Marcelo F. Montenegro, PharmD, PhD
Department of Physiology and Pharmacology, Karolinska Institute
Stockholm, Sweden
marcelo.montenegro@ki.se

The authors report no conflict of interest.

REFERENCES

1. Cluver CA, Hannan NJ, van Papendorp E, et al. Esomeprazole to treat women with preterm preeclampsia: a randomized placebo-controlled trial. Am J Obstet Gynecol 2018;219:388.e1–17.
2. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation 2013;128:845–53.
3. Montenegro MF, Sundqvist ML, Larsen FJ, et al. Blood pressure-lowering effect of orally ingested nitrite is abolished by a proton pump inhibitor. Hypertension 2017;69:23–31.
4. Sandrim VC, Montenegro MF, Palei AC, et al. Increased circulating cell-free hemoglobin levels reduce nitric oxide bioavailability in pre-eclampsia. Free Radic Biol Med 2010;49:493–500.
5. Sandrim VC, Palei AC, Metzger IF, et al. Interethnic differences in ADMA concentrations and negative association with nitric oxide formation in preeclampsia. Clin Chim Acta 2010;411:1457–60.
6. Lundberg JO, Carlström M, Weitzberg E. Metabolic effects of dietary nitrate in health and disease. Cell Metab 2018;28:9–22.

 https://doi.org/10.1016/j.ajog.2018.10.008

REPLY

Check for updates

Sandrim et al advises caution in evaluating proton pump inhibitors (PPI) to treat preeclampsia, in light of their prior work, suggesting PPI may have actions that could increase blood pressure, by interfering with nitric oxide (NO) homeostasis.

We agree that treatment trials should include interim analyses to examine the possibility of risk. However, we resolutely disagree the work they cite provides a sufficient weight of evidence to suggest PPIs should not be further investigated for their potential to treat preeclampsia, *for the following reasons*:

1) While our treatment trial did not show benefit, there was no evidence that those exposed to PPIs had an increased incidence of higher/worsening blood pressures.
2) In our preclinical laboratory work,[1] we show PPIs may have multiple actions to mitigate the vascular damage caused by preeclampsia, well beyond the singular pathway of the NO. They include: decreasing placental and endothelial secretion of soluble fms-like tyrosine kinase-1, soluble endoglin, endothelial-1, and proinflammatory cytokine secretion (these cause increased blood pressure and vascular dysfunction in preeclampsia); mitigating endothelial dysfunction in multiple assays; inducing vasodilation in whole human omental vessels; and importantly, reducing blood pressure in an animal model of preeclampsia.
3) Ghebremariam et al[2] showed omeprazole decreased expression of NO synthase (enzyme that produces NO). In contrast, we found esomeprazole significantly increased endothelial NO synthase (eNOS) expression. Hence, we could not validate a key finding of their work.
4) Their statement that PPIs are associated with an increased risk of adverse cardiovascular events refers to literature on older persons with chronic morbidities taking PPIs indefinitely. This is a very different vascular profile to pregnant women, even those with preeclampsia.
5) Supporting our preclinical findings, Saleh et al[3] independently reported that the concurrent use of PPIs among a cohort of pregnant women with suspected hypertensive disorder of pregnancy at the time of enrollment was associated with lower circulating soluble fms-like tyrosine kinase/soluble endoglin/endothelial-1, no increase in blood pressure, less gestational hypertension, longer interval to delivery, and a higher birthweight. It was in a pregnant population and identified potential benefits and certainly no tendency toward increased blood pressure.

A Royal College of Obstetricians and Gynecologists report in 2015 highlights the dire state of therapeutic development in pregnancy research.[4] Patient safely is resolute but an overly cautious approach in considering any potential treatments may mean that we will never make an impact on obstetric complications that claim the lives of thousands of women and babies. ■

Catherine Cluver, MBChB, FCOG, MMed
Mercy Perinatal, Mercy Hospital for Women, and
Translational Obstetrics Group
University of Melbourne
Melbourne, Australia
Department of Obstetrics and Gynecology, Stellenbosch University
Stellenbosch, South Africa
cathycluver@hotmail.com

Natalie Hannan, PhD
Stephen Tong, PhD
Mercy Perinatal, Mercy Hospital for Women, and
Translational Obstetrics Group
University of Melbourne
Melbourne, Australia

The authors report no conflict of interest.

REFERENCES

1. Onda K, Tong S, Beard S, et al. Proton pump inhibitors decrease soluble fms-like tyrosine kinase-1 and soluble endoglin secretion, decrease hypertension, and rescue endothelial dysfunction. Hypertension 2017;69:457–68.
2. Ghebremariam YT, LePendu P, Lee JC, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation 2013;128:845–53.
3. Saleh L, Samantar R, Garrelds IM, van den Meiracker AH, Visser W, Danser AHJ. Low soluble fms-like tyrosine kinase-1, endoglin, and endothelin-1 levels in women with confirmed or suspected preeclampsia using proton pump inhibitors. Hypertension 2017;70:594–600.
4. David AL, Thornton S, Sutcliffe A, Williams P. Developing New Pharmaceutical Treatments for Obstetric Conditions. London: Royal Collage of Obstetricians and Gyneacologist; 2015. Scientific Impact Paper No. 50.

 https://doi.org/10.1016/j.ajog.2018.10.009