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Oral contraceptive use and depression among adolescents

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ABSTRACT

Purpose: Depression is a prevalent health problem affecting U.S. women. Oral contraceptive pills (OCPs) are commonly used for pregnancy prevention, and evidence is mixed regarding any increased risk for incident depression among users, particularly adolescents.
Methods: We examined the relationship between OCP use and depressive disorders among female adolescents using validated, structured interview assessments in a general population sample of adolescents in the National Comorbidity Survey-Adolescent Supplement. Respondents were 4765 female adolescents with no history of pregnancy who reported current OCP use, lifetime OCP use, and age of OCP initiation. Lifetime and current depressive disorders, including major depressive disorder and depressive episodes, were assessed by lay interviewers.
Results: In logistic regression models adjusted for a range of confounders, there was no relationship between ever using OCPs and lifetime depressive disorder (OR 1.10, 95% CI 0.88–1.37), nor current use of OCPs and current depressive disorder (OR 0.82, 95% CI 0.50–1.35). Using survival analysis for age-of-onset data, we found that OCP use is not associated with an increased risk of depressive disorders.
Conclusions: In sum, use of OCPs in a general population sample of adolescents did not increase the risk of depressive disorders.

Introduction

Use of oral contraceptive pills (OCPs) is common: 80% of women in the United States report using OCPs [1]. OCPs are a popular choice due to their ease of use, variety of formulations, and desirable side effect profile [2]. Among young women, 22% of those aged 15–24 years report using any contraception, and OCPs are the most commonly used method [3]. Because OCP use is widespread, a small increased risk of detrimental effects can have a large clinical impact.

Women have twice the risk of depressive disorders as men [4, 5]. Evidence is needed for factors that are both more common among women and also may increase the risk of depressive disorders; such factors include exogenous hormone use [5]. OCPs contain estrogen and progesterone, both of which have purported associations with mood [6–9]. Therefore, it is of particular interest to understand whether users of OCPs may be at higher or lower risk for mood disorders, including depressive disorders, compared with nonusers.

There is no consensus on the role of OCPs in depressive disorders. Periods of estrogen instability—for example, puberty, the postpartum period, and perimenopause—show increased risk of depressive disorders. Some physicians recommend OCPs as off-label treatment for stabilizing mood or preventing depression, including among young women [10–13]. However, countervailing support suggests that initiating OCPs can lead to mood instability, which could either precipitate or exacerbate depression [14]. Mood changes are the most commonly complained side effect of OCPs and a common reason for discontinuing OCP use [15].

Two Swedish studies found that women prescribed OCPs were at increased risk for a subsequent prescription for antidepressants [16, 17]. A 2016 prospective study using the Danish drug registry found similar results [18]. Confounding by indication is a concern, namely that women may be more likely to be prescribed birth control pills to alleviate mood disorder symptoms, thus these same women are more likely to then develop depression [19]. Furthermore, both receiving a diagnosis of depression as well as receiving medication to treat depression unfortunately occurs among only a minority of individuals who experience depression; using registry

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data introduces misclassification. Therefore, the apparent relationship between OCP use and depression diagnoses could alternatively be explained by surveillance bias—women who regularly seek physicians' services are more likely to be prescribed medications in general [20]. Furthermore, individual-level confounders, such as sexual behavior, are not sufficiently accounted for in drug registries [21, 22].

Other observational studies showed OCPs may protect against depressive disorders; others show no relationship [23–27]. These studies include individuals from the community, account for covariates such as baseline depressive symptoms, and use validated depression screeners. One longitudinal study in Australia demonstrated that women who used OCPs for reasons other than birth control were more likely to experience depressive symptoms than those who used them solely for contraception; the authors suggested that associations between OCP use and increased risk of depressive disorder may be due to features of the OCP users, rather than the medications [26]. These studies are limited, although, by the possibility that women who start feeling depressed or having mood changes cease taking birth control [24,28–31]. Should this be the case, women taking OCPs for reasons other than contraception may be less likely to discontinue OCPs. Ultimately, there is not yet a consensus on whether OCPs increase or decrease depression risk, nor to what extent women's OCP use behaviors confound this relationship.

Most of this research focused on women ages 20–40 years, but depression is a debilitating illness for adolescents. It increases risk for suicide, academic difficulties, future unemployment, and criminal justice system involvement [32, 33]. Incidence of depression precipitously increases during adolescence, which is when sex differences in depression emerge [5]. The surge of physiologic sex steroids during adolescence has been hypothesized to be one driver of the female-male disparity in depression, but birth control use is often initiated during the adolescent years [5]. Coinciding with the increased risk of depression during this period, however, adolescents—especially those who experience early development—navigate sexual debut and many new social-relational insults including harassment, bullying, and sexual assault [34, 35]. To our knowledge, a single randomized controlled trial has examined OCP use and depression in adolescents, comparing OCP use with placebo use among adolescents with dysmenorrhea. It found no effect on depressive symptoms (mean exit-interview depressive symptoms score for placebo: 14.0; mean exit-interview depressive symptoms score for OCP users: 14.4; $P = 0.86$) [36].

The present study addresses the limited existing data on the OCP-depression relationship among adolescents. We examine whether OCP use is associated with increased risks of development of depression in adolescents. We consider behavioral factors that may confound the relationship, and we test the validity of the proposed mechanism between OCP use and depression.

Materials and methods

The present study examines the association between OCP use and depressive disorders in U.S. adolescents using the National Comorbidity Survey-Adolescent Supplement (NCS-A), which includes self-reported timing and duration of OCP use and timing of depressive episode onset using a structured interview. History and prevalence of depressive disorders is examined among adolescent women who ever have used OCPs, are currently using OCPs at the time of the interview, and lifetime and current nonusers. The NCS-A includes a wide range of potential confounding variables to include in our examination, including body mass index (BMI), age, smoking history, and age at first sexual intercourse.

The purported link between OCP use and depression is the action of sex steroids on the neural structures associated with emotion and cognition [6, 37]. To better understand the plausibility of the hypothesized physiological mechanism between the OCP use and depression, we consider effect modification by sexual activity. We assume that sexually active women would be more likely to be using birth control primarily for pregnancy prevention compared with nonsexually active women, who may be more likely to use OCPs for conditions such as acne control or management of polycystic ovarian or menstrual symptoms. If any association between depression and OCP use is attributable to sex steroids contained in OCPs, as previous scholars have hypothesized[6, 37], we expect an increased risk of depression among both OCP users who are sexually active and those who are not. Evidence that the relationship between OCP use and depression is modified by sexual activity would imply that the mechanism of association is not solely attributable to the physiologic action of hormones.

While this study examines the cross-sectional relationship between OCP use and depression, it may be that existing depression influences the decision to initiate OCP. To address this possibility of reverse causation, we use longitudinal methods with survival analysis to examine whether initiation of OCP use increases the subsequent reported onset of depression.

Data source

The NCS-A is a nationally representative, cross-sectional survey of 10,123 community-dwelling, school-enrolled male and female adolescents aged 13–18 years [38]. The survey was administered in 2001–2004. Data were collected using both computer and telephone interviews. Detailed information about mental health was collected in additional interviews with a parent or surrogate [39, 40]. Interviews were administered using computer-assisted personal interviewing, and both respondents and parents/surrogates received questionnaires with items related to mental health disorders. Parent questionnaires focused on only five adolescent disorders, including major depressive episode but not minor depression, irritable major depression, or irritable minor depression; adolescent questionnaires had a larger breadth of depressive disorders. In the case of a discrepancy between a respondent's and a parent's report of mental illness, reappraisal interviews were administered via telephone by trained clinical interviewers who carried out the interview first with the adolescent respondent.

Measures

Depressive disorders were assessed using the Composite International Diagnostic Interview version 3.0 [41]. A lifetime history of depressive disorder was measured as meeting criteria for major depression, minor depression, irritable major or minor depression, or a depressive episode. Current disorder included those who met criteria in the past 30 days; those who had a history of lifetime depression but did not meet qualifications for depression in the past 30 days were not considered to be currently depressed. Age of depressive disorder onset was determined by respondents' retrospective descriptions of age of onset of first qualifying condition, based on DSM-IV criteria for each condition.

Women were asked the following: "Have you ever taken birth control pills?"; "How old were you when you started taking birth control pills?"; "Do you still take them now?"; and, among former users, "How old were you when you stopped taking them?" Duration of use was measured as years from first exposure to OCPs. While discontinuation and restarting of OCP is frequent [42], we did not have detailed information and thus examined the entire span of

time from first exposure as a continuous predictor among current users. Among former users, duration of use was calculated by determining age at OCP initiation compared with age at OCP discontinuation.

We examined effect modification by sexual activity, measured as answering "yes" to the question, "Have you ever had sexual intercourse?" Those who had not had sexual debut were considered not sexually active.

Covariates included age, history of any cigarette smoking, age at sexual debut [43], BMI, and family socioeconomic status (SES). A participant was considered to have a positive smoking status if she ever smoked cigarettes; age at sexual debut was categorized as reporting sexual debut at age either younger than 13 years, ages 13–14 years, ages 15–16 years, or 17 years or older, with the reference group being those who had not reported sexual debut; in analyses stratified by sexual activity, the reference group was aged 13–14 years for those who were sexually active, and age at sexual debut was not included in models which were restricted to those who were not sexually active. BMI was categorized as underweight, normal weight, overweight, or obese as determined by age-standardized growth charts for adolescents [44]. Family SES was continuously measured as the ratio of family income, as reported by interviewee's parent, to the U.S. federal poverty thresholds for family size; for example, a family of four with an income exactly at the federal poverty level for that family size would be given a value of 1.0. Families in excess of the poverty threshold have values greater than 1.0, and families below the poverty threshold have values less than 1.0.

Analytic approach

Logistic regression was used to examine the relationships between current and lifetime OCP use with both lifetime and current depressive disorders. Results were stratified according sexual activity, defined as whether participants had or had not experienced sexual debut. Significance of sexual activity by OCP interactions was assessed using Wald χ^2 tests for multiplicative interaction.

To assess the temporality, we used Cox proportional hazards regression using age of first OCP use and age of depression onset. We matched ever users without a history of depression at age of OCP initiation to same-aged never users without a history of depression. These pairs were also matched on age of sexual debut. We followed the matched pair to examine if time to depression onset varied based on history of OCP use. Analyses were performed in SAS 9.4.

Results

Of the 5062 eligible women, 186 had missing OCP data, 94 had missing sexual activity data, and 17 had missing covariate information. Among the 297 women excluded due to missing data, 56 (19%) met the criteria for lifetime depression, and 11 (4%) met the criteria for current depression.

Of the remaining 4765 women, 671 (14%) respondents reported ever using OCPs, and of those, 405 women reported current use. Regarding the outcome, 871 women (18%) met the criteria for a history of lifetime depression. Of these, 202 (23% of those with lifetime depression, or 4% of the entire analytic sample) had current depression.

Table 1 shows demographics and covariates by OCP use. The mean age at the time of interview was 15.2 years. OCP users were older than nonusers, experienced earlier sexual debut, and a higher percentage had smoked.

As shown in Table 2, we observed an increased odds of lifetime depressive disorder among current users and ever users before covariate adjustment (OR for ever users = 1.86, 95% CI 1.54–2.24; OR for current users = 1.60, 95% CI 1.26–2.02). Examining current depressive disorders, we similarly saw an increased crude risk (OR for ever users = 1.34, 95% CI 0.92–1.94; OR for current users = 1.26, 95% CI 0.79–2.01). However, there was no evidence of an association between using OCPs (current or ever use) and lifetime or current depressive disorders in our fully adjusted models (for lifetime: adjusted OR for ever users = 1.10, 95% CI 0.88–1.37; for current: adjusted OR for current users = 1.00, 95% CI 0.77–1.29). Table 2 shows the relative impact of each confounder on the association between OCP and depression. Age at sexual debut had the largest impact on effect size, followed by age.

After stratifying by history of sexual activity (Table 3), we found no evidence of effect modification. The direction of effects across were not consistent in all models when we stratified by sexual activity. However, in all adjusted models, we found no effect of OCP use on depression. Among sexually active users, the direction of effect was slightly negative but insignificant (for lifetime: adjusted OR for ever users = 0.89, 95% CI 0.65–1.23; for current, adjusted OR for current users = 0.70, 95% CI 0.38–1.30). Among those who were not sexually active, the unadjusted and adjusted associations were slightly positive in the direction of effect but were all also consistently null. We performed a sensitivity analysis examining the association between years since the first use of OCP and depression; similarly, we found no association between years since OCP initiation and development of depression, in adjusted models or stratified by sexual history.

Table 1
Study sample characteristics among never pregnant female NCS-A respondents with complete covariate information

Measure	Women who ever used OCPs (n = 671)	Women who never used OCPs (n = 4094)	Total sample (n = 4765)
Current OCP users N (column %)	405 (60%)	N/A	405 (8%)
Mean age N (column %)	16.3 years (SD 1.14)	15.0 years (SD 1.40)	15.2 years (SD 1.46)
Smoking history N (column %)	247 (37%)	525 (13%)	772 (16%)
Age at sexual debut N (column %)			
< 13 years	23 (3%)	30 (1%)	53 (1%)
13 or 14 years	121 (18%)	164 (4%)	285 (6%)
15 or 16 years	237 (35%)	297 (7%)	534 (11%)
17 years	49 (7%)	50 (1%)	99 (2%)
N/A (Not sexually active)	241 (36%)	3553 (87%)	3794 (80%)
BMI category N (column %)			
Underweight	49 (7%)	390 (10%)	439 (9%)
Normal weight	519 (77%)	3129 (76%)	3648 (77%)
Overweight	64 (10%)	383 (9%)	447 (9%)
Obese	39 (6%)	192 (5%)	231 (5%)
Mean ratio of family income to poverty line	6.61 (SD 9.20)	6.11 (SD 7.85)	6.18 (SD 8.06)

Table 2
Unadjusted and adjusted relationships between OCP use and depressive disorder

Model	OR for ever having a depressive disorder versus never		OR for having current depressive disorder versus no current depressive disorder	
	Current users versus nonusers	Ever users versus never users	Current users versus nonusers	Ever users versus never users
	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
Unadjusted association	1.60 (1.26–2.02)	1.86 (1.54–2.24)	1.26 (0.79–2.01)	1.34 (0.92–1.94)
Adjusted for age	1.29 (1.01–1.65)	1.52 (1.24–1.86)	1.08 (0.67–1.73)	1.14 (0.77–1.68)
Adjusted for smoking history	1.33 (1.04–1.69)	1.52 (1.25–1.85)	1.03 (0.64–1.65)	1.05 (0.72–1.55)
Adjusted for BMI category	1.59 (1.25–2.02)	1.85 (1.53–2.23)	1.26 (0.79–2.01)	1.33 (0.92–1.93)
Adjusted for age at sexual debut	1.11 (0.86–1.43)	1.28 (1.03–1.58)	0.88 (0.54–1.44)	0.90 (0.59–1.36)
Adjusted for SES	1.59 (1.26–2.02)	1.85 (1.54–2.24)	1.27 (0.80–2.01)	1.35 (0.93–1.95)
Adjusted for all	1.00 (0.77–1.29)	1.10 (0.88–1.37)	0.82 (0.50–1.35)	0.80 (0.53–1.22)

Finally, Cox proportional hazards regression was used to test whether OCP ever users had a higher hazard of developing depression compared with nonusers (Table 4). OCP ever users were matched to never users by age and age of sexual debut, and they were followed from age OCP initiation for ever users to depression onset. We used simple random sampling without replacement and restricted matched participants to those who did not experience depression before the matched age of OCP initiation, or matched age among never users. The analytic sample for the matched analysis was 820 (n = 410 ever users, 410 never users). We estimated the hazard of depression from the point of OCP initiation or matching, adjusting for smoking history, BMI category, and SES. We found no relationship between OCP use and risk of depression (adjusted HR: 1.15, 95% CI 0.73–1.81).

Discussion

This study examined the relationship between use of OCPs and depressive disorders among U.S. women ages 13 to 18 years. In unadjusted models, we found increased odds of both current and lifetime depressive disorders among ever users compared with never users and among current users compared with nonusers. However, we found that these crude associations were explained by confounding: OCP users were more likely to be older, to have had sex at a younger age, and to use cigarettes than nonusers. In our examination of effect modification, we saw no meaningful differences in effect between women who were sexually active and those who were not, but we also saw no effect. Thus, we did not find evidence for the hypothesized physiologic mechanism linking OCP use to depression. Consistent with our logistic models, our matched survival analysis showed no association between OCP use and depression. Taken together, we conclude that we do not have evidence that OCPs are associated with development of depressive disorders.

These findings conflict with previous research using drug registry data, which showed that OCP use increases depression risk [16–18]. We believe behavioral patterns associated with diverse health effects have contributed to findings of the apparent risks observed in previous research, particularly among studies that were unable to sufficiently control for behavioral factors such as sexual debut and smoking. Positive association in other samples [16, 18] could be the result of confounding due to behavioral and social risk factors that increase the risk of both using OCPs and developing depressive disorders, such as precocious sexual behavior [45] and smoking [35]. Skovlund et al. (2016) found a strong positive association between OCP use and antidepressant use in the Danish drug registry: among the teenagers in their sample, current OCP users had an RR of antidepressant use of 1.8 compared with nonusers [18]. In our unadjusted association, we found a similar trend, with an OR for depressive disorder of 1.6 comparing current users with nonusers. However, this association in our sample was explained by confounding, in particular age of sexual debut. While Skovlund controlled for some individual-level covariates, such as age, education, health conditions, and BMI, our inclusion of measures of sexual activity, such as age at sexual debut, showed that behavioral factors explained the apparent risk.

While the present findings conflict with studies which used drug registry data, they are, however, consistent with other observational studies that use survey data and self-reported symptoms. Cheslack-Postava, for example, found OCPs to be either unassociated with or protective against multiple subthreshold mood disorders [23]. A 2011 study of Finnish women found that OCP use modestly protected against most psychiatric disorders [25]. A 2013 study using data from the National Longitudinal Study of Adolescent Health found that OCP use protected against depressive symptoms among U.S. women aged 25–34 years [24]. None of these studies focused on women in their teenage

Table 3
Association between OCP use and depressive disorder, stratified by history of sexual activity

Exposure group	OR for ever having a depressive disorder versus never		OR for having current depressive disorder versus no current depressive disorder	
	Current users versus nonusers	Ever users versus never users	Current users versus nonusers	Ever users versus never users
	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
Adjusted association among sexually active respondents*	0.89 (0.65–1.23)	1.14 (0.85–1.52)	0.70 (0.38–1.30)	0.69 (0.40–1.16)
Adjusted association among sexually inactive respondents*	1.20 (0.79–1.82)	1.07 (0.75–1.51)	1.08 (0.48–2.41)	1.07 (0.56–2.06)
	Maximum likelihood estimate for interaction term of current use and sexual activity in adjusted model			
	$\chi^2 = 1.486$ df = 1 $P = 0.223$	$\chi^2 = 0.0051$ df = 1 $P = 0.943$	$\chi^2 = 1.169$ df = 1 $P = 0.280$	$\chi^2 = 1.717$ df = 1 $P = 0.190$

* Adjusted for age, smoking history, BMI category, age at sexual debut (among sexually active respondents), SES.

Table 4
Hazard ratio of developing depression comparing OCP ever users with never users, matching ever users at age of OCP initiation to never users with same age at sexual debut ($n = 820$)

Exposure group	HR* for developing depressive disorder ($n = 86$) (95% CI)	AHR† for developing depressive disorder ($n = 86$) (95% CI)
Ever OCP users ($n = 410$) versus never users ($n = 410$)	1.05 (0.69–1.60)	1.15 (0.73–1.81)

* Hazard ratio, latter group is reference group.
† Adjusted hazard ratio; matched on age at sexual debut and age at OCP initiation for ever users, then further adjusted for smoking history, BMI category, SES.

years, and our findings show that this group is not dissimilar from women of other ages.

Inconsistencies between drug registry research demonstrating an increased risk and survey research showing no, or protective, associations, may be attributable to measurement of the outcome. Skovlund et al. examined not only antidepressant use but also medical discharge coding for depression and found the relationship to be much more modest, suggesting that antidepressant use is a poor proxy for an actual depression diagnosis. Both medical coding for depression and use of antidepressants require contact with a medical provider, leading to the potential risks of surveillance bias or confounding by indication. Our study's use of validated depression screeners to assess depressive disorders among community-based respondents, like others than have used this approach, are not as vulnerable to these threats to validity.

Limitations and further considerations

This study examined adolescents among whom initiation of contraceptive use is relatively recent compared with adults. Overall, 14% of our sample used OCPs. The average duration of use was 1 year in these data, which may not be a sufficient latency period to detect an association if one exists. Most research, however, shows that mood instability because of OCPs use is short-lived: Skovlund et al. [18] demonstrated that associations between OCP use and depression were strongest within the first 6–12 months after OCP usage began and attenuated with time. In our study sample, depression was ascertained in the past 30 days, the past year, and lifetime, whereas OCP use was ascertained by age of first use, age at current use, and age at discontinuation; therefore, we were unable to precisely estimate depression onset within 6–12 months of OCP initiation. Furthermore, most mood disorders in the United States occur between the ages of 18 and 43 years [46]. Although 18% of women in our sample met criteria for depressive disorders, more of them will develop depression as time progresses. We do not know how and under what circumstances these teenage exposures impact illnesses that are acquired as adults.

While the breadth and depth of the instrument used in the NCS-A is exceptional, sexual history was queried about age of first sex but not whether participants were currently sexually active, and we did not have information on the indication for birth control use (e.g., pregnancy prevention vs. another reason such as acne control). We used sexual debut to stratify women by the history of sexual activity and found no association; but sexually inactive women who have experienced debut may have been misclassified as currently sexually active due to the limitations of this measure. This misclassification likely only effected analyses that examined effect modification through stratifying by sexual activity history, as whether or not a woman has experienced sexual debut and at what age is unlikely to be misremembered or misreported.

Our measures of OCP use allowed us to estimate duration of use from onset to the nearest year, but we did not have information on periods of discontinuation between onset and most recent use. In addition, there are many types of birth control, both hormonal and not [47]. Previous studies suggest that contraception types vary in their associations with depression [24], but this survey did not have sufficient detail to explore that relationship.

Conclusion

This study found no increased risk of depressive disorders among OCP users, in contrast with drug registry studies but consistent with other studies using individual-level survey data and validated screening tools. Women deciding among birth control must weigh the risks and benefits of the side effects. Advancing information about these medications is paramount for women to make informed health decisions. The use of OCPs is a politically and culturally contentious topic and is subject to barriers such as misinformation, stigma, and shame [48]. Similarly, depression is a stigmatized illness [49, 50]. While it is important to fully understand the impact of such a common exposure, as well as the risk factors for such a common and debilitating disease, such findings can have far-reaching consequences.

While young women who experience mood disturbances while using OCPs should be consulting physicians, there is insufficient evidence to raise concern about depressive disorders among adolescents who use birth control. Use of birth control has numerous beneficial outcomes [51–54]. The impact of reducing pregnancy among teenagers has both individual and social benefits, on both health and well-being [55–57]. Indeed, one of the most well-substantiated increased depression risks for women is pregnancy [58–62]. Expanded access to safe and effective methods of birth control continues to be an important public health priority.

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