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Title	**Estimated reductions in provider-initiated preterm births and hospital length of stay under a universal aspirin prophylaxis strategy**: a cohort study
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Reviewer 1	Stéphanie Roberge
Institution	Faculté de Médecine, Université Laval, Médecine Sociale et Préventive
General comments (author response in bold)	This is an interesting study aiming at estimate the impact of a universal program of aspirin (ASA) to all pregnant in Canada using modeling simulation. The authors used a Canadian valid cohort and were strict on preeclampsia and IUGR definition, the two major outcomes that aspirin could prevent. They suggest that universal ASA program could reduce a significant number of maternal and newborn LOS. 1) While the idea and the study are interesting and well-designed, there are several major flaws that can't be overlooked: aspirin has never been tested in general population (most included RCT's estimate the impact of ASA on high-risk women). In RCTs, women are typically screened by research personal, making sure that any women with small contra-indication to ASA are excluded. In RCTs, observance to treatment is followed in women a priori interested to participate in such study. **Answer: As indicated in our response to the editors' comments, the Background now explains why we have modelled a universal approach to aspirin prophylaxis. Additionally, we speak to the assumption and limitations underlying our analyses in the Methods and Interpretation section of the paper – also as indicted above**. 2) In the current study, there are major issues that are not addressed and not enough studied; observance; potential downside or secondary effects of a universal aspirin screening program that should be included before considering publication. Moreover the author should precise what are the details of the national program, including the target population, how to screen, what dosage of aspirin should be administered, what is the time of administration, at which gestational age to stop the treatment, what are the secondary effect of aspirin on women who don't need it... I think that this study is very interesting but too early in the circumstances. Considering all those issues that needed to be clearly define, such programme cannot be implanted before those issues are completely answer, in order to really be beneficial for the women. **Answer: The intention of this study is not to call for a universal program, as we agree that current evidence does not support such a recommendation. We acknowledge that in the Background and restate it at the end of the paper as follows:** "… However, until there is compelling evidence that administration of ASA to all, or most, pregnant women can reduce the risk of preeclampsia and/or intrauterine growth restriction, clinicians should continue to follow current clinical practise guidelines.8-10. …" **Answer: We have stated and referenced in the Background the nature of dosage, timing and safety of ASA as reported in the literature.** " … Among women at increased risk of preeclampsia, clinical practice guidelines in Canada and elsewhere recommend daily low-dose (60-162 mg) aspirin (ASA) for the prevention of preeclampsia and intrauterine growth restriction,8-10 based on convincing evidence from randomized clinical trials.11-13 Initiation of ASA between 12 and 28 weeks gestation and continued until delivery, may reduce preterm preeclampsia by as much as 89% (95% CI 67 to 96)14 and intrauterine growth restriction by 56% (95% CI 35 to 70).12 … ASA is extremely inexpensive, and its adverse effects for mother and fetus appear neglible.20,21 …"
Reviewer 2	Yasseen Abdool
Institution	Ottawa Hospital Research Institute, Clinical Epidemiology, Ottawa, Ont.
General comments (author response in bold)	1) Introduction:- Wide spread adoption of ASA prophylaxis is lacking. The authors should state what information (if any) is known about current rates of ASA use within the population. **Answer: Unfortunately, data on the level of adoption of ASA prophylaxis in Canada is not available, but has been reported to be low in Sweden and South Africa where prophylactic ASA is also recommended, and anecdotal discussions with clinicians suggest that this practice remains low in Canada. We have indicated this in the Background as follows:** **"… Despite the evidence and recommendations for ASA prophylaxis, the level of adoption in Canada is uncertain, but likely low, just as elsewhere.15,16…"** 2) The objectives of this study are explained well, however, it could be improved by including the (post hoc?) assessment of cost-savings, introduced in the discussion. If however, this assessment is post hoc, this should be clearly stated within the discussion section. **Answer: The assessment of cost-savings was not a study objective, but was added as a discussion point to give an indication of potential cost savings in relation to reduced lengths of stay. Consequently, these calculations were not derived using rigorous health economics methods. For example, calculations do not take into consideration costs such as NICU care and caesarean section delivery, or life time costs of care of infants born with preterm-related disabilities such as cerebral palsy. In light of our informal approach to estimating costs (which likely underestimates costs), we think it is best to leave this as a discussion point rather than a study objective.** 3) Methods:- **Answer: As indicated in our response to the editors' comments, we have now specified key assumptions at the beginning of the Methods section, including assumption 1 and 3 specified by Reviewer 2. We did not add suggested assumption 2 – "Any severity of PE or IUGR is associated with PI-PTB". This assumption is not applicable to our analyses, as our analyses excluded cases of PE and/or IUGR that were not associated with PI-PTB.** Line 36, page 4, I disagree with the use of the term simulation in the description of this study design. Perhaps, the authors should indicate that they juxtaposed ASA efficacy rates to highlight potential health care gains. Or simply that they provided an unadjusted estimation.

Answer: We have removed the term simulation. The relevant sentences now read:

" … We completed a retrospective population-based cohort study of 269,303 singleton live born or stillborn hospital births in Canada in 2013. … Next, we juxtaposed low and high RRRs for ASA's efficacy to generate unadjusted estimates of the total number of maternal and newborn affected cases and hospital-days that might be prevented if all pregnant women took ASA prophylactically. …"

4) Line 38 on page 4, should read "269,303 singleton LIVE BORN OR STILLBORN hospital births", which is more descriptive.

Answer: As indicated the response to the preceding comment, the sentence has been revised, as suggested.

5) How was gestational age measured within this cohort, date of last menses, ultrasound, or a combination? This should be stated clearly in the methods.

Answer: The following sentence has been added to the Methods to indicate how gestational age was measured.

"… Gestational age in the Discharge Abstract Database is derived from the best clinical estimate recorded in the medical chart -- based on ultrasound dating or the last menstrual period.24 …"

6) Why not be consistent in the definition of small for gestational age 3rd percentile, rather than use it as a proxy for IUGR? This is what was measured, and it should be stated as such.

Answer: Small-for-gestational age < 3rd percentile is the study outcome measured. However, we use it as a proxy for IUGR for two reasons. First, we needed to use an "IUGR" diagnosis in the rare situation where actual birthweight was not available. More importantly, the concept of IUGR is really reflected by severe growth restriction, especially in preterm infants. Ananth argued this in his paper https://www.ncbi.nlm.nih.gov/pubmed/19786331 . It is this concept of IUGR that we are reflecting in this paper, as it is the target condition that one would be preventing with ASA use (along with preecplampsia). It is at SGA < 3rd percentile that the risk of stillbirth is much higher (http://www.nature.com/jp/journal/v32/n11/full/jp201260a.html), as is the risk of neonatal death (http://www.nejm.org/doi/full/10.1056/NEJM199904223401603#t=article). We defend our use of IUGR, accordingly.

7) The authors state that additional (less accurate) estimates could be obtained with the use of SGA10, instead of SGA3. Why not repeat the analysis on SGA10, to provide actual numbers to your contrast in the discussion. You could include this in the supplemental information, but should mention it within the discussion text.

Answer: We choose not to use SGA10 in our analysis, as this cut-off is known to include children who are not pathologically growth restricted. Although a secondary analysis using SGA10 would increase the number of IUGR cases, and therefore, also increase the number of cases and related hospital days that could be potentially averted, given that some of the assumptions underlying our analyses may overestimate the number of preventable cases, we think it is prudent to only present results for the strict definition of SGA3, as rationalized in our response to #6 immediately above.

8) Line 31 page 5, RRR needs to be defined prior to using it as an acronym.

Answer: This acronym is spelled out at the end of the Methods section, prior to its first use.

9) Line 31 page 5, I'm unsure where the range of values for ASA efficacy came from. Reference 10 looks only at PE, and shows a general reduction of 0.9. Whereas reference 11 looks both at PE and IUGR, showing reductions of 0.47 and 0.68 for PE at intervention <16 weeks and overall, respectively; and 0.44 and 0.85 for IUGR at intervention <16 weeks and overall, respectively. In the current manuscript, the origin of these estimates needs to be explained clearly.

Answer: The ranges of ASA efficacy used in the study are taken from Askie et al (2007) and Bujold et al (2010), formerly references 10 and 11 (now references 11 and 12) respectively. Table 4 in Askie et al presents relative risks of 0.9 for both preeclampsia and small for gestational age, which equates to a relative risk reduction of 10% (1-0.9). Table 4 in Bujold et al presents, for ASA initiated prior to 16 weeks, relative risk of 0.47 for both preeclampsia and IUGR (less than the 10th percentile) which equates to a relative risk reduction of 53% (1-0.47). Bujold et al presented relative risks for IUGR less than 10th percentile and IUGR any definition (0.44). These relative risks did not differ significantly, but we utilized the 10th percentile relative risk, as it was unclear what "any definition" included. The relevant section of the manuscript, reads as follows:

"… We estimated the range of piPTB that would be prevented if ASA prophylaxis conferred the lowest (10%)11 and highest (53%)12 RRR for preeclampsia, and small-for-gestational age or intrauterine growth restriction, reported in meta-analyses of randomized controlled trials. …"

10) I'm assuming that point estimates were used to produce lower and upper bounds to the efficacy of ASA treatment. However, it might be more representative to use the actual upper and lower bounds for each summary estimate reported in reference 11 (i.e. 0.68 [0.54, 0.86] for PE and 0.85 [0.87, 1.00] for IUGR, reported in figures 2 and 3 of reference 11). Additionally, these overall estimates – in contrast to the early intervention estimates (<16 weeks) – represent a more robust and inclusive representation of the efficacy of ASA.

Answer: First, we used the point estimates of relative risk reductions of 10% and 53%, rather than their associated 95% confidence intervals, because statistically these values represent the best unbiased estimate of the true effect reported in each study.

Answer: Second, the range of efficacy represented by Askie et al and Bujold et al is more representative of the literature on the potential effect of ASA than the overall estimates in Bujold et al only, noting that Askie et al's population was also not restricted to early intervention (only 59% of women began therapy before 20 weeks gestation). Askie et al's relative risks of 0.9 for preeclampsia nd small-gestational-age are more moderate than Bujold et al 0.68 for preeclampsia and 0.85 for IUGR. Askie et al therefore provides a more conservative lower bound.

11) Was there REB submission for this project, and to whom or which institutions?

	Answer: No REB submission was required for this project. The following sentence was added to the end of the Methods section. **"… No research ethics board submission was required for this project, as all analysis used denominalized hospital discharge abstract data."** 12) Results:- Line 53 page 5, LOS needs to be defined prior to its use. **Answer: The acronym LOS is no longer used in the document.** 13) Line 54, page 5, should read "among term births with birth PE and IUGR" **Answer: We verified that the wording "among term births unaffected by preeclampsia or intrauterine growth restriction" is correct.** 14) Perhaps the information in figure 2 would be better represented in a tabular form, and the information in figures 3 and 4 could be combined into one figure (as they have identical axis and subgroup categories), where maternal and infant LOS could be displayed and compared more easily for the reader. **Answer: We considered presenting figure 2 in tabular form, but prefer the visual representation as this aids in the comparison of proportions across subgroups. With respect to figures 3 and 4, although subgroup categories are identical, horizontal axes vary (0-20 for maternal results, 0-70 for newborn results). Combining the figures would result in a loss of discrimination for maternal results; we have therefore left the figures separate.** 15) Supplemental files 1 and 2 should be included as a single figure (or two sub figures) in the manuscript. **Answer: These files are now included in the manuscript, as figures 5 and 6.** 16) Interpretation:- Strengths and limitation section should spell out and explain caveats associated with the key assumptions made in conducting the analysis (see above for those identified by this reviewer). **Answer: As indicated previously, we have revised the Strengths and Limitations section to address key assumptions.** 17) A short description of the uncertainty associated with the estimated results is needed to remind the reader that these numbers are based on the above mention assumptions. **Answer: As indicated previously, we have revised the Interpretation section to describe the uncertainty associated with the results.** 18) Lines 12-19 page 7, The end sentence in the clinical and policy relevance section seems like it should be in the limitations section, as it pertains more to drawbacks in the study design. **Answer: The sentence has been moved and integrated into the Strengths and Limitations section.** 19) The potential direct cost savings section could be combined with the policy relevance section, as this pertains to the potential impact of implementing an ASA program, and has direct relevance to the development of policy. **Answer: The Potential Direct Cost Savings section has been combined with the Policy Relevance section, as suggested.**