

Association of Hormonal Contraception With Suicide Attempts and Suicides

Charlotte Wessel Skovlund, Ph.D., Lina Steinrud Mørch, Ph.D., Lars Vedel Kessing, D.M.Sc., Theis Lange, Ph.D., Øjvind Lidegaard, D.M.Sc.

Objective: The purpose of this study was to assess the relative risk of suicide attempt and suicide in users of hormonal contraception.

Method: The authors assessed associations between hormonal contraceptive use and suicide attempt and suicide in a nationwide prospective cohort study of all women in Denmark who had no psychiatric diagnoses, antidepressant use, or hormonal contraceptive use before age 15 and who turned 15 during the study period, which extended from 1996 through 2013. Nationwide registers provided individually updated information about use of hormonal contraception, suicide attempt, suicide, and potential confounding variables. Psychiatric diagnoses or antidepressant use during the study period were considered potential mediators between hormonal contraceptive use and risk of suicide attempt. Adjusted hazard ratios for suicide attempt and suicide were estimated for users of hormonal contraception as compared with those who never used hormonal contraception.

Results: Among nearly half a million women followed on average for 8.3 years (3.9 million person-years) with a mean age of 21 years, 6,999 first suicide attempts and 71 suicides were identified. Compared with women who never used hormonal contraceptives, the relative risk among current and recent users was 1.97 (95% CI=1.85–2.10) for suicide attempt and 3.08 (95% CI=1.34–7.08) for suicide. Risk estimates for suicide attempt were 1.91 (95% CI=1.79–2.03) for oral combined products, 2.29 (95% CI=1.77–2.95) for oral progestin-only products, 2.58 (95% CI=2.06–3.22) for vaginal ring, and 3.28 (95% CI=2.08–5.16) for patch. The association between hormonal contraceptive use and a first suicide attempt peaked after 2 months of use.

Conclusions: Use of hormonal contraception was positively associated with subsequent suicide attempt and suicide. Adolescent women experienced the highest relative risk.

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Hormonal contraception is used worldwide by more than 100 million women to avoid unintended pregnancies and to alleviate menstrual pain, heavy bleeding, premenstrual syndrome, and acne. Use of hormonal contraception has been associated with depression and adverse mood effects (1, 2). Apart from the daily burden depression imposes, it also increases the risk of suicide and suicide attempt (3). We found no study assessing the association between hormonal contraceptive use and risk of suicide attempt. Five studies have assessed the association between use of hormonal contraception and risk of death, including death by suicide (4–8), and most of these studies found no statistically significant association. The study with the largest number of suicides, however, showed a statistically significant relative risk of suicide of 1.4 (95% CI=1.05–1.87) among users of oral contraceptives compared with never-users (see Table S1 in the data supplement that accompanies the online edition of this article). A limitation of the published studies is the inclusion of women over the age of 25, which on average is several years after they began using hormonal contraception.

Because mood symptoms are a known reason for cessation of hormonal contraceptive use (9–11), the inclusion of women several years after they started using hormonal contraceptives is likely to cause a selection of those women who can tolerate hormonal contraception, resulting in an underestimation of any potential association between hormonal contraceptive use and risk of suicide.

In a nationwide prospective cohort study (1), we recently found an association between hormonal contraception and depression, and the association was most pronounced among adolescent women. Adolescence is a period characterized by endogenous sex hormone changes and changing external cultural and social demands, which are likely to enhance the influence of any additional factor that might cause mood disturbances, such as use of hormonal contraception.

In this study, we followed a complete national cohort of women from age 15, before their first use of hormonal contraceptives, to assess their daily use of hormonal contraception and the risk of a subsequent first suicide attempt or suicide.

METHOD

Data Sources

The Danish Sex Hormone Register Study is an ongoing national cohort study that includes all women living in Denmark. The cohort has been described previously (1, 12, 13). Briefly, the cohort was identified by the unique personal identification number assigned to all Danish citizens at birth or immigration. The personal identification number is used in all public registers, allowing reliable linkage of data between different registers. The National Prescription Register provided data on all redeemed prescriptions in Denmark for hormonal contraception (see Table S2 in the online data supplement) and antidepressants (N06A* Anatomical Therapeutic Chemical classification system code) since 1995. The Psychiatric Central Research Register provided data on psychiatric diagnoses for all inpatients and outpatients since 1995. The Cause of Death Register provided data on suicides. The National Health Register provided data on suicide attempts (see Table S3 in the data supplement) and discharge diagnoses of cancer (all first cancers except non-melanoma skin cancer) and venous thrombosis (see Table S4 in the data supplement) since 1977. The National Birth Register provided information on births since 1973. Daily updated information on immigration, emigration, and death was obtained from Statistics Denmark, which also delivered data on age and ongoing or completed education.

Study Population

We followed women who turned 15 during the study period, which extended from 1996 to 2013, and who had no prior history of hormonal contraceptive use. We excluded women with prior suicide attempts, antidepressant use, psychiatric diagnoses, cancer diagnoses, or venous thrombosis diagnoses because these factors could influence both use of hormonal contraception and risk of suicide. The year 1995 was used to assess prior medication use and prior psychiatric diagnoses. Women who immigrated after 1995 were excluded, to ensure that full exposure history was available (see Figures S1 and S2 in the data supplement).

Hormonal Contraception

Individual exposure information on prescribed and redeemed hormonal contraception was modeled as time-varying variables with information updated daily; women thus changed status from never-user to user of hormonal contraception at the date of a first redeemed prescription of hormonal contraception. Use was defined as current use or recent use (cessation within the past 6 months) to ensure that women were considered exposed to hormonal contraceptives if they ceased hormonal contraceptive use owing to mood changes but before suicide or suicide attempt. Those who stopped use were allocated to the former user category after 6 months.

Suicide Attempt and Suicide

A woman was categorized as having a suicide attempt if she had a diagnosis of suicide attempt (see Table S3 in the data

supplement) or a contact with a somatic or psychiatric hospital defined as “suicide attempt.” Only the first suicide attempt was assessed. The Cause of Death Register provided data on suicide as defined in Table S3. In the calculation of the risk of suicide, women were not censored after previous suicide attempts during the study period.

Covariates

Crude models included calendar year in addition to the exposure variable and age as the underlying time scale. Fully adjusted models additionally included ongoing or completed education: elementary school only, high school only, skilled worker, theoretical education, and theoretical education with research qualifications as a time-varying variable updated yearly.

Statistical Analysis

The study population was followed from entry at their 15th birthday until emigration, death, a first diagnosis of cancer or venous thrombosis, time of event (suicide attempt or suicide), or end of follow-up on December 31, 2013, whichever came first. Psychiatric diagnoses and antidepressant use after study start were considered intermediate variables (mediators) between use of hormonal contraception and suicide attempt or suicide and thus not confounders. Pregnant women were temporarily censored during pregnancy and for 6 months after delivery.

Cox regression analyses were used to calculate hazard ratios (relative risk) of a first suicide attempt or suicide, respectively, with 95% confidence limits and a significance threshold of 0.05. The proportional hazard assumption was checked by age stratification into 1-year age groups. The 15-year-olds had a higher risk of event than the other age groups. However, the results remained similar to those from the main analyses after exclusion of the 15-year-olds. Thus, the main results were presented combined for all age groups but also stratified into the age groups 15–19 years, 20–24 years, and 25–33 years.

We assessed the risk of first suicide attempt according to duration of hormonal contraceptive use. Finally, we assessed the risk associated with specific types of combined hormonal contraceptives according to type of progestin and route of administration, and with progestin-only products.

In a subanalysis, we calculated the proportion of the increased risk of suicide attempt in hormonal contraception users that was mediated by psychiatric diagnoses or use of antidepressants. Technically, the mediation analysis was conducted as a difference-of-coefficient analysis with standard errors determined by parametric bootstrap (14). Additionally, we conducted a quantitative bias analysis to assess how strong and how common an unknown binary risk factor for suicide attempt should be to explain our results.

Absolute incidence rates (events/person-years) were calculated for the study population, as were the absolute increase in events due to use of hormonal contraception in our study population per 1 million per year.

TABLE 1. Clinical and Demographic Characteristics of Women Living in Denmark Who Turned 15 During the Study Period (1996–2013)

Measure	Use of Hormonal Contraception								
	Never		Current or Recent ^a				Former		All
	N		N		N		N		
Suicide attempt	N		N		N		N		
Person-years	1,387,917		2,127,374		405,527		3,920,818		
Events	2,049		3,898		1,052		6,999		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Follow-up (years)	2.9	3.6	6.0	3.8	2.2	2.2	8.3	4.8	
Age (years)	17.6	2.9	21.5	3.7	24.0	4.0	21.0	4.0	
	N	%	N	%	N	%	N	%	
Education									
Basic school	84,663	6.1	168,063	7.9	59,612	14.7	313,665	8.0	
Postgraduate degree	61,068	4.4	502,060	23.6	127,335	31.4	690,064	17.6	
Polycystic ovary syndrome	11,103	0.8	21,274	1.0	6,894	1.7	39,208	1.0	
Endometriosis	5,552	0.4	19,146	0.9	4,461	1.1	31,367	0.8	
Suicide	N		N		N		N		
Person-years	1,393,940		2,154,887		418,243		3,967,070		
Events	8		42		21		71		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Follow-up (years)	2.9	3.0	6.0	3.7	2.2	2.3	8.3	4.7	
Age (years)	17.6	2.9	21.6	3.7	24.0	3.9	21.1	4.0	
	N ^b	%	N ^b	%	N ^b	%	N ^b	%	
Education									
Basic school	86,424	6.2	174,546	8.1	63,991	15.3	325,300	8.2	
Postgraduate degree	62,727	4.5	506,398	23.5	128,819	30.8	698,204	17.6	
Polycystic ovary syndrome	11,152	0.8	21,549	1.0	7,528	1.8	39,671	1.0	
Endometriosis	5,576	0.4	19,394	0.9	4,601	1.1	31,737	0.8	

^a Recent use was defined as past use with cessation within the past 6 months.

^b In person-years.

RESULTS

The study population included 475,802 women who entered the study at age 15, and the data covered 3,920,818 person-years through the study period, 1996–2013. During the mean follow-up of 8.3 years, the mean age was 21 years (SD=4), and 54% of the study population were current or recent users of hormonal contraception. A total of 6,999 first suicide attempts and 71 suicides were detected during follow-up (Table 1).

Compared with never-users, users of hormonal contraception 15–33 years of age had a relative risk of 1.97 (95% CI=1.85–2.10) for a first suicide attempt and 3.08 (95% CI=1.34–7.08) for suicide (Figure 1).

The relative risk of suicide attempt with hormonal contraceptive use was for 2.06 (95% CI=1.92–2.21) for the 15–19 age group, 1.61 (95% CI=1.39–1.85) for the 20–24 age group, and 1.64 (95% CI=1.14–2.36) for the 25–33 age group (Figure 2).

The relative risk of a first suicide attempt increased rapidly after initiation of hormonal contraceptive use, compared with never use, and it remained at least doubled until 1 year after initiation. Thereafter the risk estimates

decreased, but they remained 30% higher compared with never-users after more than 7 years of use (Figure 3).

Former users were found to have a relative risk of 3.40 (95% CI=3.11–3.71) for a first suicide attempt (see Table S5 in the data supplement) and 4.82 (95% CI=1.93–12.1) for suicide.

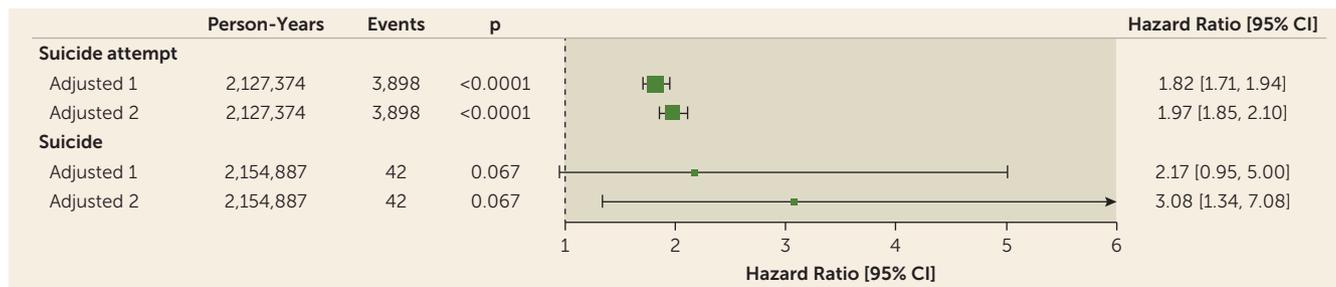
Compared with never use, use of oral combined products was positively associated with an overall first suicide attempt (relative risk=1.91, 95% CI=1.79–2.03). None of the risk estimates for specific types of oral combined products with 20–40 µg of estrogen differed significantly from risk estimates for 30–40 µg of estrogen formulated with levonorgestrel. Use of all types of oral progestin-only products was also positively associated with the risk of suicide attempt (relative risk=2.29, 95% CI=1.77–2.95) and was not statistically significantly different from the risk for oral combined products.

Oral progestin-only products with norethisterone conferred a relative risk of 2.77 (95% CI=1.89–4.05), and those with desogestrel, a relative risk of 2.01 (95% CI=1.44–2.81). Non-oral combined patch formulations showed a relative risk of 3.28 (95% CI=2.08–5.16) and vaginal ring formulations a relative risk of 2.58 (95% CI=2.06–3.22). Non-oral progestin-only implant products conferred a relative risk of 4.42 (95% CI=3.63–5.39), intrauterine devices with levonorgestrel a relative risk of 2.86 (95% CI=2.06–3.97), and medroxyprogesterone acetate depot formulations a relative risk of 6.52 (95% CI=5.03–8.46). Simple and fully adjusted estimates were similar. An exception was the relative risk with use of medroxyprogesterone acetate, which decreased substantially with full adjustment (Figure 4 and Table S5 in the data supplement; see also Table S6).

Subanalyses

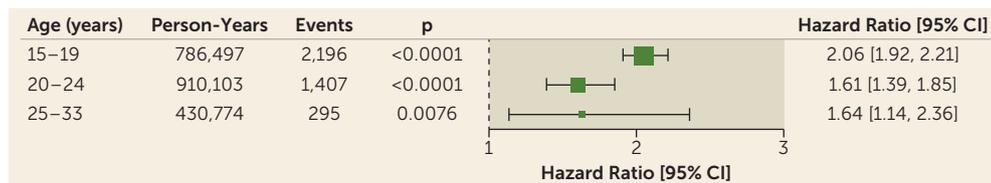
After adjusting for psychiatric diagnoses and antidepressant use as potential mediators, the hazard ratio for suicide attempt decreased to 1.58 (95% CI=1.48–1.68); this is the so-called direct effect, and accordingly the indirect effect (i.e., mediated through psychiatric diagnoses and antidepressant use) is estimated to be 1.25 (95% CI=1.14–1.36) and the mediated proportion to be 33% (95% CI=21–44).

FIGURE 1. Relative Risk of a First Suicide Attempt and Suicide Among Current Users of Hormonal Contraception Compared With Never-Users^a



^a Adjusted 1: age as underlying time, and adjusted for calendar year; adjusted 2: age as underlying time, and adjusted for calendar year, education, polycystic ovary syndrome, and endometriosis. For suicide attempt, never use (reference; hazard ratio=1.0) person-years=1,387,917, events=2,049. For suicide, never use (reference; hazard ratio=1.0) person-years=1,393,940, events=8.

FIGURE 2. Relative Risk of a First Suicide Attempt Among Current Users of Hormonal Contraceptives, Stratified by Age Group^a



^a Age as underlying time, and adjusted for calendar year, education, polycystic ovary syndrome, and endometriosis.

This quantitative bias analysis suggested that an unknown risk factor—for example, family history of suicide—with an assumed relative risk of 6.8 for suicide attempt and an odds ratio of 5 for becoming a user of hormonal contraception, should have a prevalence of one-third in the study population to be able to explain the association between hormonal contraceptive use and suicide attempt (see Figure S3 in the data supplement).

DISCUSSION

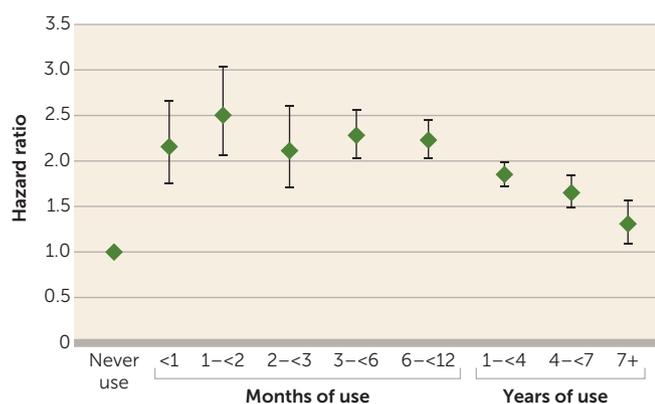
In women 15–33 years of age, hormonal contraceptive use was positively associated with a first suicide attempt, as compared with never-users. Adolescent women experienced the highest relative risks. Patch, vaginal ring, and progestin-only products were associated with higher risks than oral combined products, and a similar association was suggested for suicide. Compared with never use, the relative risk of suicide attempt rose twofold 1 month after initiation of hormonal contraceptive use, and the elevation in risk persisted with a decreasing trend after 1 year of use. The decrease in risk estimates for suicide attempt after 1 year of use was probably due to out-selection of women who develop adverse mood reactions after initiation of hormonal contraception. The women most sensitive to adverse mood reactions would thus be included in this former-user group. That circumstance is likely to explain why former use was associated with an increased risk of suicide attempt and suicide. This selection rather than their prior use of hormonal contraception more likely explains the higher relative risk of suicide attempts and suicide in former users.

Our data indicate that adolescent women are more sensitive than older women to the influence of hormonal contraceptive on risk of a first suicide attempt. This finding could be influenced by attrition of susceptible women, but also adolescent women are particularly vulnerable to risk factors for suicide attempt.

Several potential biological mechanisms have been suggested to explain how the two female sex hormones estrogen and progesterone are involved in the etiology of depressive symptoms (15–17). Because mood symptoms are a known reason for cessation of hormonal contraceptive use (9–11, 18, 19), cross-sectional studies are vulnerable to healthy-user bias, causing underestimation of a possible association between use of hormonal contraception and adverse mood reactions. Our recent study assessing the association between hormonal contraceptive use and risk of depression (1) found a 70% higher risk of depression among users of hormonal contraception compared with never-users. A recent double-blind randomized placebo-controlled study (20) found that women assigned to receive sex hormone manipulation with goserelin (a gonadotropin-releasing hormone agonist) experienced treatment-emergent subclinical depressive symptoms, and these symptoms were positively associated with the net decrease in estradiol levels.

Five studies (4–8) have assessed the association between use of hormonal contraception and risk of suicide (see Table S1 in the data supplement). Four of the studies found no statistically significant association between use of oral contraceptives and risk of suicide compared with never-users. The risk estimates were, however, above unity in three of these studies (5–7), while one study comparing users of oral contraception with users of diaphragm or intrauterine devices (4) found no elevation in the risk estimate. The other study, by Charlton et al. (8), assessed the largest number of events (241 suicides) and found a statistically significant association of 1.41 (95% CI=1.05–1.87). We found no studies

FIGURE 3. Risk of a First Suicide Attempt According to Duration of Hormonal Contraceptive Use Compared With Never Use^a



^aAge as underlying time, and adjusted for calendar year, education, polycystic ovary syndrome, and endometriosis.

assessing the association between hormonal contraceptive use and suicide attempt.

Strengths and Weaknesses

We assessed a nonselected cohort of women living in Denmark turning age 15 during the period of 1996–2013. By using data from the Danish national registers, we were able to follow these women for a mean of 8 years with no follow-up loss. The large study population allowed assessment of rare events such as suicide and suicide attempts. The information on redeemed prescriptions of hormonal contraception was obtained through bar codes from all Danish pharmacies, eliminating recall bias. It also allowed daily assessment of hormonal contraceptive use with time-dependent variables. Considering that the women paid for the contraception, the proportion of women not using the redeemed contraception is assumed to be minimal; moreover, the majority of women had repeated prescriptions and were assumed to be users only during the time the redeemed prescription was valid.

By using the personal identification number assigned to all persons in Denmark, which allows reliable linkage of data between different registers, we were able to ensure that we detected incident events of suicide attempt. Because suicide attempts are recorded by public hospitals when patients are brought in, independently of the patient's general practitioner and level of health insurance (all people in Denmark are covered by the public health insurance), it is unlikely that use of hormonal contraception would suggest better access to medical care and therefore a greater likelihood of a suicide attempt being recorded in the registers. Suicide attempts are known to be underreported (21), but there is no reason to believe that the underreporting would be distributed differently among users and never-users of hormonal contraception, so this circumstance is not likely to affect the associations assessed.

The Danish Cause of Death Register contains information on all residents who have died in Denmark since 1970. The legal regulation of death certification mandates that any case

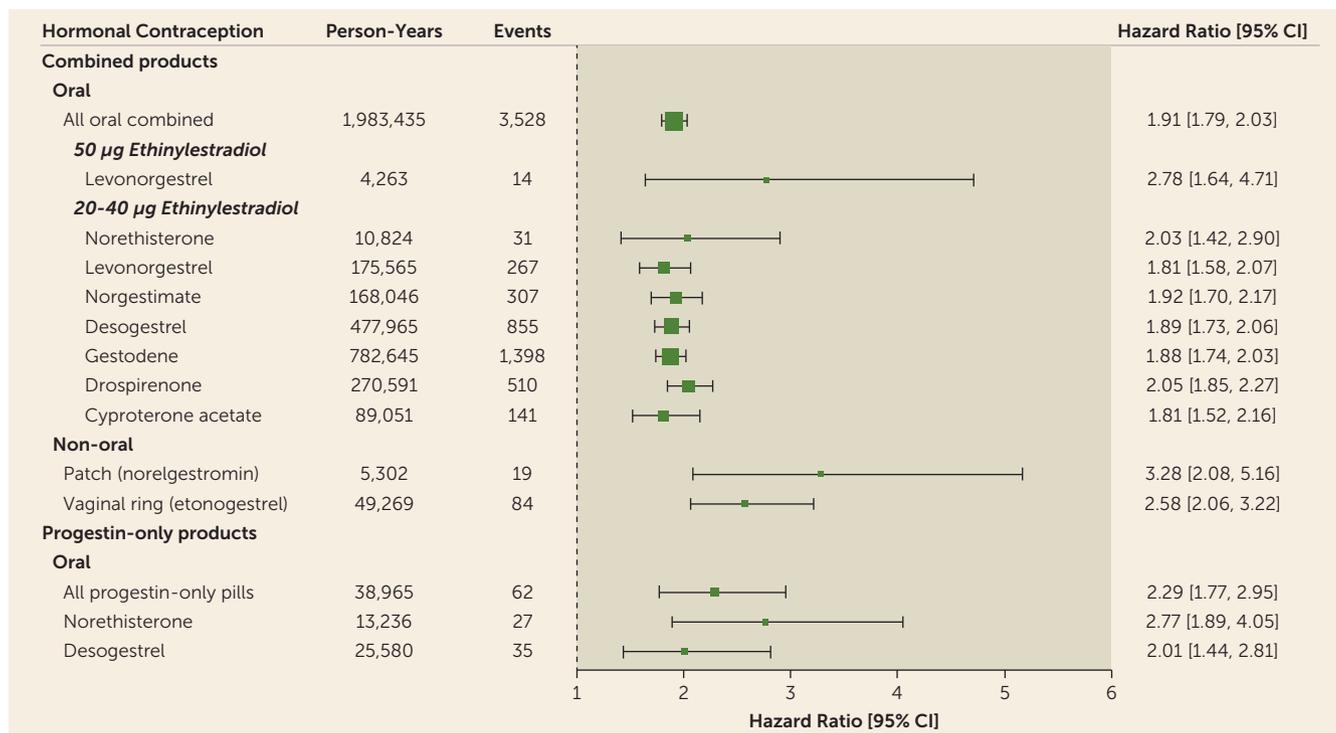
of sudden and unexpected death must be reported to the police, and the death certificate may be issued only after a medicolegal examination has been conducted. For a few deaths it is not possible to determine whether or not it was a suicide, but in most cases it is evident.

A potential confounding factor might be the initiation of a sexual relationship, since we speculate that this could influence the risk of a first suicide attempt or suicide. But with the results stratified into age groups, we still see a significant association between use of hormone contraception and suicide attempt for women over age 20, the majority of whom have had their first sexual relationship. Moreover, many women initiate use of hormonal contraceptives for their noncontraceptive benefits—to alleviate menstrual pain, heavy bleeding, premenstrual syndrome, and acne. Thus, initiation of sexual activity is by no means always the reason for prescription. Indeed, 50% of young Danes report that they became sexually active before age 17, and, of these, 69% used a condom their first time (22), which suggests that for many, sexual relationships start under use of contraceptive methods other than hormonal contraception. The reference group of never-users included women using a copper intrauterine device, women using barrier methods, and women relying on natural methods, such as rhythm methods and interrupted intercourse. Thus, this group also constitutes sexually active women. In short, sexual activity does not seem to be an important confounder for the relationship between use of hormonal contraception and suicide attempt or suicide.

The influence of postpartum depressions was diminished by censoring women temporarily during pregnancy and 6 months after delivery (23, 24). We were not able to adjust for parental suicide/suicide attempt, which is a known risk factor for suicide or suicide attempt (25, 26). To address this concern, we conducted a quantitative bias analysis to assess how strong and how common an unknown binary risk factor for suicide attempt should be if it explained our results. The analysis showed that the unknown risk factor should be very strong, with a high odds ratio for use of hormonal contraception and a prevalence in the study population of one-third, to be able to explain the observed association. We find it unlikely that there would be such a strong unmeasured confounder that at the same time had a prevalence of one-third in the population.

One could speculate on whether other risk factors for suicide or suicide attempt might be less common among the never-users of hormonal contraception, thereby potentially causing an overestimation of our results—for example, certain personality traits or religious subgroups causing both never use of hormonal contraception and a lower risk of suicide attempt (27, 28). In the youngest group of women, the never-user group will include a majority who begin hormonal contraceptive use later in life and are thus similar to the user group with respect to unknown confounders, except for time-dependent confounders. In the older age groups, it is possible that women who are still never-users could differ more from the users. However, our results did not show stronger associations among the older women, which indicates that our

FIGURE 4. Relative Risk of a First Suicide Attempt, by Type of Hormonal Contraceptive Currently Used, Compared With Never-Users^a



^a Age as underlying time, and adjusted for calendar year, education, polycystic ovary syndrome, and endometriosis.

results do not reflect overestimation due to a possible age-associated selection in the never-user group.

Our sample included only girls from the age of 15 who had no prior use of hormonal contraception. This was to avoid inclusion of a selected small group of girls who were sexually active at a very early age and received prescriptions for hormonal contraception for that reason. These girls might be at higher risk of adverse mood reactions. Women who might have a different hormonal contraceptive prescription pattern for other reasons (including various types of prior disease) that are potentially associated with the risk of adverse mood reactions or suicide attempts or suicide were excluded from the study.

Confounding by indication. Another concern could be confounding by indication. By adjusting for polycystic ovary syndrome and endometriosis, we tried to account for the increased use of hormonal contraception in these groups as well as an increased risk for depression. We expect that institutionalized women and women with either mental retardation or more severe psychiatric pathology would be more likely to receive long-acting reversible contraceptive products, such as medroxyprogesterone acetate depot, an intrauterine device with levonorgestrel, or implants. Therefore, we find confounding by indication likely and decided to omit these three specific products from the results in Figure 4. For the remaining products, women in these groups account for a vanishingly small fraction of all women using hormonal contraception. Women using combined hormonal contraception, progestin-only products, patch, or

vaginal ring are generally assumed to have similar characteristics (1), and the higher risk association among women using transdermal patch and vaginal ring compared with the corresponding pill is probably a question of dosage rather than of route of administration (29). For these products, we found confounding by indication unlikely.

Mediation through psychiatric diagnoses. Finally, in additional analyses we adjusted for any psychiatric diagnosis or use of antidepressants during follow-up and found a small influence with this adjustment on our results. The mediation analysis also establishes that the majority of the effect is not mediated through psychiatric diagnoses and antidepressant use, but this should be interpreted cautiously, as the mediator includes only diagnosed conditions before the suicide attempt, which will likely miss actual cases. This can be considered measurement error on the mediator, and it is well known (14).

It is reasonable to assume that some psychiatric disorders were unknown and untreated before the suicide attempt and that the mediated proportion is therefore higher than estimated, as patients with an untreated illness will not be included in our registers.

It is also possible that hormonal contraception may have a direct influence on the neurotransmitter and hypothalamic-pituitary-adrenal system involved in stress regulation and the neurobiology of suicidal behavior (30). This assumption is supported by Figure 3, which demonstrates a rapid increase in first suicide attempt after initiation of hormonal contraception.

Time-dependent confounders. We cannot exclude individual time-dependent confounders, such as other major life events (bad sexual experience, break-up, divorce, etc.), which could potentially confound the key associations.

Implications and Significance

Assuming that the demonstrated associations are causal, the absolute increase in events due to use of hormonal contraception in our study population of previously mentally healthy women would be 1,400 additional first suicide attempts and 12 additional suicides per 1 million person-years. More awareness of possible mood implications from exogenous female sex hormones is warranted. Considering the severity of these little-recognized potential side effects of hormonal contraceptives, health professionals and women starting hormonal contraceptives should be informed about them.

AUTHOR AND ARTICLE INFORMATION

From the Department of Gynecology and the Psychiatric Center Copenhagen, Rigshospitalet, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen; the Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen; and the Center for Statistical Science, Peking University, Beijing.

Address correspondence to Prof. Lidegaard (oejvind.lidegaard@regionh.dk).

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