

PLAIN LANGUAGE ABSTRACT

The rising rate of caesarean birth is of concern to both women and Obstetricians. One quarter of Ontario women in their first pregnancy undergo an induction of labour, and **one third of these women deliver by cesarean¹**. Prior to inducing labour, a woman's cervix often requires "ripening", a process that makes it open and soft thus facilitating the induction. Most Canadian obstetricians use prostaglandins (a chemical messenger) for cervical ripening, and a minority use Foley catheters filled to a moderate volume² (30-60 cc), both of which are equivocal in risk of cesarean delivery. However, **a recent meta-analysis from our group suggests that Foley catheters filled to a higher volume, 80cc, as compared to the usual 30cc may be associated with a decreased risk of cesarean deliveries³**.

If 80cc Foleys are found to have a lower risk of cesarean, this would have a substantial positive impact on maternity care in Ontario, Canada and beyond. To assess this, a multi-centered randomized controlled trial comparing 80cc Foleys to prostaglandins is needed. Prostaglandins have been chosen as the comparison group as they are the most widely used method of cervical ripening in Canada, and therefore the most clinically relevant comparison group. To ensure the success of such a trial, **a pilot trial must first be done. The proposed study is a pilot randomized controlled trial aimed at determining if recruitment into the large scale trial is possible, and optimizing its design. The discovery of a simple way to decrease the risk of cesarean would cause a paradigm shift in our approach to induction of labour.**

What is the main question or hypothesis for this proposal?

Foley catheters are a non-pharmacologic method of cervical ripening without the side effects of prostaglandins for a fraction of the cost. The innovation is filling a Foley used for cervical ripening to a higher volume (80cc) than the volume currently being used (30-60cc). Foleys filled to 80cc have been found on meta-analysis to trend towards a decreased risk of cesarean.

The main question: Is it feasible (defined as a recruitment rate of 20% of eligible women) to run a large scale randomized controlled trial comparing 80cc Foleys to prostaglandins for cervical ripening to decrease cesarean delivery?

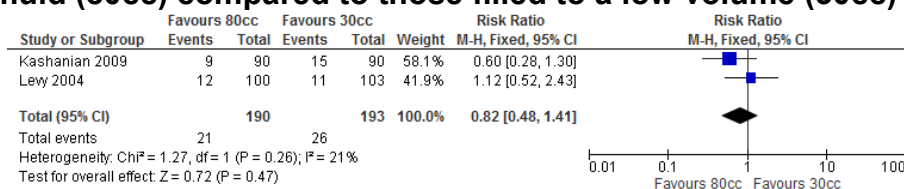
Hypothesis: The hypothesis of the large scale trial is that High volume Foleys will decrease the risk of cesarean delivery compared to prostaglandins. **The hypothesis of the current pilot study is that a randomized controlled trial is possible, in that we can enroll 20% of eligible women.**

PROJECT NARRATIVE PROPOSAL

Background:

Approximately 1/3 of first-time mothers (nulliparous women) undergoing induction of labour deliver by cesarean¹. Cesarean delivery can have negative consequences to the initial^{4,5,6} and subsequent⁷ pregnancies. Women who have a cesarean in their first pregnancy are more likely to have a cesarean in their following pregnancies¹ and this group is the largest contributor to the overall cesarean delivery rate¹. Therefore, targeting interventions that prevent cesareans in nulliparous women undergoing induction of labour will have a substantial impact on the overall cesarean delivery rate.

Adequate ripening or preparing the cervix before induction has been found to decrease the risk of cesarean⁸⁻¹¹. This can be done by a variety of methods, such as prostaglandins (a chemical messenger) or a Foley filled to a moderate volume of fluid. These methods have been found to be equal regarding the risk of cesarean delivery¹². **However, a meta-analysis by our team discovered a trend towards a decreased risk of cesarean when cervical ripening is undertaken with Foleys filled to a high volume of fluid (80cc) compared to those filled to a low volume (30cc)³.**



Most Canadian Obstetricians use prostaglandins for cervical ripening². To assess if 80cc Foleys result in a lower risk of cesarean, they need to be compared to the Canadian standard of prostaglandins. Therefore a randomized controlled trial is required.

The Greater-Toronto-Area Obstetric (GTA-OB) Network is a group of hospitals committed to facilitating research and will be the setting for the planned large scale trial. The large scale trial will aim to demonstrate a difference in the rate of cesarean from 38% to 31%, which will require the enrolment of 1442 women. It has been estimated that there are 5,437 women who will meet entry criteria in the GTA-OB network each year, if ½ are approached, 20% will need to consent to complete the trial in 3 years. **Therefore, this pilot study will determine if this recruitment rate is potentially achievable and will inform design strategies to ensure its success.**

The discovery of a simple, non- pharmacological, cost effective manner of cervical ripening that decreases the risk of cesarean would **change clinical practice and significantly improve safety for the 33,000 Canadian women and their babies who undergo cervical ripening each year.**¹³ This pilot trial is a crucial step towards this discovery.

Objectives:

The primary objective for this pilot trial is to determine the probability that an eligible woman will agree to be randomized into the trial comparing 80cc Foleys to prostaglandins for cervical ripening. This study aims to assess if it is possible to obtain a recruitment rate of 20%.

The secondary objective will be a systematic evaluation of the pilot trial process to guide full-scale study design.

Rationale:

Why is this study needed now?

Successful vaginal birth is the safest mode of delivery for both women and babies, whereas a cesarean delivery is associated with a higher rate of neonatal and maternal morbidity⁴⁻⁷. The vast majority of pregnant women would prefer to have a vaginal birth¹⁴. The goal of induction of labour is vaginal birth **and needing a cesarean section is the top fear of women undergoing induction of labour**¹⁵. Women with a failed induction have a feeling of wasted effort and pain, feel let down and disappointed¹⁶. **The healthcare system will also benefit, as first time cesarean deliveries are the leading cause of repeat cesarean deliveries**¹. **Foleys are approximately 70 times less expensive than prostaglandins**¹⁷. This project will provide the pilot study needed to discover if a Foley filled to 80cc reduces the risk of Cesarean delivery compared to prostaglandins, and will provide essential information needed for the successful execution of the large multicenter RCT. The discovery of an inexpensive method of cervical ripening that decreases the risk of cesarean delivery would have a vast impact maternal and neonatal morbidity, patient satisfaction and health care costs.

What is the clinical significance?:

The WHO recommends a cesarean section rate of 10-15%¹⁸, and the Canadian rate of 28% is significantly above this¹⁹. Induction of labour in first time mothers results in a cesarean section 1/3 of the time¹, and therefore it is essential that the process of induction is undertaken in such a way that it decreases this risk. Low volume Foleys have already proven to be a safe and cost effective method of cervical ripening¹², however, prostaglandins are used preferentially by Canadian obstetricians because of ease of use (require less set up) and perceived patient preference.² **However, if filling the Foley to 80cc was found to decrease the risk of cesarean delivery, overcoming the environmental barriers to Foley use would be justified.** By simply filling the same Foley to a higher volume, meta-analysis data suggests it is possible to decrease the risk of cesarean³. **This pilot study has the potential to lead the way towards a non-medication based intervention that has the potential to decrease the risk of cesarean and support vaginal birth in Canada and beyond.**

How will the results of this trial be used?

Rising Caesarean rates are concerning. Low volume Foleys (30-50cc) have been compared to prostaglandins in clinical trials²⁰ and meta-analysis²¹ with no difference in cesarean rate, however Foleys filled to high volumes were not included in these studies

and may decrease the risk of cesarean. The GTA-OB network has the capacity to support this needed clinical trial, however this will not be possible without ensuring that adequate recruitment will take place. This pilot will assess if adequate recruitment is achievable, and provide a platform for a rolling evaluation of recruitment strategies to improve the chance of large scale trial success.

Foundational work by the team:

A meta-analysis by the team compared high volume Foleys to low volume Foleys and a trend towards a decreased rate of cesarean with high volume Foleys was demonstrated³. **This was the foundational discovery suggesting a method to decrease the risk of cesarean delivery.**

A national survey of obstetricians showed a high degree of interest in trial participation. It also found the majority of obstetricians (85%) prefer prostaglandins because of ease of use, and a perception of patient preference,² (although this is not supported in the literature).^{22,23} This survey demonstrated sufficient interest in a trial, and that the important question to ask that would result in clinical practice change is “Do Foleys filled to 80ccs result in a lower risk of cesarean than prostaglandins?” Most obstetricians have used Foleys in the last year², demonstrating that the skills needed to make use of Foleys filled to 80cc are already in place. To facilitate the translation of Foley placement skills to our future obstetricians, we have also developed a Cervical Ripening Training Model²⁴.

Other studies have made use of Foleys filled to high volumes without evidence of adverse effects²⁵⁻²⁷, and Foleys have generally found to have a higher safety profile than prostaglandins, including decreased overall pain, decreased strong contractions causing changes in the fetal heart rate, and decreased postpartum hemorrhage^{8,20}. Our team has also done materials testing and found a standard 30cc Foley has a rupture volume of 160cc +/- 11.8cc²⁸.

A trial is needed to assess if Foleys filled to 80ccs can decrease the risk of cesarean. However, prior to this, **a pilot is required to demonstrate the feasibility of successful recruitment, and to understand unforeseen challenges and rate limiting steps that may prevent the successful completion of the trial.**

Description of the team

Anne Berndt: PI, Maternal Fetal Medicine specialist, clinician investigator at Sunnybrook Health Science Centre, MSc in Health Research Methodology. Assistant Professor, University of Toronto, Associate Scientist at the Sunnybrook Research Institute. She will oversee all aspects of the project (40% protected time).

Jon Barrett: Chief of Maternal-Fetal Medicine at Sunnybrook Health Sciences Centre, Director of Women and Babies Research Program at Sunnybrook Research Institute.

Chair of the GTA-OBS network, Professor in the department of obstetrics and gynecology at the University of Toronto. He has contributed to the design of the trial, and will provide leadership and support through Sunnybrook and the GTA-OB network (1/2 day/week)

Elizabeth Asztalos: Neonatologist at Sunnybrook Health Sciences Center, Neonatal Research Director for the Department of Newborn and Developmental Pediatrics at Sunnybrook. Associate Professor in the departments of Pediatrics and Obstetrics and Gynecology at University of Toronto. She has contributed to the design and will contribute to the analysis. (1hr/ week)

Sarah McDonald: Tier II Canada Research Chair, Associate Professor in the Department of Obstetrics and Gynecology at McMaster University, Associate Member of the Department of Clinical Epidemiology and Biostatistics. She has contributed to the design and will contribute to the analysis. Interpretation of the data, and knowledge translation (1 hr/ week).

Kellie Murphy: Maternal-Fetal Medicine specialist at Mount Sinai Hospital, Associate Professor in the Department of Obstetrics and Gynecology and Institute of Health Policy, Management and Evaluation at University of Toronto. She has contributed to the design and will contribute to the analysis, interpretation of the data, and knowledge translation (and organize recruitment through Mount Sinai. (1hr/ week)

Alex Kiss: Scientist and statistician at the Sunnybrook Research Institute, Assistant Professor in the department of health policy, management and evaluation at the University of Toronto. He will contribute to the analysis.

Approach and Work Plan

Study Design: The proposed study is a multicentre open label **randomized controlled trial pilot**. It will include nulliparous (women who have never given birth) women with term pregnancies requiring cervical ripening prior to induction of labour and takes place at Sunnybrook and NorthYork General Hospitals . The intervention involves randomizing women to cervical ripening with either a Foley filled to 80cc, or prostaglandins. We will register the trial at Clinicaltrials.gov

Primary research question: What is the probability that eligible women will agree to be randomized into the trial evaluating high volume Foleys to prostaglandins for cervical ripening.

Primary outcome: The percentage of eligible women who are approached to participate in the study that are enrolled and randomized to either the use of a high volume Foley or prostaglandin for cervical ripening.

Other outcomes: A rolling assessment of **the study process** to evaluate issues that may affect enrolment rates. These will be evaluated under the categories of technical, environmental, staff personnel, patient, and data collection issues. Other important processes outcomes include protocol compliance, ease of intervention, physician and patient satisfaction.

Inclusion criteria

- Nulliparous women 37 weeks and 0 days to 41 weeks and 6 days gestational age (term) requiring cervical ripening
- Health care provider feels it is possible to administer either method of cervical ripening.
- Bishop score of 6 or less
- Live, singleton, cephalic fetus

Exclusion Criteria

- Non-viable fetus
- Contraindication to cervical ripening, labour induction or labour
- Prior attempt at induction of labour in this pregnancy
- Spontaneous rupture of fetal membranes
- Evidence of labour or regular uterine contractions
- Lack of consent
- No one available to perform randomisation

How will participants be identified and followed?

An educational session for nurses, midwives, residents and physicians will be done at each centre. A detailed study information package will be available to give to women who meet entry criteria. Patients may choose to sign a consent form for the study in the antenatal period, or on presentation for cervical ripening.

Patients presenting for cervical ripening and meeting entry criteria will be invited to participate in the study and informed consent will be obtained by the research assistant. The research assistant will access the online randomization service at the Sunnybrook clinical trials unit, and the patient will be randomized to either prostaglandin or Foley filled to 80cc. At this time, all care and decision-making will be provided as per the woman's care provider. All approached women, whether they consent to be part of the study or not, will be invited to complete a short questionnaire regarding knowledge of the study prior to the day of induction and feelings towards research.

RAs will record in Redcap the date and time of delivery for enrolled women, as well as mode of delivery (vaginal or cesarean section) and any serious adverse events (maternal death or ICU admission, neonatal death or unplanned ICU admission)

Data Collection

Data collection for patient information will be collected electronically through RedCap. Semi-structured interviews from physicians, nurses, and residents will be conducted by the PI or delegate and recorded on paper or via email.

Patient knowledge and satisfaction surveys will be provided by the research assistant and completed by the patients when approached about participating in the study.

How will outcome measures be captured?

The primary outcome measure of percent of women recruited will be captured by the number of women who undergo the randomized intervention divided by the number of women who are eligible. These numbers will be kept by the research assistants enrolling participants in the trial. Demographic data for recruited women will be captured by the research assistants from patient charts.

For process outcomes, semi-structured interviews will be conducted with staff, chief residents and charge nurses and will be recorded in writing. Patients will be asked to fill a short patient satisfaction survey. These process outcomes will be captured every 3 months.

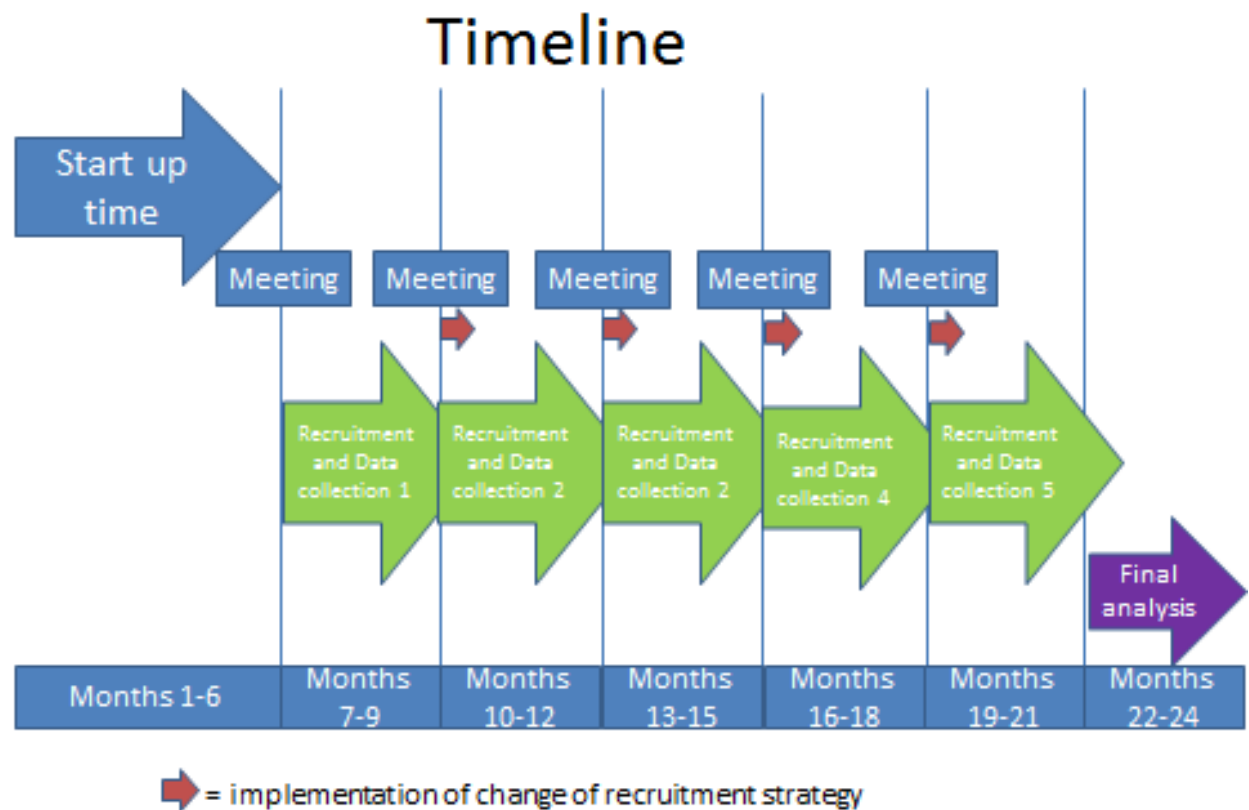
Analysis:

The primary outcome is a descriptive statistic of number of women enrolled/ number of eligible women. Process outcomes that are quantitative in nature will be described using descriptive statistics. Qualitative process outcomes will be evaluated via group discussion and consensus at each steering committee meeting.

Sample Size calculation

The primary outcome is the proportion of eligible women who consent and are randomized into the pilot trial. It is estimated that 10-15 women will be approached per week over a 15 month time frame. This is based on a total population of 4000 deliveries per year at Sunnybrook and 6000 at North York General Hospital. . One half are nulliparous, and 90% are term. 25 % of these women will undergo induction of labour, meaning approximately 24 women per week. Not all inductions will take place during day time hours or during weekdays at Sunnybrook, however almost all inductions at North York General are pre-scheduled to take place in the afternoon during the workday, resulting in an approximation of 10-15 women approached per week or 630-975 women approached over a 15 month time frame. Our target proportion is 20%. For an expected consent rate of 20%, the sample of 130-195 will provide the 95% confidence interval around this estimate to have bounds ranging from 16.9% to 23.3%, and from 17.5% to 22.7% respectively

Timeline



The start-up time includes hiring of RAs, ethics, contracts and data sharing agreements, information sessions and distribution of study information materials.

Recruitment and data collection will take place in 3 month blocks. The recruitment rate and feedback from clinicians will be assessed at a steering committee meeting every 3 months, after which strategy changes will be implemented.

The final analysis will take place in the final 3 months of the study.

Project Outcome Evaluation Metrics

Anticipated outcomes:

The primary outcome will be the percent of eligible participants approached for the trial that are enrolled in the trial and undergo randomization. **A recruitment rate of at least 20% will be considered a success.**

| Outcome | Method of capture |
|---|--|
| Recruitment rate | Number of women enrolled/ number of eligible women as found by assessing demographics of women scheduled for induction as per birth unit records |
| Pt demographics of those enrolled and not enrolled (age, indication for induction, gestational age) | Patient chart |
| Recruitment trends/ days/ time of increases recruitment | RA recruitment data |
| Staff Physician, resident and charge nurse at times of enrollment | Hospital records, RA will assess when in triage |
| Rate of protocol compliance | Assessment of appropriate inclusion/ exclusion criteria from chart, feedback from RAs |
| Physician/ resident/ nursing satisfaction and attitudes towards recruitment | Semi-structured interviews q3 months |
| Patient satisfaction/ attitudes towards recruitment | Patient surveys |
| Environmental, technical, patient, staff issues, data collection issues that facilitate recruitment or deter from recruitment | Semi structured interviews q3 months |

The study process will be evaluated every three months. The Steering committee will review the recruitment data, interviews and patient surveys, resulting in changes in the execution of the pilot for the next 3 months, with the goal of a) improving recruitment rate through strategy development and b) discovering unforeseen challenges to the success of the study. This information will ultimately be incorporated into the large scale study protocol.

Ethics:

Trained research assistants will obtain informed consent in writing from all patients. Staff, residents and nurses who provide feedback verbally will sign a consent form. Those who choose to respond by email will be assumed to be consenting by the submission of the email. All responses will be coded to a study code to maintain the confidentiality of those who participate. The master key linking these codes will be destroyed after full analysis of the study.

Canada's rising cesarean delivery rate requires creative and innovative solutions. This pilot is an essential step towards discovering a safe, cost effective way to decrease the risk of cesarean delivery and improve safety and satisfaction for women and babies.

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