05)
	25-28	5655		279	4.9	0.72	(0.63-0.83)	4317	76.3	1.04	(1.02-1.06)
	16-28	25148	11.1	1664	6.6	0.63	(0.59-0.66)	20423	81.2	1.00	(0.99-1.00)
Desogestrel only	16-19	29127		4977	17.1	1.52	(1.47-1.57)	21797	74.8	0.90	(0.89-0.91)
	20-24	14172		1719	12.1	1.29	(1.21-1.37)	9657	68.1	0.89	(0.88-0.90)
	25-28	11880		1206	10.2	1.48	(1.34-1.64)	7989	67.2	0.91	(0.90-0.93)
	16-28	55179	24.4	7902	14.3	1.35	(1.32-1.39)	39443	71.5	0.88	(0.87-0.88)
Other oral hormonal contraceptives	16-28	23948	10.6	3016	12.6	1.19	(1.15-1.24)	18179	75.9	0.93	(0.93-0.94)
Other galenic forms[a]	16-28	23875	10.6					[b]			
Total	16-28	226211	100.0	22958c	11.3c			157840[c]	78.0[c]		

[a] intrauterine systems, transdermal patches, implants and injections
[b] irrelevant here as the treatment has long term effect
[c] 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 first %
Ethinylestradiol + levonorgestrel	Midwife	83146	45.1	84.8	10.9	82.1
	Physician	14914	35.7	15.2	8.8	77.4
	All prescribers	98060	40.5	100.0	10.6	81.4
Ethinylestradiol + drospirenone	Midwife	16461	8.9	65.5	7.0	83.3
	Physician	8686	20.8	34.5	5.8	77.2
	All prescribers	25147	11.2	100.0	6.6	81.2
Desogestrel only	Midwife	47035	25.5	85.2	14.7	71.7
	Physician	8139	19.5	14.8	12.0	70.0
	All prescribers	55174	25.6	100.0	14.3	71.5
Other oral hormonal contraceptives	Midwife	19121	10.4	79.8	12.9	76.8
	Physician	4827	11.6	20.2	11.2	72.4
	All prescribers	23948	10.7	100.0	12.6	75.9
All hormonal contraceptives	Midwife	184446	100.0	81.5	11.8	78.7
	Physician	41758	100.0	18.5	9.1	75.1
	All prescribers	226204	100.0	100	11.3	78.0

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 + drospirenone. Women who received an initial prescription of ethinylestradiol combined with either levonorgestrel or drospirenone were more prone to continue with the same drug. On the contrary, women who received desogestrel-only as the initial prescribed and dispensed hormonal contraceptive had 35 % higher probability to choose another type of contraceptive within 6 months of use. Women who originally had received ethinylestradiol + drospirenone were the least likely to switch contraceptive drug during the same period of time.

The Swedish Medical Products Agency (MPA) recommends levonorgestrel containing combined pills as the first choice when prescribing oral contraceptives. 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% (13) compared to 4,5% in Denmark and 0.3% in the United States (14, 15).

The clinical implications of our findings are important as side effects or other reasons for discontinuation or switching between different contraceptives increase the risk for unwanted pregnancies. Oral desogestrel-only contraceptives have become a common choice due to fear of the increased risk for venous thromboses in both 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 for venous thrombosis and also provide a 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 previously been demonstrated that positive health effects in addition to the contraceptive effect most likely will increase continuation rates (16). 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 common prescribed hormonal contraceptive. At the same time and especially among the youngest group of women, 16 – 19 years, the percentage of switchers was the highest.

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Cerazette® (desogestrel 75µg) was registered in Sweden 2001 and the number of users, especially in the younger age categories increased rapidly during the following years. During the same time, the number of teenage abortions increased (176) and it can be speculated that the problem with bleeding control associated with progestin–only methods have ~~lead~~led to lower continuation rates ~~poorer compliance~~ in this group of users and as a consequence an increased risk of unprotected intercourse leading to unwanted pregnancies.

During the past five 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 (187-210). However these results have been contradicted by results from prospective studies (212-254). When transforming results from this kind of studies into clinical recommendations, the question of continuation/discontinuation ~~adherence and compliance~~ is crucial. A possible small increase in risk may be balanced by higher continuation rates~~a better adherence to treatment~~. The results from the present study indicate a more favourable profile for COC containing drospirenone when it comes to -continuation rates~~adherence and compliance~~. To our best knowledge this has not previously been shown. A possible more favourable thromboembolic risk profile with a COC containing ethinylestradiol + levonorgestrel may be counteracted by ~~a~~lower continuation rates ~~poorer adherence~~ compared with pills containing drospirenone and a possible increased risk of unintended pregnancies. As the risk of venous thromboembolism increases rapidly already during early pregnancy this must be taken into account.

A substantial number of women had no second dispensation in six 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 most probably the group is 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 later on started again. 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 is complete and results 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 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 of 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 six months with 14.3% changing. The RR for this type of change was 1.35, compared to ethinylestradiol + levonorgestrel. Women using drospirenone-containing COC were less likely to switch within six months than women using levonorgestrel-containing COC (RR 0.63; 0.59-0.66). The prescription pattern concerning the women's continuation rates differed overall only slightly between the physicians' and the midwives', although there was a lowered prescription and dispensation rate of ethinylestradiol + drospirenone by midwives compared to 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 guarantor of the study.

ABW 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: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work.

JB report financial relations to MSD Sweden and Bayer AB, Sweden (see attached declaration). The other investigators declared no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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

Data sharing: No additional data available.

What is already known on this topic

Compliance and adherence to contraceptive use is almost always overestimated in clinical trials. Data on difference in compliance and adherence between different formulations of oral contraception is lacking or of poor quality. Knowledge of adherence and compliance is essential when it comes to avoid unintended pregnancies.

What this study adds

Users of progestin-only pills more frequently choose another hormonal contraceptive method or discontinue use within six months. Users of drospirenone containing combined oral contraceptives were the least likely to switch method. The results indicate a more favourable profile concerning adherence to treatment for drospirenone containing combined oral contraceptives. This may be of clinical interest when it comes to a decision of what type of oral contraceptives the individual woman should be recommended.

STROBE Statement – checklist of items that should be included in reports of observational studies.

1a	Done
1b	Done
2	Done
3	*Intoduction*, last paragraph
4	*Method*, first sentence
5	*Method*, first and second paragraph
6a	*Method*, first and second paragraph
6b	We consider this as not relevant
7	In *Statistical analysis,* there are descriptions of the variables: “age groups”, “changing type” and “using same drug after 6 months”
8	Not relevant – all information is from the Swedish Prescribed Drug Register
9	In this study with an intention to solely describe the switching/ continuation rate and not to explain its underlying causes, the risk of presenting biased results is not an immediate problem. Especially not since we consider the external validity in this study as very high.
10	We consider this as not relevant
11	*Statistical analyses*
12a	Relative risks together with 95% CIs are used for the analyses, and its composition in terms of risk outcome and reference category in the ratio as well as CI interval calculations are presented in *Statistical analysis*.
12b	We consider this as not relevant
12c	We have used register data with a most probable complete registration (see *Strengths and limitations of the study*)
12d	Please see item 12c
12e	We have previously calculated the proportions for switching product within 12 months and found the pattern quite similar.
13a	See table 1 and table 2
13b	We consider this as not relevant
13c	We believe that the description of inclusion is rather uncomplicated and that the description in *Method*, first and paragraph is easy to follow.
14a	We have not included data on such information in this study
14b	There are no missing data in our chosen variables
14c	The follow-up time is exactly six months for each woman in the study.
15	Please see table 1 and table 2
16a	Please see table 1
16b	Please see *Statistical analyses*
16c	Please see table 1
17	We consider this as not relevant
18	*Discussion*, first paragraph
19	Please see *Strengths and limitations of the study*
20	*Conclusion*
21	Very high external validity (see *Strengths and limitations of the study*)
22	No funding

16th January 2013

Dear Dr. Josefsson

BMJ.2013.010282 entitled "Patterns of adherence to oral hormonal contraceptives in a cohort of first time users: a population based registry study, Sweden 2005-2010"

Thank you for sending us your paper. We read it with interest but I regret to say that we have decided not to publish it in the BMJ.

We enjoyed reading the study and were impressed by the comprehensive nature of your dataset. However we also noted the limitations and particularly that the nature of the study makes it difficult to know why people started particular preparations and also why people switched (or discontinued). The study may be appropriate for a specialist journal and hopefully lead to further research into the adverse effects of the different preparations.

We receive over 8000 submissions a year and accept less than 10%. We do therefore have to make hard decisions on just how interesting an article will be to our general clinical readers, how much it adds, and how much practical value it will be.

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Corresponding Author's Name: Ann Josefsson

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Competing interests:
Jan Brynhildsen (JB) has been reimbursed by Merck Sharpe & Dohme (MSD), Sweden, the manufacturer of desogestrel-containing contraceptives I 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.
JB has also been the member of the Swedish medical advisory board of MSD between 2008 and 2012.

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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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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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Key words: Hormonal contraceptives; Oral contraceptives; Patient adherence; Registries ; Follow-up studies

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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 rates were related to prescribing categories, i.e. physicians and midwives.

Design A longitudinal national population-based registry study

Setting The Swedish prescribed drug register

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

Main outcome measures Tendency to switch type of hormonal contraceptive within 6 months use and repeated dispensation identical to first were estimated as percentages and relative risks. 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 1977-1994 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 for first-time users, 43.3 %, 24.4 % and 11.1 %, respectively. The overall rate of switching contraceptive type in the first six months was 11.3%, highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The switching rate for all three products was highest in 16-19 year age group. Having a repeated dispensation identical to the initial 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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone compared to ethinylestradiol + levonorgestrel as reference category. The physicians' and midwives' prescription patterns concerning the women's continuation rates differed only slightly.

Conclusion Desogestrel-only users conferred the highest switcher rate to another hormonal contraceptive within a 6-months period. Users of ethinylestradiol + levonorgestrel were more prone to switch to another product within six months than women using ethinylestradiol + drospirenone. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

ARTICLE SUMMARY

Article focus

- Continuation of contraceptive use is of outmost importance to avoid unintended pregnancies
- In Sweden, a change in prescription pattern has been observed, from combined oral contraceptives to progestin-only-pills, most probably due to media alarm
- Do continuation rates differ between different formulations of combined oral contraceptives?

Key messages

- Users of progestin-only pills more frequently choose another hormonal contraceptive method, or discontinue use within six months, than users of combined oral contraceptives
- Users of drospirenone containing combined oral contraceptives were the least likely to switch method

Strengts 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, data is complete and results 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.

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 characterized by relatively high discontinuation rates and low adherence to treatment(1). Reasons for discontinuation and poor adherence have been reported to be side effects but also the fear of side effects. Reported side effects include mood disturbances, decrease in libido, weight gain and poor bleeding control and the fear also includes the risk of venous thromboembolism (2, 3). 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, discontinuation rates are still high.

A huge mass of studies has been performed, but there is only sparse evidence of differences in continuation rates between different types of hormonal contraceptives. Type of progestogen (4, 5), number of oral contraceptive pill packages dispensed (6), prescription drug or over the counter (7) 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, i.e. mono-, bi-, tri-, and four -phasic pills, patches and vaginal rings (8, 9). 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 (4-9).

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 (4,5,10). Actually, there is still a great need for studies emphasizing continuation/discontinuation and the following risk of unintended pregnancies.

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

The prescription pattern in Sweden somewhat differs from most other countries as desogestrel-only pills have a very high market share and is 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 POP-use and has been reported to be a common cause of discontinuation (2).

We hypothesised that switching product within six months is more common among desogestrel-only users compared to users of etinylestradiol + levonorgestrel and that users of ethinylestradiol + drospirenonone are least prone to switch product within six 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. Secondly to measure if rates were related to prescribing categories, i.e. physicians and midwives.

METHODS

In this study, women identified as first-time users of hormonal contraceptives were treated as a cohort and followed for six 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 (11). The inclusion criteria for data extraction were: female born 1977-1994 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 the 18 months between July 2005 - December 2006 but who had received at least one dispensation between January 2007-December 2009. This group was thus considered to be first-time users and constituted the study cohort in this study. Data from 2010 was 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 was used in this study.

The Swedish Prescribed Drug Register covers all drugs prescribed and dispensed for the entire Swedish population from June 2005 to the present. From this database we have obtained data on drugs having the Anatomical therapeutic chemical codes G03AA or G033AB (combined hormonal contraceptives) and G03AC (progestin only), from July 2005 to December 2010. We organized data by type for the three most common drugs, here referred to by their generic names: 1) ethinylestradiol + levonorgestrel, 2) ethinylestradiol + drospirenone and 3) desogestrel-only. The remaining hormonal contraceptives were placed in two other groups. The first, "Other oral contraceptives", included ethinylestradiol combined with either 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 three-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% confidence intervals for each group of oral contraceptives, with

ethinylestradiol + levonorgestrel as the reference category. The CI tails were obtained using the normal distribution approximation and delta method to derive standard errors (12). 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 prescribers, physician or midwife. Measures carried out divided on prescriber categories were the prescription distribution in percent 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 and of those who continued to use the first drug are presented in relation to 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 + drospirenone (11.1%) (Table 1). The perecentage of first-time users who switched to a different drug before six months had elapsed was 11.3%. The rate was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The group for whom 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 of age group showed the lowest rate of change. The continuation rate, i.e. having a repeated dispensation identical to the initial, was highest for ethinylestradiol + levonorgestrel (81.4%) and ethinylestradiol + drospirenone (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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone where ethinylestradiol + levonorgestrel was used as the reference category. Hence, women using ethinylestradiol + drospirenone had the lowest RR for changing to a different type of hormonal contraceptive while those using desogestrel-only had the highest. 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 did neither vary by age group for changing the type of hormonal contraceptive during the first 6 months nor for having a repeated dispensation identical to 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 + drospirenone 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).

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 first			
	Age	n	% of total	n	% per product type	Relative risk	(95% CI)	n	% per product type	Relative risk	(95% CI)
Ethinylestradiol + Levonorgestrel	16-19	73197		8234	11.2	1 (reference)		60945	83.3	1 (reference)	
	20-24	17140		1613	9.4			13158	76.8		
	25-28	7724		529	6.8			5692	73.7		
	16-28	98061	43.3	10376	10.6			79795	81.4		
Ethinylestradiol + Drospirenone	16-19	11604		952	8.2	0.73	(0.68-0.78)	9845	84.8	1.02	(1.01-1.03)
	20-24	7889		433	5.5	0.58	(0.53-0.65)	6261	79.4	1.03	(1.02-1.05)
	25-28	5655		279	4.9	0.72	(0.63-0.83)	4317	76.3	1.04	(1.02-1.06)
	16-28	25148	11.1	1664	6.6	0.63	(0.59-0.66)	20423	81.2	1.00	(0.99-1.00)
Desogestrel only	16-19	29127		4977	17.1	1.52	(1.47-1.57)	21797	74.8	0.90	(0.89-0.91)
	20-24	14172		1719	12.1	1.29	(1.21-1.37)	9657	68.1	0.89	(0.88-0.90)
	25-28	11880		1206	10.2	1.48	(1.34-1.64)	7989	67.2	0.91	(0.90-0.93)
	16-28	55179	24.4	7902	14.3	1.35	(1.32-1.39)	39443	71.5	0.88	(0.87-0.88)
Other oral hormonal contraceptives	16-28	23948	10.6	3016	12.6	1.19	(1.15-1.24)	18179	75.9	0.93	(0.93-0.94)
Other galenic forms[a]	16-28	23875	10.6			[b]					
Total	16-28	226211	100.0	22958c	11.3c			157840[c]	78.0[c]		

[a] intrauterine systems, transdermal patches, implants and injections
[b] irrelevant here as the treatment has long term effect
[c] 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 first %
Ethinylestradiol + levonorgestrel	Midwife	83146	45.1	84.8	10.9	82.1
	Physician	14914	35.7	15.2	8.8	77.4
	All prescribers	98060	40.5	100.0	10.6	81.4
Ethinylestradiol + drospirenone	Midwife	16461	8.9	65.5	7.0	83.3
	Physician	8686	20.8	34.5	5.8	77.2
	All prescribers	25147	11.2	100.0	6.6	81.2
Desogestrel only	Midwife	47035	25.5	85.2	14.7	71.7
	Physician	8139	19.5	14.8	12.0	70.0
	All prescribers	55174	25.6	100.0	14.3	71.5
Other oral hormonal contraceptives	Midwife	19121	10.4	79.8	12.9	76.8
	Physician	4827	11.6	20.2	11.2	72.4
	All prescribers	23948	10.7	100.0	12.6	75.9
All hormonal contraceptives	Midwife	184446	100.0	81.5	11.8	78.7
	Physician	41758	100.0	18.5	9.1	75.1
	All prescribers	226204	100.0	100	11.3	78.0

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 + drospirenone. Women who received an initial prescription of ethinylestradiol combined with either levonorgestrel or drospirenone were more prone to continue with the same drug. On the contrary, women who received desogestrel-only as the initial prescribed and dispensed hormonal contraceptive had 35 % higher probability to choose another type of contraceptive within 6 months of use. Women who originally had received ethinylestradiol + drospirenone were the least likely to switch contraceptive drug during the same period of time.

The Swedish Medical Products Agency (MPA) recommends levonorgestrel containing combined pills as the first choice when prescribing oral contraceptives. 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% (13) compared to 4,5% in Denmark and 0.3% in the United States (14, 15).

The clinical implications of our findings are important as side effects or other reasons for discontinuation or switching between different contraceptives increase the risk for unwanted pregnancies. Oral desogestrel-only contraceptives have become a common choice due to fear of the increased risk for venous thromboses in both 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 for venous thrombosis and also provide a 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 previously been demonstrated that positive health effects in addition to the contraceptive effect most likely will increase continuation rates (16). 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 common prescribed hormonal contraceptive. At the same time and especially among the youngest group of women, 16 – 19 years, the percentage of switchers was the highest.

Cerazette® (desogestrel 75µg) was registered in Sweden 2001 and the number of users, especially in the younger age categories increased rapidly during the following years. During the same time, the number of teenage abortions increased (17) 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 five 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 (18-21). However these results have been contradicted by results from prospective studies (2225). When transforming results from this kind of studies into clinical recommendations, the question of continuation/discontinuation is crucial. A possible 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 our best knowledge this has not previously been shown. A possible 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 possible increased risk of unintended pregnancies. As the risk of venous thromboembolism increases rapidly already during early pregnancy this must be taken into account.

A substantial number of women had no second dispensation in six 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 most probably the group is 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 later on started again. 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 is complete and results 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 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 of 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 six months with 14.3% changing. The RR for this type of change was 1.35, compared to ethinylestradiol + levonorgestrel. Women using drospirenone-containing COC were less likely to switch within six months than women using levonorgestrel-containing COC (RR 0.63; 0.59-0.66). The prescription pattern concerning the women's continuation rates differed overall only slightly between the physicians' and the midwives', although there was a lowered prescription and dispensation rate of ethinylestradiol + drospirenone by midwives compared to 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 guarantor of the study.

ABW 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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JB report financial relations to MSD Sweden and Bayer AB, Sweden (see attached declaration). The other investigators declared no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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

Data sharing: No additional data available.

What is already known on this topic

Compliance and adherence to contraceptive use is almost always overestimated in clinical trials. Data on difference in compliance and adherence between different formulations of oral contraception is lacking or of poor quality. Knowledge of adherence and compliance is essential when it comes to avoid unintended pregnancies.

What this study adds

Users of progestin-only pills more frequently choose another hormonal contraceptive method or discontinue use within six months. Users of drospirenone containing combined oral contraceptives were the least likely to switch method. The results indicate a more favourable profile concerning adherence to treatment for drospirenone containing combined oral contraceptives. This may be of clinical interest when it comes to a decision of what type of oral contraceptives the individual woman should be recommended.

STROBE Statement – checklist of items that should be included in reports of observational studies.

1a	Done
1b	Done
2	Done
3	*Intoduction*, last paragraph
4	*Method*, first sentence
5	*Method*, first and second paragraph
6a	*Method*, first and second paragraph
6b	We consider this as not relevant
7	In *Statistical analysis,* there are descriptions of the variables: “age groups”, “changing type” and “using same drug after 6 months”
8	Not relevant – all information is from the Swedish Prescribed Drug Register
9	In this study with an intention to solely describe the switching/ continuation rate and not to explain its underlying causes, the risk of presenting biased results is not an immediate problem. Especially not since we consider the external validity in this study as very high.
10	We consider this as not relevant
11	*Statistical analyses*
12a	Relative risks together with 95% CIs are used for the analyses, and its composition in terms of risk outcome and reference category in the ratio as well as CI interval calculations are presented in *Statistical analysis*.
12b	We consider this as not relevant
12c	We have used register data with a most probable complete registration (see *Strengths and limitations of the study*)
12d	Please see item 12c
12e	We have previously calculated the proportions for switching product within 12 months and found the pattern quite similar.
13a	See table 1 and table 2
13b	We consider this as not relevant
13c	We believe that the description of inclusion is rather uncomplicated and that the description in *Method*, first and paragraph is easy to follow.
14a	We have not included data on such information in this study
14b	There are no missing data in our chosen variables
14c	The follow-up time is exactly six months for each woman in the study.
15	Please see table 1 and table 2
16a	Please see table 1
16b	Please see *Statistical analyses*
16c	Please see table 1
17	We consider this as not relevant
18	*Discussion*, first paragraph
19	Please see *Strengths and limitations of the study*
20	*Conclusion*
21	Very high external validity (see *Strengths and limitations of the study*)
22	No funding

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Jan Brynhildsen (JB) has been reimbursed by Merck Sharpe & Dohme (MSD), Sweden, the manufacturer of desogestrel-containing contraceptives I 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.
JB has also been the member of the Swedish medical advisory board of MSD between 2008 and 2012.

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Continuation rates of ~~Patterns of adherence to~~ oral hormonal contraceptives in a cohort of first time users: a population based registry study, Sweden 2005-2010

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Field Code Changed

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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 rates were related to prescribing categories, i.e. physicians and midwives.

Design A longitudinal national population-based registry study

Setting The Swedish prescribed drug register

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

Main outcome measures Tendency to switch type of hormonal contraceptive within 6 months use and repeated dispensation identical to first were estimated as percentages and relative risks. 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 1977-1994 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 for first-time users, 43.3 %, 24.4 % and 11.1 %, respectively. The overall rate of switching contraceptive type in the first six months was 11.3%, highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The switching rate for all three products was highest in 16-19 year age group. Having a repeated dispensation identical to the initial 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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone compared to ethinylestradiol + levonorgestrel as reference category. The physicians' and midwives' prescription patterns concerning the women's continuation rates differed only slightly.

Conclusion Desogestrel-only users conferred the highest switcher rate to another hormonal contraceptive within a 6-months period. Users of ethinylestradiol + levonorgestrel were more prone to switch to another product within six months than women using ethinylestradiol + drospirenone. These findings may be of clinical importance when tailoring hormonal contraceptives on an individual basis.

ARTICLE SUMMARY

Article focus

- Continuation of ~~Compliance and adherence to~~ contraceptive use~~s~~ is of outmost importance to avoid unintended pregnancies
- In Sweden, a change in prescription pattern has been observed, from combined oral contraceptives to progestin-only-pills, most probably due to media alarm
- Do continuation rates ~~adherence to treatment~~ differ between different formulations of combined oral contraceptives?

Key messages

- Users of progestin-only pills more frequently choose another hormonal contraceptive method, or discontinue use within six months, than users of combined oral contraceptives
- Users of drospirenone containing combined oral contraceptives were the least likely to switch method

Strengts 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, data is complete and results 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.

INTRODUCTION

Adherence to treatment ~~Compliance~~ and continuation of contraceptive use is crucial in the efforts to avoid unwanted pregnancies. Oral contraceptive (OC) use is however; generally characterized by ~~poor compliance,~~ relatively high discontinuation rates and low adherence to treatment~~and relatively high discontinuation rates~~ (1). Reasons for discontinuation and poor adherence ~~and discontinuation~~ have been reported to be side effects but also the fear of side effects. Reported side effects include mood disturbances, decrease in libido, weight gain and poor bleeding control and the fear also includes the risk of venous thromboembolism (2, 3). 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, discontinuation rates are still high.

A huge mass of studies has been performed, but there is only sparse evidence of differences in continuation rates between different types of -hormonal contraceptives. Type of progestogen (4, 5), number of oral contraceptive pill packages dispensed (6), prescription drug or over the counter (7) 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 ~~adherence~~. Such improvements include new routes of administration and different regimens, i.e. mono-, bi-, tri-, and four -phasic pills, patches and vaginal rings (8, 9). 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 (4-9).

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 (4,5,10). Actually, there is still a great need for studies emphasizing continuation/discontinuation ~~and risks of poor compliance~~ and the following ~~as a consequence a~~ risk of unintended pregnancies.

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

The prescription pattern in Sweden somewhat differs from most other countries as desogestrel-only pills have a very high market share and is the most commonly prescribed hormonal contraceptive. This is most probably an effect of media alarm and very cautious

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recommendations by the Swedish Medical Products Agency. Poor bleeding control is, however, more common during POP-use and has been reported to be a common cause of discontinuation (2).

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We hypothesised that switching product within six months is more common among desogestrel-only users compared to users of etinylestradiol + levonorgestrel and that users of ethinylestradiol + drospirenonone are least prone to switch product within six 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. Secondly to measure if rates were related to prescribing categories, i.e. physicians and midwives.

METHODS

In this study, women identified as first-time users of hormonal contraceptives were treated as a cohort and followed for six 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 (11). The inclusion criteria for data extraction were: female born 1977-1994 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 the 18 months between July 2005 - December 2006 but who had received at least one dispensation between January 2007-December 2009. This group was thus considered to be first-time users and constituted the study cohort in this study. Data from 2010 was 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 was used in this study.

The Swedish Prescribed Drug Register covers all drugs prescribed and dispensed for the entire Swedish population from June 2005 to the present. From this database we have obtained data on drugs having the Anatomical therapeutic chemical codes G03AA or G033AB (combined hormonal contraceptives) and G03AC (progestin only), from July 2005 to December 2010. We organized data by type for the three most common drugs, here referred to by their generic names: 1) ethinylestradiol + levonorgestrel, 2) ethinylestradiol + drospirenone and 3) desogestrel-only. The remaining hormonal contraceptives were placed in two other groups. The first, "Other oral contraceptives", included ethinylestradiol combined with either 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 three-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% confidence intervals for each group of oral contraceptives, with ethinylestradiol + levonorgestrel as the reference category. The CI tails were obtained using the normal distribution approximation and delta method to derive standard errors (12). 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 prescribers, physician or midwife. Measures carried out divided on prescriber categories were the prescription distribution in percent 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 and of those who continued to use the first drug are presented in relation to 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 + drospirenone (11.1%) (Table 1). The perecentage of first-time users who switched to a different drug before six months had elapsed was 11.3%. The rate was highest for desogestrel-only (14.3%) and lowest for ethinylestradiol + drospirenone (6.6 %). The group for whom 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 of age group showed the lowest rate of change. The continuation rate, i.e. having a repeated dispensation identical to the initial, was highest for ethinylestradiol + levonorgestrel (81.4%) and ethinylestradiol + drospirenone (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 six months was 1.35 (95% CI: 1.32-1.39) for desogestrel-only and 0.63 (0.59-0.66) for ethinylestradiol + drospirenone where ethinylestradiol + levonorgestrel was used as the reference category. Hence, women using ethinylestradiol + drospirenone had the lowest RR for changing to a different type of hormonal contraceptive while those using desogestrel-only had the highest. 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 did neither vary by age group for changing the type of hormonal contraceptive during the first 6 months nor for having a repeated dispensation identical to 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 + drospirenone 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).

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 first			
	Age	n	% of total	n	% per product type	Relative risk	(95% CI)	n	% per product type	Relative risk	(95% CI)
Ethinylestradiol + Levonorgestrel	16-19	73197		8234	11.2	1 (reference)		60945	83.3	1 (reference)	
	20-24	17140		1613	9.4			13158	76.8		
	25-28	7724		529	6.8			5692	73.7		
	16-28	98061	43.3	10376	10.6			79795	81.4		
Ethinylestradiol + Drospirenone	16-19	11604		952	8.2	0.73	(0.68-0.78)	9845	84.8	1.02	(1.01-1.03)
	20-24	7889		433	5.5	0.58	(0.53-0.65)	6261	79.4	1.03	(1.02-1.05)
	25-28	5655		279	4.9	0.72	(0.63-0.83)	4317	76.3	1.04	(1.02-1.06)
	16-28	25148	11.1	1664	6.6	0.63	(0.59-0.66)	20423	81.2	1.00	(0.99-1.00)
Desogestrel only	16-19	29127		4977	17.1	1.52	(1.47-1.57)	21797	74.8	0.90	(0.89-0.91)
	20-24	14172		1719	12.1	1.29	(1.21-1.37)	9657	68.1	0.89	(0.88-0.90)
	25-28	11880		1206	10.2	1.48	(1.34-1.64)	7989	67.2	0.91	(0.90-0.93)
	16-28	55179	24.4	7902	14.3	1.35	(1.32-1.39)	39443	71.5	0.88	(0.87-0.88)
Other oral hormonal contraceptives	16-28	23948	10.6	3016	12.6	1.19	(1.15-1.24)	18179	75.9	0.93	(0.93-0.94)
Other galenic forms[a]	16-28	23875	10.6					[b]			
Total	16-28	226211	100.0	22958c	11.3c			157840[c]	78.0[c]		

[a] intrauterine systems, transdermal patches, implants and injections
[b] irrelevant here as the treatment has long term effect
[c] 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 first %
Ethinylestradiol + levonorgestrel	Midwife	83146	45.1	84.8	10.9	82.1
	Physician	14914	35.7	15.2	8.8	77.4
	All prescribers	98060	40.5	100.0	10.6	81.4
Ethinylestradiol + drospirenone	Midwife	16461	8.9	65.5	7.0	83.3
	Physician	8686	20.8	34.5	5.8	77.2
	All prescribers	25147	11.2	100.0	6.6	81.2
Desogestrel only	Midwife	47035	25.5	85.2	14.7	71.7
	Physician	8139	19.5	14.8	12.0	70.0
	All prescribers	55174	25.6	100.0	14.3	71.5
Other oral hormonal contraceptives	Midwife	19121	10.4	79.8	12.9	76.8
	Physician	4827	11.6	20.2	11.2	72.4
	All prescribers	23948	10.7	100.0	12.6	75.9
All hormonal contraceptives	Midwife	184446	100.0	81.5	11.8	78.7
	Physician	41758	100.0	18.5	9.1	75.1
	All prescribers	226204	100.0	100	11.3	78.0

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 + drospirenone. Women who received an initial prescription of ethinylestradiol combined with either levonorgestrel or drospirenone were more prone to continue with the same drug. On the contrary, women who received desogestrel-only as the initial prescribed and dispensed hormonal contraceptive had 35 % higher probability to choose another type of contraceptive within 6 months of use. Women who originally had received ethinylestradiol + drospirenone were the least likely to switch contraceptive drug during the same period of time.

The Swedish Medical Products Agency (MPA) recommends levonorgestrel containing combined pills as the first choice when prescribing oral contraceptives. 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% (13) compared to 4,5% in Denmark and 0.3% in the United States (14, 15).

The clinical implications of our findings are important as side effects or other reasons for discontinuation or switching between different contraceptives increase the risk for unwanted pregnancies. Oral desogestrel-only contraceptives have become a common choice due to fear of the increased risk for venous thromboses in both 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 for venous thrombosis and also provide a 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 previously been demonstrated that positive health effects in addition to the contraceptive effect most likely will increase continuation rates (16). 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 common prescribed hormonal contraceptive. At the same time and especially among the youngest group of women, 16 – 19 years, the percentage of switchers was the highest.

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Cerazette® (desogestrel 75µg) was registered in Sweden 2001 and the number of users, especially in the younger age categories increased rapidly during the following years. During the same time, the number of teenage abortions increased (176) and it can be speculated that the problem with bleeding control associated with progestin–only methods have ~~lead~~led to lower continuation rates ~~poorer compliance~~ in this group of users and as a consequence an increased risk of unprotected intercourse leading to unwanted pregnancies.

During the past five 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 (187-210). However these results have been contradicted by results from prospective studies (2~~1~~2-254). When transforming results from this kind of studies into clinical recommendations, the question of continuation/discontinuation ~~adherence and compliance~~ is crucial. A possible small increase in risk may be balanced by higher continuation rates~~a better adherence to treatment~~. The results from the present study indicate a more favourable profile for COC containing drospirenone when it comes to -continuation rates~~adherence and compliance~~. To our best knowledge this has not previously been shown. A possible more favourable thromboembolic risk profile with a COC containing ethinylestradiol + levonorgestrel may be counteracted by ~~a~~lower continuation rates ~~poorer adherence~~ compared with pills containing drospirenone and a possible increased risk of unintended pregnancies. As the risk of venous thromboembolism increases rapidly already during early pregnancy this must be taken into account.

A substantial number of women had no second dispensation in six 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 most probably the group is 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 later on started again. 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 is complete and results 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 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 of 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 six months with 14.3% changing. The RR for this type of change was 1.35, compared to ethinylestradiol + levonorgestrel. Women using drospirenone-containing COC were less likely to switch within six months than women using levonorgestrel-containing COC (RR 0.63; 0.59-0.66). The prescription pattern concerning the women's continuation rates differed overall only slightly between the physicians' and the midwives', although there was a lowered prescription and dispensation rate of ethinylestradiol + drospirenone by midwives compared to 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 guarantor of the study.

ABW 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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JB report financial relations to MSD Sweden and Bayer AB, Sweden (see attached declaration). The other investigators declared no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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

Data sharing: No additional data available.

What is already known on this topic

Compliance and adherence to contraceptive use is almost always overestimated in clinical trials. Data on difference in compliance and adherence between different formulations of oral contraception is lacking or of poor quality. Knowledge of adherence and compliance is essential when it comes to avoid unintended pregnancies.

What this study adds

Users of progestin-only pills more frequently choose another hormonal contraceptive method or discontinue use within six months. Users of drospirenone containing combined oral contraceptives were the least likely to switch method. The results indicate a more favourable profile concerning adherence to treatment for drospirenone containing combined oral contraceptives. This may be of clinical interest when it comes to a decision of what type of oral contraceptives the individual woman should be recommended.