Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Cervical Ripening in the Outpatient Setting*

Draft report available for public comment from August 13, 2020 to September 28, 2020.

Research Review Citation: McDonagh M, Skelly AC, Hermesch A, Tilden E, Brodt ED, Dana T, Ramirez S, Fu R, Kantner SN, Hsu F, Hart E. Cervical Ripening in the Outpatient Setting. Comparative Effectiveness Review No. 238. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I for the Agency for Healthcare Research and Quality and the Patient-Centered Outcomes Research Institute.) AHRQ Publication No. 21-EHC011. PCORI Publication No. 2020-SR-03. Rockville, MD: Agency for Healthcare Research and Quality; March 2021. DOI: 10.23970/AHRQEPCCER238.

Comments to Draft Report

Draft reports from the Effective Health Care Program undergo peer review and public comment. The Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program website or AHRQ website for public comment for a 3- to 4-week period. Comments can be submitted via the website, mail, or email. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Summary of Peer Reviewer Comments and Author Responses

This research review underwent peer review before the draft report was posted for public comment on the EHC website. The peer reviewers and Technical Expert Panel comments were largely positive. Themes that emerged included clarifications in the text, particularly the structured abstract, emphasizing flaws of the evidence base in summaries, avoiding using nonstandard abbreviations, questions over outcomes that were not prioritized for this review or where no evidence was found, and concerns over confounding. The reviewers also made several recommendations regarding future research recommendations. The review authors' responses to these common themes, and are outlined below.

- Nonstandard abbreviations (e.g. CR and CB) were removed, with each spelled out in the text. Other examples of language that were improved was the use of the word "safe" when referring to harm outcomes that were not statistically significant.
- Authors clarified text in the abstract and introduction, providing clearer language and more details where needed. Corrections were made to Appendix A, Table of Interventions.
- Reviewers expressed a desire to see more information on baseline characteristics such as body mass index (BMI) and race. These were not reported well, and were noted in study limitations and as areas for future research. Concerns over the limited or unknown applicability of the evidence, regarding race and ethnicity, were also noted in the Applicability discussion.
- Reviewers had concerns over terms and definitions used in the report, such as "post-term" and "failed induction." Authors added more details to the results text where possible, and noted the variability in how these were defined or reported as issues for study limitations and future research needs.
- The low strength of evidence, and inadequate evidence (missing or insufficient) was noted more clearly in the abstract, key messages, and conclusions.
- Specific concerns around potential confounding or effect modification were raised regarding parity, race or ethnicity, other interventions (oxytocin, epidurals), BMI, and interventions that require an open cervix (catheters, membrane sweeping). These were addressed by revising results text to be clearer on what data were available and which were not, and these concerns were addressed in the discussion section.
    - Parity: Noted that there were differences in how studies reported parity, some not reporting on it at all, and that some studies conducted subgroup analysis on this variable and others did not. Noted in study limitations that because of this variability, the results on the impact of parity are unclear.
    - Baseline Bishop score in studies of interventions that require an open cervix were rarely reported, or reported only as a median/mean for the whole group, not by intervention group. Noted this in study limitations in the discussion.
    - Other interventions such as oxytocin or epidural anesthesia were noted to have been inadequately reported to evaluate.
- Reviewers suggested additional areas for future research recommendations, such as registry and quality improvement studies, specific sample size recommendations, subgroup analyses, race and ethnicity, and evaluation of other harms or potential effect modifiers of harms. These were incorporated in to the report.

Commentator & Affiliation	Section	Comment	Response
Luci Roberts, National Institute on Aging	Title	I found the title to be misleading. The report should be titled "Induced Cervical Ripening in the Outpatient Setting" because cervical ripening happens without medical intervention in most women in the hours/days leading up to delivery, and the title suggests this ordinary phenomenon is what the report examines.	Thank you for this suggestion, the title for the report has been finalized prior to this posting.
Jean Salera-Vieira, AWHONN	Evidence Summary	Well written summary. Conclusions based on total sample 9,465 women and studies ranked as low or insufficient strength. Rare adverse outcomes did not allow for comparison between methods/groups. Fetal surveillance was not studied and therefore unable to be evaluated.Any type of outpatient monitoring for the mother and fetus was not studied and therefore unable to be evaluated. Maternal wellbeing in terms of psychological effects was not studied. Insufficient evidence on important outcomes such as perinatal mortality and time from admission to vaginal birth.	Thank you for this summary.
Sharon Ryan, American College of Nurse Midwives	Evidence Summary	The selection and inclusion of studies appears comprehensive and appropriate. The evidence summary is concise and clear, especially by starting with the main points. Nurse-midwives should be hyphenated throughout the document. A suggestion would be to move a sentence from results to the main points that the highest strength of evidence for ANY outcome was low-strength. This puts the review in context and frames the discussion and implications section. Tables of studies under each Key Question in this section is very helpful for quick looks at such a comprehensive document.	Thank you for these suggestions. We have taken your advice in the final report.

Commentator & Affiliation	Section	Comment	Response
Jean Salera-Vieira, AWHONN	Introduction	Well written.	Thank you.
Sharon Ryan, American College of Nurse Midwives	Introduction	Clear and concise Does OHSU exemplify IOL rates in all tertiary care centers? It was interesting to see one setting called out for a review such as this. The introduction section is helpful because it provides the context for the study and acknowledges many of the nuances beyond what this study covers. The second to the last sentence in the Background section is important and suggested to be moved up sooner in this section.	Thank you for this comment, we have removed this notation.
Jean Salera-Vieira, AWHONN	Methods	Appropriate, very detailed and well written.	Thank you.
Sharon Ryan, American College of Nurse Midwives	Methods	It is unfortunate that only low strength evidence is available The analytic framework is helpful and provides a grounding in the various methods employed in an ER.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Jean Salera-Vieira, AWHONN	Results	Conclusions are based on a total small sample that was unable to fully evaluate potential maternal or fetal harms and involved studies of low or insufficient evidence. The result statements, especially the statement about no studies on fetal surveillance, do not support the conclusion. The recommendations for changes include changing the conclusion to state that fetal safety is unknown because no studies included fetal surveillance.	Thank you for this comment. The Key Question on fetal surveillance was not specific to outpatient versus inpatient settings. This question was separate, and focused on identifying evidence on outcomes (benefit and harms) of fetal surveillance when a prostaglandin was used for cervical ripening. These studies could compare surveillance methods or to no monitoring. However, we did not find evidence that meet our criteria. The conclusions about fetal/neonatal harms are relevant to the evidence on outpatient versus inpatient cervical ripening, and many studies did use fetal surveillance. Please refer to our Evidence Tables, and report text for details.
Meg Seymour, National Center for Health Research	Results	Forty percent of the studies in the review were not in the United States. Depending on the health care system, insurance coverage, and procedure affordability, patients' experiences may vary significantly between countries. The review would therefore be more informative if it separately reviewed studies in the U.S. and other countries. We also note the need for studies on long-term outcomes such as breastfeeding, mother and baby health and mood, and mother-baby attachment.	Thank you for these comments. We initially hoped to be able to conduct subgroup analyses based on US vs. non-US studies. Ultimately, we did not have enough studies for a given comparison to do that. The Key Question with the largest number of non-US studies was KQ2 on mechanical methods of cervical ripening. In that question, 2 of 3 single-balloon RCTs, 0 of 1 double-balloon RCTs, and 0 of 2 catheter vs prostaglandin RCTs were conducted in the US. Removing all non-US studies would lead to insufficient evidence across the board. We searched for longer-term outcomes, such as those listed, but did not find any evidence.

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Sharon Ryan, American College of Nurse Midwives	Results	The results will have implications beyond the hospital setting. If ripening at home is considered an appropriate and safe practice patients may wish this option for their intended community birth. The baseline characteristics of subjects by each KQ was helpful as was the Key Points under each Key Question results. The narrative of the results are clear and while likely written by multiple reviewers, flows well with similar style.	Thank you.
Jean Salera-Vieira, AWHONN	Discussion	Conclusions are based on a total small sample that was unable to fully evaluate potential maternal or fetal harm and involved studies of low or insufficient evidence. The evidence is not such that conclusions can be made that outpatient cervical ripening is safe for the mother and fetus based on the sample and strength of evidence. Regarding "Research Implications" - future research recommendations include nursing care implications in caring for patients in the outpatient or inpatient cervical ripening, as well as patient centered researcn ad reported outcomes (beyond patient satisfaction).	Thank you for this summary.

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Jean Salera-Vieira, AWHONN	Discussion	Yes. However, we are not in agreement with the results and conclusions as written. The evidence strength is low, as mentioned in this draft. In our opinion, more RCTs need to be conducted to gather enough evidence to support outpatient cervical ripening with pharmacologic agents and to support development of a clinical guideline. Further, the conclusion should reflect that there is no evidence of fetal safety due to the lack of inclusion of fetal surveillance in studies. We also support clinincal options that keep mothers and infants safe, and engaging women directly in their care decisions.	(note: the "yes" is in response to a readability question about results/conclusions) Thank you for these comments. We agree that more high quality, large, RCTs are needed. Please see our Future Research section for our recommendations. With regard to the comments on "no evidence of fetal safety due to the lack of inclusion of fetal surveillance in studies", we point out that the question addressed here was very specific and does not cover all aspects of fetal safety related to fetal surveillance. The question here was about outcomes (benefits and harms) of fetal surveillance when a prostaglandin was used for cervical ripening. It is not a comparison of outpatient and inpatient surveillance. We did not find evidence that met the specific criteria for this review. For each Key Question and comparison, however, we do include descriptions of the fetal monitoring protocols used by the included studies (if reported by the authors). For example on page 10, we described: "Continuous fetal heart rate (FHR) monitoring was done for 30 minutes[61] to 1 hour[30,32,55] post dinoprostone insertion; one study reported a maximum of 2 hours of monitoring.[25]" Furthermore, on page 47, in the Discussion, we have added: "Although many of the studies on the outcomes of outpatient cervical ripening reported on the fetal heart rate (FHR) monitoring protocols used in the trials, we did not find evidence examining the benefits and harms of different protocols for FHR during cervical ripening with prostaglandins in any setting."

Commentator & Affiliation	Section	Comment	Response
Meg Seymour, National Center for Health Research	Discussion	National Center for Health Research's Comments on the Agency for Healthcare Research and Quality's Draft Systematic Review Regarding Cervical Ripening in the Outpatient Setting We are writing to express our views on the Agency for Healthcare Research and Quality's (AHRQ) draft systematic review regarding the comparative effectiveness and potential harms of cervical ripening in the outpatient versus the inpatient setting. The National Center for Health Research (NCHR) is a nonprofit think tank that conducts, analyzes, and scrutinizes research on a range of health issues, with particular focus on which prevention strategies and treatments are most effective for which patients and consumers. We do not accept funding from companies that make products that are the subject of our work, so we have no conflicts of interest. We support the review's examination of the relative risks and outcomes of outpatient interventions compared to the inpatient setting. We agree that due to the small sample sizes of many of the studies, it is not possible to assess rare outcomes. Additionally, the women in the studies were mostly young and white with few pre-existing health conditions. For this reason, the findings should not be considered generalizable; they are only applicable to a limited group of women. We recommend caution against generalizing, and encourage that future studies are not only larger, but have a more inclusive sample.	Thank you for this summary.

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Meg Seymour, National Center for Health Research	Discussion	The AHRQ review notes that the limitations of the research that has been conducted leads to limitations of their review. We agree. Although they found no difference in outcomes for inpatient and outpatient procedures, we have no confidence that the results would be similar if the studies were larger, had more diversity of the patients, assessed outcomes of greatest importance to patients, and separately analyzed for U.S. patients, since the U.S. healthcare system is so different from most other countries.	Thank you for this comment. Please see our Future Research section, which recommends more high quality, larger, RCTs.
Sharon Ryan, American College of Nurse Midwives	Discussion	The discussion section was detailed and highlighted significant findings. This section was especially useful because the narrative of the contextual factors that many providers are interested in is addressed in this section (in the strengths/limitations/applicability section. Discussion sections don't often get much attention in a large report like this, but as is often the case, there are important observations/acknowledgments in the discussion section. The considerations for clinical practice and research recommendations are very helpful.	Thank you.
Jean Salera-Vieira, AWHONN	References	Well done.	Thank you.
Sharon Ryan, American College of Nurse Midwives	References	No comments; looks good	Thank you.
Jean Salera-Vieira, AWHONN	Abbreviations and Acronyms	Helpful.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Sharon Ryan, American College of Nurse Midwives	Abbreviations and Acronyms	Helpful	Thank you.
Jean Salera-Vieira, AWHONN	Appendixes	Very thorough, complete, and helpful.	Thank you.
Sharon Ryan, American College of Nurse Midwives	Appendixes	These selected appendices are value added	Thank you.
Jean Salera-Vieira, AWHONN	General Comments	Please see attached document for the organizational response from the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). Please feel free to contact me should there be any questions. Thank you. Jean Salera-Vieira, DNP, APRN-CNS, RNC	(note: the comments from the attached document have been pasted into this disposition table under the appropriate sections)

Commentator & Affiliation	Section	Comment	Response
Jean Salera-Vieira, AWHONN	General Comments	There is not enough evidence to conclude that outpatient cervical ripening is safe for mothers and their fetuses based on the small sample of combined studies, the low and insufficient strength of the studies, the rare adverse outcome in thoses samples, lack of study of maternal and/or fetal surveillance while the outpatient procedure was being done, no study of maternal psychological well being. Applying these findings to the population of childbearing women in the United States will likely increase risk of harm as the real life sample will be much larger. There is strong pressure by some to electively induce all women at 39 weeks and this report will be seen as saying it's is safe without enought data to support that. The conclusion should be more multicenter RCTs should be done to evaluate safety. These should include a diverse population and specifically study Cervidil and Cytotec as methods with a goal of safety as an outcome rather than the focus on cesarean birth.	Thank you for this comment. We agree that the evidence is not strong, and we do recommend future RCTs, in diverse populations, with large enough sample sizes to evaluate subgroups. Please see our Future Research section.
Meg Seymour, National Center for Health Research	General Comments	Please see attached file for full comment.	(note: the comments from the attached document have been pasted into this disposition table under the appropriate sections)

Commentator & Affiliation	Section	Comment	Response
Meg Seymour, National Center for Health Research	General Comments	However, an overarching problem in the review is that it does not examine the role of patient-centered outcomes and satisfaction. Like harms and risks, these factors can impact patients' decision-making regarding inpatient versus outpatient cervical ripening. The review concludes that there is no medical difference in outcomes for cervical ripening in the inpatient or outpatient setting, but it fails to account for the subjective experiences of the patients. The outcomes for either method may not feel equal for patients, in the short or long-term.	Thank you for this comment. This is an important issue, and we have reviewed the evidence on patient preferences and satisfaction in a contextual question. Please see our report text for a narrative summary of this evidence.

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Sharon Ryan, American College of Nurse Midwives	General Comments	The report brings needed attention and information to the more and more common intervention of cervical ripening. The report gives guidance and highlights pt preferences. It does not speak so much to the burden on the facilities and staffing to accommodate the increase in the hospital setting of cervical ripening. The report acknowledges the contextual issues that are so important but rarely researched. Also, a large evidence review like this on a contemporary trend reveals that the evidence to fully answer the questions posed lag significantly behind practice trends, yet anecdotally we hear of hospitals changing practice. This illustrates the (often) chasm between evidence and practice. The comments in this document represent the compiled comments of four certified nurse-midwives who are members of the American College of Nurse-Midwives and who are in active clinical practice utilizing methods of cervical ripening in both in-patient and out-patient settings.	Thank you.