We welcome the information provided by Marin et al about efforts to ensure the rate of cesarean delivery in Brazil best serves the women and babies of the nation. The implementation of the "Adequate Childbirth Program" and the APICE-ON initiative are worthwhile attempts to amend the culture surrounding cesarean delivery while prioritizing optimal outcomes for both mothers and babies. The Robson Ten Group Classification System can assist in the continuous audit of rates of cesarean delivery along with the identification of specific patient groups for which the rate of cesarean delivery may be subjectively inappropriate. We have demonstrated that, with a robust system of data collection, the Robson Robson Ten Group Classification System can be applied not just locally but on a national level,[4] which gives individual institutions a template to compare outcomes and work to a national standard that may drive practices at a local level. ■

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Esomeprazole to treat women with preeclampsia: possible implications in the nitric oxide homeostasis

Check for updates

TO THE EDITORS: We read with interest the article by Cluver et al[1] evaluating the use of proton pump inhibitor (PPI) esomeprazole to treat women with preterm preeclampsia.[1] While the 40 mg of daily oral esomeprazole tested in their study did not prolong gestation in pregnancies with preterm preeclampsia or decrease circulating soluble fms-like tyrosine kinase-1 concentrations, the authors discuss that this dosage of esomeprazole may be too low to treat preterm preeclampsia and suggest that higher doses may still be effective.[1] We would like to bring up that the use of PPIs has been associated with increased risk of adverse cardiovascular events,[2,3] possibly due interferences in nitric oxide (NO) homeostasis. Several studies support that NO is diminished during preeclampsia, and importantly preeclampsia induces subclinical hemolysis, which results in NO scavenging.[4] PPIs also reduce endogenous formation of NO through inhibition of the enzyme dimethylarginine dimethylaminohydrolase,[2] which degrades asymmetric dimethylarginine, an endogenous NO synthase inhibitor that is increased in preeclampsia compared with healthy pregnancy.[5] In addition, we recently demonstrated that esomeprazole blocks the blood pressure-lowering effects of nitrite, preventing thus possible beneficial properties from dietary nitrate.[3] While it is most widely known that the classic NO formation is mediated by NO synthases from L-arginine, an alternative pathway for NO generation named "nitrate-nitrite-NO" has been described, in which the oxidation products of NO metabolism nitrite (NO_2^-) and nitrate (NO_3^-) are recycled back to NO in blood and tissues.[6] Nitrate is commonly found in our everyday diet and its ingestion exerts robust NO-like effects, including reduction in blood pressure and improvements in vascular function.[6] These beneficial cardiovascular effects of dietary nitrate involve an entero-salivary circulation in which nitrate is absorbed mainly in the gastrointestinal tract and then actively taken up and concentrated in salivary glands, resulting in high nitrate levels in saliva.[6] Commensal bacteria in the mouth then reduce salivary nitrate to nitrite and when saliva enters the acidic stomach, nitrite is rapidly protonated to form nitrous acid, which decomposes further to form NO affecting blood pressure.[3] The use of PPIs increases gastric pH and this contributes to impairments of the nitrate-nitrite-NO pathway described above. In summary, PPIs may alter NO homeostasis by inhibition of dimethylarginine dimethylaminohydrolase and preventing NO generation from dietary nitrate-nitrite. We believe these recently discovered properties of PPIs should be considered in future studies using PPIs, especially in patients in cardiovascular risk. ■

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REPLY

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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. ■

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