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Original Publication:

Malou Lindberg, Anniqa Foldemo, Ann Josefsson and Ann-Britt Wiréhn, Differences in prescription rates and odds ratios of antidepressant drugs in relation to individual hormonal contraceptives: A nationwide population-based study with age-specific analyses, 2012, European journal of contraception & reproductive health care, (17), 2, 106-118.
http://dx.doi.org/10.3109/13625187.2012.658925

Differences in prescription rates and odds ratios of antidepressant drugs in relation to individual hormonal contraceptives: a nationwide population-based study with age-specific analyses

Malou Lindberg[1,2], Anniqa Foldemo[1,3], Ann Josefsson[4], and Ann-Britt Wiréhn[1,4]

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

[2]Department of Medical and Health Sciences, Primary Care, Linköping University, Linköping, Sweden

[3]Department of Medical and Health Sciences, Division of Nursing Sciences, Faculty of Health Sciences, Linköping University, Linköping, Sweden

[4]Division of Obstetrics and Gynaecology, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Department of Obstetrics and Gynaecology in Linköping, County Council of Östergötland, Linköping, Sweden

Short title: Contraceptives and antidepressant therapy

Key words: Antidepressants; Combined hormonal contraceptives; Depression; Hormonal contraceptives; Progestin-only contraceptives; Mood; Registries

Correspondence: Malou Lindberg, Local Health Care Research and Development Unit in Östergötland, SE-582 24 Linköping, Sweden. Tel: +46 10 38 510. Fax: +46 10 38 501. E-mail: malou.lindberg@lio.se

ABSTRACT

Objectives To examine, among young women, the association of individual hormonal contraceptives, within two broad groupings, with antidepressant therapy.

Methods In a nationwide register-based study, we examined the prescription rates of antidepressant drugs in relation to individual combined hormonal and progestin-only contraceptives among Swedish women aged 16–31 years (N=917,993). Drug data were obtained from the Swedish Prescribed Drug Register for the period 1 July 2005-30 June 2008. Data on the total population of women aged 16-31 in 2008 were obtained from the Total Population Register of Statistics Sweden. The proportion of women using both hormonal contraception *and* antidepressants, and odds ratios (ORs) for antidepressant use for hormonal contraceptive users versus non-users, were calculated, the latter by logistic regression, for each formulation.

Results The highest antidepressant OR in all age groups, particularly in the 16–19 years age group, related to medroxyprogesterone-only, followed by etonogestrel-only, levonorgestrel-only and ethinylestradiol/norelgestromin formulations. Oral contraceptives containing ethinylestradiol combined with lynestrenol or drospirenone had considerably higher ORs than other pills. ORs significantly lower than 1 were observed when ethinylestradiol was combined with norethisterone, levonorgestrel or desogestrel.

Conclusion The association between use of hormonal contraceptives and antidepressant drugs varies considerably within both the combined hormonal contraceptive and the progestin-only groups.

INTRODUCTION

Despite the side effects they are claimed to elicit (e.g., nausea, weight gain, depression, and mood disturbances), hormonal contraceptives are a widely used means of birth control[1]. The general opinion is that their efficacy in preventing undesired pregnancy largely offsets their adverse effects. Several formulations of hormonal contraceptives are available in Sweden; they are administered via different routes (pills, transdermal patches, vaginal rings, implants, injections, intrauterine systems [IUSs]). The plasma levels of steroids achieved and the way they are metabolised partly depend on the galenic form[1].

Studies on side effects of oral contraceptives (OCs), including depression and other mood disturbances, have produced divergent results[2–7]. Because of methodological limitations and methodological differences, findings in this field are difficult to interpret and to compare[7].

The use of hormonal contraceptives alters the levels of circulating sex steroids. One of the hypotheses formulated is that fluctuating oestrogen levels might cause mood disturbance in hormone-sensitive women[8].

Depression increases dramatically during adolescence and its prevalence in late adolescence reaches the level seen among adults[9]. Depression is thought to be caused by a combination of genetic, developmental, pharmacologic and interpersonal factors[10]. One explanation for the increased risk in early adolescence is the greater exposure to negative life events, particularly those involving difficulties in intimate relationships and family relationships[11]. With regard to females, an alternative explanation is a heightened sensitivity to the important fluctuations in sex hormones characterising reproductive events. Oestrogen and progesterone affect brain regions and share common pathways and receptor sites in areas of the brain known to be involved in the modulation of mood[12].

In a previous publication on the relation between hormonal contraceptives and antidepressant therapy among young Swedish women, Wiréhn *et al.*[13] reported that nearly 60% of women aged 16–31 years had used hormonal contraceptives at least once during a three-year period. Of these, about 75% had used combined hormonal contraceptives (CHCs) and 41% had used progestin-only drugs. The results showed that progestin-only contraceptive users, particularly teenagers, were prescribed antidepressant drugs more than users of CHCs. However, the various progestin components contained in CHCs and progestin-only contraceptives may differ in their association to antidepressant therapy. To our knowledge, this matter has not been thoroughly investigated. Therefore, the purpose of this study was to further elucidate the link between the use of hormonal contraceptives and antidepressant therapy among young women, for each CHC and progestin-only drug, and to assess differences between age groups.

METHODS

Study population

The total Swedish female population aged 16–31 years in 2008 comprised 917,993 persons. Use of hormonal contraceptives and antidepressant drugs by that population was analysed in this study. The data for each hormonal contraceptive were analysed for all women aged 16-31, and for the following age groups: 16–19, 20–23, 24–27 and 28–31 years. The reason why this particular age bracket (16–31 years of age) was taken into consideration is the higher risk for depression in younger women[14]. The study population was divided into women who had not used hormonal contraceptives at all (n=377,744), those who had used solely one formulation (n= 385,784), and those who had changed from one formulation to another (switched within-, as well as between, the CHC and progestin-only contraceptive groups; n= 154,465; Tables 1-3).

Table1. Number and proportion of women aged 16-31 years, residing in Sweden in 2008, who used antidepressant therapy and/ or hormonal contraceptives during the three-year period from 1 July 2005 to 30 June 2008, presented for different age groups and in total (data obtained from the Swedish Prescribed Drug Registry).

Drug usage	Galenic form	Age in 2008										
		16-19 years		20-23 years		24-27 years		28-31 years		16-31 years		
		n	%*	n	%*	n	%*	n	%*	n	%*	%**
Antidepressant drugs		9 961	3.9	19 069	8.3	23 265	10.8	26 411	11.9	78 436	8.5	
Hormonal contraceptives		121 619	48.3	158 241	69.1	137 329	63.5	123 060	55.7	540 249	58.9	
CHC												
Ethinylestradiol / lynestrenol	Pill	20	0.0	112	0.0	279	0.1	430	0.2	841	0.1	*0.2*
Ethinylestradiol / norethisterone	Pill	2 502	1.0	6 504	2.8	7 357	3.4	7 211	3.3	23 574	2.6	*4.9*
Ethinylestradiol / levonorgestrel	Pill	50 723	20.2	50 852	22.2	32 971	15.2	24 137	10.9	158 683	17.3	*26.7*
Ethinylestradiol / desogestrel	Pill	760	0.3	2 914	1.3	8 533	3.9	8 673	3.9	20 880	2.3	*3.9*
Ethinylestradiol / norgestimate	Pill	5 066	2.0	9 920	4.3	6 490	3.0	2 631	1.2	24 107	2.6	*5.7*
Ethinylestradiol / drospirenone	Pill	4 692	1.9	10 063	4.4	13 417	6.2	10 857	4.9	39 029	4.3	*8.9*
Ethinylestradiol / norelgestromin	Tdp	456	0.2	1 014	0.4	1 154	0.5	834	0.4	3 458	0.4	*1.1*
All users of one CHC and no other HC		64 219	25.5	81 379	35.5	70 201	32.4	54 773	24.8	270 572	29.5	
Switchers within CHC		14 611	5.8	17 948	7.8	10 668	4.9	6 227	2.8	49 454	5.4	
Progestin-only												
Norethisterone-only	Pill	220	0.1	951	0.4	1 796	0.8	2 261	1.0	5 228	0.6	*1.6*
Lynestrenol-only	Pill	125	0.0	861	0.4	1 670	0.8	2 536	1.1	5 192	0.6	*1.5*
Levonorgestrel-only	IUD/Implant	346	0.1	1 435	0.6	2 664	1.2	5 729	2.6	10 174	1.1	*2.4*
Medroxyprogesterone-only	Injection	371	0.1	1 421	0.6	2 291	1.1	2 807	1.3	6 890	0.8	*1.6*
Etonogestrel-only	Implant	3 474	1.4	6 733	2.9	4 933	2.3	2 540	1.1	17 680	1.9	*4.7*
Desogestrel-only	Pill	15 045	6.0	16 797	7.3	17 713	8.2	20 493	9.3	70 048	7.6	*15.9*
All users of one progestin-only and no other HC		19 581	7.8	28 198	12.3	31 067	14.4	36 366	16.5	115 212	12.6	
Switchers within progestin-only		4 043	1.6	6 189	2.7	5 441	2.5	6 433	2.9	22 106	2.4	
All switchers		37 819	15.0	48 664	21.3	36 061	16.7	31 921	14.4	154 465	16.8	
All non-switchers		83 800	33.3	109 577	47.9	101 268	46.8	91 139	41.2	385 784	42.0	
No. of women residing in Sweden		251 597		228 993		216 384		221 019		917 993		

* percent of all women

** percent irrespective of switching between formulations

HC: hormonal contraceptive; CHC: combined hormonal contraceptive; IUS: Intrauterine systems ; Tdp: Transdermal patch

Table 2. Number and proportion of women aged 16-31 years, residing in Sweden in 2008, who used antidepressant therapy *and* hormonal contraceptives during the three-year period from 1 July 2005 to 30 June 2008, presented for different age groups and in total (data obtained from the Swedish Prescribed Drug Registry).

Contraceptive used	Age in 2008														
	16-19 years			20-23 years			24-27 years			28-31 years			16-31 years		
	n	%[#]	95% CI	n	%[#]	95% CI	n	%[#]	95% CI	n	%[#]	95% CI	n	%[#]	95% CI
CHC															
Ethinylestradiol / lynestrenol	0		-	112	8.9	(4.4 - 16.1)	40	14.3	(10.4 - 19.1)	64	14.9	(8.7 - 22.1)	114	13.6	(11.3 - 16.1)
Ethinylestradiol / norethisterone	111	4.4	(3.7 - 5.4)	450	6.9	(6.3 - 7.6)	651	8.8	(8.2 - 9.5)	688	9.5	(4.7 - 15.5)	1900	8.1	(7.7 - 8.4)
Ethinylestradiol / levonorgestrel	1693	3.3	(3.2 - 3.5)	3084	6.1	(5.9 - 6.3)	2716	8.2	(7.9 - 8.5)	2506	10.4	(5.3 - 16.5)	9999	6.3	(6.2 - 6.4)
Ethinylestradiol / desogestrel	59	7.8	(6.0 - 10.2)	256	8.8	(7.8 - 9.9)	655	7.7	(7.1 - 8.3)	833	9.6	(4.7 - 15.5)	1803	8.6	(8.3 - 9.0)
Ethinylestradiol / norgestimate	240	4.7	(4.2 - 5.4)	718	7.2	(6.7 - 7.8)	555	8.6	(7.9 - 9.3)	288	10.9	(5.7 - 17.3)	1801	7.5	(7.1 - 7.8)
Ethinylestradiol / drospirenone	294	6.3	(5.6 - 7.0)	1116	11.1	(10.5 - 11.7)	1736	12.9	(12.4 - 13.5)	1648	15.2	(9.1 - 21.9)	4794	12.3	(12.0 - 12.6)
Ethinylestradiol / norelgestromin	39	8.6	(6.2 -12.0)	111	10.9	(9.1 - 13)	168	14.6	(12.6 - 16.7)	129	15.5	(9.2 - 22.5)	447	12.9	(11.8 - 14.1)
All users of one CHC and no other HC	2436	3.8	(3.1 - 4.7)	5745	7.1	(6.4 - 7.8)	6521	9.3	(8.6 - 10.0)	6156	11.2	(5.9 - 17.5)	20858	7.7	(7.4 - 8.1)
Progestin-only															
Norethisterone-only	17	7.7	(4.6 - 13.2)	81	8.5	(6.8 - 10.5)	204	11.4	(9.9 - 12.9)	221	9.8	(4.8 - 15.9)	523	10.0	(9.2 - 10.8)
Lynestrenol-only	7	5.6	(2.3 - 13.7)	76	8.8	(7.0 - 10.9)	158	9.5	(8.1 - 11.0)	268	10.6	(5.5 - 16.7)	509	9.8	(9.0 - 10.6)
Levonorgestrel-only	41	11.8	(8.6 - 16.3)	219	15.3	(13.4 - 17.2)	388	14.6	(13.2 - 16.0)	873	15.2	(9.1 - 22.0)	1521	14.9	(14.3 - 15.7)
Medroxyprogesterone-only	51	13.7	(10.4 - 18.1)	208	14.6	(12.8 - 16.6)	402	17.5	(16.0 - 19.2)	585	20.8	(13.9 - 28.1)	1246	18.1	(17.2 - 19)
Etonogestrel-only	309	8.9	(8.0 - 9.9)	777	11.5	(10.8 - 12.3)	672	13.6	(12.7 - 14.6)	388	15.3	(9.2 - 22.1)	2146	12.1	(11.7 - 12.6)
Desogestrel-only	772	5.1	(4.8 - 5.5)	1518	9.0	(8.6 - 9.5)	1976	11.2	(10.7 - 11.6)	2198	10.7	(5.6 - 16.9)	6464	9.2	(9.0 - 9.4)
All users of one progestin-only and no other HC	1197	6.1	(4.8 - 7.8)	2879	10.2	(9.1 - 11.4)	3800	12.2	(11.2 - 13.3)	4533	12.5	(6.8 - 19.0)	12409	10.8	(10.2 - 11.3)
All non-switchers	3633	4.3	(3.7 - 5.1)	8624	7.9	(7.3 - 8.5)	10321	10.2	(9.6 - 10.8)	10689	11.7	(6.3 - 18.0)	33267	8.6	(8.3 - 8.9)
Switchers															
Switchers within CHC	770	5.3	(3.8 - 7.4)	1444	8.0	(6.7 - 9.6)	1144	10.7	(9.0 - 12.7)	933	15.0	(8.9 - 22.0)	4291	8.7	(7.9 - 9.6)
Switchers within progestin-only	354	8.8	(6.0 - 12.8)	696	11.2	(9.0 - 13.8)	764	14.0	(11.7 - 16.7)	894	13.9	(8.0 - 20.7)	2708	12.3	(11.0 - 13.5)
Switchers between CHC and progestin-only	1385	7.2	(5.9 - 8.9)	2573	10.5	(9.3 - 11.7)	2394	12.0	(10.7 - 13.4)	2288	11.9	(6.4 - 18.3)	8640	10.4	(9.8 - 11.1)
All switchers	2509	6.6	(5.7 - 7.8)	4713	9.7	(8.9 - 10.6)	4302	11.9	(11.0 - 12.9)	4115	12.9	(7.2 - 19.4)	15639	10.1	(9.7 - 10.6)

[#] Antidepressant therapy by hormonal contraceptive users x 100; CHC: combined hormonal contraceptive; CI: confidence interval

Table 3. Odds ratios (ORs) of antidepressant use (hormonal contraceptives vs. no hormonal contraceptives) according to contraceptive formulation, by age group and for the total sample (age-adjusted) of women aged 16-31 years, residing in Sweden in 2008.

Contraceptive used	Age in 2008														
	16-19 years			20-23 years			24-27 years			28-31 years			16-31 years		
	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)	n	OR	(95% CI)
No hormonal contraceptives[#]	129978	1.00		70752	1.00		79055	1.00		97959	1.00		377744	1.00	
CHC															
Ethinylestradiol / lynestrenol	20			112	1.07	(0.56 - 2.05)	279	1.35	(0.97 - 1.89)	430	1.30	(1.00 - 1.70)	841	1.39	(1.14 - 1.69)
Ethinylestradiol l / norethisterone	2502	1.34	(1.11 - 1.63)	6504	0.83	(0.75 - 0.92)	7357	0.79	(0.73 - 0.86)	7211	0.79	(0.73 - 0.85)	23574	0.91	(0.87 - 0.96)
Ethinylestradiol / levonorgestrel	50723	1.08	(1.01 - 1.14)	50852	0.74	(0.71 - 0.78)	32971	0.74	(0.70 - 0.77)	24137	0.87	(0.83 - 0.91)	158683	0.86	(0.84 - 0.88)
Ethinylestradiol / desogestrel	760	2.47	(1.88 - 3.23)	2914	1.04	(0.91 - 1.19)	8533	0.67	(0.62 - 0.73)	8673	0.79	(0.74 - 0.85)	20880	0.87	(0.83 - 0.92)
Ethinylestradiol / norgestimate	5066	1.47	(1.28 - 1.68)	9920	0.88	(0.81 - 0.96)	6490	0.77	(0.71 - 0.85)	2631	0.92	(0.81 - 1.04)	24107	1.02	(0.97 - 1.07)
Ethinylestradiol / drospirenone	4692	2.00	(1.76 - 2.26)	10063	1.39	(1.29 - 1.48)	13417	1.21	(1.15 - 1.28)	10857	1.34	(1.26 - 1.41)	39029	1.48	(1.43 - 1.53)
Ethinylestradiol l / norelgestromin	456	2.71	(1.95 - 3.77)	1014	1.38	(1.13 - 1.68)	1154	1.39	(1.18 - 1.65)	834	1.36	(1.13 - 1.65)	3458	1.62	(1.46 - 1.79)
All users of one CHC and no other HC	64219	1.40	(1.33 - 1.48)	81379	0.86	(0.83 - 0.90)	70201	0.84	(0.81 - 0.87)	54773	0.95	(0.92 - 0.98)	270572	0.99	(0.97 - 1.01)
Progestin-only															
Norethisterone-only	220	2.43	(1.47 - 3.99)	951	1.02	(0.81 - 1.28)	1796	1.04	(0.90 - 1.21)	2261	0.81	(0.70 - 0.93)	5228	1.03	(0.94 - 1.13)
Lynestrenol-only	125	1.65	(0.77 - 3.55)	861	1.05	(0.83 - 1.33)	1670	0.85	(0.72 – 1.00)	2536	0.88	(0.77 - 1.00)	5192	0.97	(0.88 - 1.07)
Levonorgestrel-only	346	3.73	(2.69 - 5.19)	1435	1.99	(1.72 - 2.30)	2664	1.38	(1.23 - 1.54)	5729	1.33	(1.24 - 1.44)	10174	1.52	(1.43 - 1.61)
Medroxyprogesterone-only	371	4.59	(3.40 - 6.19)	1421	1.89	(1.63 - 2.20)	2291	1.73	(1.55 - 1.93)	2807	1.96	(1.78 - 2.15)	6890	2.10	(1.97 - 2.24)
Etonogestrel-only	3474	2.91	(2.58 - 3.29)	6733	1.47	(1.36 - 1.59)	4933	1.30	(1.20 - 1.42)	2540	1.35	(1.21 - 1.50)	17680	1.69	(1.61 - 1.77)
Desogestrel-only	15045	1.70	(1.57 - 1.84)	16797	1.13	(1.06 - 1.20)	17713	1.02	(0.97 - 1.08)	20493	0.89	(0.85 - 0.94)	70048	1.11	(1.08 - 1.14)
All users of one progestin-only and no other HC	19581	2.32	(2.17 - 2.48)	28198	1.28	(1.22 - 1.34)	31067	1.14	(1.09 - 1.18)	36366	1.06	(1.02 - 1.10)	115212	1.27	(1.24 - 1.30)
Switchers															
Switchers within CHC	14611	1.61	(1.48 - 1.74)	17948	1.01	(0.95 - 1.07)	10668	0.99	(0.93 - 1.05)	6227	1.32	(1.23 - 1.42)	49454	1.23	(1.19 - 1.28)
Switchers within progestin-only	4043	2.82	(2.52 - 3.17)	6189	1.44	(1.33 - 1.57)	5441	1.33	(1.23 - 1.44)	6433	1.20	(1.12 - 1.29)	22106	1.52	(1.46 - 1.59)
Switchers between CHC and progestin-only	19165	2.27	(2.13 - 2.42)	24527	1.35	(1.28 - 1.41)	19952	1.11	(1.06 - 1.17)	19261	1.00	(0.96 - 1.05)	82905	1.35	(1.31 - 1.38)
All switchers	37819	2.53	(2.40 - 2.67)	48664	1.22	(1.17 - 1.27)	36061	1.10	(1.06 - 1.15)	31921	1.10	(1.06 - 1.14)	154465	1.33	(1.30 - 1.36)

[#] = Reference category;
HC: hormonal contraceptive; CHC: combined hormonal contraceptive; CI: confidence interval

Data collection

Data were anonymously extracted from the Swedish Prescribed Drug Register, which covers the entire Swedish population[15]. This register contains data on all drugs prescribed and dispensed after 30 June 2005. Data on drugs with the Anatomical Therapeutic Chemical (ATC) codes G03AA or G03AB (CHC), G03AC (progestin-only) (vaginal rings have ATC code G02B and are not included in this study), and N06A (antidepressant drugs) from 1 July 2005 to 30 June 2008 were extracted from the register and divided into seven hormonal formulations from the CHC group (ethinylestradiol [EE] combined with lynestrenol, norethisterone, levonorgestrel [LNG], desogestrel, norgestimate, drospirenone [pills containing drospirenone were available in three different dosage forms during the study period] or norelgestromin) and into six formulations from the progestin-only group (norethisterone, lynestrenol, LNG, medroxyprogesterone, etonogestrel and desogestrel). The drugs are referred to by their generic names.

Data on the number of women with prescribed drugs in each age group together with data from the Total Population Register (available on the Statistics Sweden's website)[16] on all women residing in Sweden in each specific group, made it possible to derive the number of non-users in each age group. The data handling has been described in greater detail previously[13]. In this article, prescribed and dispensed drugs are included in the term 'used drugs'. The study does not control for the sequence of drug use.

Statistical analyses

The use of different formulations of hormonal contraceptives and the use of antidepressants are given as numbers and percentages of the total population, and stratified by age group. Data on the formulations were categorised into the following groups: use of only one specific

formulation in the three-year period; switchers within the CHC and progestin-only groups; and switchers between the CHC- and progestin-only groups. The modality of administration (i.e. implants, injections, IUSs, pills, transdermal patches) was described for each formulation.

Use during the three-year study period of *both* hormonal contraceptives *and* antidepressants (i.e., both were *prescribed* and *dispensed* during the aforementioned period) is presented as the number of persons and the percentage, with 95% confidence intervals (CIs), of persons using the two types of treatment among the total number of hormonal contraceptive users who had used a single hormonal contraceptive. Calculation of the binomial tail area via the F distribution was employed to determine the exact lower limit in the CIs and thus avoid negative values due to small proportions[17]. Comparisons of proportions between all pairs of formulations within the CHC and progestin-only groups were made with one-way ANOVA using the F-test. The Tukey–Kramer[18] procedure was used to achieve a simultaneous 5% significance level for multiple comparisons and these *p*-values are presented in appendices 1 and 2. The use of the term statistically significant in the text means that the *p*-value found in the corresponding test was < 5%.

Employing logistic regression, with antidepressant use as a dependent variable, odds ratios (ORs) with 95% CIs were calculated per age group and according to the type of hormonal contraceptive versus non-use of hormonal contraceptives. Age as a continuous variable was included in the regression models and all ORs were thereby adjusted for age.

Ethical approval

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

RESULTS

Drug use

The EE/LNG formulation was the most commonly employed hormonal contraceptive; it was used by 26.7% of Swedish women aged 16–31 years. The second most frequent was desogestrel-only, followed by EE/drospirenone (Table 1).

Antidepressant therapy was used by 8.5% of the Swedish women, increasing from 3.9% in the 16–19 years age group to 11.9% among those aged 28–31 years (Table 1). The most commonly prescribed antidepressant drugs (86.5%) were selective serotonin reuptake inhibitors (SSRIs; data not shown).

Note to the Publisher: Insert Table 1 about here.

Hormonal contraceptives in relation to antidepressant therapy

Combined hormonal contraceptives

With regard to women aged 16-31 who were dispensed or prescribed only one CHC for contraception, the use of antidepressant medications was significantly higher among those taking EE/lynestrenol, EE/norelgestromin and EE/drospirenone than among women using a single one of the remaining CHCs. The proportion of women who were dispensed or prescribed an antidepressant while taking EE/LNG, was significantly lower than among women using any other CHC, also in the youngest age group (Table 2).

Note to the Publisher: Insert Table 2 about here.

The ORs for antidepressant therapy for the 16–31 years age group (hormonal contraceptive users vs. non-users) mainly followed the proportions for users of antidepressant drugs and hormonal contraceptives; for instance, EE/LNG had the lowest OR together with

EE/norethisterone and EE/desogestrel although the ORs in the youngest age group were significantly above 1 in all combinations (Table 3).

Progestin-only preparations

The prevalence of antidepressant therapy among users of medroxyprogesterone acetate, over all ages, was significantly higher than in women using any single one of the other progestin-only products, whereas that prevalence was lowest among women taking desogestrel-only. Use of LNG-only was associated with the second highest prevalence rate of antidepressant therapy, which also was significantly higher than those related to the remaining progestin-only products (Table 2).

The ORs for antidepressant therapy (hormonal contraceptive users vs. non-users) in the progestin-only group were significantly greater than 1 in all age groups for medroxyprogesterone acetate-only, LNG-only and etonogestrel-only. The highest ORs in total and in the youngest age group were for medroxyprogesterone acetate-only (Table 3, each $p \leq 0.05$).

Note to the Publisher: Insert Table 3 about here.

Routes of administration

The highest ORs for antidepressant therapy were associated with the use of injections, IUSs and implants, all of which released progestin-only products (Table 3).

DISCUSSION

Main findings

This study presents the total and age-specific association between antidepressant therapy and use of diverse hormonal contraceptives among women aged 16–31 years. The highest prevalence of antidepressant treatment for all age groups, as absolute values and relative to non-users of hormonal contraceptives, was among women receiving medroxyprogesterone acetate-only injections. Other high consumers of antidepressant drugs were those using the etonogestrel-only implant, the LNG-IUS, the transdermal patch releasing EE and norelgestromin, or combined oral contraceptives (COCs) containing EE and either drospirenone or lynestrenol. Users of desogestrel-only pills also had significantly increased antidepressant use, but this increase was small. With the exception of those aged 20 years or less, women taking the six remaining formulations studied had an equal or even lower antidepressant drug dispensed rate than women not using hormonal contraceptives.

Strengths and weaknesses

Major strengths in register research are the possibility of studying large populations and the gathering of information that is free from recall bias. Yet, misclassification of data is possible. In this study, misclassification is probably negligible as the Swedish Prescribed Drug Register covers all dispensed drugs and data are transferred directly from the cashier's computer to the register. The limitations in this study are related to the study design and, more particularly, to the inability to study the sequence of drug use. Since there is no indication in the register for first time use, there has to be a reasonable period free from drug use to secure that the possible effect, i.e. antidepressant use, *followed* the use of the hormonal contraceptive, and not the other way around. In our opinion that period has to last at least 18-24 months which

gives an analysable follow-up period of only 12 months. Without a time period free from hormonal contraceptive and antidepressant drug use it would not be possible to know what drug was used first, the contraceptive or the antidepressant. Consequently, risk and causality *cannot* be determined from these data, only associations and thus, our findings merely reflect *usage patterns* of hormonal contraceptives and antidepressants.

Vaginal rings have not been included in this study and this might be an oversight.

Variations in antidepressant ORs (hormonal contraceptive users vs. non-users) invite speculation on whether certain formulations and/or routes of hormonal contraceptives affect mood, positively or negatively. Longitudinal evaluation is necessary to establish a more meaningful theory on increased risk for mood disorders depending on formulations and/or routes of hormonal contraceptive usage. A further limitation is that, from these data, it is not possible to adjust for confounders, i.e. conditions associated with antidepressant use as well as hormonal contraceptive use. One such example might be antidepressant treatment used for chronic pain. However, conditions distributed equally between antidepressant users and non-users do not affect the ORs.

Differences in relation to other studies

In their review of the relevant literature, Oinonen and Mazmanian conclude that oral contraceptives have mostly favourable effects on the mood of women[19]. This is in line with the results of a comparable analysis we carried out, concerning solely pills, from which COCs containing EE and drospirenone or lynestrenol (which account for about 10% of total OC use) were excluded. Comparable calculations in the present study yielded an antidepressant OR of less than 1 indicating that antidepressant use was lower among COC users than non-users (these specific figures are not presented in the Results section). However, the similarity of

these results depends on whether antidepressant use (the outcome measure in our study) and negative mood (the outcome measure in the review[19]) relate to similar phenomena.

Whatever the hormonal contraceptive formulation, ORs for antidepressant use were consistently highest in the youngest age groups, although they varied in magnitude. This might result from a lack of adjustment for potential confounders. However, it could also reflect a biological basis of mood disturbances due to an underlying hormonal instability in adolescence similar to that proposed for mood disturbances during the climacterium[20]. The effect of irregular oestrogen production on mood is well known from previous studies. Douma et al.[8] showed that fluctuating oestrogen levels correlate significantly with mood disturbance. In their recent review, Deecher et al. concluded that hormonal changes increase vulnerability for depression in a subset of women, especially during crucial periods of the reproductive life, and that fluctuations in hormonal levels appear to increase the risk for depression[21]. Similar findings have also been reported by other authors[22,23] and it seems that some women are more vulnerable than others to rapid and radical changes in steroid hormone levels[24,25].

There are fewer studies on depressive episodes around the time of menarche. The youngest age group in this study was 16–19 years and this age group presented the highest antidepressant OR (hormonal contraceptive user vs. non-user) compared with the older groups irrespective of the formulation and administration route studied. What causes this is still unclear; further studies are needed to clarify if and how the use of different formulations and routes affect antidepressant use.

Some studies suggested that there is an association between the injectable contraceptive, depot medroxyprogesterone acetate (DMPA), and changes in mood or an increase in depressive symptoms[26–29]. The US Food and Drug Administration warned against its use in patients with a history of depression. However, there are also studies indicating that DMPA

does not cause any changes in mood over time[30–32]. An explanation that cannot be ruled out for the results in our study is that women who have been non-compliant with hormonal contraceptives have higher odds of being prescribed injections or implants and that those women may have a higher degree of psychological distress.

Unanswered questions and future research

Follow-up analyses are required to examine causality between certain types of hormonal contraceptives and antidepressant therapy. Thus, there is a need for data over a wider span than the three years that were available in the Swedish Prescribed Drug Register at the time of this study. This is an important topic for future research. To increase our understanding of young women's mental health associated with hormonal contraception in the early adolescence, a qualitative comparative study of psychological aspects between users and non-users would be valuable. A recent meta-analysis on women's experience of menarche including 14 qualitative studies was performed by Chang et al.[33]. However, none of the studies addressed this question. Our results need to be confirmed in prospectively designed studies.

The differences in antidepressant use between CHC formulations bring up the question whether certain galenic forms of hormonal contraceptives are related to mood disorders. This question is especially interesting when studying the results pertaining to LNG. In combination with EE, this progestin has a relatively weak association with antidepressant drugs, whereas LNG-only released from an IUS or implant has a high association. Whether this is due to differences in serum levels of progestin and/or oestrogen remains to be determined.

Conclusion

We have previously reported that antidepressant drug usage is higher among users of progestin-only compared with CHC formulations[13]. The present study, with hormonal contraceptives stratified by formulations, shows that the association between use of hormonal contraceptives and antidepressant drugs varies considerably within the CHC and progestin-only groups. These formulation-specific analyses reveal that antidepressant drug use was generally higher among young women using hormonal contraceptives other than pills, namely, IUSs, implants, injections and transdermal patches.

ACKNOWLEDGEMENT

The study was supported by the Swedish Society of Medicine Soderstrom-Konigska Foundation.

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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Appendix 1

Statistical software output presenting Tukey-Kramer multiple comparisons for combined hormonal contraceptives (CHCs) in table 2.

Multiple comparisons

(I) CHC	(J) CHC	Mean difference (I-J)	Std. error	*p*-value[#]	95% Confidence interval	
					Lower bound	Upper bound
Ethinylestradiol / Lynestrenol	Ethinylestradiol / Norethisterone	.05	.009	.000	.03	.08
	Ethinylestradiol / Levonorgestrel	.07	.009	.000	.05	.10
	Ethinylestradiol / Desogestrel	.05	.009	.000	.02	.08
	Ethinylestradiol / Norgestimate	.06	.009	.000	.03	.09
	Ethinylestradiol / Drospirenone	.01	.009	.816	-.01	.04
	Ethinylestradiol / Norelgestromin	.01	.010	.996	-.02	.04
Ethinylestradiol / Norethisterone	Ethinylestradiol / Lynestrenol	-.05	.009	.000	-.08	-.03
	Ethinylestradiol / Levonorgestrel	.02	.002	.000	.01	.02
	Ethinylestradiol / Desogestrel	-.01	.003	.255	-.01	.00
	Ethinylestradiol / Norgestimate	.01	.002	.191	.00	.01
	Ethinylestradiol / Drospirenone	-.04	.002	.000	-.05	-.04
	Ethinylestradiol / Norelgestromin	-.05	.005	.000	-.06	-.03
Ethinylestradiol / Levonorgestrel	Ethinylestradiol / Lynestrenol	-.07	.009	.000	-.10	-.05
	Ethinylestradiol / Norethisterone	-.02	.002	.000	-.02	-.01
	Ethinylestradiol / Desogestrel	-.02	.002	.000	-.03	-.02
	Ethinylestradiol / Norgestimate	-.01	.002	.000	-.02	-.01
	Ethinylestradiol / Drospirenone	-.06	.002	.000	-.06	-.06
	Ethinylestradiol / Norelgestromin	-.07	.005	.000	-.08	-.05
Ethinylestradiol / Desogestrel	Ethinylestradiol / Lynestrenol	-.05	.009	.000	-.08	-.02
	Ethinylestradiol / Norethisterone	.01	.003	.255	.00	.01
	Ethinylestradiol / Levonorgestrel	.02	.002	.000	.02	.03
	Ethinylestradiol / Norgestimate	.01	.003	.000	.00	.02
	Ethinylestradiol / Drospirenone	-.04	.002	.000	-.04	-.03
	Ethinylestradiol / Norelgestromin	-.04	.005	.000	-.06	-.03
Ethinylestradiol / Norgestimate	Ethinylestradiol / Lynestrenol	-.06	.009	.000	-.09	-.03
	Ethinylestradiol / Norethisterone	-.01	.002	.191	-.01	.00
	Ethinylestradiol / Levonorgestrel	.01	.002	.000	.01	.02
	Ethinylestradiol / Desogestrel	-.01	.003	.000	-.02	.00
	Ethinylestradiol / Drospirenone	-.05	.002	.000	-.05	-.04
	Ethinylestradiol / Norelgestromin	-.05	.005	.000	-.07	-.04
Ethinylestradiol / Drospirenone	Ethinylestradiol / Lynestrenol	-.01	.009	.816	-.04	.01
	Ethinylestradiol / Norethisterone	.04	.002	.000	.04	.05
	Ethinylestradiol / Levonorgestrel	.06	.002	.000	.06	.06
	Ethinylestradiol / Desogestrel	.04	.002	.000	.03	.04
	Ethinylestradiol / Norgestimate	.05	.002	.000	.04	.05
	Ethinylestradiol / Norelgestromin	-.01	.005	.821	-.02	.01
Ethinylestradiol / Norelgestromin	Ethinylestradiol / Lynestrenol	-.01	.010	.996	-.04	.02
	Ethinylestradiol / Norethisterone	.05	.005	.000	.03	.06
	Ethinylestradiol / Levonorgestrel	.07	.005	.000	.05	.08
	Ethinylestradiol / Desogestrel	.04	.005	.000	.03	.06
	Ethinylestradiol / Norgestimate	.05	.005	.000	.04	.07
	Ethinylestradiol / Drospirenone	.01	.005	.821	-.01	.02

[#] A *p*-value < 0.05 denotes a significant difference between the formulation groups

Appendix 2

Statistical software output presenting Tukey-Kramer multiple comparisons for progestin-only products in table 2.

Multiple comparisons

(I) Progestin-only	(J) Progestin-only	Mean difference (I-J)	Std. error	*p*-value[#]	95% Confidence interval	
					Lower bound	Upper bound
Norethisterone	Lynestrenol	.00	.006	.999	-.02	.02
	Levonorgestrel	-.05	.005	.000	-.06	-.03
	Medroxyprogesterone	-.08	.006	.000	-.10	-.06
	Etonogestrel	-.02	.005	.000	-.04	-.01
	Desogestrel	.01	.004	.497	.00	.02
Lynestrenol	Norethisterone	.00	.006	.999	-.02	.02
	Levonorgestrel	-.05	.005	.000	-.07	-.04
	Medroxyprogesterone	-.08	.006	.000	-.10	-.07
	Etonogestrel	-.02	.005	.000	-.04	-.01
	Desogestrel	.01	.004	.788	-.01	.02
Levonorgestrel	Norethisterone	.05	.005	.000	.03	.06
	Lynestrenol	.05	.005	.000	.04	.07
	Medroxyprogesterone	-.03	.005	.000	-.05	-.02
	Etonogestrel	.03	.004	.000	.02	.04
	Desogestrel	.06	.003	.000	.05	.07
Medroxyprogesterone	Norethisterone	.08	.006	.000	.06	.10
	Lynestrenol	.08	.006	.000	.07	.10
	Levonorgestrel	.03	.005	.000	.02	.05
	Etonogestrel	.06	.004	.000	.05	.07
	Desogestrel	.09	.004	.000	.08	.10
Etonogestrel	Norethisterone	.02	.005	.000	.01	.04
	Lynestrenol	.02	.005	.000	.01	.04
	Levonorgestrel	-.03	.004	.000	-.04	-.02
	Medroxyprogesterone	-.06	.004	.000	-.07	-.05
	Desogestrel	.03	.003	.000	.02	.04
Desogestrel	Norethisterone	-.01	.004	.497	-.02	.00
	Lynestrenol	-.01	.004	.788	-.02	.01
	Levonorgestrel	-.06	.003	.000	-.07	-.05
	Medroxyprogesterone	-.09	.004	.000	-.10	-.08
	Etonogestrel	-.03	.003	.000	-.04	-.02

[#] A *p*-value < 0.05 denotes a significant difference between the formulation groups