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**Use of hormonal contraceptives in relation to antidepressant therapy:
a nationwide population-based study**

Ann-Britt Wiréhn, PhD¹

Anniqa Foldemo, RN, PhD^{1,2}

Ann Josefsson, MD, PhD³

Malou Lindberg, RN, PhD¹

¹Local Health Care Research and Development Unit, County Council in Östergötland, Linköping University, Linköping, Sweden

²Department of Medical and Health Sciences, Division of Nursing Sciences, Faculty of Health Sciences, Linköping University, Linköping, Sweden

³Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynaecology, Faculty of Health Sciences, Linköping University, Linköping, Sweden

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Corresponding author:

Ann-Britt Wiréhn,
Local Health Care Research and Development Unit in Östergötland,
SE-582 24 Linköping,
Sweden.

Tel: +46 13 228506
Fax: +46 13 228501
E-mail: ann-britt.wirehn@lio.se

ABSTRACT

Objectives The relation between the use of different hormonal contraceptives and antidepressant therapy was investigated.

Methods In a nationwide cross-sectional study among all women in Sweden aged 16-31, drug expenditure data on hormonal contraceptives and antidepressants were obtained from the Swedish Prescribed Drug Register. Odds ratios (ORs) for antidepressant use were calculated by logistic regression for progestin-only users versus non-users as well as for combined hormonal contraceptive (CHC) users versus non-users.

Results In the study population (n=917 993), 58.9 % were hormonal contraceptive users, and 8.5 % were antidepressant users. The age-pattern for antidepressant ORs differed between the two types of users of contraceptives; progestin-only users had significant ORs above 1 in all age groups whereas among CHC users the OR was above 1 solely in those aged 16-19. The largest difference between types of users was seen in the age group 16-19 in which women resorting to a progestin-only contraceptive had a 67% (95% confidence interval: 57% - 78%) higher antidepressant use than women treated with a CHC.

Conclusion Progestin-only contraceptive users resorted to antidepressants more than users of CHCs. This phenomenon is particularly pronounced among teenagers. Therefore, special attention should be given to young women's mental history when prescribing hormonal contraceptives and vice versa: **the** contraceptive history should be taken into account when prescribing antidepressants.

INTRODUCTION

Mental disorders are among the most burdensome of diseases due to their high prevalence and they are positively related to socioeconomic measures of disadvantage.¹ Depression and anxiety are common in adolescence, the stage at which most mental disorders begin¹⁻³, although they are often first detected later in life.² Epidemiological research from different parts of the world has revealed that the lifetime prevalence of depression in women is roughly twice that in men.⁴ Likewise, self-reported studies on behavioural and emotional problems report differences between genders in adolescents.⁵⁻⁸ However, major depression is a multifactor disorder including predisposing genetic influences⁹ and no fully satisfactory explanation for the gender difference has been proposed.^{4,10}

Many different combined hormonal contraceptives (CHCs) and progestin-only hormonal contraceptives are available worldwide. They are effective means of preventing pregnancy¹¹ and of achieving a proper cycle control¹². Although ideas about their association with mental disorders vary, it is commonly believed that hormonal contraceptives have no impact on depressive symptoms and only minimal, if any, impact on mood.¹³⁻¹⁵ On the other hand, emotional side effects are suggested as reasons for discontinuing/switching treatment.¹⁶ Furthermore, different side effects of hormonal contraceptive use on mood have been described; these appear to depend on the relation between oestrogen and progestin, and on the type of progestin.¹⁷

Mental disorders such as depression and anxiety are more common in women who have reported adverse mood effects from either current or past treatment with combined oral contraceptives (COCs) than in those without such side effects during COC treatment.¹⁸ This finding may support the theory that it is not the hormonal contraceptives as such that induce the mood swings but instead a vulnerability to mood deterioration in certain individuals. In order to further investigate the occurrence of mood disorders in users of different hormonal contraceptives we assessed the simultaneous use of antidepressants among the entire population of young women in Sweden. Hence, the aim of this study was to explore the relation between use of different hormonal contraceptives and antidepressant therapy.

METHODS

Design and study population

This register study comprised all 917 993 female residents in Sweden aged 16 to 31 on 1 November 2008. Sweden has a total population of about 9.3 million. The study employed a cross-sectional design and the study population was separated into hormonal contraceptive users and non-users as well as into antidepressant users and non-users.

Data collection

Since July 2005, data on all dispensed drug prescriptions in Sweden are available in the Swedish Prescribed Drug Register. The register covers the whole Swedish population and contains data on the following: dispensed amount per drug for each patient; a unique patient identifier, age, sex, place of residence; prescribing and dispensing dates; type of health care level; and the prescriber's profession.¹⁹ Data on all dispensed drugs with the Anatomical Therapeutic Chemical (ATC) code G03A (hormonal contraceptives) and N06A (antidepressants) were extracted from the registry for a three-year period from 1 July 2005 to 30 June 2008. The contraceptives were separated into two groups, one consisting of combined oestrogen- and progestin contraceptives (CHCs) and the other of progestin-only products. CHCs have ATC-codes G03AA or G03AB whereas progestin-only contraceptives have the ATC-code G03AC. Thus, the contraceptive data included oral contraceptives as well as other contraceptive formulations. In addition to the ATC-code, the year of birth was extracted for each individual. All data were anonymous. Although the correct designation for data from the Swedish Prescribed Drug Register is, strictly speaking, "prescribed and dispensed drugs", the term used in this article is "drug users". To be considered as a contraceptive or antidepressant user the woman had to have the actual drug dispensed at least once during the three-year period. All of the drugs referred to in this article are generic drugs.

The total number of women in each specific group in the nation was identified from the Total Population Register, which is available on Statistics Sweden's website.²⁰ The difference between the total number of individuals and the number obtained from the Swedish Prescribed Drug Register represented data on non-users of both contraceptives and antidepressants. Each non-user was given a unique code which was inserted into the data set. Thus, a data set was obtained consisting of all Swedish women aged 16 to 31.

Statistical analyses

Numbers and percentages of users are given for the whole group of women aged 16-31, as well as for the age subgroups 16-19, 20-23, 24-27, and 28-31 years. By logistic regression, with antidepressant user as a dependent variable, age-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for those using solely a CHC and those using solely a progestin-only contraceptive versus non-hormonal contraceptive users. Similar analyses were carried out on subjects using both of these generic drugs, i.e. those who switched from using a CHC to using a progestin-only compound – or vice versa - during the three-year period. Analogous ORs were determined for each age group separately. The magnitude of the difference between ORs for CHC and progestin-only use in relation to antidepressant use was calculated as a ratio between these ORs.

Ethical approval

This study was approved by the Local Ethics Committee at Linköping University; Dnr M125-08.

RESULTS

Drug use

In the female Swedish population aged 16-31 on 1 November 2008, 540 249 (58.9%) subjects were hormonal contraceptive users and 78 436 (8.5%) antidepressant users, i.e. they had received a prescription and had it filled at least once during the three-year period. Among the hormonal contraceptive users, 402 931 (74.6 %) had used a CHC at least once, 220 233 (40.8%) had used a progestin-only contraceptive at least once (Table 1) (the presented percentages exceed 100 % since a number of the hormonal contraceptive users switched from one type of hormonal contraceptive to another during the three-year period (15.4 %)). The mean ages in the progestin-only, CHC and antidepressant groups were 24.1, 23.1 and 25.0 years, respectively.

In proportion to all antidepressant users, the selective serotonin reuptake inhibitor (SSRI) users constituted 86.5% of the studied population (data not shown). A negligible number (n=208) of hormonal emergency contraception users were included in the progestin-only group (data not shown).

The frequency of dispensing contraceptive drugs during the three-year period ranged from 1 to 84 times (median = 3), and 10% of the individuals collected a prescription between 9-84

times. For antidepressant drugs the frequency of dispensing ranged from 1 to 304 times (median = 5), and 10% of the individuals took out the prescribed drug between 16 and 304 times.

Relation between the use of antidepressants and hormonal contraceptives

In the age interval studied, the OR for antidepressants was 1.31 (95% CI: 1.29 – 1.34) in progestin-only users and 1.02 (1.00 – 1.04) in CHC users (Table 2). The OR of progestin-only users decreased with increasing age, from 2.14 (2.01 – 2.28) in the youngest age group to 1.08 (1.04 – 1.12) in the oldest age group. For CHC users, this statistic had a different pattern, still showing the highest OR in the youngest age group (OR = 1.28 [1.22 – 1.35]) and then decreasing to just below 0.9 in the group 20 to 27 years old and rising again to about 1 in the oldest age group. Thus, progestin-only users had antidepressant ORs above 1 regardless of age whereas the OR for CHC users was greater than 1 only in the age group 16-19 (Figure 1).

Antidepressant ORs (hormonal contraceptives versus no hormonal contraceptives) are higher among progestin-only users in every age group than among CHC users in the corresponding age groups but the magnitude of the difference decreases with age: it amounts to 67% (95% CI: 57-78%) among women 16-19 years old and to only 10% (95% CI: 6-14%) among those in the age group 28-31.

DISCUSSION

In this nationwide population-based study we explored the relation between the use of different hormonal contraceptives and antidepressants among young women of different ages. Our main finding is that antidepressant therapy is more common among progestin-only users in every age group than among users of combined contraceptives. The largest difference was observed in the youngest age group with 67% higher antidepressant use among progestin-only users than among CHC users.

Hormonal contraceptives are easy to use, are highly effective and provide women means of controlling their reproductive and sexual health. Still, questions remain about their potential for causing symptoms of depression. Duke et al.¹³ studied oral contraceptive use in young Australian women and found no independent effect on symptoms of depression. To be able to compare their study to ours, we carried out a non-stratified analysis (i.e. progestin-only and CHC users were combined) of data on women grouped according to age in the same way as the Australian authors had done, and reached a similar result: we found a non-significant OR amounting to 0.97 whereas the OR they calculated, which was also non-significant, was 1.05.

In contrast to the study by Duke et al.¹³, Kulkarni et al. found that COCs can cause mood disorders as an unwanted side-effect.¹⁷ This finding corresponds with our results for the CHC users in the youngest age groups but not for the total population of CHC users. Interestingly, for those aged 20 to 27, our findings suggest that CHC users employ antidepressants less often than do non-contraceptive users. However, it is important to be aware of differences in data constitution between the different studies when comparing results. For example, we included data on all hormonal contraceptives; in addition to contraceptive pills, hormonal contraceptive formulations such as subcutaneous implants, injections, vaginal rings and transdermal patches were taken into consideration as well. Implants and injections are progestin-only contraceptives whereas the vaginal ring and the transdermal patch are CHCs. Since the relation between the use of hormonal contraceptives and antidepressant therapy, at least in our study, seems to depend strongly on age, the discrepancies between results from different studies may to some extent be an effect of the different ages of the study populations. In addition, factors such as a history of mental disorder, personality, troublesome relationships, socioeconomic problems, etc., may intervene in different combinations. They thus may influence and thereby confound the relation between use of hormonal contraceptives and the state of mood if no adjustment is made for these factors. However, the difference in antidepressant use between CHC and progestin-only users observed in our study might be a real unfavourable effect of progestin-only use on mood which is compensated for by ethinylestradiol in the CHC group. Another possible explanatory factor might be that the effects of progestins are more pronounced in teenagers than in older women.

Kendler et al. proposed a comprehensive model for depression suggesting that a combination of genetic, developmental, pharmacological and interpersonal factors may predict the development of depression and thereby explain the aetiology of this disorder.^{9,21} Apart from the daily burden that depression places on individuals, in young people depression also increases the risk of suicide. Since adolescence is already a period of greater risk of suicide any additional factor is of great importance.²² Women are twice as likely as men to experience depression and are particularly vulnerable to mood disorders during their reproductive years.^{4,5} This might support Kendler's theory of a biological basis and a relation between mood disorders and changes in sex steroid levels as these hormones exert pronounced effects on brain areas that are involved in mood and cognition.^{6,23-26} In a review article by Kuehner²³, presenting gender differences in unipolar depression, it has also been postulated that the explanation lies in differences in gender roles.

Our analyses lack adjustments for possible confounding factors such as stressful life events, which are strong risk factors for depression in women,⁹ and also for any history of mental disorder, personality problems, troublesome relationships, socioeconomic problems and the crises that are regarded as an ordinary part of growing up. These factors would only have an effect on the differences in antidepressant ORs (contraception / no contraception) between users of generic drugs if they were associated solely with users of CHCs or solely with users of progestins. This might arise, for example, if caregivers would believe that prescribing progestin-only treatment is preferable to prescribing CHC for women with former mood problems. It is important to bear in mind that this definitely is a possible confounder.

In a population-based survey on mental health conducted in 2005 in the county of Östergötland, Sweden,²⁷ it was shown that the percentage of individuals (of both genders) aged 18-29 who needed mental health care was higher among those who had not visited a health care clinic than among those who had. Hodges et al. observed that only one out of four young Australians with mental health disorders receive professional help.²⁸ Likewise, the meta-analysis carried out by Mitchell et al. demonstrated that in primary health care GPs generally identify only about half of the true cases of depression.²⁹ These findings suggest that a substantial number of women in our study may have suffered from mood disorders but have not had any antidepressant treatment. This raises the question whether the relation between mood disorders and hormonal contraceptives differs from that between antidepressant therapy and hormonal contraceptives. It seems likely that women who visit a health care clinic to get a prescription for hormonal contraceptives would tend to raise questions about their mental health in an earlier phase than those who do not visit a health care clinic – a phenomenon called Berkson's bias.³⁰ This bias might have resulted in overestimating the antidepressant ORs (contraception / no contraception) but it would affect the antidepressant ORs (progestin-only / CHC) only if the tendency to cause problems differs between users of one generic drug or the other.

In general, when using register data in research, major advantages are large populations and information free from recall bias. However, the possible misclassification of data must be taken into consideration. This concerns, for instance, the completeness of registration of individuals and the accuracy and degree of completeness of the registered data and the registration period.³¹ The Swedish Prescribed Drug Register covers all drugs dispensed from all

Swedish pharmacies and thus, since data are transferred directly from the cashier's computer to the register, the completeness of the register is reasonably high. Therefore, misclassification problems are probably a minor issue and the registered frequency of dispensed drugs is almost certainly correct. Only a small percentage of women can be identified as having purchased large numbers of prescription drugs; quite a few of them probably had switched from one type of hormonal contraceptive to another and/or from one antidepressant to another.

A registration period of three years was the period for which data were available when this study was planned and a longer time-frame would probably not change or strengthen the results. A weakness in this study is possibly the cross-sectional approach over the three-year period. We do not know the sequence of drug use for an individual i.e. whether a person was an antidepressant user before starting to use a contraceptive or the other way around. Therefore it is possible that the results are to some extent an effect of the preferential prescription of progestin-only contraceptives for women already identified as having a tendency to have mood problems. Future, prospectively designed studies registering data for a longer period will allow the sequence of drug use to be evaluated.

CONCLUSION

To our knowledge, this is the first study comparing the relation between age-specific drug use of different types of hormonal contraceptives and antidepressant therapy, using a national register of prescribed and dispensed drugs. Stratification of age and generic drugs showed variations between age groups and type of hormonal contraceptives and demonstrates therefore the importance of analysing subgroups. We conclude that progestin-only users are more liable to use antidepressants than are users of CHCs; this is particularly evident among teenagers. As progestin-only contraceptives seem to be a precipitating and/or perpetuating factor in mood disorders in vulnerable women, counsellors and prescribers of hormonal contraception should pay careful attention to women with a history of mood disorders and to those who have experienced lowered mood when taking a hormonal contraceptive. Likewise, mental healthcare givers should take contraceptive histories from their female patients.

Declaration of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Age-specific number of women residing in Sweden with *at least one drug expenditure* of antidepressant or hormonal contraceptive during the three-year period July 2005 - July 2008. Data obtained from the Swedish Prescribed Drug Registry.

Age (years)	No of female residents in Sweden	Drug expenditures							
		Hormonal contraceptives						Antidepressants	
		Any type		Progestin-only		Combined hormonal contraceptives		n	%*
		n	%*	n	%**	n	%**		
16-19	251 597	121 619	48.3	42 789	35.2	97 995	80.6	9 961	3.9
20-23	228 993	158 241	69.1	58 914	37.2	123 854	78.3	19 069	8.3
24-27	216 384	137 329	63.5	56 460	41.1	100 821	73.4	23 265	10.8
28-31	221 019	123 060	55.7	62 060	50.4	80 261	65.2	26 411	11.9
<i>16-31</i>	<i>917 993</i>	<i>540 249</i>	<i>58.9</i>	<i>220 223</i>	<i>40.8</i>	<i>402 931</i>	<i>74.6</i>	<i>78 436</i>	<i>8.5</i>

* Percentage of the Swedish female population

** Percentage of hormonal contraceptive users

Table 2. Odds Ratios (ORs) for antidepressant use (hormonal contraceptives versus no hormonal contraceptives), adjusted by age among female inhabitants aged 16-31 years.

Hormonal contraceptive usage July 2005-June 2008			
	n	OR	95% CI
No hormonal contraceptives*	377 744	1.00	
CHCs	320 026	1.02	1.00 -1.04
Progestin-only	137 318	1.31	1.29 -1.34
CHCs and progestin-only	82 905	1.35	1.31-1.38
<i>Total</i>	<i>917 993</i>		

* Reference category

CHCs: combined hormonal contraceptives; CI: confidence interval