

Bayesian Meta-Analyses Could Be More: A Case Study in Trial of Labor After a Cesarean-section Outcomes and Complications

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Abstract

The meta-analysis's utility is dependent on previous studies having accurately captured the variables of interest, but in medical studies, a key decision variable that impacts a physician's decisions was not captured. This results in an unknown effect size and unreliable conclusions. A Bayesian approach may allow analysis to determine if the claim of a positive effect is still warranted, and we build a Bayesian approach to this common medical scenario. To demonstrate its utility, we assist professional OBGYNs in evaluating Trial of Labor After a Cesarean-section (TOLAC) situations where few interventions are available for patients and find the support needed for physicians to advance patient care.

1 Introduction

Meta-analysis is one of the most important and critical tools in medical research (Lee 2018; Haidich 2010) used to collect results from prior studies and coalesce them into a single, more robust conclusion. Medical research broadly is dominated by the use of the two simplest kinds of meta-analysis, fixed and random effects (Reis et al. 2023; K. Hackenberger 2020), which are useful tools but assume that the underlying studies have all the needed details and context. This becomes problematic when under-served areas like women's health result in systemic missing information in medical studies. Neither a random nor fixed effect model will reach a reliable conclusion in such a situation, and this results in the inadequate study of conditions that impact vast portions of the population. Lack of thorough and rigorous studies in obstetric care is unfortunately common due to a lack of representation of minority groups (Steinberg et al. 2023), lack of statistical rigor and power in OBGYN studies (Bruno and Blue 2022), and the lowest rate of research funding (Parchem et al. 2022). Existing meta-analysis techniques for dealing with confounding factors require specifying the size of the confounding effect (VanderWeele and Ding 2017). Since the confounding effect size is often unknown, this becomes unfalsifiable and leaves medical researchers no path forward beyond an expensive re-study of the problem, which is challenging due to the aforementioned lack of funding (Parchem et al. 2022). The

question then becomes, how can we leverage prior studies and data, even when it may have missing confounders to be corrected for?

In this article, we argue and show that a Bayesian approach to performing a meta-analysis can be used to help mitigate these prior errors and provide evidence for alternative hypotheses. Specifically, we address a common scenario where a decision variable is not incorporated into the meta-analysis. We then present a meta-analysis approach that can be rapidly adapted to new situations and describe our collaboration with clinicians in setting the hyper-priors. If an effect is still detected, the process can proceed. If no effect is detected, the known missing variable should be collected in a new study, and no reliable evidence exists to counter the null hypothesis.

This is critical in the medical field as it is unacceptable to begin a clinical trial without having a valid reason to conduct the trial in the first place due to managing the risks (i.e., to patients) and rewards (i.e., reasonable expectation of efficacy). Specifically, it may occur that the issue is not in the mechanical application of the statistics but that full consideration of the medical procedures, process, and decision-making may reveal causal considerations that would invalidate the result of a standard statistical analysis. In our case study, we are concerned with the usage of Pitocin and mechanical dilation (a.k.a., a catheter) as methods of induction of labor for patients with a history of cesarean delivery. Prior work has identified Pitocin as a (allegedly) superior and safer method for achieving this goal, which is clinically relevant as a failed TOLAC has more complications than a scheduled elective repeat cesarean section (Cesarean section, further abbreviated as CS). However, this conclusion was drawn by performing standard statistical tests on observational data without accounting for how the choice to use Pitocin vs mechanical dilation is made in practice. By using a Bayesian approach to the meta-analysis design, we can correct for these missing factors.

To understand this issue, we present the decision process with additional context in Fig. 1. By hand, a medical provider will measure a *Bishop score* (Bishop 1964). The primary purpose of a Bishop score is to indicate the likelihood of a successful vaginal induction, whereas higher scores indicate a higher likelihood. This is thus directly causal to the target outcome. For example, a component of the Bishop score is dilation of the cervix (i.e., how open your cervix is), and a

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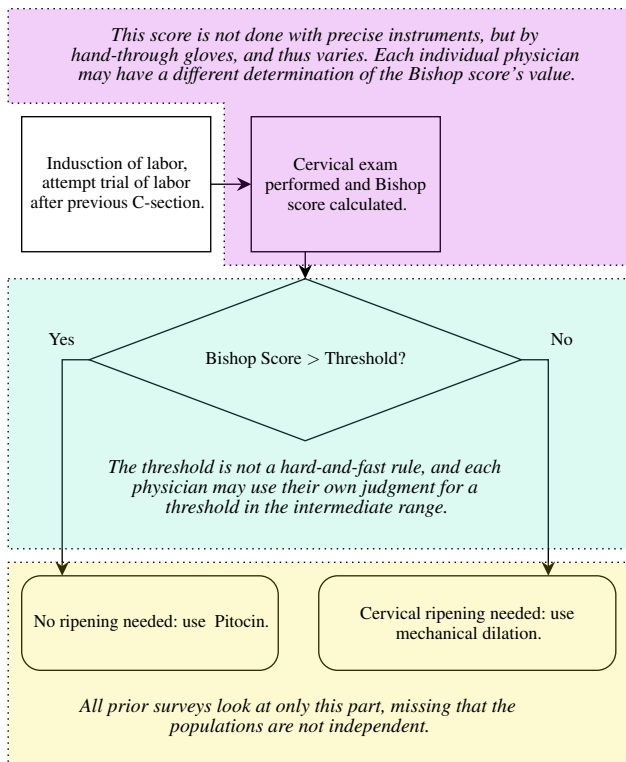


Figure 1: Cervical ripening is achieved with the application of Pitocin or mechanical dilation (a catheter). Whether one method has a higher rate of successful vaginal delivery after a C-section is of clinical relevance to the decision, as a failed TOLAC has higher rates of complications than a scheduled repeat C-section. The choice is made by computing a Bishop Score in clinical practice but creates a shared dependency (i.e., in the same Markov blanket), and this factor was ignored in previous studies. This creates an unaccounted causal impact between the two groups.

closed cervix can not physically pass a baby.

If a patient had a sufficiently high Bishop score (e.g., 13 out of a maximum of 13 points), no cervical ripening is needed, and so neither Pitocin nor mechanical dilation would be used. However, Pitocin is prescribed only when the Bishop score is sufficiently high; thus, less ripening is needed. Ergo, prior studies that have shown Pitocin as being statistically better are failing to disentangle that *a patient receiving Pitocin has already been determined to have a more favorable cervix, and thus closer to a successful delivery at the onset.*

We turn to Bayesian machine learning and probabilistic programming to answer this clinical research question and to act as a case study on how incorporating Bayesian methods with physician guidance can help correct historical inequities. Using the prior knowledge of how the decision process is made in Fig. 1, we will develop a graphical model that accounts for the Bishop score as a hidden variable. Further, we can model the impact of this unobserved variable by using the Pitocin vs catheter populations against a truncated hidden variable, where the provider's discretion on a Bishop

threshold informs the truncation of the hidden variable. *This allows us to replace subjective approaches from the literature that require already knowing the impact of the confounder with more objective hyper-priors that can be set by clinical guidance and prior published evidence.* In doing so, we can leverage the incomplete data (Bishop scores have not been reported in prior studies) to determine that there is no adverse statistical difference between Pitocin and mechanical dilation when accounting for the unobserved Bishop scores. This conclusion is important for women's healthcare, enabling more options when adverse reactions occur, aligning with provider skill, and providing the justification to pursue an RCT for confirmation. All research was carried out under strict guidance and cooperation with professional OBGYNs to ensure clinical relevance and transition to clinical practice.

The rest of our article is organized as follows. First, we will provide the detailed medical context of our study in §2. Second, we will describe the Bayesian model we construct and additional tests that will be performed in §3. The results of our methods and clinical relevance will be demonstrated in §4 with further discussion in §5. Finally, we will end with a comparison to prior methods for meta-analysis with confounding factors in §6 and our conclusion in §7.

2 Medical Context

Our approach is readily adaptable to stations where a single decision variable was not factored into the original analysis or included in the data. Such single-variable deciders occur regularly due to differences in care due to provider discretion (Cook et al. 2018) and the use of simple decision criteria (Bae 2014; Podgorelec et al. 2002) that are prevalent throughout healthcare as a means of reducing research findings into easy-to-remember actionable rules that can be applied in fast-moving clinical environments.

Our case study is chosen in part because of its applicability to most women in the world. The rate of cesarean sections has been increasing globally from 12.1% in 2000 to 21.1% in 2015 (Boerma, Ronsmans, and Melesse 2018; JA et al. 2021). In the United States, the rate of cesarean section in 2019 was 31.7% (Osterman 2020). Cesarean sections have a higher rate of adverse consequences, including infection, hemorrhage, and increased risk of complications, such as abnormal placentation, in future pregnancies. Vaginal delivery is, therefore, the preferred method of delivery when clinically possible. Optimal methods for trial of labor after cesarean section (TOLAC) for vaginal birth after cesarean section (VBAC) have been under investigation as an alternative to repeat cesarean section in hopes of reducing complications.

In 2018, the rate of VBAC in the United States was 13.3% (Osterman 2020). Successful VBAC has fewer adverse outcomes than repeat cesarean sections and reduces the risk associated with multiple cesarean sections (SC et al. 2015; Silver, Landon, and Rouse 2006; Nisenblat et al. 2006). Failed TOLAC, however, is associated with increased morbidity and mortality compared to an elective repeat cesarean section (Hibbard et al. 2001). Uterine rupture results in the most significant increase of morbidity and mortality with TOLAC. The rate of uterine rupture with one prior low-transverse

cesarean delivery is $<1\%$; however, it is an obstetrical emergency if it occurs (Landon, Hauth, and Leveno 2010; Lydon-Rochelle et al. 2010). This risk leads to policies by hospitals and obstetricians to forbid induction of labor for patients desiring TOLAC or to limit induction to Pitocin and artificial rupture of membranes (AROM). The increase in the number of TOLACs has prompted further interest in optimizing the clinical management of patients attempting a VBAC to improve the likelihood of success.

Induction methods for TOLAC have recently been under investigation. In 2013, Jozwiak and Dodd attempted to compare methods of labor induction for TOLAC, but there was insufficient evidence to make a conclusion (West, Jozwiak, and Dodd 2017). The effect of prostaglandins and risk of uterine rupture during TOLAC has shown mixed results (Landon, Hauth, and Leveno 2010; Lydon-Rochelle et al. 2010). Multiple studies show that misoprostol significantly increases risk of uterine rupture (Plaut, Schwartz, and Lubarsky 1999; Aslan et al. 2004). The American College of Obstetricians and Gynecologists (ACOG) recommends that misoprostol should not be used for cervical ripening in patients with previous cesarean section or uterine surgery, but does not set clear guidelines on the use of other prostaglandins. Studies on the use of mechanical dilation for induction for TOLAC, such as a cervical ripening balloon and foley catheter, have also had mixed results (Ravasia, Wood, and Pollard 2000; Bujold, Blackwell, and Gauthier 2004; Hoffman et al. 2004). (Kehl, Weiss, and Rath 2016) published a meta-analysis in 2016 that looked at induction methods in TOLACs. They found mechanical dilation to be as effective as prostaglandins, with a lower risk for uterine rupture. However, the review was limited by number and quality of studies. Multiple studies have been published since in an attempt to evaluate the effectiveness of mechanical dilation. (Wingert, Hartling, and Sebastiani 2019) published a meta-analysis in 2019 that evaluated clinical interventions impacting VBAC rates but included limited information on the impact of mechanical dilation. This study aims to evaluate the safety and outcomes of mechanical dilation for cervical ripening during TOLAC.

3 Methods

The data collection of our meta-analysis will follow standard clinical protocols used by physicians to perform such studies. Multiple OBGYN physicians performed this step of the work to collect the data, specify all search terms, and perform all data filtering, to ensure that our data for the study is clinical meta-analysis data as collected by OBGYNs attempting to elucidate a clinical research question. A result of this work is the start of new clinical trials to test the efficacy without the decision threshold, and our results cover the literature at the time the initial study was completed.

In §3.1, our approach to a Bayesian meta-analysis will be detailed. A set of distributions are chosen that are clinically relevant to how the Bishop score is calculated, and broadly applicable to other scenarios. The generative story will be presented in the general form, with comments denoting how the hyper-priors and variables were set for our case study. The standard fixed-effect meta-analysis will be covered in §3.2 and used in comparison to show how results change and

in the analysis of outcomes that are not related to the Bishop score.

3.1 Meta-Analysis Method

By default, and when applicable, we used the standard fixed-effect model to perform a meta-analysis across studies (V. and I 2001). We used the fixed effect model primarily due to the small number of studies that have looked at this problem. While a random-effects model is often preferred in medical studies (Higgins, Thompson, and Spiegelhalter 2009), the small number of $n=6$ total studies makes the estimation of random-effects models unreliable, and so a fixed-effects model is generally preferred (Higgins, Thompson, and Spiegelhalter 2009; Lin et al. 2020). We use the relative risk measure as the effect size of the intervention (mechanical dilation) since the outcome is binary (cesarean delivery versus vaginal delivery) and an event of regular occurrence (Nakayama, Zaman, and Tanaka 1998). The fixed-effect model (and all other results) were computed using Python-Meta.

However, the above-cited papers recommend taking a Bayesian approach to better handle difficult low-sample size situations when possible. We do so for the relative risk calculations because the data strongly violates the heterogeneity assumption of the fixed-effect modeling. We also note the mediating factor that the studies included select the use of a catheter based on physician's clinically recommended discretion, often in regard to unreported Bishop scores. This means the standard hypothesis testing assumes $\mathbb{P}(\text{CS}|\text{intervention})$, when the actual data reflects a second unobserved conditional on the Bishop score, giving $\mathbb{P}(\text{CS}|\text{intervention}, \text{Bishop})$.

Specification of Priors For each prior that needed to be set, they were done so by having the machine learning researcher(s) in this study consult with the physician(s) involved. The goal was to make the priors as informative to the underlying true generative process, rather than convenience in statistical inference (hence, the use of a truncated normal distribution between populations). To develop a shared and agreed approach for setting these priors, the following question process was developed and asked in this order:

1. Is this event recorded at a national, state-wide, or hospital database — with aggregate statistics available? If yes, the largest available population rate was used to specify a prior.
2. Is there a maximum plausible range of values one might expect (e.g., is going from minimum to maximum Bishop score plausible?) in the most extreme cases? Another framing that was helpful was “what is an impact that would be so large to shock you that it was so effective”. This helped with deciding between normal vs. heavy-tailed priors, and if any prior should have a limited range or scope.
3. What would you expect to see in normal clinical practice, and how consistent is that observation?

The order in which we recommend these questions is based on the degree to which we found them useful in this study. Large-scale statistics are the most objective, and maximum

ranges were useful in specifying the τ priors on the degree of impact on the population rates (lines 16 and 17). The third question was still useful, but not to the same degree. We found question three often resulted in “it-depends” responses and ambiguity, but was valuable in driving the discussion into *why* “it depends”. This further discussion would eventually lead to evolution in the graphical model or other questions that would help derive a prior.

We note that the Bishop prior and threshold, by their nature as the unobserved decision variable, would not benefit from more nuanced prior specification because there are no direct observations to benefit from appropriate scaling. For this reason, normal distributions were chosen for ease of inference. We also note that in Fig. 1, there are multiple sources of variation: the measurement error of the Bishop score, the provider discretion on the threshold to use, and the bias of individual providers on their own measurements¹. These are more effects than our model can account for because the different types of errors are outside the Markov blanket of the observed variables, and so they collapse into a smaller number of discrete items we can infer.

Bayesian-Meta Analysis Method We develop a general-purpose hierarchical Bayesian model to handle our situation: an unobserved (or otherwise not recorded) factor is used as a decision criterion, acting as a mediator on the apparent effectiveness of a control and an intervention on the occurrence of some adverse event E . The Plate diagram of our method is shown in Fig. 2, with key groups of variables. The δ variables model the unobserved decision variable, which will be left/right truncated for the intervention and control effects, respectively. β , μ , and η will control the base rate of occurrence in each population, which is mediated by the decision variable δ . The θ variables will control the effect of the intervention. Finally, the τ variables are hyper-priors common to Bayesian meta-analyses.

To perform a meta-analysis with our approach, only one hyper-prior *needs* adjustment by the user for their own problems. A population-wide adverse-event rate μ must be specified as a weakly informative prior. For our case study we use statistics from the US population rate of C-sections overall births in 2019 (Moher, Shamseer, and Clarke 2015), which indicates a population-wide cesarean section rate of 31.7%. We will now detail how and why we set each of these priors to specific distributions, and their precise interactions, which are summarized in algorithm 1.

We select a weakly informative prior of $\log(\eta) \sim \text{Logistic}(\log(30))$ for the strength of the hyper prior of the Beta distributions that will be used for the probability of a C-section across studies. We model the intervention effect on the $\text{logit}(\mu) + \beta \cdot \text{Truncated} + \theta_i$ as a hyper prior, where *Truncated* indicates the control or mediator truncated portion of the (inferred latent) distribution. $\theta \sim \text{Normal}(0, \tau^2)$ and study level prior $\theta_i \sim \text{Normal}(\theta, \tau^2)$,

¹To clarify the difference in the latter two, note that the provider making the decisions may not be the same individual measuring the Bishop score. For example, a medical resident operating under the guidance of an attending physician will have two different entities involved rather than one.

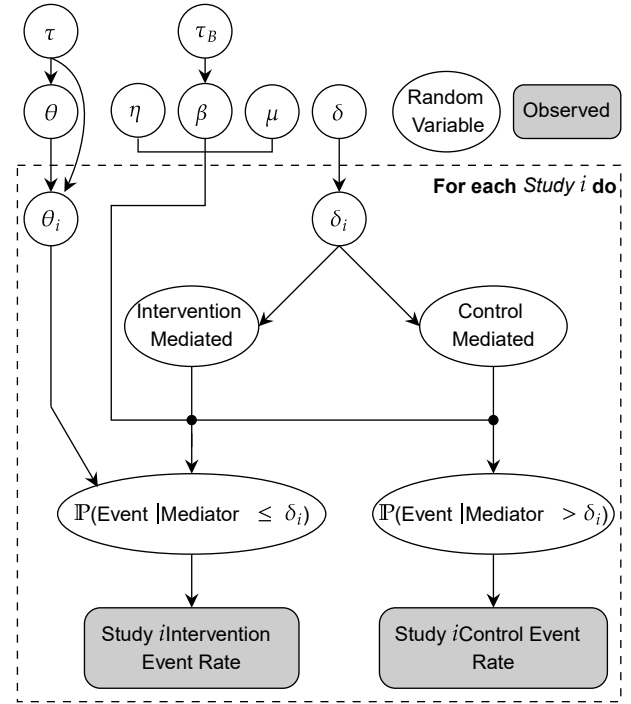


Figure 2: The Plate Diagram for our model. Grey nodes are observed variables, white are sampled, and dashed lines are subgraphs that repeat together. The key observation is that there is a bifurcation of variables modeling the outcome given a mediating decision variable (in this study, a Bishop score) for the control (Pitocin) and intervention (catheter). This shows how our algorithm accounts for a single mediator (Bishop score) and threshold (outside the num_samples plate) that is altered by a provider’s discretion δ_i and then causes the two groups to have different underlying Bishop scores.

with $\tau \sim \text{HalfCauchy}(\frac{\sqrt{0.5}}{3})$. The use of τ is dual purpose. First, it is recommended by (Harrer et al. 2021) for Bayesian meta-analysis to account for the between-study heterogeneity. Second, it also corresponds to a Horseshoe prior (Brennan 2021; Carvalho, Polson, and Scott 2009) to correspond to a default of no-impact, which is easy for the model to overcome given such an observation (Bhadra et al. 2019). The scale is chosen so that at the logit scale, the prior impact of τ will be that the impact of the intervention should be within ± 50 percentage points, making it a weak prior informative to the likely range of impact based on OBGYN feedback. The θ_i is dropped from the control group (i.e., they have no intervention). Similarly, β models the unobserved Bishop score, and $\beta \sim \text{Normal}(0, \tau_B^2)$ models the impact of the Bishop score on the logits of needing a CS (τ_B^2 is modeled the same way as τ for the same reasons).

As noted, we need to specify the problem-specific parameter μ . For us, the population-wide C-section rate $\mu \sim \text{Beta}(12, 25)$ is chosen correspond with an expectation that $\mu = 12/(12 + 25) = 32\% \approx 31.7\%$. For any other problem, the user can use $\mu \sim \text{Beta}(P, N)$ where P and N are posi-

Algorithm 1: Generative story for decision mediated meta-analysis. Comments describe the purpose of variables, with the TOLAC example in parenthesis.

Data: Observed counts of the event (C-section) and non-event (vaginal birth) for each study segregated by the use of a catheter (mechanical dilation) for low Bishop scores and the use of Pitocin for the high Bishop scores.

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1  $\log(\eta) \sim \text{Logistic}(\log(30));$ 
2  $\eta \leftarrow \exp(\log(\eta));$ 
3  $\mu \sim \text{Beta}(12, 25);$  // Population-wide cesarean section rate prior
4  $\tau \sim \text{HalfCauchy}(\sqrt{0.5/3})$ 
5  $\tau_B \sim \text{HalfCauchy}(\sqrt{0.5/3});$ 
6  $\theta \sim \mathcal{N}(0, \tau^2);$  // Impact of the intervention (mechanical dilation)
7  $\beta \sim \mathcal{N}(0, \tau_B^2);$  // Unobserved impact of the mediator (Bishop score) has on the outcome (needing a C-section)
8  $\text{MediatorPrior} \sim \mathcal{N}(0, 1);$  // Unobserved mediator (Bishop score)
9  $\delta \sim \mathcal{N}(0, 1);$  // Mediator (Bishop) threshold location
10 foreach Study  $i$  do
11    $\theta_i \sim \mathcal{N}(\theta, \tau^2)$ 
12    $\text{MediatorDist} \leftarrow \mathcal{N}(\text{MediatorPrior}, 1)$ 
13    $\delta_i \sim \mathcal{N}(\delta, 1);$  // The study specific threshold that is inferred.
14    $\text{InterventionMediated} \sim \text{MediatorDist}_{(-\infty, \delta_i)}$ 
15    $\text{ControlMediated} \sim \text{MediatorDist}_{[\delta_i, \infty)}$ 
16    $\mu_{\text{control}} \leftarrow \exp(\text{logit}(\mu) + \beta \cdot \text{ControlMediated})$ 
17    $\mu_{\text{intervention}} \leftarrow \exp(\text{logit}(\mu) + \beta \cdot \text{InterventionMediated} + \theta_i)$ 
18    $p_E^\uparrow \sim \text{Beta}(\mu_{\text{control}} \cdot \eta, (1 - \mu_{\text{control}}) \cdot \eta);$  // Probability of event in the control population ( $\mathbb{P}(\text{C-section}|\text{High Bishop})$ )
19    $p_E^\downarrow \sim \text{Beta}(\mu_{\text{intervention}} \cdot \eta, (1 - \mu_{\text{intervention}}) \cdot \eta);$  // Probability of event in the intervention population ( $\mathbb{P}(\text{C-section}|\text{Low Bishop})$ )
20    $RR \leftarrow p_E^\downarrow / p_E^\uparrow$ ; // Compute the Relative Risk
21   Observe likelihoods of  $p_E^\downarrow$  and  $p_E^\uparrow$  against the observed study rate of event (C-sections).
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tive/negative occurrences, respectively, such that $P/(P + N)$ approximates a known population-wide occurrence rate. A reasonable heuristic when using a known population rate X is to set $P = X * 50$, $N = (1 - X) * 50$.

To account for the Bishop score being used in determining if a catheter is needed, we model the effect as Truncated distributions. The *MediatorDist* represents the hidden distribution of Bishop scores, which is truncated by a low and

high range (denoted by a subscript of [low,high]). In this manner, the fundamental decision process as outlined in Fig. 1 is incorporated into the model and allowed to have an impact itself.

The global Bishop score is modeled with a prior of $\text{Normal}(0, 1)$ as it is unobserved, and our interest is in the impact on the model, making the scale irrelevant. The threshold of provider preference on Bishop scores is hierarchical with $\delta \sim \text{Normal}(0, 1)$ as and provider level preference $\delta_i \sim \text{Normal}(\delta, 1)$. The values *InterventionMediated_i* and *ControlMediated_i* are then sampled from a lower/upper truncated (at δ_i) Normal distribution reflecting the lower/higher Bishop scores in the catheter/control groups respectively (performed on lines 14 and 15). These hyperpriors provide valuable prior information to enable the possibility of reaching a conclusion despite few studies being available and provide population-wide estimates. As the model we choose is hierarchical to account for the potential heterogeneity in studies, we model each study’s baseline rate of cesarean section as sampled from $\text{Beta}(\mu \cdot \eta, (1 - \mu) \cdot \eta)$.

Our model algorithm 1 is computed using Markov Chain Monte Carlo (Metropolis et al. 1953) using the NUTS sampler (Hoffman and Gelman 2014) and implemented with Numpyro (Phan, Pradhan, and Jankowiak 2019) with highest density regions (HDR) of 95%.

3.2 Standard Fixed-Effect Models for Other Cases

In the medical context of this work, we also wish to compare the risk of adverse uterine and neonatal events, so we calculated the odds ratio. These variables do not have the same bias with Bishop scores, and so a standard fixed-effect model is desirable for both familiarity and appropriateness given the context. Both of these events are rare, often with 0-5 occurrences in either group. This makes relative risk infeasible to estimate, and so the odds ratio is preferred under the “rare-disease assumption” (Greenland and Thomas 1982; Cummings and Koepsell 2001; Greenland, Thomas, and Morgenstern 1986). Even still, the odds ratio of significantly rare events is error prone, especially when no occurrences are detected in the control or intervention group (Chang and Hoaglin 2017). We choose to use Peto’s method of estimating the approximate odds ratio of rare events in a fixed-effect meta-analysis (Yusuf et al. 1985). Peto’s method has received significant study and has been found to be sufficient so long as the event’s rareness is on the order of $\leq 1\%$ and the control/intervention groups are not lopsided in sample sizes, which our data satisfies (Greenland and Salvani 1990; Brockhaus, Bender, and Skipka 2014; Brockwell and Gordon 2001). While a similar Bayesian treatment is possible, the extremely limited number of occurrences makes the impact of uninformative priors let alone weakly informative, especially large and nuanced (Efthimiou 2018). Such nuanced statistical modeling is beyond the scope of study. Thus, a well-studied and valid fixed-effect model is preferred.

4 Results

4037 patients that underwent TOLAC, were identified (Bulough, Southward, and Sharp 2021; Eriksen, Chandrasekaran,

and Delaney 2019; Koenigbauer, Schalinski, and Jarchau 2021-08; Radan, Amylidi-Mohr, and Mosimann 2017; Ralph et al. 2020; Sarreau, Isly, and Poulain 2020) The patients had a mean age of 31.46 years and a mean gestational age of 39.22 weeks. These patients were divided into a cohort of patients who underwent TOLAC with the use of mechanical dilation (n = 1039 patients) and a cohort who did not receive mechanical dilation (n = 2998 patients). The cohort of patients using mechanical dilation included those who used a foley balloon, Cook catheter, and osmotic dilators. 231 patients had a prior vaginal delivery in this group. In the studies that included the indications for prior cesarean delivery, these included labor dystocia (29%), non-labor dystocia (i.e., fetal heart tracing abnormalities or fetal malpresentation; 50.6%), and unspecified (21%).(Brockhaus, Bender, and Skipka 2014; Bullough, Southward, and Sharp 2021; Koenigbauer, Schalinski, and Jarchau 2021-08)

The first outcome we consider is the relative risk of a cesarean delivery under intervention (mechanical dilation) compared to a control group (pitocin, AROM, dinoprostone). The vaginal delivery rate in the mechanical dilation group was 51.4% compared to the control group 69.1%.

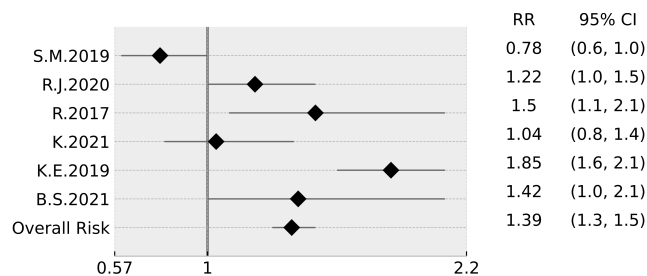


Figure 3: Forest Plot of mechanical dilation (intervention) vs. Pitocin when ignoring the unaccounted Bishop score as outlined in Fig. 1. Because a Fixed-Effect meta-analysis fails to account for this mediating variable, and fails assumption tests, we do not recommend using its conclusion. It is presented to show why a Bayesian approach with a hidden variable for the Bishop score is needed.

Using a standard fixed-effect model (which ignores the causal impact of Bishop scores), the results are significant with $p < 0.001$ and a mean cesarean section estimated relative risk of 1.39 (CI 1.27-1.51), indicating the risk of cesarean section in the mechanical dilation group is 39% higher (Fig. 3), but a Cochran's Q test shows significant heterogeneity ($p < 0.001$) that, combined with the impact of mechanical dilation selected by physician preference, leads us to be doubtful of this result.

Our Bayesian model in algorithm 1 accounts for these factors and reports a risk ratio of 1.04 (CI 0.93-1.18). This indicates that there is no difference in risk of cesarean section when conditioned on physician preference to select for intervention based on Bishop scores (Fig. 4).

For TOLAC inductions, our results show that mechanical dilation is as effective and safe as Pitocin. This should alleviate hospital and provider concerns about the use of mechanical dilation to safely perform cervical ripening. This

is important because in the case of a TOLAC, mechanical dilation is the only potentially available option for cervical ripening. In future studies the statistics of Bishop scores of each group should be reported for more robust conclusions and modeling.

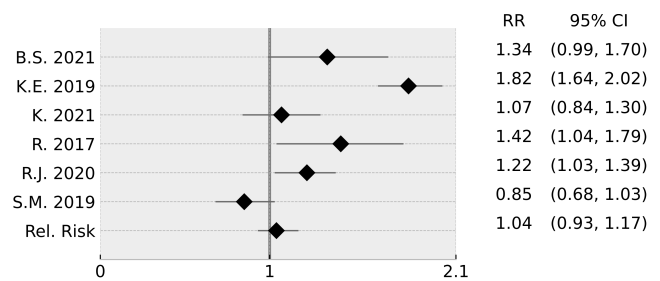


Figure 4: An improved meta-analysis that accounts for the hidden variable of the Bishop score, which is used to determine whether mechanical dilation (intervention) or Pitocin (control) is used. This shows that current evidence is not sufficient to conclude there is any difference in the outcome of C-section rates.

4.1 APGAR and Uterine Results

Also of clinical interest in our meta-analysis is the rate of adverse uterine events (ruptures) and the APGAR² score is < 7 by 5 minutes. Because the Bishop score is a direct measure of progress toward what Pitocin and mechanical dilation are attempting, the Bayesian model is necessary. The Bishop score does not have the same direct causal relationship with adverse uterine events or APGAR scores, and so a classic fixed-effect model is appropriate. Per our discussion in §3, we use a Odds Ratio fixed-effect model congruent with standard practice. We note that applying our algorithm 1 to this data results in the same conclusion.

The mechanical dilation cohort has an adverse uterine event rate of 2.98% (31 uterine rupture/dehiscence) and a 5-minute APGAR <7 rate of 1.92%. The control cohort has an adverse uterine event rate of 1.73% (52 uterine rupture/dehiscence) and an APGAR <7 at 5-minute rate of 1.83%. The resulting odds indicate no significant difference for adverse uterine events ($p = 0.136$; CI 0.89-2.48) or APGAR < 7 at 5min ($p = 0.434$; CI 0.71-2.22).

5 Discussion of Medical Context

Management of induction of labor for TOLAC has an ever-increasing importance with the increasing rates of cesarean section. The risk of TOLAC failure and, more importantly, uterine dehiscence and rupture are of utmost concern when deciding induction methods. ACOG currently recommends avoidance of misoprostol due to the increased risk of uterine dehiscence and rupture, but there are limited recommendations regarding other methods of prostaglandins versus mechanical dilation with an unfavorable Bishop score.

²This is the common method of writing APGAR, though it is not an acronym — it is named for its developer Virginia Apgar.

The current study compared complication rates and outcomes during TOLAC when using mechanical dilation. Overall, the results show no difference in the number of complications with both uterine and neonatal adverse events. When using the Bayesian model that also accounts for unreported Bishop scores, there was no statistical difference in VBAC rates between the mechanical dilation group and the control.

Like every meta-analysis, there are limitations. The main limitation is the small number of cohorts, which limits the power of this study. There is a paucity of high-quality literature describing the use of mechanical dilation in patients undergoing a TOLAC. This low number of studies gives us a cautionary pause. The risk of uterine rupture/dehiscence, while generally rare, is a catastrophic event. This leads to some hospitals and obstetricians not allowing induction of labor for patients wishing to undergo a TOLAC or limiting the induction agents used to Pitocin without allowing the use of mechanical dilation. Therefore, it is of utmost importance to determine if the use of mechanical dilation in patients undergoing TOLAC are at increased risk of complications. The current data does not support uterine scar as a contraindication for mechanical dilation for induction of labor. However, larger studies are warranted to provide additional evidence.

6 Prior Methods In Confounded Meta-Analysis

The issue of statistical errors in medical work has long been known (Glantz 1980). Most prior works have focused on errors in the form of lack of assumption testing (Karadeniz et al. 2019; Slutsky 2013; Hanif and Ajmal 2011) or of malfeasance or data entry errors (Carlisle 2017; Ercan and Demirtas 2015). To be clear, we are not accusing prior papers in the area of TOLAC in this article of these types of errors. Instead, our study is concerned with a type of error that physicians are not generally trained with regard to statistical study design: violations of the independently and identically distributed assumption via a shared causal factor (Klein et al. 2024). In our case, the use of Pitocin vs. mechanical dilation is not independent because of the process that is used to decide between these factors. By accounting for this missing factor, we have determined there is no detectable statistical difference in outcomes.

The issue of hidden variables impacting results is not unknown to the medical research community. The “Many labs” project explored this by replicating a study multiple times by different teams to attempt to quantify impediments to reproducibility and determined that unobserved hidden variables did have a measurable impact on results (but did not prevent replication in their case) (Klein et al. 2014). The key difference is our work considers a known unknown, whereas ManyLabs considers unknown unknowns.

Our meta-analysis is predicated on addressing a known mediating variable that was not accounted for in previous TOLAC studies. One previous line of work in confounded meta-analysis is to calculate an E-Value, which indicates the minimum effect size necessary to explain away a significant result (VanderWeele and Ding 2017). If applied to our study we obtain a relatively small E-value of 2.13, which can be

interpreted as saying the unaccounted impact of the Bishop score would need to be associated with at least a 2.13-fold reduction in relative risk across all studies to explain the apparent relation. This is not a statement of what is true, but a sensitivity analysis bounding the amount of unexplained effect that would need to exist. Given the Bishop score is a direct predictive and causal variable to the outcome of a TOLAC (Parveen, Rengaraj, and Chaturvedula 2022), we consider this E-value informative to the need for more careful design and study of Pitocin vs dilation for a TOLAC.

While the E-Value is easy to apply, it does not inform a corrected estimate of the effect size we seek to study. In the review by (Mathur and VanderWeele 2022), other options that can be used to produce a corrected estimate are grouped into one-stage and two-stage. Broadly, both one and two-stage methods require expert or data-informed assumptions to be made about the size of the effect imposed by the confounding variable. *These methods are most useful when the effect of the confounding variable can be meaningfully estimated.* There is no method for us to measure this effect absent first establishing the valid reason to pursue an RCT to obtain such data, thus the necessity of our approach. Though bounds have been developed for results under unobserved confounding (Kilbertus et al. 2020; Byun et al. 2024), to wit, we are the first to look at meta-analysis.

Last, we note that power analysis is confounded by the hidden variable itself. A study with low power is unlikely to detect an effect if one exists. The purpose of our study is not to try and maximize power, but to determine if a *previously detected effect is actually supported by the data available.* From a clinical decision-making process, running the Bayesian meta-analysis is directly productive because if the study has an effect, then it supports the importance of the difference irrespective of the missing variable. But if not, the ideal next action is to build evidence that includes the missing variable — to which the power analysis of the meta-analysis does not provide any benefit or change in action taken.

7 Conclusion

To demonstrate the utility of our method, we have applied it to a real-world case study in OBGYN care of laboring mothers. Working with physicians, we develop the generative story and specification of priors in a manner that is easy to adapt to other problems. Our case study is important as the rate of cesarean delivery has steadily increased, which, in turn, has led to an increase in TOLAC. Induction of labor in patients undergoing TOLAC is challenged by the limited agents available for cervical ripening. No significant difference was observed in the number of complications or in the rate of successful VBAC for patients undergoing TOLAC with the use of mechanical dilation compared to usual methods such as Pitocin. The results of this study are being used to help inform medical management of patients, provide the patients with increased options, and design Randomized Controlled Trials to further verify the results.

References

- Aslan, H.; Unlu, E.; Agar, M.; and Ceylan, Y. 2004. Uterine rupture associated with misoprostol labor induction in women with previous cesarean delivery. *Eur J Obstet Gynecol Reprod Biol*, 113(1): 45–48.
- Bae, J.-M. 2014. Clinical Decision Analysis using Decision Tree. *Epidemiology and Health*, e2014025.
- Bhadra, A.; Datta, J.; Polson, N. G.; and Willard, B. 2019. Lasso meets horseshoe: A survey. *Statistical Science*, 34(3): 405–427. ArXiv: 1706.10179 Citation Key: Bhadra2019.
- Bishop, E. H. 1964. Pelvic scoring for elective induction. *Obstet. Gynecol.*, 24: 266–268.
- Boerma, T.; Ronsmans, C.; and Melesse, D. 2018. Global epidemiology of use of and disparities in caesarean sections. *Lancet*, 392(10155): 1341–1348.
- Brennan, J. 2021. Horseshoe priors in numpyro.
- Brockhaus, A.; Bender, R.; and Skipka, G. 2014. The Peto odds ratio viewed as a new effect measure. *Stat Med*, 33(28): 4861–4874.
- Brockwell, S.; and Gordon, I. 2001. A comparison of statistical methods for meta-analysis. *Stat Med*, 20(6): 825–840.
- Bruno, A. M.; and Blue, N. R. 2022. Challenges in Interpreting Obstetrics and Gynecology Literature. *Clinical Obstetrics & Gynecology*, 65(2): 225–235.
- Bujold, E.; Blackwell, S.; and Gauthier, R. 2004. Cervical ripening with transcervical Foley catheter and the risk of uterine rupture. *Obstet Gynecol*, 103(1): 18–23.
- Bullough, S.; Southward, J.; and Sharp, A. 2021. Vaginal prostaglandin E2 versus double-balloon catheter for induction of labour for vaginal birth after caesarean section: A retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol*, 259: 90–94.
- Byun, Y.; Sam, D.; Oberst, M.; Lipton, Z.; and Wilder, B. 2024. Auditing Fairness under Unobserved Confounding. In Dasgupta, S.; Mandt, S.; and Li, Y., eds., *Proceedings of The 27th International Conference on Artificial Intelligence and Statistics*, volume 238 of *Proceedings of Machine Learning Research*, 4339–4347. PMLR.
- Carlisle, J. B. 2017. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trials in anaesthetic and general medical journals. *Anaesthesia*, 72(8): 944–952.
- Carvalho, C. M.; Polson, N. G.; and Scott, J. G. 2009. Handling Sparsity via the Horseshoe. In van Dyk, D.; and Welling, M., eds., *Proceedings of the Twelfth International Conference on Artificial Intelligence and Statistics*, volume 5 of *Proceedings of Machine Learning Research*, 73–80. Hilton Clearwater Beach Resort, Clearwater Beach, Florida USA: PMLR.
- Chang, B.-H.; and Hoaglin, D. 2017. Meta-analysis of Odds Ratios: Current Good Practices. *Med Care*, 55(4).
- Cook, D. A.; Pencille, L. J.; Dupras, D. M.; Linderbaum, J. A.; Pankratz, V. S.; and Wilkinson, J. M. 2018. Practice variation and practice guidelines: Attitudes of generalist and specialist physicians, nurse practitioners, and physician assistants. *PLOS ONE*, 13(1): e0191943.
- Cummings, P.; and Koepsell, T. D. 2001. On the need for the rare disease assumption in some case-control studies. *Injury Prevention*, 7: 254 – 254.
- Efthimiou, O. 2018. Practical guide to the meta-analysis of rare events. *ebmh.bmj.com*, 21(2): 72–76.
- Ercan, I.; and Demirtas, H. 2015. Statistical errors in medical publication. *Biometrics & Biostatistics International Journal*, Volume 2(Issue 1).
- Eriksen, J.; Chandrasekaran, S.; and Delaney, S. 2019. Is Foley Catheter Use during a Trial of Labor after Cesarean Associated with Uterine Rupture? *Am J Perinatol*, 36(14).
- Glantz, S. A. 1980. Biostatistics: how to detect, correct and prevent errors in the medical literature. *Circulation*, 61(1): 1–7.
- Greenland, S.; and Salvan, A. 1990. Bias in the one-step method for pooling study results. *Stat Med*, 9(3): 247–252.
- Greenland, S.; Thomas, D.; and Morgenstern, H. 1986. Reviews and Commentary THE RARE-DISEASE ASSUMPTION REVISITED A CRITIQUE OF “ESTIMATORS OF RELATIVE RISK FOR CASE-CONTROL STUDIES. *Am J Epidemiol Formtriy Am J Hyg*. Accessed September 12, 2021.
- Greenland, S.; and Thomas, D. C. 1982. On the need for the rare disease assumption in case-control studies. *American journal of epidemiology*, 116 3: 547–53.
- Haidich, A. B. 2010. Meta-analysis in medical research. *Hippokratia*, 14(Suppl 1): 29–37.
- Hanif, A.; and Ajmal, T. 2011. Statistical Errors in Medical Journals (A Critical Appraisal). *Annals of King Edward Medical University*, 17(22): 178–178.
- Harrer, M.; Cuijpers, P.; A, F. T.; and Ebert, D. D. 2021. *Doing Meta-Analysis With R: A Hands-On Guide*. Boca Raton, FL and London: Chapman & Hall/CRC Press, 1st edition. ISBN 9780367610074.
- Hibbard, J.; Ismail, M.; Wang, Y.; Te, C.; Karrison, T.; and Ismail, M. 2001. Failed vaginal birth after a cesarean section: How risky is it?: I. *Maternal morbidity. Am J Obstet Gynecol*, 184(7): 1365–1373.
- Higgins, J.; Thompson, S.; and Spiegelhalter, D. 2009. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A (Statistics Soc)*, 172(1): 137–159.
- Hoffman, M.; and Gelman, A. 2014. The No-U-Turn Sampler: Adaptively Setting Path Lengths in Hamiltonian Monte Carlo. *J Mach Learn Res*, 15: 1593–1623. Accessed September 12, 2021.
- Hoffman, M.; Sciscione, A.; Srinivasana, M.; Shackelford, D.; and Ekbladh, L. 2004. Uterine Rupture in Patients with a Prior Cesarean Delivery: The Impact of Cervical Ripening. *Am J Perinatol*, 21(04): 217–222.
- JA, M.; BE, H.; MJK, O.; and Births, A. 2021. Final Data for 2019. *Natl Vital Stat Rep*, 70(2): 1–51. Accessed September 12, 2021.
- K. Hackenberger, B. 2020. Bayesian meta-analysis now – let’s do it. *Croatian Medical Journal*, 61(6): 564–568.

- Karadeniz, P. G.; Uzabacı, E.; Kuyuk, S. A.; Kesin, F. K.; Can, F. E.; Seçil, M.; and Ercan, I. 2019. Statistical errors in articles published in radiology journals. *Diagnostic and Interventional Radiology*, 25(2): 102–108.
- Kehl, S.; Weiss, C.; and Rath, W. 2016. Balloon catheters for induction of labor at term after previous cesarean section: a systematic review. *Elsevier*. Accessed September 12, 2021.
- Kilbertus, N.; Ball, P. J.; Kusner, M. J.; Weller, A.; and Silva, R. 2020. The Sensitivity of Counterfactual Fairness to Unmeasured Confounding. In Adams, R. P.; and Gogate, V., eds., *Proceedings of The 35th Uncertainty in Artificial Intelligence Conference*, volume 115 of *Proceedings of Machine Learning Research*, 616–626. PMLR.
- Klein, A.; Raff, E.; Seamon, E.; Foley, L.; and Bussert, T. 2024. More Options for Prelabor Rupture of Membranes, A Bayesian Analysis. In *2024 IEEE 11th International Conference on Data Science and Advanced Analytics (DSAA)*, 1–9.
- Klein, R. A.; Ratliff, K. A.; Vianello, M.; Adams, R. B.; Bahnik, S.; Bernstein, M. J.; Bocian, K.; Brandt, M. J.; Brooks, B.; Brumbaugh, C. C.; Cemalcilar, Z.; Chandler, J.; Cheong, W.; Davis, W. E.; Devos, T.; Eisner, M.; Frankowska, N.; Furrow, D.; Galliani, E. M.; Hasselman, F.; Hicks, J. A.; Hovermale, J. F.; Hunt, S. J.; Huntsinger, J. R.; IJzerman, H.; John, M.-S.; Joy-Gaba, J. A.; Barry Kappes, H.; Krueger, L. E.; Kurtz, J.; Levitan, C. A.; Mallett, R. K.; Morris, W. L.; Nelson, A. J.; Nier, J. A.; Packard, G.; Pilati, R.; Rutchick, A. M.; Schmidt, K.; Skorinko, J. L.; Smith, R.; Steiner, T. G.; Storbeck, J.; Van Swol, L. M.; Thompson, D.; van 't Veer, A. E.; Ann Vaughn, L.; Vranka, M.; Wichman, A. L.; Woodzicka, J. A.; and Nosek, B. A. 2014. Investigating Variation in Replicability. *Social Psychology*, 45(3): 142–152.
- Koenigbauer, J.; Schalinski, E.; and Jarchau, U. 2021-08. Cervical ripening after cesarean section: a prospective dual center study comparing a mechanical osmotic dilator vs. prostaglandin E2. *J Perinat Med*.
- Landon, M.; Hauth, J.; and Leveno, K. 2010. Maternal and Perinatal Outcomes Associated with a Trial of Labor after Prior Cesarean Delivery.
- Lee, Y. H. 2018. An overview of meta-analysis for clinicians. *The Korean Journal of Internal Medicine*, 33(2): 277–283.
- Lin, E.; Tong, T.; Chen, Y.; and Wang, Y. 2020. Fixed-effects model: the most convincing model for meta-analysis with few studies. Accessed September 12, 2021.
- Lydon-Rochelle, M.; Holt, V.; Easterling, T.; and Martin, D. 2010. Risk of Uterine Rupture during Labor among Women with a Prior Cesarean Delivery.
- Mathur, M. B.; and VanderWeele, T. J. 2022. Methods to Address Confounding and Other Biases in Meta-Analyses: Review and Recommendations. *Annual Review of Public Health*, 43(1): 19–35.
- Metropolis, N.; Rosenbluth, A.; Rosenbluth, M.; Teller, A.; and Teller, E. 1953. Equation of state calculations by fast computing machines. *J Chem Phys*, 21(6): 1087–1092.
- Moher, D.; Shamseer, L.; and Clarke, M. 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*, 41. 2015;4(1):1–9.
- Nakayama, T.; Zaman, M.; and Tanaka, H. 1998. Reporting of attributable and relative risks, 1966–97. *Lancet*, 351(9110).
- Nisenblat, V.; Barak, S.; Griness, O.; Degani, S.; Ohel, G.; and Gonen, R. 2006. Maternal complications associated with multiple cesarean deliveries. *Obstet Gynecol*, 108(1): 21–26.
- Osterman, M. 2020. Recent trends in vaginal birth after cesarean delivery : United States, 2016–2018. Accessed September 12, 2021.
- Parchem, J. G.; Townsel, C. D.; Wernimont, S. A.; and Afshar, Y. 2022. More than grit: growing and sustaining physician-scientists in obstetrics and gynecology. *American Journal of Obstetrics and Gynecology*, 226(1): 1–11.
- Parveen, S.; Rengaraj, S.; and Chaturvedula, L. 2022. Factors associated with the outcome of TOLAC after one previous caesarean section: a retrospective cohort study. *Journal of Obstetrics and Gynaecology*, 42(3): 430–436.
- Phan, D.; Pradhan, N.; and Jankowiak, M. 2019. Composable Effects for Flexible and Accelerated Probabilistic Programming in NumPyro. December 2019.
- Plaut, M.; Schwartz, M.; and Lubarsky, S. 1999. Uterine rupture associated with the use of misoprostol in the gravid patient with a previous cesarean section. *Am J Obstet Gynecol*, 180(6): 1535–1542.
- Podgorelec, V.; Kokol, P.; Stiglic, B.; and Rozman, I. 2002. Decision Trees: An Overview and Their Use in Medicine. *Journal of Medical Systems*, 26(5): 445–463.
- Radan, A.-P.; Amylidi-Mohr, S.; and Mosimann, B. 2017. Safety and effectiveness of labour induction after caesarean section using balloon catheter or oxytocin. *Swiss Med Wkly*, 45. 2017;147(45):w14532.
- Ralph, J.; Leftwich, H.; Leung, K.; Zaki, M.; Della, T. M.; and Hibbard, J. 2020. Morbidity associated with the use of Foley balloon for cervical ripening in women with prior cesarean delivery.
- Ravasia, D.; Wood, S.; and Pollard, J. 2000. Uterine rupture during induced trial of labor among women with previous cesarean delivery. *Am J Obstet Gynecol*, 183(5): 1176–1179.
- Reis, D. J.; Kaizer, A. M.; Kinney, A. R.; Bahraini, N. H.; Holliday, R.; Forster, J. E.; and Brenner, L. A. 2023. A practical guide to random-effects Bayesian meta-analyses with application to the psychological trauma and suicide literature. *Psychological Trauma: Theory, Research, Practice, and Policy*, 15(1): 121–130.
- Sarreau, M.; Isly, H.; and Poulain, P. 2020. Balloon catheter vs oxytocin alone for induction of labor in women with a previous cesarean section: A randomized controlled trial. *Acta Obstet Gynecol Scand*, 99(2): 259–266.
- SC, C.; KD, G.; LM, K.; and SF, U. 2015. Maternal Morbidity for Vaginal and Cesarean Deliveries, According to Previous Cesarean History: New Data From the Birth Certificate, 2013. *Natl Vital Stat Rep*, 64(4): 1–13. Back cover.

Silver, R.; Landon, M.; and Rouse, D. 2006. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol*, 107(6): 1226–1232.

Slutsky, D. J. 2013. Statistical Errors in Clinical Studies. *Journal of Wrist Surgery*, 2(4): 285–287.

Steinberg, J. R.; Turner, B. E.; DiTosto, J. D.; Weeks, B. T.; Young, A. M. P.; Lu, C. F.; Wolgemuth, T.; Holder, K.; Laasiri, N.; Squires, N.; Zhang, N.; Richardson, M. T.; Magnani, C. J.; Anderson, J. N.; Roque, D. R.; and Yee, L. M. 2023. Race and Ethnicity Reporting and Representation in Obstetrics and Gynecology Clinical Trials and Publications From 2007-2020. *JAMA Surgery*, 158(2): 181.

V., H. L.; and I, O. 2001. Statistical methods for meta-analysis.

VanderWeele, T. J.; and Ding, P. 2017. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Annals of Internal Medicine*, 167(4): 268–274.

West, H.; Jozwiak, M.; and Dodd, J. 2017. Methods of term labour induction for women with a previous caesarean section. *Cochrane Database Syst Rev*, 2017(6).

Wingert, A.; Hartling, L.; and Sebastianski, M. 2019. Clinical interventions that influence vaginal birth after cesarean delivery rates: Systematic Review & Meta-Analysis. *BMC Pregnancy Childbirth*, 2019;19(1):1-19.

Yusuf, S.; Peto, R.; Lewis, J.; Collins, R.; and Sleight, P. 1985. Beta blockade during and after myocardial infarction: An overview of the randomized trials. *Prog Cardiovasc Dis*, 27(5): 335–371.