

## Comparing aspirin 75 to 81 mg vs 150 to 162 mg for prevention of preterm preeclampsia: systematic review and meta-analysis: questionable quality and small study effects?

To the Editor:—Low-dose aspirin prevents preterm preeclampsia, but it is not innocuous. It incurs an increased risk of postpartum hemorrhage, vaginal hematomas, and neonatal intracranial hemorrhage.<sup>1</sup> Hence, targeted treatment with the lowest effective dose is important.

We are concerned by the conclusion of Ghesquiere et al<sup>2</sup> that higher doses of aspirin (150–162 mg) are more effective. Only 3 prevention trials (consisting of 107–210 women) were included in the primary analysis. All were small trials, and 2 trials were not prospectively registered.

Moreover, we have particular concerns about the trial by Kasraeian et al,<sup>3</sup> who randomized 210 women at high risk of developing preeclampsia to 80 or 150 mg of aspirin. Our concerns are as follows:

1. The trial reports an exceptionally high nonsignificant risk reduction of 80% for preeclampsia before 37 weeks of gestation (1/89 women vs 6/101 women; relative risk [RR], 0.19; 95% confidence interval [CI], 0.02–1.54).<sup>2</sup> Given aspirin reduces the risk of preterm preeclampsia by, at most, 60%, this effect is well beyond those reported by larger trials. Particularly given the comparison was 80mg of aspirin and not placebo.
2. The authors report risk reductions of 81% for term preeclampsia cases (2/80 women vs 12/101 women; RR, 0.19; 95% CI, 0.04–0.82) and 91% for all preeclampsia cases (3/89 women vs 18/101 women; RR, 0.09; 95% CI, 0.01–0.71).<sup>2</sup> Larger studies have not found aspirin to reduce the risk of term preeclampsia by this large degree.
3. The exposure groups are not equal; women in the 80-mg group had a higher body mass index and were more likely to have used antihypertensive and antidiabetic medications (preeclampsia risk factors).<sup>3</sup>
4. The authors did not use an intention-to-treat analysis.
5. The trial was registered to recruit 100 participants (identifier: IRCT20140317017035N6) but randomized 210 participants, with no explanation or sample size calculation.
6. There are inconsistencies within their tables. For instance, they stated that 89 of 101 women (88.0%) and 85 of 89 women (95.5%) developed late preeclampsia.<sup>3</sup>

In contrast to this study, the trial by Tapp et al,<sup>4</sup> which does not share the same methodological concerns, reported a more modest and plausible reduction in preterm preeclampsia (1/53 women vs 2/51 women; RR, 0.48; 95% CI, 0.05–5.14).

Aspirin at higher doses may provide a greater benefit for preventing preeclampsia. However, given the limitations of this meta-analysis, the jury is still out. We agree that further high-quality trials are needed, which also assess adverse outcomes. This meta-analysis should not alter clinician practice. ■

Catherine Cluver, MD, PHD  
Department of Obstetrics and Gynaecology  
Stellenbosch University  
Cape Town, South Africa  
Mercy Perinatal  
Mercy Hospital for Women  
Melbourne, Australia

Ellen Kupka, MD  
Department of Obstetrics and Gynecology  
Institute of Clinical Science  
Sahlgrenska Academy  
University of Gothenburg  
Gothenburg, Sweden  
Department of Research and Higher Education  
Center for Clinical Research Dalarna  
Uppsala University  
Region Dalarna  
Falun, Sweden

Susanne Hesselman, MD, PHD  
Department of Research and Higher Education  
Center for Clinical Research Dalarna  
Uppsala University  
Region Dalarna  
Falun, Sweden  
Department of Women's and Children's Health  
Uppsala University  
Uppsala Sweden

Stephen Tong, MD, PHD  
Mercy Perinatal  
Mercy Hospital for Women  
Melbourne, Australia  
Department of Obstetrics and Gynaecology  
The University of Melbourne  
Heidelberg, Australia

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Roxanne Hastie, PHD  
Mercy Perinatal  
Mercy Hospital for Women  
Melbourne, Australia  
Department of Women's and Children's Health  
Uppsala University  
Uppsala Sweden  
Department of Obstetrics and Gynaecology  
The University of Melbourne  
Heidelberg, Australia

Lina Bergman, MD, PHD  
Department of Obstetrics and Gynaecology  
Stellenbosch University  
Cape Town, South Africa  
Department of Obstetrics and Gynecology  
Institute of Clinical Science  
Sahlgrenska Academy  
University of Gothenburg  
Gothenburg, Sweden  
Department of Women's and Children's Health  
Uppsala University  
Uppsala Sweden  
[lina.bergman.2@gu.se](mailto:lina.bergman.2@gu.se)

R.H. and L.B. have joint last authorship.

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## REFERENCES

1. Jiang Y, Chen Z, Chen Y, et al. Low-dose aspirin use during pregnancy may be a potential risk for postpartum hemorrhage and increased blood loss: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2023;5:100878.
2. Ghesquiere L, Guerby P, Marchant I, et al. Comparing Aspirin 75 to 81 mg vs 150 to 162 mg for prevention of preterm preeclampsia: systematic review and meta-analysis. *Am J Obstet Gynecol MFM* 2023; 5:101000.
3. Kasraeian M, Asadi N, Vafaei H, et al. The effect of 150 and 80 mg doses of aspirin on preventing preterm birth in high-risk pregnant women. *J Perinat Med* 2022;50:1264–70.
4. Tapp S, Guerby P, Girard M, et al. A pilot randomized trial comparing the effects of 80 versus 160 mg of aspirin on midtrimester uterine artery pulsatility index in women with a history of preeclampsia. *J Obstet Gynaecol Can* 2020;42:1498–504.

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