

Comment on: Prediction and secondary prevention of preeclampsia from the perspective of public health management – the initiative of the State of Rio de Janeiro

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Dear Editor,

We read with interest the article “Prediction and secondary prevention of preeclampsia from the perspective of public health management—the initiative of the State of Rio de Janeiro,” published by Braga and colleagues.⁽¹⁾ The authors recommend universal treatment (for all pregnant women) with elemental calcium at 1500 mg per day and identification of women at high-risk of preeclampsia (PE) based on the presence or absence of maternal risk factors alone, followed by aspirin at a dose of 100 mg in those cases. In this letter, we express our concerns with these simplistic strategies which, despite best intentions, are unlikely to work in clinical practice or reduce the PE rates at the population level.

First, the evidence that 1500 mg of elemental calcium supplementation is useful in preventing preeclampsia (PE) is, at best, questionable. There is no evidence to support universal use of calcium, or cost-effectiveness data supporting such universal treatment strategy. It is true that the World Health Organization (WHO) guideline⁽²⁾ issued in 2011 and updated in 2018,^(2,3) supported by Cochrane Systematic Reviews,^(4,5) recommended calcium supplementation during pregnancy in areas with low dietary calcium intake. However, a sensitivity analysis evaluated the validity of these Cochrane systematic reviews and meta-analyses,⁽⁶⁾ and found that conclusions about the benefits of calcium supplementation to prevent PE are misleading because of a high degree of heterogeneity [$I^2 = 76\%$] between trials, with results mainly driven by a large number of small studies included in the metanalysis. Small studies tend to overestimate treatment effects (“small-study effects”) and are more likely to be published when positive findings are reported than when no treatment effect is evident (publication bias).⁽⁷⁾ Of note, the three larger randomized trials of calcium for the prevention of PE reported negative findings and had no heterogeneity when combined.⁽⁶⁾

Second, pregnant women are naturally resistant to medication use due to concerns regarding safety, risk perception, and effectiveness⁽⁸⁾ that can be aggravated by non-convincing medical advice. Considering this suboptimal medication adherence during pregnancy, incorporating a complex dose scheme of 1500 mg of calcium supplement per day can also jeopardize dietary nonheme iron and iron absorption⁽⁹⁾ and interfere with compliance to aspirin indicated for pregnant women classified as high-risk of developing PE.

Although the risk of preterm PE can be reduced by the prophylactic use of aspirin with a daily dose ≥ 100 mg and starting the therapy < 16 weeks,⁽¹⁰⁾ the ASPRE trial⁽¹¹⁾ utilized 150 mg of aspirin per day, based on previous evidence showing a dose-dependent benefit of the therapy,⁽¹²⁾ and achieved a 62% reduction in the risk of PE. Thus, we agree that it would be ideal for the pharmaceutical industry to commercialize this dosage, as Braga et al.⁽¹⁾ suggested. However, until this is achieved, a dose of 150mg of aspirin can be easily achieved by administering 1 + 1/2 tablet of 100 mg and discarding the other half.⁽¹³⁾

Last but not least, the proposed risk factor checklist approach is known to perform poorly, detecting less than a third of patients who will later develop PE.⁽¹⁴⁾ The most effective way of identifying the high-risk group to receive prophylactic aspirin is by combining maternal factors with biophysical and biochemical markers,⁽¹⁵⁾ as used in the ASPRE trial employing an algorithm freely provided by Fetal Medicine Foundation (FMF),⁽¹⁶⁾ through software, website, and mobile device applications with a user-friendly interface available at <https://fetalmedicine.org/research/assess/preeclampsia>.^(16,17) The most significant components of combined screening, such as mean arterial pressure measurement and ultrasound, are readily available and widely used in most clinical settings, even in low/middle-income countries such as Brazil, and do not incur additional costs. Even without biochemical markers, the FMF algorithm outperforms risk factor-based checklists and could be rapidly implemented, leading to a significant increase in the identification of high-risk women who would benefit from aspirin prophylaxis. More than half of these women would likely be missed by the traditional risk factor-based approach.⁽¹⁸⁾

The Rio de Janeiro State Secretariat for Health misses a critical window of opportunity to effectively mitigate the burden of PE by not considering implementing a feasible universal PE screening program with effective prophylactic measures based on the screening result, in line with recent recommendations from the International Federation of Gynecology and Obstetrics (FIGO),⁽¹³⁾ the International Society for the Study of Hypertension in Pregnancy (ISSHP),⁽¹⁹⁾ and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).⁽²⁰⁾ The FMF algorithm with biophysical markers and without using biochemical markers has been previously validated in Rio de Janeiro and achieved a detection rate of 71%,⁽²¹⁾ similar to the reference study.⁽²²⁾ A pragmatic FIGO recommendation is to use a combination of maternal risk factors with mean arterial pressure as a baseline screening test to estimate each individual's risk of developing preterm PE, where it is not possible to measure uterine artery pulsatility index and biochemical markers. It is better to use this simple combined test rather than using maternal risk factors as binary (yes/no) variables alone, as the latter approach leads to suboptimal prediction.⁽¹³⁾ In light of these considerations, we advise that all pregnant women should be screened for preterm PE during early pregnancy by the FMF algorithm, women identified at high risk should receive aspirin prophylaxis at a dose of 150 mg and, calcium supplementation should be reserved for women at high-risk for PE and low dietary calcium intake, rather than universally.


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Reply to:

Author´s reply to Comment on: Prediction and secondary prevention of preeclampsia from the perspective of public health management – the initiative of the State of Rio de Janeiro

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Dear Editor,

We thank the authors Rezende et al.⁽¹⁾ the opportunity to continue discussing the preeclampsia prevention strategies adopted by the State of Rio de Janeiro and which was the reason for our editorial in RBGO.⁽²⁾

The first of the criticisms targeted the World Health Organization's (WHO) recommendation⁽³⁾ for universal calcium supplementation for pregnant women from areas with low intake.⁽⁴⁾ There were two questions raised on this topic.

The first of them would be that taking 3 calcium tablets a day (for a total of 1500mg) could be a complex scheme, with potential harm to iron absorption or even adherence to acetylsalicylic acid (AAS) when necessary. We agree that calcium supplementation can impair iron absorption and, therefore, we advise in our Editorial that calcium tablets should be ingested with some food, but not those rich in phytates, oxalates, or iron, as these substances hinder the calcium absorption.⁽²⁾ Furthermore, calcium supplements should be taken at least 2 hours apart from iron supplements or multivitamins containing iron, as this mineral reduces calcium absorption.⁽²⁾ We believe that, with this guidance, and the correct encouragement to adhere to this supplementation, coordinated by the prenatal care provider, showing that calcium is not a medicine, but a supplement, just like iron and folic acid, whose supplementation is well accepted among our pregnant women, that these issues will be resolved.

The other question concerns the effectiveness of preventing preeclampsia with calcium supplementation in populations with low intake. The authors cite Wright's et al.⁽⁴⁾ study that analyzed Hofmeyr's et al.⁽⁵⁾ meta-analysis which supported the WHO recommendation⁽³⁾ regarding universal calcium supplementation during pregnancy in areas with low intake. Wright's et al.⁽⁴⁾ analysis evaluating the heterogeneity of the studies

included in the meta-analysis had already been presented by Hofmeyr et al.⁽⁵⁾ in the original study. In response to Wright's et al.⁽⁴⁾ questions, the authors of the meta-analysis emphasized that: "The composite outcome maternal death or serious morbidity was reduced with calcium supplementation (four trials, 9732 women; RR: 0.80, 95% CI: 0.66–0.98). There was one maternal death with calcium supplementation versus six maternal deaths with placebo. These important outcomes were not subject to heterogeneity or small trial effects".⁽⁶⁾ We are convinced that our main target in this action to prevent preeclampsia in the State of Rio de Janeiro is to reduce maternal mortality. And the data points in our favor. Furthermore, we can not lose sight of the fact that hypertension (all forms) is the main cause of maternal death in the state of Rio de Janeiro and we have evidence that the incidence of hypertension during pregnancy affect 12% of women⁽⁷⁾ and seems higher in Brazil than in other countries. Therefore, any reduction in the occurrence of this problem is of special interest to public health.

We are certainly looking forward to the inclusion of two recent simultaneous trials in this meta-analysis, as their results reinforce the benefits of universal calcium supplementation during pregnancy in populations with low intake, even at lower doses.⁽⁸⁾ We hope the WHO can reduce its supplementation recommendation from 1500-2000mg of daily calcium to 500mg (that would certainly facilitate adherence to supplementation), which seems to provide the same protection against the ominous outcomes of preeclampsia. Until then, we are staunch that following the WHO does not seem unreasonable.

The authors' other relevant question concerns the use of AAS in preventing preeclampsia. And then there are also two issues that were raised: the dose of AAS and the type of screening used to predict it.

Regarding the dose of AAS, the authors advocate the advantages of using 150mg compared to the 100mg that we propose, according to the Brazilian Ministry of Health⁽⁹⁾ and the Brazilian Network for the Study of Hypertension in Pregnancy (Rede Brasileira de Estudos de Hipertensão na Gestação – RBEHG).⁽¹⁰⁾ It is worth highlighting that the majority of the 77 trials included in the Cochrane review that evaluated the role of antiplatelet agents for preventing pre-eclampsia and its complications used low doses of AAS.⁽¹¹⁾ Only one trial with 1,776 women used 150mg of AAS in this metanalysis. Thus, the results of this Cochrane review demonstrated the effectiveness of prophylaxis with 100mg of AAS not only in consistently reducing preeclampsia, but also in the occurrence of preterm birth, infant deaths, neonatal deaths or death before hospital discharge, and other adverse outcomes.⁽¹¹⁾

The benefits of using higher doses of AAS were validated by the ASPRE study,⁽¹²⁾ and led to a greater response in preventing preeclampsia. Specifically regarding the AAS dose of 150mg, it is worth noting that Brazil does not sell AAS in this dosage. As organizers of care, state public managers need to anchor their policies by prioritizing medicines included in the Brazilian National List of Essential Medicines (*Relação Nacional de Medicamentos Essenciais – RENAME*).⁽¹³⁾ And a simple consultation of this list shows that AAS is available through the Brazilian Unified Health System (Sistema Único de Saúde – SUS) in doses of 100 and 500mg. The authors point to two solutions to this problem that bring major concern. The first of these is the instruction to break the tablets in order to obtain a dosage of 150mg. The Brazilian National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*) does not regulate this practice⁽¹⁴⁾ and does not require that any grooves in the tablets be related to the division of the active ingredient into halves of the product.⁽¹⁵⁾ Of special relevance in the case of AAS is the protection that certain tablets of this product have to avoid gastric action, which is lost when the tablet is split. Furthermore, pharmaceutical companies do not recommend this practice and the responsibility for any error in the dosage administered will be attributed to the professional who advised this practice.⁽¹⁵⁾ The authors' other recommendation would be to discard the other half of the AAS tablet not immediately used, which would lead to a loss of 25% of all AAS used in an eventual government preeclampsia prevention program.

Regarding the fiscal responsibility required of public managers, this policy does not meet the rigors of public pharmacoeconomics and would probably be rejected by control agencies and the public ministry itself. Finally, in relation to the dose of AAS, it is also worth highlighting the WHO's concern with the lack of evidence on the comparative risk of postpartum haemorrhage among women who received 75mg [dose recommended by WHO to preeclampsia prevention] compared with those who received 150mg of aspirin and noted it as a research priority.⁽¹⁶⁾

Regarding organized screening for the prediction of preeclampsia, we agree with the authors about its importance, including the use of biochemical and biophysical markers for this. However, budgetary limitations prevent this strategy from being implemented at this moment. Even among Brazilian university centers, which serve a tiny portion of the obstetric population, we do not know of any service that performs this screening in its routine. Even in well-resourced clinical settings, as highlighted by Magee et al.,⁽¹⁷⁾ uterine-artery Doppler ultrasonography and placental growth factor assays are not routinely performed. In addition to the costs of biochemical markers, the use of uterine-artery Doppler ultrasonography implies the availability of this test in the SUS routine, which has not yet been validated by the Brazilian Ministry of Health. Considering that a significant proportion of pregnant women in the State of Rio de Janeiro begin prenatal care at more than 12 weeks of gestation, the imposition of biophysical variables for the onset of AAS, which would certainly take time, would postpone the start of prophylaxis for preeclampsia beyond the 16th weeks of pregnancy, which could reduce its effectiveness. Even the use of just mean arterial pressure, something clinically simple to do, as a strategy also recommended by the International Federation of Gynecology and Obstetrics (FIGO),⁽¹⁸⁾ encounters some limitations, including the lack of computers/internet networks, especially in rural areas of 92 municipalities that make up the State of Rio de Janeiro. However, adding mean arterial pressure to maternal risk factors increases the detection rate of preeclampsia before the 37th weeks of gestation from 41.5% [33.3-50.1] to 49.3% [40.8-57.8],⁽¹⁹⁾ which we consider important. Therefore, we predict that this strategy could be the next target we should pursue.

Organizing the prediction of preeclampsia in the State of Rio de Janeiro considering only clinical factors, in accordance with the recommendations of the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), the U.S. Preventive Services Task Force (USPSTF)⁽²⁰⁾ and the RBEHG⁽¹⁰⁾ do not seem like a missed window of opportunity. Considering that calcium is not supplemented for almost no pregnant woman in the State of Rio de Janeiro and the use of AAS is extremely limited, even among patients with unequivocal clinical risk factors for preeclampsia, organize the obstetric care network with the introduction of prediction model and actions of preeclampsia prevention with universal physical activity and calcium supplementation, as well as AAS in cases selected based on clinical variables, will pave the way for more refined strategies that, we hope, will not be delayed. In public management, science must go hand in hand with wisdom. Or as St. Francis of Assisi would say: "Start by doing what is necessary, then what is possible, and suddenly you are doing the impossible!"

For now, and while the universal use of biophysical and biochemical markers in screening for preeclampsia, as recommended in ASPRE, is not possible, we consider that universal calcium supplementation for pregnant women in the State of Rio de Janeiro, whose diet is known to be deficient in this mineral⁽²¹⁾ as well as 100mg of AAS prophylaxis carried out in those cases of clinical risk factors obtained during the first prenatal consultation seems to be appropriate for our obstetric population.⁽²⁾ Considering the high rates of maternal mortality in our State, led by hypertension during pregnancy/preeclampsia/eclampsia, the impossibility of offering a screening capable of predicting preeclampsia, with greater precision, should not invalidate the policy now established. As Voltaire said: "the best is the enemy of good". Strengthening the line of care for pregnant women, especially universalizing the prediction of preeclampsia through organized screening, even if

only with clinical factors, is a valuable initiative and one that we consider worthy. A more precise guideline, but not applicable in clinical practice (for whatever reason) is worth less than a less comprehensive protocol but widely and immediately implementable in the obstetric routine of the SUS. After all, we are left with Confucius' maxim "better a diamond with a flaw than a pebble without".

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