

Article details: 2019-0014	
Title	<b>Prenatal bed rest in developed and developing regions: A systematic review and meta-analysis</b>
Authors	Brittany Matenchuk BSc, Rshmi Khurana MD, Chenxi Cai PhD, Normand G. Boulé PhD, Linda Slater MLIS and Margie H. Davenport PhD
Reviewer 1	Review withheld
Institution	
General comments and author response	<b>Author response:</b> We thank the reviewer for this thoughtful comment. Our results indicate that in developed regions, bed rest increases the odds of having a very premature baby by 169%. Further, women placed on prenatal bed rest in developed regions were twice as likely to deliver a baby <1500g compared to women who were not placed on bed rest. We believed these are strong evidence to support that bed rest in developed countries has a poor fetal outcome. We only included RCT, therefore there are not systematic factors which could bias why some a prescribed bed rest or not. Moreover, a sensitivity analysis was performed to evaluate whether the effects were different when examining relationships between the different indications for bed rest and maternal/infant outcomes. Our analysis suggested that there were not significant between the different indications for bed rest and maternal/infant outcomes.
Reviewer 2	Natalie Dayan
Institution	McGill University Health Center, Medicine, Montréal, Que.
General comments and author response	<p><b>COMMENTS FROM REVIEWER 2:</b></p> <p>This is a well-written systematic review on the effect of bedrest in pregnancy on maternal and fetal/neonatal outcomes. The methodology is sound and up to date. The study was registered on PROSPERO. The authors found overall no impact of bedrest when compared to no bedrest on maternal and fetal/neonatal outcomes in developed countries but not in Zimbabwe.</p> <p><b>C1:</b> Was there a language restriction? This is important because the authors attempt to stratify on developed versus underdeveloped countries and are only able to include studies from Zimbabwe in the underdeveloped stratum. Perhaps extending to non-English language articles would yield more studies from underdeveloped areas.</p> <p><b>R1:</b> Thank you for your comment about the rationale for language restriction. We emphasize the importance of non-English language articles, so our analysis was not restricted by language (method section, page 6, line 155-156).</p> <p><b>C2:</b> In the methods section, how many studies per outcome were required before pooling and what was the maximum <math>I^2</math> statistic required for pooling (typically no more than 70%)?</p> <p><b>R2:</b> We thank the reviewer for this thoughtful comment. There is no minimum number of studies per outcome was required before pooling. We agree with you that 70% is considerable heterogeneity and the statement has been added in the revised manuscript. We have added the following information to the revised version of the manuscript on page 8. <i>Line 207: Meta-analysis for a given outcome was not performed if the <math>I^2</math> was above 70%.</i></p> <p><b>C3:</b> I am not sure why the authors are presenting the quality along with the pooled results. Typically, quality is presented for each study separately. It is distracting. Please report the results by outcome and then have a separate section for quality.</p> <p><b>R3:</b> Thank you for your comment about presenting the quality. The GRADE committee suggests that GRADE rates the quality of evidence for each outcome across studies rather than for each study<sup>1</sup>. We added a risk of bias table for each study in the online supplemental document (online supplement table 3).</p> <p><b>C4:</b> Please reference the studies included in each outcome and indicate the <math>n</math> of each pooled result. This was forgotten for some. I would also suggest separating maternal from</p>

	<p>fetal/neonatal outcomes in the results section, and using subheadings.</p> <p><b>R4:</b> We thank the reviewer for this comment. We reference the studies included in each outcome and indicate the n of each pooled result in our revised manuscript. We also separated maternal from fetal/neonatal outcomes in the results section and using subheadings in our revised manuscript.</p> <p><b>C5:</b> The authors offer very little explanation or thought as to why the results are distinct by developed versus underdeveloped nations. One possibility might be that standard care differs between studies, sites and geographic areas. In fact, this would explain much of the heterogeneity. A more in-depth discussion of the variety of “standard care” across studies would be helpful.</p> <p><b>C5:</b> We thank the reviewer for this comment. The discussion of the ‘standard care’ across studied were inappropriately removed in reformatting to fit the word count for CMAJ. Thank you for highlighting this error.</p> <p>The following statement has been added o the conclusion (page 15, line 369-379):</p> <p><i>It is important to note that all trials of bed rest in undeveloped countries were conducted in Zimbabwe. As Zimbabwe has one of the highest rates of maternal and fetal morbidity and mortality in the world, our findings from undeveloped countries may not be generalizable to other developing countries. In the analysis of undeveloped countries (Zimbabwe), bed rest treatment was conducted in hospital and no-bed rest treatment was conducted at home. In undeveloped countries, low birth weight is associated with hypertensive disorders of pregnancy and pre-eclampsia, nutritional status of the mother, anemia, and access to health care 2. Hospitalization may afford improved access to skilled healthcare workers, sanitation, and nutritional status monitoring, thereby reducing the risk of low birth weight infants 2. It is beyond the scope of this review to determine if bed-rest or hospitalization itself improved birthweight.</i></p> <p><b>C6:</b> Do not use the term “pregnancy induced hypertension” — it is no longer a standard accepted term. “Gestational hypertension” is preferred.</p> <p><b>C6:</b> We thank the reviewer for this comment. We replaced the term Pregnancy Induced Hypertension by hypertensive disorders of pregnancy in the revised manuscript.</p> <p><b>C7:</b> The authors should be cautious in stating that bedrest did not improve maternal outcomes. Based on this review, there is insufficient evidence for this statement (few studies of low quality).</p> <p><b>C7:</b> We thank the reviewer for this comment. We have changed our statement in the revised paper.</p> <p>The following statement has been revised (page 14, line 345-347):</p> <p><i>The primary indication for bed rest is to prolong gestation and promote development towards term; however, the findings of our meta-analysis from limited studies do not support the use of bed rest to improve those outcomes.</i></p>
<b>Reviewer 3</b>	David Henry
Institution	Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre, Toronto, Ont.
General comments and author response	<p><b>COMMENTS FROM REVIEWER 3:</b></p> <p><b>General comments:</b></p> <p>The authors set out to conduct a systematic review of randomized trials of bed rest in pregnancy after 20 weeks gestation. They then go on to apply the GRADE instrument to determine the quality of evidence and some recommendations that can be based on this literature. Their main conclusion is that “In developed regions, treatment of complicated pregnancies with prolonged bed rest results in worse newborn outcomes.” At one level the authors appear to have done a solid job. They registered their protocol and followed the recommended process for planning and conducting a systematic review. However, more detailed assessment of their work raises some important questions and some serious doubts. In view of those doubts I don’t think its appropriate to apply a GRADE assessment until the</p>

numbers are agreed upon, so my comments are confined to the systematic review and I focus on a few specific issues.

**C1:** The authors' PICO is not clear. Studies in the literature have defined a setting in which bed rest was considered useful – eg PROM, multiple fetuses, pre-eclampsia etc. The authors appear to include all women at 20 weeks or later. I am unclear which population of patients they were interested in and how that maps to the populations in the trials that they included. It is also unclear which outcomes they were most interested in – either maternal or fetal.

**R1:** Thank you for your comment about the PICO. The PICO was applied in the revised manuscript for better clarity.

The following sentences has been revised (page 5):

*Eligibility Criteria*

*The PICOS (population, intervention, comparison, outcome, study design) framework was used to guide this review.*

*Population*

*The population of interest was pregnant women.*

*Intervention*

*The intervention was standard care (including tocolytics, anti-hypertensive medications) plus bed rest (including activity restriction; hospitalized or at home). Bed rest was defined as a prescribed restriction of activity encompassing the majority of waking hours for >1 week (13).*

*Comparison*

*Eligible comparators were: standard care without activity restriction (no bed rest).*

*Outcome*

*Fetal outcomes included birth weight, small at birth (birth weight <1500 g and <2500g), or small for gestational age (SGA: less than the 10th percentile for gestational age and sex), gestational age, premature delivery (<37 weeks at birth), very premature delivery (as defined by the author <35, <34 or <32 weeks at birth), perinatal death and admission to the neonatal intensive care unit (NICU). Maternal outcomes included preterm rupture of membranes (PROM), hypertensive disorders of pregnancy, pre-eclampsia, and gestational diabetes mellitus (GDM).*

*Studies were not excluded due to language of publication or publication format (e.g., abstracts only).*

*Study design*

*Eligible studies are randomized controlled trials.*

**C2:** There is no rationale given for studying outcomes by 'developed' and 'undeveloped' countries. The term 'undeveloped' hasn't been used for some time. It is better to talk about 'developing' or more appropriately about 'middle' and 'low' income countries. Zimbabwe certainly qualifies for the latter. However, it is doubtful if trials run at an urban hospital in Harare in the 1990s by an experienced Australian investigator truly reflect the challenges of providing obstetric care to complicated pregnancies in resource-poor settings. So, I question the authors' stratification of the results.

**R2:** Thank you for your comment. The developmental status of the region in the year the study took place based on the World Bank country definition in the World Development Indicators database. These definitions intend to reflect basic economic region conditions<sup>3</sup>. We believed Zimbabwe in the 1990s belonged to 'undeveloped' country instead of 'developing country'. The trials run by an experienced Australian investigator, but the women have received the normal hospital care which reflected the obstetric care in Harare.

**C3:** I am concerned about the authors' premise that their work is original and advances knowledge significantly. My reason for saying this is that there are three relevant Cochrane Reviews that don't seem to be mentioned in the paper. One of them is authored by the principal investigator of the Zimbabwe trials (Crowther) referred to in this paper. The details of the reviews are given below. I may have missed a reference to them in the document, but I searched on authors' names and could find nothing. The authors should be very clear in

showing how this present review builds on the information in the Cochrane reviews.

**R3:** Thank you for your comment. Discussion of the previously published reviews was inappropriately removed in reformatting to fit the word count for CMAJ. Thank you for highlighting this error. Previous reviews of bed rest and pregnancy outcomes generally demonstrated that there were no harms or benefits of bedrest during pregnancy; however, high heterogeneity was highlighted as an issue for several outcomes. In contrast, our review demonstrated that bedrest is harmful in developed (but not undeveloped countries) such as Canada or the United States. This finding was associated with low, often 0% heterogeneity.

A discussion of previous reviews was added in the revised manuscript (page 4, line 114-117; page 14, line 358-359).

Page 4: *However, previous meta-analyses focus on multiple or singleton pregnancy suggested there is little evidence to support a policy of routine hospitalization for bed rest 4,5. However, high heterogeneity was highlighted as an issue for several outcomes.*

Page 14: *Overall, bed rest increased birth weight by 80g in twin/triplet pregnancies compared to the no bed rest group. This finding is in line with other review on bed rest for multiple pregnancy 4.*

**C4:** I have trouble reconciling the numbers in some of the Figures with those in Online Supplement Table 1. For instance, the sample sizes for the individual trials in Figure 4 agree with Table 1. But the sample sizes in Online Supplement Figure 2 are larger for each trial and this discrepancy is not explained clearly.

**R4:** Thank you for your comment. The different sample size between online supplement figure 1 and 2 because figure 1 reported the number of women while figure 2 reported the number of births. Some of the women have twin or triplet pregnancies, so the sample size was different. All the sample size (women and births) was based on the reports of studies.

**C5:** I also have trouble with the calculations they have made. First, the actual event rates are very variable across trials. For instance, very preterm birth rates in developed regions vary from 0% (Mathews) to 100% (Bigelow). This should give rise to great caution about whether these results should or can be combined. In addition, the OR is not a good estimator of the RR when event rates are as high as in some of the studies included here.

**R5:** Thank you for your comment about the Mathews study and the Bigelow study. These two studies have a huge difference in very preterm birth rates. We did not exclude them because their Odds Ratio could not be estimated (since both groups had either 0% or 100% events) in RevMan so they did not contribute to the data.

**C6:** In relation to 5) the standard software will not include Mathews and Bigelow when trying to calculate a pooled odds ratio or rate ratio (as seen in Fig 4). But these studies contribute important information. In contrast, all the studies can be included in an analysis of risk differences. Using the data in Fig 4 (very pre-term birth), I estimate a pooled risk difference of 0.042 (95% CI = -0.029 to 0.11 - DSL). Notably the I2 value is 61% with inclusion of Mathews and Bigelow, very different from what the authors found. Set against a background rate of 14.4% (no bed rest) this gives an indicative pooled RR of 1.3 (95% CI 0.79, 1.79) in otherwords not statistically significant. These calculations are approximations, but they indicate that the conclusions depend very much on the method of analysis and the studies that are included. One of the authors' main findings of an increase in very premature births with bed rest is not supported.

**R6:** Thank you for your comment. We agree with your C5 comment suggesting that these two studies which should not be combined with the others in the meta-analysis. We mentioned how the very preterm birth rates were very different in these two studies and why (statistically) they did not contribute to the ORs in our revised paper for better clarity. We believe that using OR to report the outcome is more suitable than RR as these two studies did not contribute to the data. We carefully checked the manuscript and avoided using "risk" instead of "odds" for better clarity.

A statement was added in the revised manuscript (page 10, line 259-261).

*However, it should be noted two studies in developed regions did not contribute to the pooled ORs due to the very preterm birth rates in 0% and 100%<sup>6,7</sup>.*

**C7:** I am not going to comment on the authors' use of the GRADE process as it rests entirely on the validity of their systematic review and meta-analysis. I think it is premature to develop strength of recommendation statements when the underlying data are in doubt. I think the GRADE table they present should be replaced by a detailed risk of bias assessment for the candidate RCTs, including a discussion of the main threats, including lack of concealed randomization. It would also be helpful to assess the quality and completeness of their methods using the revised AMSTAR 2 instrument available full text from the BMJ website.  
**R7:** Thank you for your comment. We added a risk of bias table for each study in the online supplemental document).

#### **Reference**

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3. World Bank Country and Lending Groups. <http://data.worldbank.org/about/country-classifications>. Published 2018. Accessed 2018.
4. Crowther CA, Han SJ, Do SR. Hospitalisation and bed rest for multiple pregnancy. 2010(7).
5. Sosa CG, Althabe F, Belizan JM, Bergel E. Bed rest in singleton pregnancies for preventing preterm birth. *Cochrane Database Syst Rev.* 2015(3):CD003581.
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7. Bigelow CA, Factor SH, Miller M, Weintraub A, Stone J. Pilot Randomized Controlled Trial to Evaluate the Impact of Bed Rest on Maternal and Fetal Outcomes in Women with Preterm Premature Rupture of the Membranes. *Am J Perinatol.* 2016;33(4):356-363.