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Hydroxychloroquine early in pregnancy and risk of birth defects: don't throw out the baby with the bathwater

Check for updates

TO THE EDITORS: We read with interest the article by Huybrechts et al[1] that reported increased major congenital anomalies among first-trimester hydroxychloroquine-exposed pregnancies. The methods used by this excellent research group are sound. Using claims data, they compared hydroxychloroquine-exposed pregnancies with matched unexposed pregnancies and found a 1.26 adjusted relative risk of all major malformations among exposed pregnancies. No particular pattern of anomalies was found. The authors concluded that first-trimester hydroxychloroquine exposure leads to a small increased risk of congenital anomalies. We worry that the findings presented in this paper will be interpreted by practicing clinicians as causally related. This information could tip the balance in clinical decision-making toward anticipated risk rather than the established benefit of hydroxychloroquine during pregnancy.

The authors' conclusions imply that hydroxychloroquine is potentially teratogenic. Establishment of teratogenicity requires several criteria.[2] This study fulfills the tenet of identifying exposure to an agent at a critical time in gestation. However, the study does not satisfy other criteria, such as careful delineation of the clinical cases, exposure associated with a specific pattern of defects, and the association making biologic sense. The study's large sample size provided sufficient statistical power to demonstrate a small but significant increased risk of congenital anomalies with hydroxychloroquine exposure. Although the authors used state-of-the art methods to adjust for confounders, small effect sizes can sometimes be explained by unmeasured confounding. As in all claims data, there is insufficient information to control for exposures to tobacco, alcohol, other drugs, folic acid supplements, and over-the-counter medications that may have impacted the risk of malformations. Most importantly, given the lack of any specific pattern of congenital anomalies, these results could be spurious. Evaluation of increased risks for specific congenital anomalies with hydroxychloroquine exposure in case-control studies could help clarify this issue.

In contrast, several studies have now clearly established the critical role of hydroxychloroquine in controlling systemic lupus erythematosus disease activity in pregnancy and improving outcomes. Currently, several professional societies recommend continuing hydroxychloroquine during lupus pregnancies.[3] Moreover, this medication reduces the risk of congenital heart block in offspring of women who are anti-Ro and anti-La positive.[4]

We would caution readers in their interpretation of the results presented. This study has not proven that hydroxychloroquine is teratogenic, whereas data supporting the benefits of hydroxychloroquine during pregnancy for malarial prophylaxis, lupus pregnancy outcome, and prevention of congenital complete heart block are sound. ■

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Hydroxychloroquine early in pregnancy and risk of birth defects: absence of evidence is not the same as evidence of absence

Because pregnant women are generally excluded from randomized controlled trials, virtually all evidence about medication safety during pregnancy in humans must come from observational studies. Therefore, causality can never be "proven" in this context, regardless of the study design. However, we should evaluate new evidence on its merits and not on the basis of whether it supports prior beliefs.

We restricted the cohort to women with a treatment indication and matched patients based on propensity scores comprising >80 variables. Although residual confounding can never be excluded, the likelihood of imbalances large enough to explain the observed associations after conditioning on such a broad set of prespecified variables is small. Indeed, the ability to account for rich sets of potential confounders is a major benefit of cohort studies nested in large healthcare utilization databases.

The letter suggests that the fact that there was no evidence of an increased risk of malformation syndromes casts doubt on the validity of our findings. However, many teratogens are associated with one or more specific malformation subtypes while not being associated with syndromes (eg, valproate, diabetes). Furthermore, although the mechanism is not always known (eg, thalidomide), in this case, there is biologic plausibility. Hydroxychloroquine crosses the placenta[1] and inhibits cell division and DNA synthesis[2]; therefore, hydroxychloroquine could have effects on rapidly dividing embryonic cells.

Until now, studies evaluating the teratogenicity of hydroxychloroquine were too small (36−194 exposed) to be able to detect small to moderate risk increases, especially with an unjustified reliance on statistical significance of underpowered comparisons.[3] However, absence of evidence should not be equated with evidence of absence. Furthermore, 2 previous studies reported relative risks >2, although estimates were imprecise. Our study is the largest study (2045 exposed) conducted and, importantly, the first to be able to conclude that hydroxychloroquine does not seem to be a major teratogen, given that the upper limit of the 95% confidence interval for malformations overall suggests a risk increase of not more than 50%.

Although the benefits of hydroxychloroquine for pregnant women with malaria or rheumatic disorders are undisputed, we cannot dismiss signals of a potential small increased risk of congenital anomalies. It is our responsibility to present the best available evidence on both benefits and risks, allowing clinicians to make informed treatment decisions. As we clearly stated in the study and reiterate here, for most patients with autoimmune rheumatic disorders, the balance will tip toward the established benefits of hydroxychloroquine during pregnancy. ■

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