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RESEARCH

Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10


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Abstract

Objective To assess the risk of venous thrombosis in current users of non-oral hormonal contraception.

Design Historical national registry based cohort study.

Setting Four national registries in Denmark.

Participants All Danish non-pregnant women aged 15-49 (n=1 626 158), free of previous thrombotic disease or cancer, were followed from 2001 to 2010.

Main outcome measures Incidence rate of venous thrombosis in users of transdermal, vaginal, intrauterine, or subcutaneous hormonal contraception, relative risk of venous thrombosis compared with non-users, and rate ratios of venous thrombosis in current users of non-oral products compared with the standard reference oral contraceptive with levonorgestrel and 30-40 µg oestrogen. Diagnoses were confirmed by at least four weeks of anticoagulation therapy after the diagnosis.

Results Within 9 429 128 woman years of observation, 5287 first ever venous thrombosis events were recorded, of which 3434 were confirmed. In non-users of hormonal contraception the incidence rate of confirmed events was 2.1 per 10 000 woman years. Compared with non-users of hormonal contraception, and after adjustment for age, calendar year, and education, the relative risk of confirmed venous thrombosis in users of transdermal combined contraceptive patches was 7.9 (95% confidence interval 3.5 to 17.7) and of the vaginal ring was 6.5 (4.7 to 8.9). The corresponding incidences per 10 000 exposure years were 9.7 and 7.8 events. The relative risk was increased in women who used subcutaneous implants (1.4, 0.6 to 3.4) but not in those who used the levonorgestrel intrauterine system (0.6, 0.4 to 0.8). Compared with users of combined oral contraceptives containing levonorgestrel, the adjusted relative risk of venous thrombosis in users of transdermal patches was 2.3 (1.0 to 5.2) and of the vaginal ring was 1.9 (1.3 to 2.7).

Conclusion Women who use transdermal patches or vaginal rings for contraception have a 7.9 and 6.5 times increased risk of confirmed venous thrombosis compared with non-users of hormonal contraception of the same age, corresponding to 9.7 and 7.8 events per 10 000 exposure years. The risk was slightly increased in women using subcutaneous implants but not in those using the levonorgestrel intrauterine system.

Introduction

Several studies have assessed the risk of venous thrombosis in women using oral contraceptives.[1-10] However, none has assessed the risk in women using subcutaneous hormonal implants. A recent study reported a 48% higher risk of venous thrombosis in women using a vaginal ring compared with those using combined oral contraceptives containing levonorgestrel,[11] and a few studies have reported the risk in women using a transdermal combined contraceptive patch, although the results were conflicting.[12-16]

Using a historical national registry based cohort study design, we assessed the absolute and relative risk of venous thrombosis in Danish women using non-oral hormonal contraception.

Methods

Information on the four national data sources that provided information for the study is provided in detail elsewhere.[10] Briefly, from Statistics Denmark we obtained data on length of schooling, ongoing or finished education, vital status, and emigration of all Danish women aged 15-49 from 1 January 2001 to 31 December 2010. We censored women in cases of death or emigration.

Since 1977 the national registry of patients has collected discharge diagnoses from all public and private hospitals in Denmark (see appendix for a list of the relevant diagnoses and

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Disease codes (international classification of diseases, 10th revision)

codes used in this study). To include only first ever events, we excluded women with any type of venous or arterial thrombotic event before the study period (1977-2000), those with cancer, those who had undergone bilateral oophorectomy or hysterectomy, and those who had been sterilised. From study follow-up we censored a woman's risk time during pregnancy, calculated from conception to three months after delivery, and women with a coagulation disorder from the first time such a diagnosis was recorded (appendix). The registry records only women admitted alive to hospital. Lethal events from venous thrombosis were captured in the national cause of death registry.

A diagnosis of venous thrombosis was confirmed through prescribed anticoagulation therapy recorded in the national registry of medicinal products for at least four weeks after the diagnosis. Since 1 January 1994, and validated from 1995, information on filled prescriptions, including hormonal contraception, collected by the national registry of medicinal products has been complete. From this database we obtained information that had been updated daily on redeemed prescriptions of hormonal contraception from 1995 to 2010. We categorised the products in use according to progestogen type, oestrogen dose, and route of being administered. Duration of use was estimated from the prescribed defined daily doses from the date of prescription until the end date of defined daily doses of the last redeemed prescription or date of a study event. When hormonal contraception was switched without pause, we calculated duration as the sum of use before switch and current use of the new preparation. If a pause lasted for more than four weeks, we reset the length of use. To account for use before study start (left censoring bias), we allocated continuous users of hormonal contraception to the relevant duration of use category on 1 January 2001 by assessing use before the study period back to 1995.

Women who used the levonorgestrel intrauterine system were censored after three years and included again when a new prescription of a hormonal contraceptive product was recorded. This was done owing to missing information on removal of these devices.

Length of schooling and level of education were used as proxies for social class. Four strata were applied: elementary school education only, ongoing or completed high school education, high school and ongoing or ended middle length education, and high school and ongoing or ended long education. A fifth category included women without information on education, typically the youngest women.

We controlled for calendar year to deal with potential secular confounding of increasing adiposity by time.

Data on smoking were not available. Smoking is a weak risk factor for venous thrombosis in young women. However, we have no reason to believe in preferential prescribing of specific types of hormonal contraception among smokers. In Denmark the correlation between smoking and length of education is strong. Thus, controlling for years of schooling and length of education may have captured most confounding (if any) influenced by smoking.

As women treated for infertility with ovarian stimulation drugs (Anatomical Therapeutic Chemical code G03G) are anticipated to be at an increased risk of venous thrombosis, we censored these women during such treatment.

Statistical analysis

Using multiple Poisson regression we analysed data in five year age groups: 15-19, 20-24, and 45-49 years. The non-oral contraceptive products included transdermal patches containing norelgestromin (the active metabolite of norgestimate) and ethinylestradiol, a vaginal ring with etonogestrel (third generation progestogen) and ethinylestradiol, subcutaneous implants containing etonogestrel only, and the levonorgestrel intrauterine system (hormone intrauterine device). Two reference oral contraceptives with levonorgestrel and norgestimate, respectively, were assessed for comparison.

We stratified the estimates into three categories according to length of contraceptive use (<1 year, 1-4 years, >4 years). Absolute as well as relative risk estimates were calculated. The reference group for the relative risk estimates was non-users of all types of hormonal contraception (never users+former users). We calculated rate ratios for the different product types, with users of oral contraceptives containing 30-40 µg oestrogen and levonorgestrel as reference. Tests for interaction with age and year were carried out.

Relative risk estimates were adjusted for age, calendar year, length of schooling and education, and eventually for length of contraceptive use. For all relative risk estimates and incidence rate ratios we calculated 95% confidence limits. We set the level of significance at $P<0.05$.

Results

After exclusions and censoring, 1 626 158 non-pregnant women free of previous thrombotic diseases or cancer contributed 9 429 128 woman years of observation. During this time 5287 diagnoses of first ever venous thrombosis events were recorded, corresponding to 8.1 per 10 000 woman years. Current users of hormonal contraception contributed 3 536 946 woman years and of these, 325 849 concerned non-oral products. Non-users of hormonal contraception contributed 5 892 182 woman years, with an overall incidence of confirmed venous thrombosis of 2.1 per 10 000 woman years. The incidence of venous thrombosis increased by 42.9% during the 10 year study period, or by 4.3% per year (table 1⇓). After adjustment for calendar year and use of hormonal contraception, the incidence increased by 6.3-fold with increasing age and decreased by 51.2% with increasing length of education.

Hormonal contraception and venous thrombosis

Current use of combined oral contraceptives with 30-40 µg oestrogen and levonorgestrel increased the risk of confirmed venous thrombosis by 3.2 (2.7 to 3.8), corresponding to an incidence of 6.2 events per 10 000 exposure years (table 2⇓).

During 6178 woman years, six confirmed events of venous thrombosis were observed in association with transdermal combined contraceptive patches, corresponding to an incidence of 9.7 per 10 000 exposure years. Compared with non-users of hormonal contraception, the adjusted relative risk was 7.9 (3.5 to 17.7) and compared with users of oral contraceptives containing levonorgestrel the rate ratio was 2.5 (1.1 to 5.6, tables 2 and 3⇓). After adjustment for length of use, the rate ratio was reduced to 2.3 (1.0 to 5.2). When compared with oral contraceptives containing the corresponding progestogen (norgestimate), the adjusted rate ratio was 2.2 (1.0 to 5.0).

During 50 334 woman years, 39 confirmed venous thrombosis events were observed with the combined contraceptive vaginal ring, corresponding to an incidence of 7.8 per 10 000 exposure years and an adjusted relative risk of 6.5 (4.7 to 8.9) compared with non-users of hormonal contraception. Compared with users of combined oral contraceptives with levonorgestrel, the rate

ratio was 2.0 (1.4 to 2.9), which after adjustment for length of use was reduced to 1.9 (1.3 to 2.7, tables 2 and 3).

During 29 497 woman years, five confirmed venous thrombosis events were observed with progestogen only subcutaneous implants, corresponding to an incidence rate of 1.7 per 10 000 exposure years and an adjusted relative risk of 1.4 (0.6 to 3.4, table 2) compared with non-users of hormonal contraception. Compared with users of combined oral contraceptives with levonorgestrel, the rate ratio was 0.4 (0.2 to 1.1, table 3).

The adjusted relative risk of confirmed venous thrombosis with the levonorgestrel intrauterine system was 0.6 (0.4 to 0.8, table 2). Compared with users of combined oral contraceptives with levonorgestrel, the rate ratio was 0.2 (0.1 to 0.3, table 3).

After stratification according to length of use, the relative risk of venous thrombosis in women using combined oral contraceptives was reduced with increasing length of use (table 4⇓). No reduction by time was seen in users of transdermal combined contraceptive patches or progestogen only contraception, and no consistent changes were seen for women who used the vaginal ring.

Discussion

Women who use combined hormonal transdermal patches or vaginal rings for contraception have a 7.9 or 6.5 times increased risk of venous thrombosis compared with non-users of hormonal contraception of the same age, corresponding to 9.7 and 7.8 events per 10 000 exposure years. The risk was slightly increased in women using subcutaneous implants but not in those using the levonorgestrel intrauterine system.

An incidence rate of confirmed venous thrombosis in users of transdermal patches of 1 in 1000 exposure years was found in a recent American study,[11] and a relative risk of 7.9 compared with non-users of hormonal contraception or twice the risk with use of the corresponding combined oral contraceptive containing norgestimate in several previous studies[11 14-16] although not all[12 13] (table 5⇓). These results are supported by pharmacokinetic studies showing 60% higher plasma levels of oestrogen in women who use transdermal patches compared with those using the corresponding combined oral contraceptive.[17]

With an incidence of 7.8 confirmed events per 10 000 exposure years, the vaginal ring conferred a 90% higher risk of venous thrombosis than did combined oral contraceptives containing levonorgestrel, bringing the risk to the same level as that of combined oral contraceptives with third and fourth generation progestogens, and compatible with the Food and Drug Administration study.[11] Supporting our and the FDA results is the three[18] and five times[19] increase in sex hormone binding globulin in users of vaginal ring contraception compared with users of combined oral contraceptives containing levonorgestrel, and the activated protein C sensitivity ratio 3.75 times higher than with oral contraceptives,[19] both considered as surrogate markers for the risk of venous thrombosis.

The modest non-significant 40% increased relative risk of venous thrombosis in women using subcutaneous implants is not surprising, as other types of progestogen only contraception do not confer an increased risk,[10] and it is less than half the risk found in users of combined oral contraceptives containing levonorgestrel.

The low risk of venous thrombosis in users of the levonorgestrel intrauterine system has been shown in previous studies.[7 10] In the present study this product actually significantly decreased the risk of venous thrombosis, suggesting that the influence of progestogen only contraception on risk of venous thrombosis may depend on dose.

The inconsistent changes with length of use for the non-oral products could be influenced by the low power in some of the length of use categories. Another possibility, however, is that the non-oral route influences the coagulation system and liver differentially compared with the oral route. Nor did the FDA report show any consistent change in risk with length of use of either the patch or the vaginal ring.

The clinical implications of the findings can be expressed in terms of the number of women who should change their hormonal contraceptive from the transdermal patch or the vaginal ring to combined oral contraceptives containing levonorgestrel to prevent one event of venous thrombosis in a year. If the incidence rate of venous thrombosis in women using combined oral contraceptives containing levonorgestrel is 6 per 10 000 exposure years, the vaginal ring is 11 per 10 exposure years, and the transdermal patch is 14 per 10 000 exposure years, then 2000 women using the vaginal ring and 1250 using the transdermal patch should shift to combined oral contraceptives with levonorgestrel to prevent one event of venous thrombosis in one year. A risk of 10 per 10 000 woman years implies a risk of venous thrombosis of more than 1% over a 10 year user period. Therefore women are generally advised to use combined oral contraceptives with levonorgestrel or norgestimate, rather than to use transdermal patches or vaginal rings.

Strengths and limitations of the study

The inclusion of all Danish non-pregnant women over a decade ensures outstanding external validity. Information on use of hormonal contraception from a prescription database is the most reliable data on exposure available today for four reasons. Firstly, each pharmacy transfers data electronically by bar codes, eliminating typing errors. Secondly, the collection of these data in a central national database is done primarily for reimbursement purposes and therefore should not be biased by the pursuit of pharmacoepidemiological studies. Thirdly, the continued daily update of information on use eliminates recall bias, as we know from case-control studies, and the problems of continuous updating of data on exposure in cohort studies. Fourthly, we eliminated the problem of left censoring bias by assessing exposure to hormonal contraception over a six year period before our study started. And we were able to validate each venous thrombosis event by linking individual data on diagnosis to succeeding anticoagulation therapy.

We could not control for family disposition or for body mass index. Adiposity is a well documented risk factor for venous thrombosis. So far no study has shown any confounding influence from adiposity, as the rate ratio between hormonal contraception with different progestogens was not changed in studies adjusting for this information.[6 8 20]

Conclusion

Use of transdermal patches and vaginal rings conferred incidence rates of 9.7 and 7.8 confirmed venous thromboses per 10 000 exposure years, and relative risks of 7.9 and 6.5 compared with non-use of hormonal contraception, respectively. A subcutaneous progestogen only implant may increase the risk by 40%, whereas the levonorgestrel intrauterine system did not confer any increased risk, but perhaps even protection.

This study was approved by the Danish Data Protection Agency (J No 2010-41-4778).

What is already known on this topic

Combined oral contraceptives with levonorgestrel or norgestimate confer half the risk of venous thrombosis than oral contraceptives containing desogestrel, gestodene, or drospirenone

Progestogen only pills do not confer an increased risk of venous thrombosis

What this study adds

Women who use combined contraceptive transdermal patches are at an increased risk of venous thrombosis about eight times that of non-users of hormonal contraception, corresponding to 9.7 events per 10 000 exposure years

Vaginal rings increased the risk of venous thrombosis 6.5 times compared with non-use of hormonal contraception, corresponding to 7.8 events per 10 000 exposure years

The risk of venous thrombosis was not significantly increased with use of subcutaneous implants or the levonorgestrel intrauterine system compared with non-use of hormonal contraception

Contributors: ØL planned the study, supervised the analysis, interpreted the results, and wrote the manuscript. He is guarantor of the study. EL planned the study, interpreted the results, and revised the manuscript. LHN made the statistical analyses and interpreted the results. CWS prepared all data from the national registry of patients and national death registry. All authors discussed and approved the final manuscript. ØL decided when and where to attempt publication.

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Ethical approval: Ethical approval is not requested for registry based studies in Denmark, and consent from participating patients is not required.

Data sharing: No additional data available.

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Tables

Table 1| Crude incidence rate and adjusted relative risk of confirmed venous thrombosis according to age, calendar year, and length of education

		Venous thrombosis				
Variables	**Woman years**	**All**	**Confirmed**	**Incidence per 10 000 woman years**	**Adjusted relative risk* (95% CI)**	**P value**
Age:						
15-19	1 403 925	365	251	1.79	0.16 (0.13 to 0.19)	<0.001
20-24	1 198 098	479	326	2.72	0.19 (0.16 to 0.22)	<0.001
25-29	1 145 729	594	387	3.38	0.30 (0.27 to 0.33)	<0.001
30-34	1 299 645	715	448	3.45	0.44 (0.40 to 0.48)	<0.001
35-39	1 509 447	930	601	3.98	0.60 (0.55 to 0.66)	<0.001
40-44	1 510 042	1105	705	4.67	0.82 (0.75 to 0.89)	<0.001
45-49	1 362 242	1099	716	5.26	1.00 (reference)	—
Year:						
2001	994 095	444	315	3.17	0.70 (0.61 to 0.79)	<0.001
2002	979 715	466	331	3.38	0.72 (0.64 to 0.82)	<0.001
2003	963 470	438	304	3.16	0.68 (0.60 to 0.77)	<0.001
2004	953 604	512	319	3.35	0.79 (0.70 to 0.89)	<0.001
2005	939 935	525	362	3.85	0.81 (0.72 to 0.91)	0.0005
2006	929 975	537	363	3.90	0.84 (0.74 to 0.94)	0.0028
2007	921 713	615	391	4.24	0.97 (0.87 to 1.09)	0.6531
2008	918 349	538	347	3.78	0.87 (0.77 to 0.98)	0.0171
2009	911 825	599	365	4.00	0.98 (0.87 to 1.09)	0.6597
2010	916 449	613	337	3.68	1.00 (reference)	—
Education:						
1 (low)	2 164 635	1819	1159	5.35	1.25 (1.11 to 1.42)	0.0004
2	1 026 525	475	314	3.06	0.72 (0.62 to 0.83)	<0.001
3	2 236 972	1456	974	4.35	0.83 (0.73 to 0.95)	0.0087
4 (high)	1 385 214	602	382	2.76	0.61 (0.53 to 0.71)	<0.001
Not available	2 615 782	935	605	2.31	1.00 (reference)	—

*Adjusted for age, calendar year, education, and use of hormonal contraception.

Table 2| Crude incidence rate and adjusted relative risk of venous thrombosis in current users of non-oral hormonal contraception and combined oral contraceptives (COC) with non-users as reference

Outcome, contraception type	Woman years	No with venous thrombosis	Incidence per 10 000 exposure years	Adjusted relative risk* (95% CI)	P value
All venous thromboses:					
Non-use	5 892 182	2262	3.84	1.00 (reference)	—
COC with levonorgestrel and 30-40 µg oestrogen	231 675	201	8.68	2.37 (2.05 to 2.74)	<0.001
COC with norgestimate	298 566	198	6.63	2.63 (2.27 to 3.05)	<0.001
Patch	6178	7	11.33	4.40 (2.09 to 9.24)	<0.001
Vaginal ring	50 334	55	10.93	4.29 (3.27 to 5.62)	<0.001
Implant	29 497	15	5.09	2.08 (1.25 to 3.46)	0.005
Levonorgestrel IUS	239 841	88	3.67	0.80 (0.65 to 0.99)	0.040
Confirmed events:					
Non-use	5 892 182	1209	2.05	1.00 (reference)	—
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	6.22	3.21 (2.70 to 3.81)	<0.001
COC with norgestimate	298 566	135	4.52	3.57 (2.98 to 4.27)	<0.001
Patch	6178	6	9.71	7.90 (3.54 to 17.65)	<0.001
Vaginal ring	50 334	39	7.75	6.48 (4.69 to 8.94)	<0.001
Implant	29 497	5	1.70	1.40 (0.58 to 3.38)	0.450
Levonorgestrel IUS	239 841	33	1.38	0.57 (0.41 to 0.81)	0.002

Patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD; NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD, NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena: Bayer Pharma, Berlin, Germany).
*Adjusted for age, calendar year, and education.

Table 3| Rate ratio estimates of venous thrombosis between users of different types of non-oral hormonal contraception and users of combined oral contraceptives (COC) with levonorgestrel and 30-40 µg oestrogen (reference group)

Outcome, contraception type	Woman years	No with venous thrombosis	Adjusted rate ratio (95% CI)*	P value
All venous thrombosis:				
COC with levonorgestrel and 30-40 µg oestrogen	231 675	201	1.00 (reference)	—
COC with norgestimate	298 566	198	1.11 (0.91 to 1.35)	0.305
Patch	6178	7	1.85 (0.87 to 3.94)	0.109
Vaginal ring	50 334	55	1.81 (1.34 to 2.44)	0.0001
Implant	29 497	15	0.88 (0.52 to 1.48)	0.623
Levonorgestrel IUS	239 841	88	0.34 (0.26 to 0.43)	<0.001
Confirmed events:				
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	1.00 (reference)	—
COC with norgestimate	298 566	135	1.11 (0.88 to 1.41)	0.378
Patch	6178	6	2.46 (1.09 to 5.58)	0.031
Vaginal ring	50 334	39	2.02 (1.41 to 2.89)	0.0001
Implant	29 497	5	0.44 (0.18 to 1.07)	0.070
Levonorgestrel IUS	239 841	33	0.18 (0.12 to 0.26)	<0.001
Confirmed events adjusted for length of use:				
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	1.00 (reference)	—
COC with norgestimate	298 566	135	1.09 (0.86 to 1.38)	0.465
Patch	6178	6	2.31 (1.02 to 5.23)	0.045
Vaginal ring	50 334	39	1.90 (1.33 to 2.71)	0.001
Implant	29 497	5	0.43 (0.18 to 1.05)	0.064
Levonorgestrel IUS	239 841	33	0.18 (0.12 to 0.26)	<0.001

Patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD; NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD, NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena; Bayer Pharma, Berlin, Germany).
*Adjusted for age, calendar year, and education.

Table 4| Relative risk of confirmed venous thrombosis in current users of different types of hormonal contraception according to length of use

Hormonal contraception	No with confirmed venous thrombosis	Adjusted relative risk (95% CI)*		
		<1 year	1-4 years	>4 years
Non-use	1209	1 (reference)	1 (reference)	1 (reference)
COC with levonorgestrel and 30-40 µg oestrogen	144	4.25 (3.17 to 5.69)	3.07 (2.28 to 4.13)	2.71 (2.06 to 3.58)
COC with norgestimate	135	4.97 (3.86 to 6.39)	2.97 (2.19 to 4.03)	2.67 (1.82 to 3.92)
Patch	6	6.89 (2.22 to 21.4)	11.9 (3.82 to 36.9)	NA
Vaginal ring	39	8.36 (5.73 to 12.2)	3.83 (1.91 to 7.69)	5.37 (1.73 to 16.7)
Implant	5	1.63 (0.41 to 6.52)	1.43 (0.46 to 4.45)	NA
Levonorgestrel IUS	33	0.59 (0.34 to 1.05)	0.61 (0.39 to 0.94)	NA

COC=combined oral contraceptive; patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD, NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD; NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena; Bayer Pharma, Berlin, Germany); NA=not available.

*Adjusted for age, calendar year, and education.

Table 5| **Incidence of venous thrombosis in users of transdermal contraceptive patch and corresponding combined oral contraceptive (COC) with norgestimate, and rate ratio of venous thrombosis in users of patch versus users of combined oral contraceptives with norgestimate**

			Incidence per 10 000 exposure years		
Study	Sampling period	No with venous thrombosis	Patch	COC with norgestimate	Rate ratio (95% CI)
Jick 2006[12]	2002-05	68	5.3	4.2	1.1 (0.7 to 1.8)
Jick 2007[13]	2002-06	56	NA	NA	1.1 (0.6 to 2.1)
Jick 2010[14]	2002-07	38	NA	NA	2.4 (1.2 to 5.0)
Cole 2007[15]	2002-04	57	4.1	1.8	2.2 (1.3 to 3.8)
Dore 2010[16]	2002-06	201	NA	NA	2.0 (1.2 to 3.3)
FDA 2011[11]	2001-07	625	9.6	6.6*	1.3* (0.9 to 1.7)
Lidegaard 2011[10]	2001-10	3434	9.7	4.5	2.2 (1.0 to 5.0)

NA=not available; FDA=Food and Drug Administration.

*Reference group was users of combined oral contraceptives with levonorgestrel and 30-40 µg oestrogen.