Invited Commentary: How Can We Reconcile the Findings of Keyes et al.’s Study With the Experience of Our Patients in Clinical Practice?

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Although the accompanying study by Keyes et al. (Am J Epidemiol. 2013;000(00):000–000) shows us that women currently using hormonal contraception (HC) have better scores on the Center for Epidemiologic Studies Depression Scale and report fewer suicide attempts, it does not show us that HC protects women from mood disorders or that HC is free of the mood-related side effects which cause high rates of discontinuation. The groups compared in the Keyes et al. study were different in many ways; the women using HC were younger, were more likely to engage in positive health behaviors, and had lower depression scores at each prior interview. Women with mood disorders are more likely to avoid or discontinue HC and more likely to experience worsening mood while on HC. The negative mood-related side effects experienced by women using HC (irritability and lability) are not captured by a screening tool for clinical depression, such as the depression scale used in this study. The database used in this study was longitudinal and multiwave, so the authors could have compared changes in depressive symptoms among women who switched from hormonal to nonhormonal contraceptive methods (and vice versa) across different waves. Only if the same women experienced greater levels of depressive symptoms after discontinuing HC and fewer symptoms when they restarted HC could we conclude that HC may protect women from mood disorders.

depression; hormonal contraception; mood; oral contraceptives; screening

Abbreviations: CES-D, Center for Epidemiologic Studies Depression; HC, hormonal contraception; HRT, hormone replacement therapy.

The study by Keyes et al. (1) in this issue of the Journal is an important addition to our knowledge about the safety of hormonal contraception (HC). In particular, the lower level of suicide attempts in a large population sample of women using HC is reassuring. Every day in clinical practice, at least one woman tells me she has discontinued use of HC because “the Pill makes me go crazy!” How can we reconcile the conclusion of Keyes et al. that “Hormonal contraception may reduce levels of depressive symptoms among young women” (1, p. 000) with the experience of our patients in clinical practice?

The sampling method used in the Keyes et al. study is a concern. The groups compared in the study were different; the women using HC were “younger than women in other groups, less likely to have children, more likely to have a college degree, more likely to engage in individual sports (e.g., running), more likely to engage in positive health behaviors such as undergoing a routine physician’s checkup and visiting the dentist, less likely to be a regular smoker, and more likely to have used hormonal contraception in the past. Women using hormonal contraceptives also had a lower mean body mass index than other groups and a lower depression score in each prior interview” (1, p. 000). Although the authors used propensity scores to “match” women in terms of different confounders, this can only be done for observed (and observable) covariates. In other words, it is equally plausible that the apparent difference between these 4 groups of women may have depended more on whether or not a given contraception method was chosen or tolerated rather than on the effect of the method.

Approximately 30% of women using HC discontinue use because of dissatisfaction, and mood-related side effects are frequently listed as a reason for discontinuation (2, 3). Current and former users of HC are different, because the former users...
stopped HC for a particular reason. Surveying a population sample of current and former HC users in Germany, Oddens (4) found a significant difference in reported side effects of HC. For example, irritation was reported by 17.6% of former users and less irritability by 4.2%, as compared with 13.0% and 8.8% of current users ($P < 0.01$); more depression was reported by 18.6% of former users and less depression by 2.4%, as compared with 10.3% and 5.7% of current users ($P < 0.001$). Keyes et al. compared women who were currently using HC with women who were not, but many of those women not currently on HC must have been former users and may have discontinued use because of mood-related side effects.

Women who experience mood-related side effects from HC may have a higher incidence of clinical depression; therefore, they may score higher on the Center for Epidemiologic Studies Depression (CES-D) Scale and may have more reported suicide attempts (5). Physicians may also discourage women with mood disorders from using HC. Therefore, the group of women in this study who were current users of HC probably included fewer women with depressive mood disorders and suicidal behavior.

The discrepancy between the findings in this study and clinical practice reminds me of what we learned about the association of hormone replacement therapy (HRT) with heart disease from the Nurses’ Health Study (6) and the Women’s Health Initiative randomized controlled trial (7). From the Nurses’ Health Study, we learned that women who choose to take HRT have better cardiovascular health outcomes (6); from the Women’s Health Initiative study, we learned that women randomized to HRT have poorer cardiovascular health outcomes (7). One aspect of the HRT debate is clear—that women who choose to use HRT differ from those who do not in many ways: they’re thinner; they have fewer risk factors for heart disease; and they tend to be more educated and wealthier, to exercise more, and to be generally more health-conscious. In the same way, from the Keyes et al. study (1), we learn that women who choose to use HC have better mental health outcomes. Women who choose not to use HC are different people and include many of the women who had symptoms which led them to tell their doctors, “The Pill makes me go crazy!”

The CES-D Scale was designed to screen for clinical depression, not to measure side effects of HC. The various reports validating the measure compared it with standardized psychiatric interviews and other measures of clinical depression (8). When my patient says to me, “The Pill makes me go crazy!”, she is not describing clinical depression. When we designed our recent study, “Characteristics of Women Who Complain of Mood and Sexual Side Effects From Hormonal Contraception” (9), I spent time talking to some of my patients who had discontinued HC because of mood-related side effects and asked them what words they would use (besides “crazy”) to describe those effects. We then asked more of them whether the questions we created captured their experience. The questions we used were: Did you notice any of the following side effects while you were on the contraceptive and which went away after you stopped it?—1) crying more easily (no/yes); 2) feeling depressed or sad (no/yes); 3) getting angry or irri-
tated more easily (no/yes); and 4) being more anxious than usual (no/yes). In order to score high on the CES-D Scale, one must also report some other depressive symptoms, such as anhedonia, despair, suicidal ideation, etc., which are part of clinical depression but not part of the more common mood-related side effects of HC.

The database used in this study was longitudinal and multivariate, so there were some interesting opportunities to further explore these associations which were not taken. For example, one could focus on the women who switched from hormonal to nonhormonal contraceptive methods (and vice versa) across different waves and examine whether there were corresponding changes in their depressive symptoms.

In conclusion, although this study shows us that women currently using HC have better scores on the CES-D Scale and report fewer suicide attempts, it does not show us that HC protects women from mood disorders or that HC is free of the mood-related side effects which cause high rates of discontinuation. This is because women with mood disorders are more likely to avoid or discontinue HC and more likely to experience worsening mood while on HC, and because the mood-related side effects experienced by women on HC are not captured by a screening tool for clinical depression.

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