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Response to Behrens and Edwards: Atovaquone-proguanil exposure in pregnancy should not be condemned from current evidence

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Dear Editor

We read with interest Prof Behrens' and Dr. Edwards' letter regarding our article on atovaquone-proguanil (AP) exposure in pregnancy [1]. They highlight a critical point, which is the crux of our article-there remain to date extremely limited data on the safety of AP in pregnancy. However, their interpretation of our conclusion needs clarification. We stated in our article that we recommend AP not be used for prophylaxis or treatment in pregnant women if other suitable alternatives are available [2]. In circumstances where no other options exist, AP prophylaxis is preferable to no prophylaxis, as highlighted in the podcast accompanying our article [3]. We recommend that when making these decisions, providers present women with the available options, risks, and benefits, and together with their patient, use all available data to make the best decision for their patient.

Our current study was underpowered and did not have statistically significant findings. However, we found that 28% of AP exposed pregnancies ended in fetal loss compared to only 17.6% of unexposed pregnancies, and 16%, and 6% of pregnancies exposed to mefloquine, and chloroquine, respectively [2]. The differences in proportions cannot be completely discounted. Our earlier literature review found eight articles which reported on miscarriage, with a total of only 95 exposed women, with 21 miscarriages reported [4]. Thus, the current sample of 50 women, while small, substantially increases the available evidence on AP. A strength of the recent paper is that the rate of miscarriage among exposed women was compared to a largely similar population of unexposed women, whereas the previous review compared rates of miscarriage between other published reports (i.e., a more heterogenous population).

While the available data do not suggest an increased risk of major birth defects with AP, the largest study to date included only 151 infants exposed in first trimester [5], and our prior review included only 446 women [4]. These are sufficient data to exclude an issue occurring at a rate of 1/148 pregnancies, and not nearly enough data upon which to be confident that

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the lack of association previously found truly represents that no harm occurs as a result of *in utero* AP exposure. There is an urgent need for analysis of existing data, especially in countries where the use of AP in pregnancy is recommended. This would set the stage to potentially provide stronger rationale for a randomized controlled trial (RCT). It should be noted, however, that to provide sufficient evidence of a lack of harm requires a large sample size, on the order of 3000 exposed participants, which will impact the feasibility of conducting an RCT. Patients will benefit most through care based on all available data; women should be fully informed of the possible risks and benefits of any prophylactic regimen used during pregnancy.

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