The REDUCE-I Pilot Trial: REDucing the Utilization of CEsarean sections with Induction

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BACKGROUND: The cesarean section (CS) epidemic appears to be continuing unabated and rising rates are being observed in the developing world. Recent data suggests that 21% of births worldwide are by CS and that this rate has doubled since 2000(1). While there is no doubt that CS is lifesaving in many circumstances for both mothers and babies, CS rates have risen significantly without any corresponding improvement in outcomes. CS, while protective of some pelvic floor outcomes, increases the rates of abnormal placentation in subsequent pregnancies, which increases the risk of severe maternal morbidity and hysterectomy(2). Reducing the risk of CS has proved challenging, and no clearly effective interventions have been identified in clinical trials(3, 4). Modelling studies suggest that the target population to reduce the overall CS rate should be first time mothers(5).

Currently the rate of CS in first time mothers with singleton fetuses ≥35 weeks with cephalic presentation being induced in Alberta is 32.6%(6). This has increased from 23.1% in 1992 and a recent study from our group found that increasing CS for fetal distress are the most important factor in explaining this rise(7). Induction of labor often overstimulates uterine contractions (hyperstimulation) and can lead to fetal distress. Therefore, an intervention to decrease uterine hyperstimulation may lead to a reduction in fetal distress and therefore CS. Additionally, uterine hyperstimulation can lead to the reduction of oxygen transport to the fetus potentially leading to asphyxia and hypoxic-ischemic encephalopathy (HIE) which can result in chronic neurodevelopmental impairment.

For the vast majority of women who are induced in Alberta (and worldwide), this is accomplished by intravenous oxytocin. An approach that could reduce uterine hyperstimulation with induction of labor is to discontinue the oxytocin infusion once the active phase of labor is reached. This is consistent with bench research that shows that oxytocin stimulates prostaglandin production in the chorio-decidua, which induces positive feedback loops to continue production(8). Furthermore, this idea has been tested in a number of small single centre clinical trials with encouraging results. The 10 trials to date have been summarized by two meta-analyses(9, 10). The number of randomized subjects was modest n=1,538 and the sample sizes ranged from 100-250. Most of trials were not of high quality with either high or unclear risk of bias. Only two of the trials were in populations comparable to Canada: one in Europe and one in the USA(11, 12). All trials that reported CS rates documented a reduction with oxytocin discontinuation; pooled OR 0.64 (0.48–0.87). The USA trial observed a reduction in the rate of CS with oxytocin discontinuation compared to continuing from 19.2% (24/125) to 25.2% (32/127) and the European trial the rates were 15% (15/100) vs 22% (22/100). The baseline rates of CS are comparable to our population and the differences they observed were clinically significant. The meta-analyses also observed reductions in the rates of uterine hyperstimulation with oxytocin discontinuation 0.53 (0.33–0.84). While these results are promising, a definitive large randomized controlled trial (RCT) is required to assess important safety outcomes. We propose an initial small pilot study, which will allow us to refine our protocol and will ensure the success of a large multi-centre cluster RCT. Additionally, we also wish to examine serial urine prostaglandin (PG) metabolite levels in a subset of the study population. Our group has completed a large study of PG metabolites (unpublished data) in over 200 women pre-labor and in labor. We have found that prostaglandin F and E metabolites are increased during induced and

spontaneous labor. We hypothesize that patients who do not need oxytocin restarted may have higher levels or will not have a drop in their urinary PG metabolites. This data could help with improving compliance in future trials. This will also permit a precision medicine approach whereby in the larger trial, the intervention can be offered to those women most likely to benefit.

AIMS: In this REDucing the Utilization of Cesarean sections with Induction (REDUCE-I) Pilot Trial, we propose to answer the following question: Does discontinuation of oxytocin during the active stage of labor (≥6 cm dilation) decrease the rate of cesarean section (CS) in induced primiparous women, at term (≥37 weeks), with a cephalic presenting singleton fetus without increasing maternal or neonatal morbidity?

METHODS: The REDUCE-I Pilot Trial is a randomized controlled trial (RCT).

Proposed interventions: We will use the modern definition to define the active stage of labor to be ≥6 cm dilation(13). The intervention will be to stop oxytocin infusion when a dilation of ≥6 cm has been documented. The intervention will be continued until delivery unless contractions decrease to less than 2 in 10 minutes or if no further cervical dilation is noted 4 hours after discontinuation.

Randomization: A computer-generated random allocation sequence will be created by the study statistician. Randomization will stratified by need for cervical ripening and randomization will be blocked. Randomization will take place prior to the initiation of oxytocin.

Blinding: Once a patient is found to be ≥6 cm dilation, the study medication will be initiated. Pharmacy will make up identical vials of oxytocin or saline, which will be numbered according to the random allocation sequence created by the study statistician. Nurses will use the blinded vials for ongoing infusion. Patients and caregivers will be blinded.

Inclusion/exclusion criteria: Primiparous women 18 years old or older, at term (≥37 weeks) with a cephalic presenting singleton fetus undergoing induction of labor with oxytocin. Multiple pregnancies and known fetal congenital or chromosomal anomalies will be excluded.

Duration of treatment: The treatment period will continue until delivery. If the frequency of the patient's contractions are reduced to less than 2 in 10 minutes or there has been no change in dilation for 4 hours then oxytocin can be restarted.

In the event a physician or midwife makes a decision to stop the study medication, they have the option to become unblinded by making a request to pharmacy to make it easier for them to know at what dose to continue or re-start oxytocin.

Duration of follow up: Maternal and neonatal follow up until discharge. Postpartum readmission and outcomes will be obtained up to 4 weeks postpartum.

Primary outcomes: 1) CS in labor. 2) Uterine hyperstimulation (occurrence of >5 contractions in 10 minutes). 3) Proportion of screened subjects who agree to enroll in the trial.
Secondary outcomes: Adverse neonatal and maternal outcomes including:
Neonatal: a) Perinatal death; b) Neonatal asphyxia: intrapartum stillbirth or neonatal death from asphyxia (Perinatal Society of Australia and New Zealand coding)(14) or NICU admission and at least two of: i. Apgar score of ≤5 at 10 minutes; ii. Mechanical ventilation or chest compressions for resuscitation within 10 minutes; iii. Cord pH <7.00 (venous or arterial), or arterial base excess ≥12 at birth; c) moderate or severe asphyxia (Sarnat)(15) or meets criteria for therapeutic cooling; and d) sepsis or suspected sepsis.

Maternal: a) postpartum hemorrhage (PPH); b) blood transfusion; c) postpartum uterine artery/pelvic artery embolization; d) postpartum hysterectomy; and e) postpartum maternal intensive care unit (ICU) admission.

Compliance: Duration of oxytocin discontinuation. Rate of reintroduction of oxytocin infusion.

Urine Prostaglandin metabolites: Urine samples will be collected every 2 hours during labor from a minimum of 13 women in the intervention group and a minimum of 13 women in the control group. Samples will be aliquoted, frozen, and stored at -80°C prior to analysis. The following five assays will be performed: Prostaglandin E2 ELISA kit (Cayman 514010); Prostaglandin E2 metabolite ELISA kit (Cayman 514531); Prostaglandin F2α ELISA Kit(Cayman 516011),PGF2a metabolite, 13,14-dihydro-15-keto Prostaglandin F2α ELISA Kit (Cayman 516671); and creatinine ELISA kit. Assays will be performed according to manufacturer instructions with appropriate dilutions.

Measurement of Outcomes: The primary and secondary outcomes will be obtained by detailed chart review by an experienced nurse blinded to allocation. To assess neonatal outcomes, such as hypoxic-ischemic encephalopathy (HIE), data will be obtained by linkage to a specialized asphyxia database in Calgary. This database has collected data on all neonates in Calgary diagnosed with HIE since 2010. Loss to follow-up is not applicable for the current trial as data on all hospital-based deliveries are routinely captured in the medical chart.

Sample Size: The proposed sample size is 200. Approximately 1250 primiparous women are induced each year at Foothills Medical Centre; their CS rate is approximately 30%. A sample of 200 subjects has 30% power to detect an absolute difference of 10% in CS rate and 44% power to detect a difference consistent with previous trials. While under-powered for clinical outcomes, this pilot RCT will allow us to determine an effect size in our population (which will be required to perform a sample size calculation for a larger trial) and will allow us to assess the feasibility of moving forward with a larger study.

Recruitment: We would expect approximately 1250 primiparous women to be induced at Foothills Medical Centre (FMC) over the study period, therefore, we are anticipating approximately a 16% recruitment rate.

Compliance: Compliance to the treatment is a potential problem. Not all previous studies reported compliance but it is noteworthy that in the USA study that oxytocin was continued in 25% of subjects randomized to discontinuation and restarted in a further 25%(12). This may have been due to concerns regarding the potential adverse effects of longer labor. We note that all the previous studies were performed prior to the release of recent guidelines on labor management (13), which advocated for accepting slow progress in labor and allowing longer labors. These recent guidelines were the intervention we tested in the REDUCED trial, a clustered multi-centre trial which is now completed. Our results did not find any evidence of increased maternal or neonatal risks with longer labors. The intervention site for this study (Foothills Medical Centre [FMC]) was a control site but we plan to move toward adoption of the guidelines at FMC over the next 3-6 months (pandemic permitting). We anticipate that our data will alleviate physician concerns regarding longer labors and encourage patience in managing labor.

Location: Two academic centres will be used for the pilot: FMC in Calgary will be the treatment site, and Royal Alexandra Hospital in Edmonton will be used as a contemporaneous non-intervention control site.

Statistical Analysis: The analysis will be conducted independently by the study statistician (Dr. Brant). The primary outcome will not be changed during analysis. The trial, with an explicit statement of the primary outcome, will be registered at clinicaltrials.gov. For dichotomous outcomes relative risks will be calculated and Fisher exact test will be used to assess statistical significance. For continuous outcomes mean differences will be assessed with t-tests after appropriate transformations. Sub-group analysis will be performed by need for cervical ripening. The analyses will be conducted after recruitment for the pilot study has been completed. We will conduct a differences-in-differences analysis using contemporanous control data from the Royal Alexandra Hospital in Edmonton to monitor for temporal trends in outcomes and changes in labor management.

Timeline: This study will be completed in two years (see figure).

EXPERTISE, EXPERIENCE & RESOURCES: We are a strong interdisciplinary and well-established team with expertise in obstetrics, epidemiology, neonatology, molecular biology, clinical trials, and biostatistics. The principal applicant (Dr. Stephen Wood, Obstetrician/Epidemiologist) will be responsible for directing trial. The co-principal applicant (Dr. Amy Metcalfe, Epidemiologist) will co-manage the trial and will analyze the results of the Childbirth Experience Questionnaire 2 (CEQ2). The data will be collected and prepared for analysis by Ms. Selphee Tang and Ms. Susan Crawford (Epidemiologist for APHP). The

neonatal HIE data will be obtained by the study neonatologist (Dr. Khorshid Mohammad). The co-principal applicant, Dr. Donna Slater will supervise the measurement of the urinary prostaglandins. The analysis will be carried out independently by the study statistician (Dr. Rollin Brant). Two clinical collaborators, Dr. Philippa Brain and Dr. Jennifer Soucie from the obstetrics group at FMC will aid in recruitment.

ALIGNMENT WITH THE CHW STRATEGY AND RELEVANT PROJECT METRICS: Our research project is aligned with the Maternal and Child Health research program, which is outlined in University of Calgary's Child Health and Wellness Strategy(19). Safely decreasing the cesarean section rate in induced women will benefit maternal and infant health. As described above, cesarean sections increase the risk of severe maternal morbidity and hysterectomy, and CS may impact the development of the normal neonatal microbiome, which may have long term effects on child health. In addition, discontinuation of oxytocin during the active phase of labor may decrease the risk of neonatal asphyxia, which can have devastating and long-term consequences to child health.

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Ethics & operational approvals	x							
Recruit participants and conduct trial		x	x	x	x	x		
Laboratory analyses							X	
Data cleaning and analysis							X	X
Manuscript preparation								x

Our project is relevant to the Better Beginnings grand challenge area in child health and wellness, which is related to optimizing maternal, fetal, newborn and child health with accurate prediction, prevention, and interventions. If successful, this trial will prevent cesarean sections, which will provide infants the best start in life and improvements to maternal health. We will be utilizing two approaches to solving this grand challenge. As a registry-based trial, we will be 'harnessing big data for optimal child outcomes' given that we are using the Alberta Perinatal Health Program database, as well as the southern Alberta asphyxia database, to obtain most of the data for our project. Secondly, we will be 'transforming health care for children and families' as this clinical intervention is designed to change the way care is delivered.

SUSTAINABILITY: If REDUCE-I suggests a safe reduction in the CS rates, we will apply to CIHR for a Project Scheme grant for a multi-center randomized controlled trial to test this intervention in our trial network from the REDUCED trial.

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