Response to: "Comment on 'Infertility and teratogenicity after paternal exposure to systemic dermatologic medications: A systematic review'"

To the Editor: We would like to thank Enriquez-Gutierrez et al[1] for their thoughtful comments on our article, "Infertility and Teratogenicity after Paternal Exposure to Systemic Dermatologic Medications: A Systematic Review,"[2] in which we curated the available data to facilitate patient-provider discussion on the potential risks of systemic dermatologic medications following paternal exposure. In preparing our review, we were aware of issues of quality and risk of bias in the studies available on this topic. Study of fertility and teratogenicity is inherently both methodologically and ethically challenging. To improve the clinical utility of our literature review, we incorporated information from 2 additional sources: the US Food and Drug Administration Adverse Events Reporting System and the US Food and Drug Administration—approved prescribing information for each medication.

We agree that the issue of reporting on bias is widespread in medicine. In a study of systematic reviews, Moher et al found that fewer than a quarter (23.1%) of all systematic reviews and meta-analyses assessed the included studies for risk of bias.[3] This may be due in part to a lack of validated tools for assessing the variety of study designs that exist in the literature. Enriquez-Gutierrez et al[1] correctly point to the Cochrane Risk of Bias Tool[4] for assessing randomized controlled trials included in systematic reviews and meta-analyses; however, of the 19 studies included in our review, only 4 were randomized controlled trials. There is a paucity of validated tools to assess bias in nonrandomized trials or in vitro studies, and there is a lack of consensus on this issue. In systematic reviews with qualitative analysis, the Newcastle-Ottawa Scale[5] suggested by Enriquez-Gutierrez et al[1] has limited utility for bias assessment. Instead, this tool was "developed to assess the quality of nonrandomised studies with its design, content, and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results." The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement strongly emphasizes the difference between study quality and risk of bias and calls for focus on the latter.[6] Similarly, the Scottish Intercollegiate Guideline Network critical appraisal checklists are designed to assess methodologic quality rather than to assess the risk of bias.[7] A tool to address risk of bias in the in vitro studies of semen parameters included in this review is yet more elusive.

Ultimately, we commend Enriquez-Gutierrez et al[1] for highlighting the importance of the assessment of bias in systematic reviews and meta-analyses. This is an issue throughout the medical literature that requires a systemic effort to improve across the board. We look forward to using assessment of bias in future reviews that include studies of a more homogeneous randomized controlled trial methodology. Nevertheless, we believe that our review achieves its goal of curating all of the available information for patient-centered discussions on risk tolerance surrounding the sensitive topic of fertility and pregnancy. We will continue to point to this comprehensive summary of the limited evidence on this topic in response to our patients' concerns.

George A. Zakhem, BS,[a] Catherine C. Motosko, BS,[a] Euphemia W. Mu, MD,[a,b] and Roger S. Ho, MD, MS, MPH[a]

From the Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, New York,[a] and Mount Sinai Beth Israel, Department of Dermatologic Surgery, New York, New York.[b]

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Correspondence to: Roger S. Ho, MD, MS, MPH, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, 240 E 38th St, Floor 12, New York, NY 10016

E-mail: Roger.Ho@nyumc.org

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