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Association of Use of Oral Contraceptives With Depressive Symptoms Among Adolescents and Young Women

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IMPORTANCE Oral contraceptives have been associated with an increased risk of subsequent clinical depression in adolescents. However, the association of oral contraceptive use with concurrent depressive symptoms remains unclear.

OBJECTIVES To investigate the association between oral contraceptive use and depressive symptoms and to examine whether this association is affected by age and which specific symptoms are associated with oral contraceptive use.

DESIGN, SETTING, AND PARTICIPANTS Data from the third to sixth wave of the prospective cohort study Tracking Adolescents' Individual Lives Survey (TRAILS), conducted from September 1, 2005, to December 31, 2016, among females aged 16 to 25 years who had filled out at least 1 and up to 4 assessments of oral contraceptive use, were used. Data analysis was performed from March 1, 2017, to May 31, 2019.

EXPOSURE Oral contraceptive use at 16, 19, 22, and 25 years of age.

MAIN OUTCOMES AND MEASURES Depressive symptoms were assessed by the *DSM-IV*–oriented affective problems scale of the Youth (aged 16 years) and Adult Self-Report (aged 19, 22, and 25 years).

RESULTS Data from a total of 1010 girls (743-903 girls, depending on the wave) were analyzed (mean [SD] age at the first assessment of oral contraceptive use, 16.3 [0.7]; (mean [SD] age at the final assessment of oral contraceptive use, 25.6 [0.6] years). Oral contraceptive users particularly differed from nonusers at age 16 years, with nonusers having a higher mean (SD) socioeconomic status (0.17 [0.78] vs −0.15 [0.71]) and more often being virgins (424 of 533 [79.5%] vs 74 of 303 [24.4%]). Although all users combined (mean [SD] ages, 16.3 [0.7] to 25.6 [0.6] years) did not show higher depressive symptom scores compared with nonusers, adolescent users (mean [SD] age, 16.5 [0.7] years) reported higher depressive symptom scores compared with their nonusing counterparts (mean [SD] age, 16.1 [0.6] years) (mean [SD] score, 0.40 [0.30] vs 0.33 [0.30]), which persisted after adjustment for age, socioeconomic status and ethnicity (β coefficient for interaction with age, −0.021; 95% CI, −0.038 to −0.005; $P = .0096$). Adolescent contraceptive users particularly reported more crying (odds ratio, 1.89; 95% CI, 1.38-2.58; $P < .001$), hypersomnia (odds ratio, 1.68; 95% CI, 1.14-2.48; $P = .006$), and more eating problems (odds ratio, 1.54; 95% CI, 1.13-2.10; $P = .009$) than nonusers.

CONCLUSIONS AND RELEVANCE Although oral contraceptive use showed no association with depressive symptoms when all age groups were combined, 16-year-old girls reported higher depressive symptom scores when using oral contraceptives. Monitoring depressive symptoms in adolescents who are using oral contraceptives is important, as the use of oral contraceptives may affect their quality of life and put them at risk for nonadherence.

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Supplemental content

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Oral contraceptive pills (OCPs) are often used by women to prevent pregnancies or diminish menstrual symptoms. Successful fertility control engenders many social and economic benefits for women, such as better education and personal autonomy.[1] However, 32% to 60% of women discontinue OCP use within 6 months for varying reasons, including mood changes.[2-4] Research findings regarding OCP use and concurrent mood changes are inconsistent, and range from improved mood or having fewer mood swings[5-11] to worsened mood[12-17] or having no effect at all.[18-25] These results suggest that some women may benefit from OCP use whereas others do not, or are even negatively affected.

The above-described heterogeneity in findings may be related to differences in study populations, as previous research showed that the incidence of adverse OCP effects may depend on age. In a large Swedish population-based observational study, adolescents were more likely than adult women to subsequently start using psychotropic drugs after initiation of OCP use.[26] A comparable pattern was found in a Danish observational study that showed that adolescents were more prone than adult women to seek psychiatric help when using OCPs.[12] This finding suggests that the first onset of clinical depression associated with OCP use is particularly salient during early adolescence. Whether this phenomenon also holds true for the concurrent presence of depressive symptoms is unknown. Alternatively, the inconsistent results might also be because of the use of diverse (unvalidated) mood questionnaires.[27] Assessment of separate symptoms with validated questionnaires is of interest, as a randomized clinical trial revealed that OCP use increased mood swings and irritability symptoms, but improved depressive symptoms.[28]

Therefore, we aimed to examine the associations between OCP use and concurrent depressive symptoms, test whether these associations are affected by adolescence, and determine which particular symptoms—if any—are associated with OCP use. We used data from a large longitudinal survey of adolescents in the Netherlands, including 1010 adolescent girls whose depressive symptoms were assessed using validated and sensitive questionnaires for depressive symptoms in up to 4 waves for 9 years.[29]

Key Points

Question What is the association between oral contraceptive use and concurrent depressive symptoms in adolescents and young women?

Findings In this cohort study of 1010 adolescents followed up for 9 years, 16-year-old oral contraceptive users showed higher concurrent depressive symptom scores compared with their counterparts not using oral contraceptives. Oral contraceptive users particularly reported more crying, eating problems, and hypersomnia compared with nonusers.

Meaning It is important to monitor for depressive symptoms in adolescents who are using oral contraceptives, as it may affect their quality of life and put them at risk for nonadherence.

Methods

Study Population

Data were derived from the Dutch population survey TRAILS (Tracking Adolescents' Individual Lives Survey), conducted from September 1, 2005, to December 31, 2016. TRAILS is a large prospective cohort designed to investigate the psychological, social, and physical development of adolescents. Children were recruited from primary schools in 2001 and 2002.[30] Exclusion criteria were serious health or language problems that would hamper full participation in the study. In total, 2230 children (mean [SD] age, 11.1 [0.6] years; 1137 girls) were enrolled in the study. After baseline assessment, children were followed up at the median ages of 13 (T2), 16 (T3), 19 (T4), 22 (T5), and 25 (T6) years.[31] All follow-up assessments had good retention rates (the proportion of the baseline sample) of 96.4% (2149 of 2230; T2), 81.4% (1816 of 2230; T3), 84.3% (1881 of 2230; T4), 79.7% (1778 of 2230; T5), and 72.6% (1618 of 2230; T6). The present study included girls and young women who had filled out at least 1 and up to 4 assessments of oral contraceptive use and depressive symptoms from wave T3 to T6 (ages, 16-25 years). Oral contraceptive pill use was assessed at waves T3 to T6 with the question: "Do you use an oral contraceptive pill?" and as part of a medication list provided by the participants. Fourteen data points were excluded owing to discrepancies between the OCP use question and the medication list. An additional 37 observations were excluded as participants were using sex steroids other than OCPs or were pregnant at that point. These exclusions resulted in a final sample of 3317 data points from 1010 girls and young women (mean, 3.3 observations per participant). Excluded participants (T3, 107 of 952 [11.2%]; T4, 80 of 983 [8.1%]; T5, 111 of 937 [11.8%]; T6, 49 of 792 [6.2%]) more often had a non-Dutch ancestry (percentile difference, 5.3% at age 16 years; 8.2% at age 19 years; 8.4% at age 22 years; 9.3% at age 25 years) and a lower socioeconomic status (SES) (difference in SES score, 0.34 at age 16 years; 0.39 at age 19 years; 0.42 at age 22 years; 0.40 at age 25 years) than included girls at all waves (eTable 1 in the Supplement). The national ethical Central Committee on Research Involving Human Subjects approved the study design. At baseline (T1) parents provided written consent and children provided oral assent. At wave T2 and T3, both parents and children provided written consent and assent for participation in the new wave. From T4 to T6, children were at least 18 years of age and provided written consent.

Depressive Symptoms

Depressive symptom scores at age 16 years were assessed with the *DSM-IV*-oriented affective problems scale of the Youth Self-Report.[32] This self-report version of the Child Behavior Checklist consists of items on crying, eating, sleeping, suicidal ideation, self-harm, feelings of worthlessness and guilt, energy, activity, sadness, and anhedonia. Items were rated as 0 = not true, 1 = a little or sometimes true, or 2 = very or often true for the preceding 6 months. At ages 19, 22, and 25 years, depressive symptoms were assessed with the affective problems scale of the Adult Self-Report,[33] the adult version of the Youth Self-Report. This scale includes the above-mentioned items plus 2 items on decision-making and feelings of not being

able to succeed. The scale scores represent the mean item scores (range, 0-2), with a score of more than 1 corresponding closely to the *DSM-IV* criteria for major depressive disorder.[34] Cronbach α in our samples were 0.78 at age 16 years, 0.84 at age 19 years, 0.85 at age 22 years, and 0.87 at age 25 years.

Statistical Analysis

Statistical analysis was performed from March 1, 2017, to May 31, 2019. Population characteristics of OCP users and nonusers were compared by mean values of χ^2 tests or *t* tests, depending on the type of variable. First, the association between OCP use and depressive symptoms was examined with a linear mixed model considering OCP use as a fixed factor. A random intercept and random slope were added to the model as they lowered the Akaike information criterion. The random intercept accounted for between-participant variability of depressive symptoms and the random slope (modeled by age) allowed for individual slopes for depressive symptoms over time. Mixed models with different covariance structures were fitted using restricted maximum likelihood estimation and, in this case, variance components was chosen based on the Akaike information criterion. The final model was estimated with maximum likelihood estimation. Second, the interaction term age × OCP use was added to the model to investigate whether age modified the association. Stratified analyses were performed to examine the association per age category using linear regression analyses. Third, associations between OCP use and specific depressive symptoms were determined using binary logistic regression analyses in the age groups that showed significance in the interaction analysis.

Exploratory Analyses

Women who experience psychological adverse effects are more likely to discontinue their OCP use (the "healthy survivor effect").[26] As this healthy survivor effect would underestimate the association between OCP use and depressive symptoms, the same mixed model was repeated in girls who had never used OCP before, in comparison with never users. As an alternative approach, duration of use (0, no OCP use; 1, 1 month-3 years; 2, 3-6 years; 3, 6-9 years, and 4, 9-12 years, based on the number of subsequent assessments with reported OCP use) was added to the model as a covariate. To explore whether the potential association between OCP use and depressive symptoms could be bidirectional, we adjusted the association between OCP use and depressive symptoms at age 16 years for depressive symptom scores at age 13 years (T2).

All analyses were conducted with and without adjustment for age (time varying), SES, and ethnicity. Age was centered and divided by 3 to ease interpretation for the effect per each 3-year increase in age. Socioeconomic status was assessed on a continuous scale based on the educational level, job, and income of the parents at study entry, with higher values indicating a better social and economic position. Ethnicity was categorized as having a Dutch or non-Dutch ancestry.

Data were analyzed using IBM SPSS Statistics, version 24 (IBM Corp) using 2-sided tests. $P < .01$ for the main analyses and $P < .05$ for the exploratory analyses were considered statistically significant.

Results

Data from 743 to 903 girls, depending on the wave, were used for the analyses. Girls had a mean (SD) age of 16.3 (0.7) years at the first assessment of OCP use (T3) and 25.6 (0.6) years at the final assessment (T6). Descriptive statistics of OCP users and nonusers are shown in the **Table**. Oral contraceptive pill users differed particularly from nonusers at age 16 years. During this assessment, nonusers had a higher mean (SD) SES than users (0.17 [0.78] vs -0.15 [0.71]), were more likely to be of non-Dutch ethnicity (76 of 536 [14.2%] vs 24 of 309 [7.8%]), and were more likely to be virgins (424 of 533 [79.5%] vs 74 of 303 [24.4%]).

For the cohort as a whole, OCP use was not associated with higher adjusted mean scores on depressive symptoms (β coefficient, 0.006; 95% CI, -0.013 to 0.025; $P = .52$) (eTable 2 in the Supplement). As depicted in **Figure 1**, age significantly affected the association (β coefficient for age × OCP use, -0.021; 95% CI, -0.038 to -0.005; $P = .0096$); this association was driven by differences in 16-year-old girls. At this age, girls who used OCP had higher concurrent depressive symptom scores than their nonusing counterparts (mean [SD] score, 0.40 [0.30] vs 0.33 [0.30]; β coefficient, 0.075; 95% CI, 0.033-0.120; $P < .001$). The depressive symptom item scores at age 16 years are depicted in **Figure 2**. Use of OCPs was associated with more crying (odds ratio, 1.89; 95% CI, 1.38-2.58; $P < .001$), eating problems (odds ratio, 1.54; 95% CI, 1.13-2.10; $P = .009$), and hypersomnia (odds ratio, 1.68; 95% CI, 1.14-2.48; $P = .006$) compared with nonusers.

Exploratory Analyses

Excluding girls who used OCP previously (regardless of whether they continued or discontinued use) strengthened the association between OCP use and depressive symptoms for the whole cohort (β coefficient for first-time OCP use, 0.021; 95% CI, -0.005 to 0.046; $P = .11$) (eTable 2 in the Supplement). Also, long-term OCP use (up to 3, 6, 9, and 12 years) decreased the likelihood of higher depressive symptoms scores, although this finding was not significant (β coefficient, -0.007; 95% CI, -0.024 to 0.009; $P = .39$). Adjustment for depressive symptom scores before OCP use weakened the association in 16-year-old girls (β coefficient for OCP use, 0.040; 95% CI, 0.001-0.079; $P = .046$).

Post Hoc Analyses

To investigate whether the age-specific association may be explained by residual confounding or preexisting differences, we explored which differences between OCP users and nonusers were already present at the age of 13 years, when OCP use was unlikely. At age 13 years, the 16-year-old user group was more often sexually active, experienced more stressful events, and more often had menstrual-related pain and acne than the 16-year-old nonuser group (eTable 3 in the Supplement). In subsequent analyses, these factors were added one by one to the adjusted model (that already included age, ethnicity, and SES) to examine whether they individually affected the association. All 4 factors weakened the association (change in

Table. Sociodemographic and Clinical Characteristics of the Participants per Wave

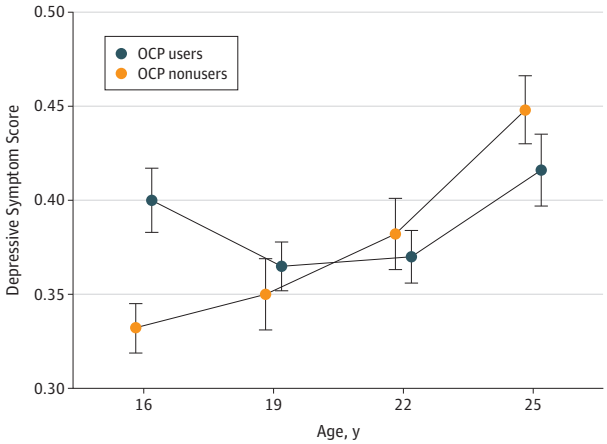
Characteristic	16 y of Age			19 y of Age			22 y of Age			25 y of Age		
	No OCP Use (n = 536)	OCP Use (n = 309)	*P* Value[a]	No OCP Use (n = 290)	OCP Use (n = 613)	*P* Value[a]	No OCP Use (n = 283)	OCP Use (n = 543)	*P* Value[a]	No OCP Use (n = 398)	OCP Use (n = 345)	*P* Value[a]
Age, mean (SD), y	16.1 (0.6)	16.5 (0.7)	<.001	18.9 (0.6)	19.0 (0.6)	.01	22.3 (0.6)	22.2 (0.7)	.004	25.6 (0.6)	25.6 (0.6)	.55
Dutch ethnicity, No./total No. (%)	460/536 (85.8)	285/309 (92.2)	.006	235/290 (81.0)	564/613 (92.0)	<.001	235/283 (83.0)	501/543 (92.3)	<.001	352/398 (88.4)	317/345 (91.9)	.14
SES, mean (SD)[b]	0.17 (0.78)	−0.15 (0.71)	<.001	0.11 (0.77)	0.03 (0.76)	.15	0.03 (0.78)	0.12 (0.74)	.13	0.07 (0.77)	0.16 (0.74)	.09
BMI, mean (SD)	21.5 (3.1)	22.0 (3.1)	.01	23.3 (4.3)	23.0 (3.7)	.26	24.1 (4.7)	23.6 (4.2)	.12	24.1 (4.7)	24.0 (4.8)	.58
Virgin, No./total No. (%)	424/533 (79.5)	74/303 (24.4)	<.001	157/287 (54.7)	85/613 (13.9)	<.001	54/283 (19.1)	44/542 (8.1)	<.001	25/395 (6.3)	17/344 (4.9)	.43
Age at menarche, mean (SD), y	13.0 (1.2)	12.6 (1.1)	<.001	12.9 (1.2)	12.9 (1.1)	.97	12.8 (1.2)	12.9 (1.1)	.50	12.8 (1.1)	13.0 (1.1)	.01
Antidepressant use, No./total No. (%)	0/536 (0.0)	1/308 (0.3)	.37	4/290 (1.4)	6/613 (1.0)	.74	11/283 (2.0)	11/543 (2.0)	.17	16/398 (4.0)	15/345 (4.3)	.86
Outcome measures, No./total No. (%)												
Depressive Symptom Score, mean (SD)	0.33 (0.30)	0.40 (0.30)	.001	0.36 (0.34)	0.36 (0.32)	.96	0.39 (0.34)	0.37 (0.32)	.29	0.45 (0.37)	0.42 (0.34)	.19
Sadness	184/535 (34.4)	196/304 (35.5)	.76	106/290 (36.6)	231/613 (37.7)	.77	100/283 (35.3)	178/542 (32.8)	.49	182/398 (45.7)	146/345 (42.3)	.37
Anhedonia	89/534 (16.7)	63/306 (20.6)	.16	39/290 (13.4)	99/613 (16.2)	.32	46/283 (16.3)	72/542 (13.3)	.25	91/398 (22.9)	53/345 (15.4)	.01
Worthlessness	129/534 (24.2)	72/306 (23.5)	.87	80/289 (27.7)	139/613 (22.7)	.11	84/283 (29.7)	137/543 (25.2)	.19	140/398 (35.2)	101/345 (29.3)	.10
Inappropriate guilt	132/533 (24.8)	70/306 (22.9)	.56	60/290 (20.7)	110/613 (17.9)	.36	60/283 (21.2)	100/542 (18.5)	.35	109/398 (27.4)	72/345 (20.9)	.04
Indecisiveness	NA	NA	NA	150/290 (51.7)	286/613 (46.7)	.18	131/283 (46.3)	266/542 (49.1)	.46	225/398 (56.5)	181/345 (52.5)	.27
Tiredness	277/534 (51.9)	183/305 (60.0)	.03	121/290 (41.7)	301/613 (49.1)	.04	142/283 (50.2)	321/542 (59.2)	.02	229/398 (57.2)	217/345 (62.9)	.15
Loss of energy	242/535 (45.2)	160/306 (52.3)	.05	123/290 (42.4)	285/613 (46.5)	.25	150/283 (53.0)	261/542 (48.2)	.19	224/398 (56.3)	203/345 (58.8)	.50
Insomnia	181/536 (33.8)	120/305 (39.3)	.12	96/290 (33.1)	214/613 (34.9)	.60	139/282 (49.3)	214/542 (39.5)	.008	158/398 (39.7)	142/345 (41.2)	.71
Hypersomnia	77/535 (14.4)	73/304 (24.0)	<.001	77/290 (26.6)	177/613 (28.9)	.48	71/282 (25.2)	149/541 (27.5)	.51	118/398 (29.6)	115/345 (33.3)	.30
Eating problems	225/536 (42.0)	144/305 (47.2)	.15	119/290 (41.0)	257/613 (41.9)	.83	120/283 (42.4)	216/543 (39.8)	.50	198/398 (49.7)	175/345 (50.7)	.83
Not succeeding	NA	NA	NA	101/290 (34.8)	171/613 (27.9)	.04	95/283 (33.6)	146/542 (26.9)	.05	175/398 (44.0)	109/345 (31.6)	<.001
Self-harm	32/536 (6.0)	21/306 (6.9)	.66	15/290 (5.2)	16/613 (2.6)	.05	9/283 (3.2)	11/543 (2.0)	.34	11/398 (2.8)	6/345 (1.7)	.46
Suicidal ideation	37/536 (6.9)	22/305 (7.2)	.89	16/290 (5.5)	26/613 (4.2)	.40	13/283 (4.6)	21/543 (3.9)	.71	29/398 (7.3)	13/345 (3.8)	.04
Crying	179/534 (33.5)	146/304 (48.0)	<.001	104/290 (35.9)	274/613 (44.7)	.01	126/283 (44.5)	268/543 (49.4)	.21	171/398 (43.0)	142/345 (41.2)	.66

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; OCP, oral contraceptive pill; SES, socioeconomic status.

[a] Based on 2-tailed χ^2 tests for dichotomous variables or *t* tests for continuous variables. All variables were assessed at every wave, except for SES, ethnicity, and menarche; the first 2 were determined at study entry (T1) and the latter at age 16 years (T3).

[b] Continuous scale based on the educational level, job, and income of the parents.

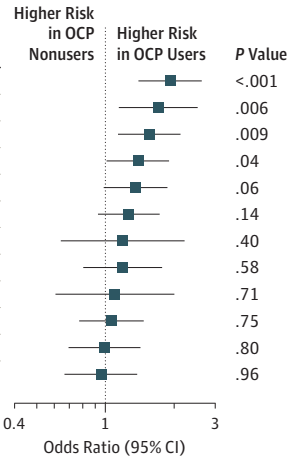
Figure 1. Oral Contraceptive Pill (OCP) Use and Depressive Symptom Scores by Age Groups



Data are (adjusted) mean values with 1 SE for the depressive symptom score through multilevel analysis (ie, mixed models). Analyses were adjusted for age, ethnicity, and socioeconomic status (β coefficient for interaction = −0.021 [95% CI, −0.038 to −0.005; *P* = .0096]).

Figure 2. Depressive Item Scores According to Oral Contraceptive Pill (OCP) Use in Youngest Age Group

Symptom	Odds Ratio (95% CI)	*P* Value
Crying	1.89 (1.38-2.58)	<.001
Hypersomnia	1.68 (1.14-2.48)	.006
Eating problems	1.54 (1.13-2.10)	.009
Tiredness	1.38 (1.01-1.87)	.04
Insomnia	1.35 (0.98-1.84)	.06
Loss of energy	1.26 (0.93-1.70)	.14
Self-harm	1.19 (0.65-2.18)	.40
Anhedonia	1.18 (0.80-1.74)	.58
Suicidal ideation	1.10 (0.61-1.97)	.71
Sadness	1.06 (0.77-1.46)	.75
Worthlessness	0.99 (0.70-1.41)	.80
Inappropriate guilt	0.96 (0.67-1.36)	.96



Data are (adjusted) odds ratio with 95% CIs for severe and moderate symptoms vs the reference group (no symptoms) through binary logistic regression analysis. The mean (SD) age in the youngest age group was 16.3 (0.7) years.

β coefficient for OCP use: virginity, -9.3%; stressful events, -26.7%; menstrual-related pain, -21.3%; acne, -17.3%). However, none of the factors diminished the association between OCP use and depressive symptoms at age 16 years.

Discussion

In this large cohort study of adolescents, we did not find support for an overall association between OCP use and depressive symptoms among young women. However, 16-year-old girls using OCPs did report higher concurrent depressive symptom scores compared with their nonusing counterparts. When individual depressive symptoms were examined, 16-year-old girls using OCPs particularly reported more crying, hypersomnia, and eating problems, while the required symptoms for the diagnosis of depression—anhedonia and sadness—were unaffected. Adjusting the association between OCP use and depressive symptoms for pre-OCP use depressive symptoms in 16-year-old girls reduced the magnitude of the association, but did not eliminate the significance of the findings.

Earlier clues of a possible association between OCP use in adolescence and vulnerability for depressive symptoms come from 2 large population-based studies.[12,26] These studies showed that adolescent girls using OCP were the most likely to subsequently start using psychotropic drugs or be admitted to a psychiatric hospital compared with nonusers. Our study provides important evidence that this vulnerable group is the most likely to report more concurrent depressive symptoms.

This age-specific vulnerability is complex and likely bidirectional. Important emotion-related regions of the brain, such as the amygdala, prefrontal cortex, and hippocampus, are still maturing during adolescence and therefore may be particularly sensitive to sex hormone–related changes at age 16 years.[35] In addition, ages 15 to 18 years may be a critical time for the development of depression in girls, as the sex gap in the incidence of depression dramatically increases during this period.[36] Neurobiological studies support this idea, as sex hormones are capable of directly influencing gene expression in the cell nuclei in the brain.[37] Furthermore, the use of OCPs affects sex hormone levels, including androgens and stress hormones.[38] Although almost nothing is known about the effect of OCP use on the maturation of the brain,[35] these findings confirm its potential capability to do so.

In addition to the possibility that OCP use leads to more depressive symptoms, the weakened strength of the association after adjustment for pre-OCP use depressive symptoms in 16-year-old girls also points toward an association in the reverse direction. A previous study demonstrated that mood worsening among individuals using OCPs was more likely in users with a history of depression.[25] This finding might suggest that a subset of women with depression may be at risk for OCP-associated mood deterioration because they are particularly sensitive to interactions between cycling gonadal steroids and affect. Also, treatment with OCPs is standard care for cycle-related mood problems[39] and for polycystic ovarian syndrome, which is associated with depressive symptoms.[40] Therefore, mood-related physical problems may also be involved in the association between OCP use and depressive symptoms. Hence, some girls in our sample may have initiated OCP use because they experienced mood problems.

Residual confounding could have led to overestimation of the association. Differences between OCP users and nonusers that were likely present before the initiation of OCP use weakened the strength of the association at age 16 years, although none of the differences completely diminished the association. However, future studies should replicate and consider the importance of these factors. In contrast, the healthy survivor effect may have led to underestimation of the association between OCP use and depressive symptoms. In sup-

port of this possibility, comparing first-time users with never-users yielded a stronger association. This finding is in line with findings from a Danish study in which the highest relative risks (RRs) for a diagnosis of depression were found after 6 months (RR, 1.5) of use, whereas RRs were smaller when individuals had used OCP for longer periods (RR, 1.2 for use of 1-3 years; RR, 0.9 for use of 4-6 years; RR, 0.8 for use of 7-9 years).[12] Our finding, combined with these data, suggests that the absence of an association in older individuals may be owing to the healthy survivor effect. The possibility of an underestimation in our younger participants cannot be excluded either, because information on OCP use before the age of 16 years was not available and thus could not be explored.

One may wonder why hypersomnia, eating problems, and increased crying, rather than core symptoms of depression such as sadness, were reported more commonly among adolescent OCP users. These symptoms fit well in symptom profiles of adolescent depression, where, in contrast to adult depression, the emphasis is more on vegetative or physical disturbances (eg, loss of energy, changes in weight, and appetite and sleep changes) than on anhedonia.[41] The symptom-specific findings are also in line with results from a randomized clinical trial, which showed that OCP use worsened mood swings and irritability symptoms, but improved depressive symptoms such as sadness,[28] suggesting that associations between OCP use and mood may be symptom specific.

Strengths and Limitations

Strengths of this study are the availability of multiple time points when depressive symptoms were assessed with the use of well-validated instruments. Also, we were able to adjust for important covariates such as SES and ethnicity. The assessment of depressive symptoms provides a complementary, more inclusive perspective on the association between OCP use and depression across the severity spectrum to existing studies using proxies such as incident clinical depression. More important, subclinical depressive symptoms may also cause distress in adolescents, and many adolescents with psychiatric problems in the clinical range do not seek help.[42] Moreover, the concurrent examination of OCP use and depressive symptom severity over several years contributes to a better insight into the real-time risks associated with OCP use.

This study has some limitations. Use of observational data precludes any causal inference. Also, this longitudinal analysis does not provide information about specific OCPs. Because very few girls specified OCP use as medication use, we were unable to conduct separate analyses for different kinds of OCPs. However, we checked which OCPs were used in a comparable cohort of girls born in the same year and postal code as the girls included in this study (InterActive DataBase [IADB] cohort).[43] In that cohort, most of the girls used either monophasic (81.1%) or triphasic ethinyl estradiol and levonorgestrel (2.5%), followed by ethinyl estradiol and drospirenone (4.6%) and ethinyl estradiol and desogestrel (1.8%). Hence, testing for specific components was not useful, as probably almost all participants were using the same type of progestin. Finally, generalizability of results to other countries might be limited owing to differences in the acceptability of and access to contraception across societies.[44] For example, unlike Dutch teenagers, not all teenagers in the United States have access to no-cost contraception.[45,46] Such differences have implications for group characteristics of girls using OCPs and, hence, associated outcomes.

Although we cannot be conclusive about the direction of the association, awareness of the possible existence of mood problems among OCP-using adolescents is critical to the health and development of adolescents. Depressive symptoms may reduce quality of life[47] and OCP use adherence,[48] because, for example, girls may attribute these depressive symptoms to the use of OCPs, potentially resulting in unwanted teenage pregnancies. To lower the probability of an unintended conception, long-acting reversible contraceptives are recommended as a first-line option.[49,50] However, those are only used by a minority of teenagers in both the Netherlands and the United States.[51,52] We do not suggest limiting OCP use to counterbalance this risk for depressive symptoms. In fact, previous research has shown benefits of OCP use such as improvement of dysmenorrhea and premenstrual syndrome[49]; additionally, OCP use is much safer than pregnancy and associated postpartum depression risks.[50]

Conclusions

In this study, 16-year-old OCP users showed higher concurrent depressive symptom scores compared with their nonusing counterparts. Overall, adolescent girls are more likely to report increased crying, hypersomnia, and eating problems while taking OCPs, but these symptoms seem to diminish once they enter adulthood. Monitoring these symptoms is important, as they may affect their quality of life and put them at risk for nonadherence.

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