A randomized double-blinded controlled trial comparing dilation and evacuation outcomes with and without oxytocin use

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List of Abbreviations

ACOG = American Congress of Obstetricians & Gynecologists
AE = adverse event
BMI = body-mass index
D&E = dilation and evacuation
DIC = disseminated intravascular coagulation
DSMP = data safety monitoring plan
DSMB = data safety monitoring board
EBL = estimated blood loss
NAF = National Abortion Federation
IUD = intrauterine device
IV = Intravenous
LMP = last menstrual period
QMC = Queens Medical Center
SAE = serious adverse events
UH = University of Hawaii
UW = University of Washington
VAS = visual analog scale
WIRB = Western Institutional Review Board

Project Summary/Abstract

Study Title: A randomized double-blinded controlled trial comparing dilation and evacuation outcomes with and without oxytocin use

Objective: Our study objective is to determine whether routine use of intravenous (IV) oxytocin will affect bleeding outcomes at the time of dilation and evacuation (D&E) at 18 to 24-weeks gestation.

Background: Abortion is one of the most common procedures performed in the United States. While surgical abortion is considered to be a safe procedure, rates of hemorrhage, the most common complication that occurs at the time of surgical abortion, increase with gestational age. Few studies have identified effective interventions to manage blood loss during D&E (dilation and evacuation), the procedure used to terminate pregnancy above 14 weeks gestation. Many practitioners use uterotonics, including oxytocin, to help minimize blood loss, however, oxytocin administration has never been studied with D&E.

Design: We propose a randomized, double-blinded, placebo-controlled trial at two sites, the University of Hawaii (UH) and the University of Washington (UW). Subjects who present for D&E at 18 to 24-weeks gestation will be recruited and randomized to IV oxytocin versus IV fluid alone. Bleeding will be measured during the procedure and until the time of discharge from the postoperative care unit.

Outcomes: The primary outcome is the rate at which providers intervene to control blood loss during D&E procedures. Interventions include bimanual massage, administration of medications (i.e. misoprostol, methergine) and performing additional procedures (i.e. placement of an intrauterine tamponade balloon, exploratory laparoscopy or laparotomy). Secondary outcomes include measured blood loss, complication rates, procedure length, and postoperative pain and satisfaction.

Sample size & population: We designated a 15% decrease in provider interventions to control blood loss to be clinically significant. To achieve this, with 80% power and two-sided alpha of 0.05, we need 83 subjects per group for a total sample of 166 women. Patients will be recruited in Honolulu, HI at the UH site and Seattle, WA at the UW site. Eligible participants include women 14-years and above presenting for termination of pregnancy including those with fetal demise or fetal anomalies. Exclusion criteria include placenta accreta, preoperative misoprostol use, or women unable or unwilling to provide written informed consent.

1. Background & Rationale

Nearly 1.2 million abortions are done in the United States each year, making it one of the most common surgical procedures performed (1). Only a small number of surgical abortions, 1.9 per 1000 procedures, result in a complication (1, 2). Dilation and evacuation (D&E), the surgical procedure used to terminate pregnancy above 14 weeks gestation, has a higher risk of complication. Hemorrhage, defined as blood loss over 500-ml, occurs in 0.8% to 2.1% of all D&E procedures and is the most common complication of D&E (3, 4). The rate of hemorrhage increases with gestational age; up to 6.3% of D&Es performed above 18 weeks gestation are affected by hemorrhage (5).

In an attempt to decrease hemorrhage with D&Es, many abortion providers routinely administer uterotonics like oxytocin (6). The ability of oxytocin to decrease bleeding is extrapolated from the obstetric literature where clear evidence demonstrates that it decreases hemorrhage when used routinely at the time of a full-term delivery. Studies evaluating routine oxytocin for first-trimester surgical abortion failed to show any change in blood loss (7, 8). To date, no randomized trials have evaluated routine oxytocin administration at the time of D&E in the second trimester. Because of its effect on blood loss at the time of a term delivery, oxytocin is often used during surgical termination of pregnancy at a variety of gestational ages. There is no documented "standard of care" in the literature regarding prophylactic use of any uterotonics during D&E. At The Queen's Medical Center (QMC), many providers very commonly use oxytocin at the time of D&E. We seek to determine whether this intervention decreases blood loss and the need to perform interventions to control bleeding.

We have performed a preliminary retrospective analysis of a subset of patients (n=23) undergoing D&E at 18- to 24-weeks (Study Title: Abortion Database, WIRB Approved, Study ID 2013-88). This study included procedures performed by UH/UCERA Faculty Physicians. Eight of 23 (34.8%) patients included in this subset received oxytocin. We found that those who received oxytocin had a mean estimated blood loss (EBL) of 112.5-ml while those who did not receive oxytocin had a mean EBL of 135.3-ml. A difference in blood loss of 22.8-ml (about 5 teaspoons) does not have any clinical consequences for the patient. In other words, the patient does not experience a drop in their blood count (hemoglobin), would not have any symptoms of anemia (lightheadedness or weakness), and would not require any additional treatment because an additional 22.8-ml of blood was lost during a procedure.

Importantly, this retrospective analysis does not properly answer our clinical question. For a research study to answer a question it is important to be able to properly assess the following:

1. Exposure – In this case the exposure is whether or not the patient received oxytocin and the dose of oxytocin. With a retrospective analysis, we are "stuck" with whatever information is available in the medical record. In terms of collecting

information on the exposure (oxytocin), we have information on whether a patient received oxytocin but the amount infused was not always recorded.

2. Outcome – In this case, the outcome is estimated blood loss. In terms of collecting information on the outcome, estimated blood loss recorded in the medical record, is known to be unreliable, inconsistent, and not uniformly collected. Typically in the operating room, the surgeon and anesthesiologist estimate blood loss by visually inspecting the amount of blood in the collection canister and the blood on surgical sponges. It is no surprise that one obstetrical study comparing estimated and measured blood loss demonstrated a difference of nearly 300-ml between the two groups (9, 10).
3. Confounders – A confounder is something that "mixes" or "blurs" the effect. A researcher may be attempting to relate an exposure to an outcome but is actually measuring the effect of a third factor, known as a confounding variable to the outcome. For example, the results of our preliminary analysis show that patients who did not receive oxytocin had slightly less bleeding. However, what if some confounding factor (i.e. low platelets, higher gestational age, multiple gestation, etc.) made it more likely for patients who had a higher risk of bleeding to get oxytocin? Although we were trying to measure the effect of oxytocin on bleeding we may have in fact been measuring the hidden effect of confounders on bleeding. Sometimes confounders are easily identifiable, sometimes they are unknown, yet-to-be identified factors.

The retrospective analysis we conducted does not adequately address our scientific question because of the three factors listed above. In our randomized controlled trial we will be able to improve on the quality of data collected in the following ways;

1. Exposure – We will know if a patient received oxytocin and those who get oxytocin will get a standard amount of the medication
2. Outcome – Blood loss will be accurately measured rather than estimated.
3. Confounders - Conducting a randomized controlled trial is the best way to avoid confounding because assignment of participants into one group or another happens purely by chance. In other words, possible confounders don't affect whether the patient receives or does not receive the intervention.

Though oxytocin is a safe, inexpensive medication, no medication is administered without some risk. Some abortion providers hypothesize that use of oxytocin can make it more difficult to remove pregnancy tissue because the uterine muscle contracts around the surgical instrument making them difficult to manipulate (5). Oxytocin may increase postoperative uterine cramping causing the patient unnecessary discomfort (11). Though no published reports describe adverse events when oxytocin is used at the time of D&E, when used during labor and delivery at term or induction termination in the second and third trimester, oxytocin related complications such as anaphylaxis, uterine rupture, arrhythmias and water intoxication have been reported (12-15). Unnecessary use of oxytocin would raise abortion related healthcare costs both directly, via the cost of the medication, and indirectly, via the cost of treating related adverse events and pain.

This study will be conducted in compliance with the protocol approved by the Research and Institutional Review Committee, and according to Good Clinical Practice standards, applicable federal regulations, and QMC institutional policies, and QMC research policies and procedures.

2. Specific Aims/Objective/Purpose:

Primary Objective: Our primary objective is to determine whether routine use of oxytocin decreases the rate of intervention to decrease excess blood loss compared to IV fluid alone in women having D&E between 18- and 24 -weeks gestations (for special considerations for 22- to 23-week and 6-day gestations see Inclusion Criteria). Interventions to decrease bleeding have been defined as bimanual massage, use of uterotonics (misoprostol, methylergonovine, carboprost tromethamine), injection of additional vasopressin, balloon tamponade or packing, re-aspiration, exploratory laparotomy or laparoscopy, need for uterine artery embolization or hysterectomy.

Secondary Objectives:

- Measured blood loss (described in section 6 under "Surgical Protocol")
- Procedure length, measured from placement of the speculum to removal of speculum
- Complications including uterine perforation, cervical or vaginal laceration, hemorrhage (blood loss greater than 500 ml), need for transfusion, exploratory laparotomy or laparoscopy
- Postoperative pain: recorded 60-minutes after the end of the procedure using a 10-cm visual analog scale (VAS) and compared to preoperative baseline score
- Patient Satisfaction: measured 60-minutes after the procedure using 5-point scale and compared to preoperative baseline score

3. Study Design

Overall Study Design

We propose a randomized, double-blind, placebo-controlled trial of women undergoing D&E at 18- to 24-weeks gestation (for special considerations for 22- to 23-week and 6-day gestations see Inclusion Criteria). Women will be randomized to receive 30-units of IV oxytocin versus IV fluid alone. This study will be performed at two sites: The Queen's Medical Center (UH site, Honolulu, Hawaii) and University of Washington Hospital and Clinics and Cedar River Clinic (UW sites, Seattle, WA). The gestational-age limits were selected for two reasons. First, studies have shown rates of hemorrhage increase significantly past 18-weeks gestation and are reported to be as high as 6.3% (5). Second, a survey of abortion providers who participate in

the Family Planning Fellowship LISTSERV found that providers who routinely use oxytocin during D&E generally do so starting at 18-weeks gestation.

Description of the drug to be studied

Pitocin®, or synthetic oxytocin, is made by JHP Pharmaceuticals in Rochester, MI. The research pharmacists at each site will be given a randomization scheme and will accordingly prepare an IV solution that contains either 500-ml of lactated ringers or 500-ml of fluid mixed with 30-units of oxytocin. Study medications will be labeled with study identification numbers based on allocation (see Randomization).

Sample Size & Duration

We designated a 15% decrease in intervention rates to control blood loss as clinically significant. To achieve this, with 80% power and two-sided alpha of 0.05, we need 83 subjects per group for a total sample of 166 women. At the UH site (QMC), we estimate 100 D&E procedures between 18- and 24-weeks gestation will be performed over the next 12-months. We estimate 50% of all eligible patients will agree to participate giving us an enrollment of approximately 55-60 patients over a 14-month period. UW site investigators have estimated 180 abortions at 18- to 24-weeks will occur over the next year. Similar to the UH-site, we estimate 50% of eligible subjects will be recruited and we should therefore enroll about 100-120 patients in 14-month period. Each subject's involvement lasts from the time of the pre-operative visit until discharge from post-operative unit.

Randomization

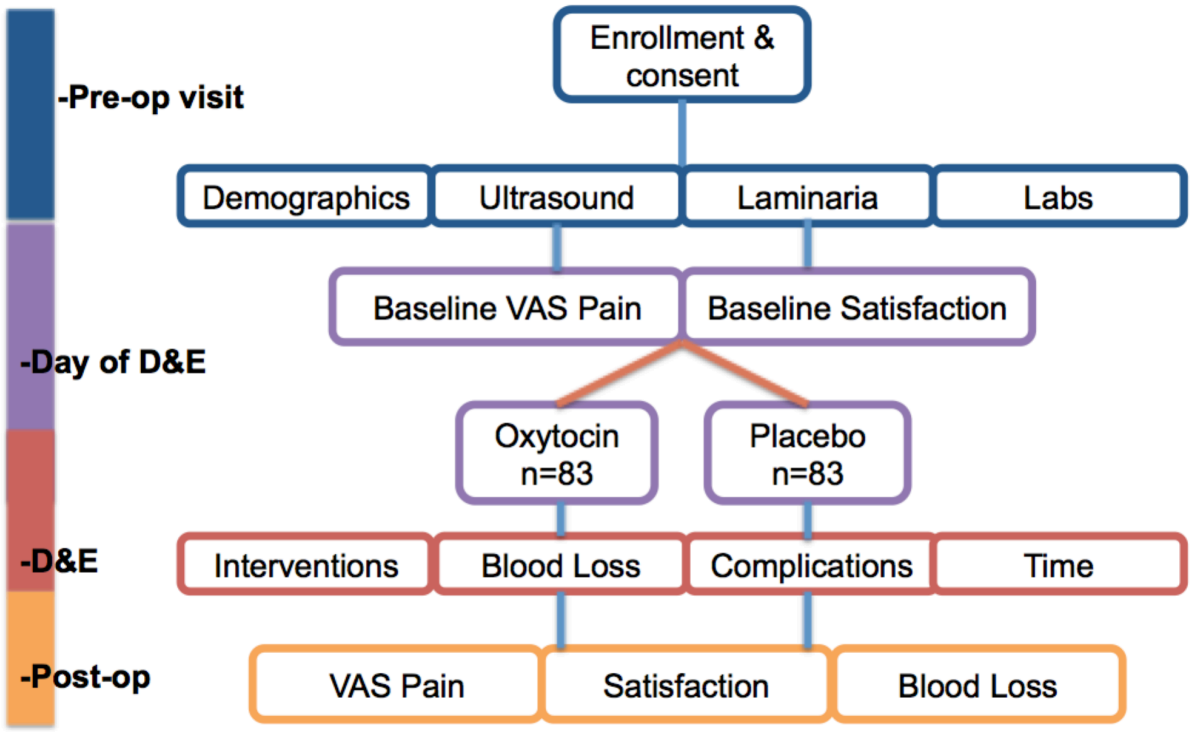
An individual not involved with subject recruitment, enrollment or follow-up will determine allocation of subjects by computer-generated random numbers in block sizes to be determined by that individual. The investigators will provide research pharmacists sealed, sequentially-numbered, opaque envelopes containing study group assignment which will be decided on the day of surgery. The research pharmacists will prepare study medication (either IV fluid alone or IV fluid with oxytocin) and will label the fluid bag with a study identification number. Investigators will assign each subject a study identification number in sequential order. Study medication will be delivered to the operating room prior to the procedure.

The research pharmacist will be the only individual not blinded to group assignment and will not have contact with study investigators or the research coordinators prior to the procedure. An opaque sealed envelope outlining group assignment (oxytocin or IV fluid alone) will accompany each solution of IV fluid. The research assistant will keep this envelope with them during the procedure. The surgeon, anesthesiologist and all assistants will be blinded to group assignment. However, the surgeon or anesthesiologist may instruct the research assistant to open the envelope to determine group assignment if the patient exhibits signs of complications directly related to oxytocin such as anaphylaxis, arrhythmia, or water intoxication or in case of emergency where the physician feels unblinding is necessary.

Follow-up procedure

Study procedures will end when the patient is discharged from the medical facility. Patients will receive standard post-abortion care as performed at the various practice sites. In terms of post-operative pain and satisfaction assessment, this will be assessed approximately 1-hour after the D&E in the recovery room. Any complications that occur before the patient is discharged from the medical facility will be recorded.

Study Flow Schematic



4. Eligibility Criteria

A. Inclusion Criteria:

- Age greater than or equal to 14-years
- Requesting pregnancy termination
- Intrauterine pregnancy at 18- to 23 weeks and 6 days gestation
    - Gestational-age to be confirmed by ultrasound (See section 6)
    - We will perform procedures in full compliance with QMC Abortion Policies. At QMC, intentional termination is performed at 18- to 21-weeks and 6-days gestation but may be performed up to 23-weeks and 6-days gestation in the following circumstances:
        - Fetal anomaly

253 - Intrauterine fetal demise
254 - Victims of rape or incest
255 - Woman's life is in danger
256 • Subjects must be willing and capable of giving informed consent and able to understand
257 and sign written consents in English.
258
259
260 *B. Exclusion Criteria:*
261 • Ultrasound findings suggestive of placenta accreta
262 • Patients requiring preoperative misoprostol
263
264 In clinical research, pregnant patients are considered to be a vulnerable research population
265 due to the interplay of maternal and fetal health risks. In the case of patients seeking abortion,
266 the focus is turned solely to the health of the woman as the pregnancy is undesired and will be
267 terminated.
268
269 Minors are also considered a vulnerable research population and we will seek IRB approval to
270 include patients aged 14-years and older. In both Hawaii and Washington State, parental
271 consent is not required for minors age 14-years and older to receive pregnancy care, including
272 an abortion. According to the American College of Obstetricians and Gynecologists (ACOG)
273 Committee Opinion on "Guidelines for Adolescent Health Research", the Code of Federal
274 Regulations allows parental consent to be waived in clinical situations where parental
275 permission is not typically required. The Code of Federal Regulations also states that, "in
276 certain research studies, adolescent minors would not be considered children and parental
277 permission would not be required. Such research includes certain clinical studies involving
278 pregnancy, family planning, and treatment of STDs where the adolescent can legally consent to
279 such services." (16) There is no published medical evidence or theoretical reason why
280 adolescents would have a higher risk of complications during D&E than adults.
281
282 Through our consent process, we will make it clear that participation in this study is voluntary.
283 Participants will not be approached until after they have already secured medical care for the
284 abortion procedure (i.e. preoperative evaluation, consent for the abortion procedure, and
285 scheduling are complete). We will not post advertisements for recruitment and will only
286 approach patients who have already consented to the abortion procedure. Subjects will not be
287 provided with any remuneration for study participation. We will make it clear that if patients
288 are not willing to participate in the study, they will still be provided the same standard of care.
289

290 ## 5. Recruitment/Enrollment

291
292 **Study Population**

The study population will consist of female patients aged 14 and older who request D&E at 18- to 24-weeks gestation (for special considerations for 22- to 23-week and 6-day gestations see Inclusion Criteria). This study will be conducted at UH (QMC) and UW.

Subject recruitment, admission and allocation

Providers (listed in Appendix C – Roles of Personnel) will approach patients who meet inclusion criteria about study participation at the preoperative visit, which takes place in UH Faculty Practice Sites at least one- to two-days before the procedure. Invitation to participate will be offered only after patients have received standard counseling and have provided written consent for the abortion procedure itself. It will be made clear to all patients that their decision to enroll or not enroll in the study will not affect their access to requested abortion care. Consent for the study will be obtained by study investigators. In the rare instance that the investigators recruit another physician's patient, attending physician permission will be obtained first, before approaching the patient. After enrollment, a copy of the study consent will be given to the subject (see Consent Form attachment).

No advertisements will be posted for this study. Subjects will be recruited at UH Faculty Practice sites (i.e. not part of QMC). At the UW site, subjects will be recruited at Cedar River Clinic or UW Hospital and Clinics where they will also perform the procedures in the outpatient setting. On the day of the procedure, the surgeon will meet with the subjects one- to two-hours before the procedure to confirm they are still willing to participate.

Criteria for Discontinuation

Participants may end study participation upon request at any point in the study. For example, they may withdraw any time prior to the procedure or they may decline to complete postoperative the postoperative satisfaction and pain score. After study consent and randomization but prior to the procedure, patients may be discontinued if it is revealed that the patient meets any of the exclusion criteria.

We will follow intention-to-treat principles and analyze all data based on its allocation regardless of whether or not the intervention was received.

6. Study Procedures/Protocol

Procedure setting

At UH faculty practice sites, surgical abortions above 18-weeks gestation are performed in an operating room setting. One of six experienced D&E providers will perform all procedures. At the UW site, one of two experienced D&E providers will perform all abortions in either the operating room or outpatient surgical center setting. At both sites, fellows may participate in the procedure under direct supervision**.** In study documents, we will record the name of the surgeon, whether a fellow participated in the procedure and their level of training.

Screening/Preoperative evaluation

Patients requesting abortion procedures who meet inclusion criteria will be recruited at the preoperative visit which typically occurs one- to two-days before the procedure at the UH faculty practice sites, however, if patients have any doubts or ambiguity about the abortion, they can be given as much time as they need to consider their options before scheduling surgery. Study investigators will thoroughly consent patients for the study (see Subject Recruitment, Admission, Allocation).

Standard pre-operative counseling and assessment (including routine blood or laboratory tests) will be done, contraceptive counseling will be performed and surgical consent will be obtained. For patients with HMSA insurance, we have received pre-approval status. Therefore, no additional actions need to be taken on the part of the subject or investigators to assure health insurance coverage. The preoperative care of study participants will differ from usual care in the following way:

- Components of demographic and health related information will be recorded in study documents. All information recorded in study documents is part of usual preoperative assessment. We will not be obtaining any additional information from study participants

Pre-operative evaluation on the day of surgery

In the pre-operative area, the following study procedures will be performed:

- Approximately one- to two-hours before the procedure, providers will confirm that subjects are willing to participate.
- Pain/Satisfaction Assessment: The research assistant will assess subject's pain score using a 10-cm VAS and patient satisfaction using a 5-point scoring system within 60-minutes of the procedure. Assessment will be made before any anesthetic medications have been given. These values will serve as a baseline to compare with the postoperative assessment described later.

Intraoperative Evaluation

Participation in this study does not alter the key portions of the surgical procedure. Standard D&E procedures will be performed under ultrasound guidance according to the usual standard of care. Each patient will receive general anesthesia or deep sedation with choice and dosage amounts of anesthetic agents decided by the anesthesiologist. Unless there is a contraindication, surgeons will give all patients 5-units of vasopressin mixed with 10-mL of saline in a paracervical block. This is the current practice at QMC based on scientific evidence (17) and recommendations by the National Abortion Federation (NAF) (18) and Society of Family Planning (SFP) (3). As is the usual practice, amniotic fluid is drained from the uterus prior to removing products of conception. Intraoperative care of study participants will differ from usual care in the following ways:

- Study Drug Administration: Upon speculum insertion, 500-ml of lactated ringers or 500-ml of lactated ringers with 30-units of oxytocin will be given as an IV fluid bolus infusion over approximately 15-minutes. The dose of oxytocin is extrapolated from the obstetric literature; oxytocin is used at this does at the time of term delivery at QMC and throughout the US (16). Currently, the same dose of oxytocin is very commonly administered at QMC on labor & delivery and during D&Es.
- Blood Loss Measurement: It is the usual practice at QMC for the surgeon to handle all products of conception throughout the procedure until it is sealed in a specimen container and they will continue to do so. Simple visual inspection is known to be inaccurate in estimating blood loss (9, 10). Thus, following the procedure, the surgeon or research assistant will measure blood loss with a graduated cylinder.
- Weighing of gauze and sponges: Used gauze or sponges will be weighed and the dry weight of the gauze or sponge will be subtracted and converted from grams to milliliters using a one-to-one ratio.
- Measurement of procedure length: The research coordinator will measure and record length of procedure in seconds starting from when the speculum is placed and ending when the speculum is removed from the vagina.

In rare cases, the surgeon may not able to separate amniotic fluid from blood. In these cases, hematocrit of the blood-amniotic fluid mixture will be checked at completion. This hematocrit will be compared to the patient's preoperative serum hematocrit to determine the dilution ratio and ascertain blood loss. We plan to validate this process by performing the same hematocrit assessment on a subset of patients whose amniotic fluid was separated at the start.

Intraoperative complications such as hemorrhage (blood loss greater than 500-ml), need for transfusion, uterine perforation, cervical laceration, vaginal laceration, or need for laparoscopy or laparotomy will be documented. Complications such as cervical or vaginal laceration, or uterine perforation, will be managed according to current standards of care. The research coordinator will record all such events in the study documents. If the surgeon is concerned for excessive bleeding due to uterine atony, measures will be taken to manage it. The decision to intervene will be based on signs of impending hemorrhage such as the presence of brisk and/or prolonged, bright red, vaginal bleeding or accumulation of over 200ml of blood loss with ongoing significant bleeding or signs of hemodynamic instability. Ultimately, the provider involved must use their best clinical judgment to decide when to intervene. When providers feel it is necessary to intervene, they will perform the following interventions in the order described below (3):

1. Bimanual uterine massage
2. Intramuscular methylergonovine 0.2-milligrams (may repeat dose in 2- to 4-hours)
3. Rectal misoprostol 800-micrograms
4. 250-micrograms of intramuscular carboprost tromethamine (may repeat dose every 15- to 90-minutes)
5. Intra-uterine balloon tamponade

6. Additional surgical procedures such as re-aspiration after procedure completion, exploratory laparotomy or laparoscopy (including those resulting in hysterectomy), or uterine artery embolization.

The rationale for using an algorithm is to standardize the care of patients and more accurately assess our main study outcome, the need for intervention to control bleeding. Study investigators agreed upon the order of interventions because it so closely mirrors current clinical practice, though a written algorithm does not currently exist. The algorithm does not dictate that a provider must wait a certain amount of time between steps. If the provider feels they need to move on to the subsequent step in the algorithm to best care for the patient, they may do so at any time. If contraindications to one of the uterotonics exist, the provider may skip to the next step in the algorithm and this will be documented. Providers may use additional injections of vasopressin at any time during the procedure at their discretion to control excess bleeding; these additional injections will be noted in the study documents.

Postoperative Evaluation

After the procedure is complete, the surgical team will transfer the patient to the recovery unit where she will spend a minimum of 60-minutes (6). The following will be performed in the postoperative care unit:

- Pain management: All patients will receive 15-milligrams of IV ketorolac or 500-milligrams of oral naproxen at the time of procedure completion unless they have contraindications to these medications (18, 19). Anesthesiologists may give alternative or additional doses of pain medication if the patient does not obtain relief with initial dose. All pain medications administered will be recorded in study documents.
- Pain/Satisfaction Assessment: The research assistant will assess patient satisfaction and postoperative pain 60-minutes after the procedure. Satisfaction will be assessed using a 5-point scoring system and pain will be assessed using a 10-cm VAS (19-21).
- Postoperative Bleeding Assessment: Before the patient is discharged, the research assistant will collect and weigh all used pads to quantify postoperative bleeding, subtracting out the weight of a dry pad from the used pad.
- Monitoring for Signs of Adverse Events: Respiratory rate, heart rate and oxygen saturation will be continuously monitored from the time oxytocin is administered until subject arrives in the post-operative area as is the usual routine for patients having surgery. Blood pressure will be measured at frequent intervals as determined by the anesthesiologist. When patients are in the postoperative recovery area, vital signs will be checked per the QMC Same Day Surgery protocol which includes continuous heart rate and oxygen saturation with blood pressure checked every five-minutes for the first 15-minutes, every 15-minutes for the next hour, then every hour. Patients will be asked every 30-minutes if they are experiencing symptoms of pain, bleeding, heart palpitations. Any complications that occur postoperatively will be recorded.

Please see attached Data Collection forms, which will be used throughout the above processes. See Study Flow Schematic for visual representation of the above.

7. Drug Supply, Packaging, Labeling and Storage

Pitocin ® or synthetic oxytocin is made by JHP Pharmaceuticals in Rochester, Michigan. It is currently stocked by the pharmacy and a supply of study medication may be ordered by the QMC pharmacy. Oxytocin is supplied as packages of twenty-five oversized 1-mL vials, each containing 10 units of oxytocin or as a 10-mL multiple-dose vial containing 10 units of oxytocin per mL (total = 100 units of oxytocin). It must be stored at 15°–25°C (59°–77°F). With proper storage, the shelf life of this medication is up to 3-years. Once mixed in a bag of IV fluids, the solution expires after 90-days. The manufacturer provides standard labeling of oxytocin vials; however, study drugs will be re-labeled by the research pharmacist to conceal the randomization status of the subject. All listed providers have prescribing privileges for study medications.

8. Statistical Methods

Patients may discontinue from the study at any time. If a patient withdraws, we will follow intention-to-treat principles and will analyze subjects in the groups they were assigned to.

Primary Outcome: Use of any of the following interventions to control bleeding:

- Bimanual massage
- Uterotonics including: misoprostol, carboprost tromethamine, methylergonovine
- Injection of additional vasopressin
- Balloon tamponade
- Re-aspiration after procedure completion
- Exploratory laparotomy or laparoscopy
- Uterine artery embolization
- Hysterectomy

We will compare intervention rates between treatment and control groups using a chi-square test. If significant differences in demographic or abortion related characteristics exist between study groups, we will employ multiple logistic regressions to control for these differences.

Secondary Outcomes:

- Measured blood will be compared using a student's t-test.
- Procedure length will be compared using a student's t-test
- Complications (described in Section 6) will be compared using a chi-square test
- Postoperative pain will be compared using a student's t-test
- Patient Satisfaction will be compared using a student's t-test

We anticipate that some outcomes such as measured blood loss and procedure length may not be normally distributed. If this is the case, we will use an appropriate transformation to normalize the data distribution prior to analysis.

No interim analysis is planned. A Data Safety Monitoring Board (DSMB) has been assembled to review data (See Section 10B, Page 20). Otherwise, the principal investigators will be responsible for protecting and monitoring the rights, safety and welfare of the subjects at each site. Statistical analysis will be performed with R-software®. Data will be analyzed using intention to treat principles. Missing data will be noted. Only the primary investigators and research assistants will have access to study records, which will be kept in locked file cabinets in the study investigator's office. All data will be entered into a database without personal health identifiers for analysis. Any publications or presentations will be reported without reporting any personal health identifiers. Any deviations from the planned statistical analysis will be documented.

Number of subjects and statistical power

Hemorrhage, defined as EBL greater than 500-ml, is a rare outcome that occurs in less than one to 6.3% of D&Es above 18-weeks gestation (3-5). Given this, a study to decrease the rate of hemorrhage would not be feasible because it would require a large sample. Our primary outcome, the rate of provider intervention to decrease bleeding, represents a meaningful clinical outcome. When an intervention is required to prevent excessive blood loss it adds time and expense to the procedure. Each intervention poses some increased risk of morbidity. Importantly, when additional interventions are required, it increases the level of concern for the surgeon. If our study is successful, decreasing surgical time and healthcare costs will be a strong motivation for others to adopt this intervention.

Though a study may have several measured outcomes, the sample size is based on the study's primary outcome. In this study, the primary outcome is the rate of intervention to decrease excess blood loss. Our primary outcome, the rate of provider intervention to decrease bleeding, represents a meaningful clinical outcome. When an intervention is required to prevent excessive blood loss it adds time and expense to the procedure. Each intervention poses some increased risk of morbidity. Importantly, when additional interventions are required, it increases the level of concern for the surgeon. We think the rate of provider intervention is the most important factor a surgeon will consider when deciding whether to use a medication like oxytocin. If our study is successful, decreasing surgical time and healthcare costs will be a strong motivation for others to adopt this intervention.

Other outcomes we will collect data on in this study include measured blood loss, procedure time, complications (uterine perforation, cervical or vaginal laceration, hemorrhage (blood loss greater than 500-ml), need for transfusion, exploratory laparotomy or laparoscopy, postoperative pain, and patient satisfaction. Though each of these is important, the sample size in a research study is based on the ability to demonstrate differences in the primary outcome.

Based on an unpublished study from Oregon Health and Science University (OHSU) that was performed with patients in the same gestational age as proposed here, we have estimated our baseline need for intervention to be 20% (22). We have deemed a decrease of 15% from 20% to 5% to represent a clinically significant change. In other words, we are trying to show that

prophylactic oxytocin will change the provider intervention rate from 20% in the unexposed (placebo) group to 5% in the exposed (treatment) group. A clinically significant decrease means that the effect size is large enough to be important to physicians and patients. Thus, we believe that a surgeon will be willing to use a medication, in this case oxytocin, if it will decrease their need to perform additional interventions from 20% to 5%.

For results to be meaningful scientifically, they must also be statistically significant. Statistical significance is based on two parameters, power and alpha. By convention, research studies typically set power at 0.80 or 80% meaning there is an 80% chance of detecting a difference between two treatments if a real difference exists and a 20% of making a false-negative conclusion. Alpha is conventionally set at 0.05 or 5% meaning there is a 5% chance that results were due to chance rather than a true difference (false-positive conclusion).

We based our sample size calculations on these conventions: power of 0.80 and alpha of 0.05. Based on these parameters, we calculated that a sample size of 75-subjects per group is needed to demonstrate a difference of 15%. To account for a projected 10% dropout rate, we will randomize 83-subjects to each group for a total enrollment of 166-subjects. If we meet our recruitment goals, we will have the ability to demonstrate a decrease of 15% or more in the need for interventions to decrease bleeding.

9. Risks/Benefit Assessment

Risk Category

This study presents minimal risk to the subjects involved. Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests." The study involves routine venipuncture which would be done regardless of whether an individual participated in this study.

Any patient who undergoes a D&E is at risk for bleeding. For patients in the treatment group, although oxytocin has a theoretical risk of adverse events including cardiac arrythmia, water intoxication, uterine rupture, and allergic reaction, these events are rare and have not been documented during D&E (12-15). These adverse events are more likely to occur to patients who are exposed to large and/or prolonged doses of oxytocin, such as doses used for labor induction (23, 24). No cases of water intoxication have been reported with a single 30-unit infusion diluted in 500-ml of IV fluid at the time of D&E. Because oxytocin is already very commonly used during D&E at QMC, the risk posed to the patient by this study is minimal as it is not outside of the standard of care for this procedure. Care will be taken throughout the surgery and in the post-operative area to identify any signs of side effects from study drug usage.

If bleeding occurs to patients in the placebo group, many other suitable medications and procedures, aside from oxytocin, are readily available if needed. Furthermore, many

practitioners throughout the country do not use oxytocin routinely so the placebo protocol would not be considered outside the current standard-of-care.

Experiencing an unplanned pregnancy or a fetal demise can be a stressful time for a patient. However, this study does not add any additional psychological or social risks to the subject. The patient will not incur any additional economical costs for study participation nor will remuneration be provided. Patient will be made aware that she can discontinue the study at any time and that she will still be offered the procedure she requests. We will utilize a data safety-monitoring plan (DSMP) (see Section 10B) to monitor and track adverse events that may be related to the investigation. If this study meets criteria for an interim analysis and a review of the data demonstrates the study posing significant risk to the subjects, we will stop the study at that time.

Potential Benefits

There are likely no direct benefits to the subjects who participate in this study. Because we do not believe that oxytocin will significantly affect bleeding during D&E, we do not think that the treatment group will receive any direct benefits over the placebo group. Overall, the results of the study will help patients having D&Es in the future. If oxytocin is ineffective at decreasing the need for interventions to control bleeding during D&E, we can stop administering it, thereby decreasing health care costs. If it is found to be effective, routine use of it could help women avoid complications of excess bleeding in the future and decrease overall morbidity and mortality associated with this procedure. Because there is currently no established "standard of care" regarding uterotonic use during D&Es, results from this study may help to develop future guidelines that would direct providers in how to optimally care for their patients.

Financial Obligations/Cost:

It will be made clear that subjects will not be billed for study drug or additional hematocrit tests necessary to determine blood loss. All standard of care labs, medications and procedures will be billed through the subjects' insurance. There will be no compensation offered for injury or adverse events of this study.

10. Safety & Adverse Events

A. Adverse Event (AE) Reporting

An adverse event is defined as any adverse finding, temporally associated with drug use. These findings include an abnormal physical finding or sign, a new or increased symptom, and abnormal test or laboratory study, or a cluster of signs, symptoms, and abnormal assessments. An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or has been previously observed in relation to this medication.

A severe adverse event is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. An unexpected adverse event is defined as any adverse drug experience, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed. Any SAE, whether or not related to the study product, will be reported to the IRB and if appropriate, the FDA, within 24-hours. The initial SAE report will be followed by submission of a completed SAE report.

Adverse events due to oxytocin are anticipated to be extremely unusual in this study. Possible AEs include, electrolyte imbalances, severe allergic reactions, and heart beat abnormalities. Of note, none of these adverse events have been reported during D&E procedures. The healthcare providers will monitor subjects for signs of adverse events during the procedure and in the post-operative area via routine frequent vital sign assessments. (See Section 6, Postoperative Evaluation) All subjects will be informed about the definitions of AEs and SAEs, and asked to report these events during participation. All AEs and SAEs occurring during the course of the study will be collected, documented, and reported to the Principal Investigator on an AE or SAE Forms. Each week, study investigators will review these forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs and SAEs to the point of a satisfactory resolution. Unanticipated non-serious adverse events will be reported within 30 days. All SAEs will be reported to one of the PIs within 24-hours.

In the event that a subject is withdrawn from the study or the investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem identified has resolved or stabilized with no further change expected, is clearly unrelated to the study product, or results in death. Outcomes of SAEs and unexpected AEs that occurred during the previous year will be included in progress reports to the IRB.

B. Data & Safety Monitoring (DSM)

The principal investigators will be primarily responsible for protecting and monitoring the rights, safety and welfare of the subjects. These investigators will meet regularly (i.e. weekly or bimonthly depending on subject enrollment) with the research coordinators to monitor data quality.

We will create a DSMP to track and monitor any potential adverse outcomes to study subjects. The DSM report summary will be sent to the IRB on a twice-annual basis or more frequently if requested as part of an ongoing progress report. Included in the DSM report will be: subject sociodemographic characteristics, expected versus actual recruitment rates, retention rates,

any quality assurance or regulatory issues occurring during that period, summary of AEs and SAEs, and any action or changes to the protocol since last report. Routine documented meetings will be held to review study progress, AEs, SAES, and update changes to the protocol at least every six weeks. If there is a clear trend in adverse events, unblinding can be done at any time and the study may be terminated early if it is felt that the study poses untoward effects on subjects.

All Adverse Events (AE) as defined in Section 10 (Safety & Adverse Events, Page 18) occurring during the course of the study will be collected and documented. Each week, a study investigator will review accumulated AE events from the previous week. The study investigators will follow all AEs to the point of a satisfactory resolution. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE) or unexpected adverse event (UAE), also defined in Section 10. Any SAE or UAE will be reported to the PI (or a co-investigator if the PI is not available) within 24-hours.

Any UAE and SAE, whether or not related to the study drug, will be reported to the DSMB within 24 hours. The DSMB will meet at the start of the study and will reconvene after the first 10 patients have been recruited from the UH site. Thereafter, they will meet after a total of 30 patients and 50 patients have been recruited from the UH site. If it takes more than 6 month intervals to reach these recruitment milestones, a meeting will be convened so that no longer than 6 months will pass without a meeting. If an SAE or UAE occurs, the DSMB will be convened within a week to review the SAE or UAE.

At scheduled meetings, the DSMB will review and evaluate accumulated study data for participant safety, study conduct and progress, and make recommendations concerning the continuation, modification, or termination of the trial. As recommended by the National Institutes of Health, the DSMB will be responsible for defining its processes, including event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review (25). These event triggers would include but not be limited to: serious adverse events (see Page 18, Section 10) or a trend in increased rates of side effects or complications to study subjects.

Data Safety Monitoring Plan will include the following protection elements:

- Subject Safety & Protection: No data collection activities will begin until IRB approval has occurred. To screen for adverse events, vital signs will be continuously monitored during the surgical procedure and patients will be frequently assessed until discharged home (See Section 3, Postoperative Evaluation). Subjects will be removed from the study at any point if they request to do so or if there are any unanticipated problems involving risks to subjects or others, unexplained adverse outcomes, or life threatening adverse events. Any such issues will be reported to the IRB (See Section 10, Adverse Event Reporting). We will still follow an intent-to-treat analysis.

- Data Integrity: Primary investigators will assure that subject inclusion criteria are being met, transcription of data is accurate and complete, units of measure are recorded

appropriately, and calculations are standardized and performed accurately. This will occur on a biweekly or monthly schedule depending on subject enrollment.

- Subject Privacy: Subjects will be consented privately and in-person by the investigators (See Section 5, Subject Recruitment, Admission, Allocation). All questions will be answered before subject signs consent.

- Data Confidentiality & Study Documentation: All subjects will be assigned a unique study ID number. No identifying information will be used in data analysis procedures or in research reports. Only Principal Investigators, and research coordinator(s) involved in the conduct of this study will have access to patient data that include personal identifiers. Data will be recorded in a paper chart and converted into electronic file. We will keep paper charts in a locked drawer and password-protect electronic files. We will keep codes linking the study identification number with the name of the subject confidential, secured by password-protected data file within the locked research unit of the Principal Investigator. All information collected during this study will be kept private to the extent allowed by federal, state and local law. Data will be de-identified prior to analysis. Patient identifiers that link them to data collected during the conduct of this study will be destroyed at the earliest possible opportunity consistent with study conduct and applicable research regulations. Records will be destroyed by the UH-contracted shredder service when applicable.

- Product Accountability: The research pharmacist will be responsible for ordering, mixing, labeling, storing, and disposing of expired/unused study drugs. This will be done in accordance with study specifics (see Section 6, Description of Drug to be Studied) and will be overseen by the Primary Investigators.

- Rights of Refusal and Withdrawal: Patients will be free to refuse enrollment or withdraw from the study at any time. Participants may refuse to answer individual questions posed throughout the study.

11. Data Handling & Record Keeping

A. Confidentiality & Data Security

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

i. What protected health information (PHI) will be collected from subjects in this study
ii. Who will have access to that information and why
iii. Who will use or disclose that information
iv. The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Consent forms are drafted and included in Appendix D. These consent forms will be approved by each institutions' IRB. The consent forms at UH (QMC), will be provided in the English language only and therefore study will only be available to those patients with command of the English language. Consent forms will be reviewed with each subject when they are admitted to the study. Subjects will be given a copy of the signed document for their records

Hard copies of clinical information and data will always be kept in a secured place in our research offices, and only study team members will be able to access them on an as-needed basis. Key personnel may not alter the data in any database without specific cause and approval of the Investigator. For de-identification, all subjects will be assigned a unique study ID number when they enter the study. Data will be recorded in a paper chart and converted into electronic file database. Study databases will be password protected, and all portable devices will be fully encrypted. No data will be sent over the Internet unless it is de-identified; data will be sent from UW to UH but not from UH to UW. Data will be de-identified prior to any analysis. We will keep codes linking the study identification number with the name of the subject confidential, secured by password-protected data file within the locked research unit of the Principal Investigators at each site. Further measures to ensure data security will adhere to security standards set by the QMC and the Research and Institutional Review Committee.

B. Record Retention

Study documents will be retained for at least three years after the formal discontinuation of this project. They will be stored in locked, secured cabinets in the PI's office. All data will be de-identified. Any electronic files will be password protected and encrypted. If both Primary Investigators leave Hawaii, they will make arrangements to store the data with the UH Department of OBGYN to be destroyed at the designated time.

C. Direct Access to Source Data/Documents

The investigators will permit study-related monitoring, audits, RIRC review, and regulatory inspections/audits by providing direct access to all study related data/documents. This will be indicated in the consent process with the potential subjects.

12. Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to The Queen's Medical Center Research and Institutional Review Committee (RIRC) for formal approval to conduct the study. The decision of the RIRC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided an informed consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the RIRC for the study. The formal consent of a subject, using the RIRC-approved consent form, must be obtained before that subject has any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining consent.

For other "Ethical considerations of study population," see Section 4.

13. Study Finances

- Study funds from this project are through a grant from the Society of Family Planning (see attached grant letter). These funds will go towards salaries of staff, paying for the study drug (oxytocin), any additional blood work that is done solely to help ascertain blood loss instead of treat patient, and all additional equipment not otherwise typically present in an operating room and clerical necessities. (see Appendix B – Budget for more information). All of the other healthcare costs are standard-of-care that would be billed to the patient or her insurance regardless of whether or not she was participating in a study.
- Study funds will pay for the research medications (oxytocin) and an additional laboratory tests (like hematocrit) that are outside the standard-of-care. Otherwise, patient or patient's insurance will pay for the costs of the procedure.
- The PI or the physician performing the procedure will provide emergency medical treatment, but the subject's insurance will be billed for this treatment. No other payment is available.
- There is no remuneration being offered for the subjects.
- The PIs have no financial or personal conflict-of-interest with this study medication.

14. Publication & Presentation Plans

Findings from this study will be disseminated by multiple means. Results will be presented at the Annual Family Planning Fellowship meeting in 2015. We plan presentation at a national meeting such as the North American Forum on Family Planning or the Annual National Abortion

Federation Meeting. This study will be submitted for publication to a nationally recognized peer-reviewed journal such as Obstetrics & Gynecology, Contraception, or the American Journal of Obstetrics & Gynecology.

15. Timeline

After IRB approval is granted, we anticipate completing recruitment and enrollment in about 12- to 14-months with data analysis to occur within a month after completion of enrollment. Please see attached study timeline

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