



Response to Invited Commentary

Keyes et al. Respond to “Hormonal Contraception and Mood”

Katherine M. Keyes*, Keely Cheslack-Postava, Carolyn Westhoff, Christine M. Heim, Michelle Haloosim, Kate Walsh, and Karestan Koenen

* Correspondence to Dr. Katherine M. Keyes, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th Street, Suite 503, New York, NY 10032 (e-mail: kmk2104@columbia.edu).

Initially submitted June 11, 2013; accepted for publication July 15, 2013.

We thank Dr. Wiebe for her thoughtful commentary (1) on our study examining the association between hormonal contraceptive use and depressive symptoms and suicide attempts (2). It is true that women using hormonal contraceptives are different in myriad ways from women who are not, complicating inferences made from an observational study in which treatment is not assigned. Dr. Wiebe notes that the inferential problems faced in our analysis are analogous to findings in the observational literature on postmenopausal hormone treatment and other observational studies on the effects of particular treatment protocols. The larger question, then, is whether we can learn something about treatment effects from observational data. We submit that the field has made significant strides in developing innovative methods with which to infer treatment effects from observational data (e.g., see Hernán et al. (3)). These advances have been motivated in part by the conflicting results from observational and clinical trials. The challenge of using observational evidence lies in employing creative strategies for mitigating potential confounding (4) and in appropriately interpreting results while remaining vigilant to threats to validity.

Mood-related discontinuation of hormonal contraception among former users would affect our results to the extent that women who discontinue use because of mood-related side effects are also more likely to have depressive symptoms and/or to attempt suicide at a later date (5). Unfortunately, there are few population-based data on the extent to which women who discontinue hormonal contraception because of nondiagnostic factors related to “mood” or “irritability” are more likely to experience depressive symptoms or attempt suicide. Further, while the population-based German study indeed found that former users were more likely to report irritability than current users (6), the totality of population-based research in the area of oral contraceptives and mood/affect side effects is decidedly mixed; a 2002 review of the literature, while largely based on small, nonepidemiologic samples, indicated that there was little consistent evidence for an effect of oral contraceptives on negative mood and affect but consistent evidence for less variability

in affect across the menstrual cycle among hormonal contraceptive users (5). To address concerns about discontinuation effects, we controlled for prior use of hormonal contraceptives and prior level of depressive symptoms in our analyses. The results were robust, at least partially mitigating discontinuation effects.

We appreciate the suggestion to examine within-individual differences in hormonal contraceptive use and depressive symptoms. We reanalyzed the data with a fixed-effects within-person regression approach. Use of hormonal birth control was inversely associated with past-week depressive symptoms ($\beta = -2.22$, 95% confidence interval (CI): $-2.40, -2.04$), high levels of depressive symptoms (odds ratio = 0.61, 95% CI: 0.55, 0.67), and suicide attempts (odds ratio = 0.59, 95% CI: 0.50, 0.71). Thus, a within-person approach yields the same associations as a between-person analysis. We note that there are limitations to this approach (e.g., only stable characteristics are controlled).

We submit that the role of sex hormones in mental health, including but not limited to exogenous hormone use in the form of contraception, remains understudied in population-based epidemiologic samples. There are no questions on family planning or reproductive health in the major nationally representative psychiatric epidemiologic surveys, aside from questions on number of livebirths and current pregnancy status. Conversely, nationally representative surveys that routinely collect information on family planning often have limited, nondiagnostic measures of psychiatric disorders. Decisions regarding contraception and family planning are among the most central in women’s lives; we cannot fully understand women’s mental health without considering aspects of family planning, including the pharmacological actions of particular treatments, as well as the psychological processes involved in reproductive health decisions. Examination of the intersection of hormone use and mental health, including potential factors that select women into certain contraceptive options and the potential effects of those contraceptives on mental health, is critical yet overlooked in the field of women’s health.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York (Katherine M. Keyes, Keely Cheslack-Postava, Carolyn Westhoff, Michelle Haloossim, Kate Walsh, Karestan Koenen); Department of Obstetrics and Gynecology, Mailman School of Public Health, Columbia University, New York, New York (Carolyn Westhoff); and Center for Human and Health Sciences, Institute of Medical Psychology, Charité—Universitätsmedizin Berlin, Berlin, Germany (Christine M. Heim).

REFERENCES

1. Keyes KM, Cheslack-Postava K, Westhoff C, et al. Association of hormonal contraceptive use with reduced levels of depressive symptoms: a national study of sexually active women in the United States. *Am J Epidemiol.* 2013;178(9):1378–1388.
2. Wiebe ER. Invited commentary: how can we reconcile the findings of Keyes et al.'s study with the experience of our patients in clinical practice? *Am J Epidemiol.* 2013;178(9):1389–1391.
3. Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology.* 2008;19(6):766–779.
4. Davey Smith G. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol.* 2008;102(2):245–256.
5. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord.* 2002;70(3):229–240.
6. Oddens BJ. Women's satisfaction with birth control: a population survey of physical and psychological effects of oral contraceptives, intrauterine devices, condoms, natural family planning, and sterilization among 1466 women. *Contraception.* 1999;59(5):277–286.