PREDICTORS OF FAILED MEDICAL MANAGEMENT IN WOMEN WITH EARLY PREGNANCY LOSS

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ABSTRACT

Objectives: While medical management has been used to treat early pregnancy loss for over two decades, there remains a paucity of reliable predictors of treatment efficacy. The principal goal of this thesis is to identify new factors influencing medical management failure in women with first trimester pregnancy loss. Two objectives will be discussed. The first aim is to assess the effect of menstrual gestational age on the efficacy of misoprostol, in a population of women with a low sonographic gestational age. The second objective is to assess the value of uterine content ultrasound (US) measurements in predicting medical management failure in women with early pregnancy loss.

Research design and methods: Two retrospective observational studies were conducted, each corresponding to a thesis objective. Both studies are based on a cohort of women with early pregnancy loss having visited the Emergency Department (ED) of the Jewish General Hospital, Montreal, Canada, between 2011 and 2013. Only women having been discharged with an outpatient prescription for misoprostol were included in out studies. With respect to the first objective, women had to have an US gestational age below 8 weeks. Exposure of interest consisted of menstrual age. In regards to the second objective, all women with US imaging available for review were included. Exposure of interest was uterine content measurements including: content anteroposterior distance (CAPD), content longitudinal distance, content transverse distance and uterine content volume. For both studies, logistic regression was used to estimate the effect of exposure on failed medical management defined as need for dilatation and curettage (D&C) or unplanned return to the ED (URED).

Results: Increasing menstrual age was associated with an increased risk of D&C and URED. Specifically, risk of D&C and URED was 13.64% at ≤ 8 weeks and 26.32% at > 8 weeks, $p < 0.05$. Among uterine content measurements evaluated, CAPD was found to be independently associated with D&C and URED. When using an APD cutoff of 15mm, women were more likely to require D&C, 2.65 (1.31 - 5.36), $p < 0.01$ and to have an URED, 2.59 (1.41 - 4.79), $p < 0.01$.

Conclusion: Both clinical and sonographic factors play a role in predicting successful medical management of early pregnancy loss. Increasing menstrual gestational age is associated with an increased risk of failed medical management regardless of US estimated gestational age. Furthermore, women with a uterine CAPD below 15mm on US should be considered good candidates for successful medical management. Although there is a need for further validation, combining current predictors of misoprostol efficacy with menstrual gestational age and ultrasonographic measurements of uterine CAPD may be helpful in selecting patients with first trimester pregnancy failure that can safely be managed medically.

Keywords: Misoprostol; Abortion, Spontaneous; Abortion, Missed; Abortion, Incomplete; Pregnancy Trimester, First; Gestational Age; Ultrasonography, Prenatal

RÉSUMÉ

Objectifs : Bien que nous traitons les fausses couches spontanées précoces de façon médicale depuis plus de 20 ans, il existe peu de facteurs fiables pouvant prédire l'efficacité du traitement. Le but principal de cette thèse est d'identifier de nouveaux facteurs pouvant influencer le risque d'échec du traitement médical chez des femmes ayant une fausse couche au premier trimestre. Cette thèse comprend deux objectifs. Le premier est d'évaluer l'effet des semaines d'aménorrhées sur l'efficacité du misoprostol chez des femmes ayant un bas âge gestationnel par échographie. Le deuxième objectif vise à évaluer l'effet de différentes mesures échographiques du contenu utérin pour prédire le risque d'échec du traitement médical de fausses couches spontanées précoces.

Recherche et méthodes : Deux études observationnelles rétrospectives ont été menées, chacune selon les objectifs de thèse. Les deux études sont basées sur une cohorte de femmes atteintes de fausses couches spontanées précoces qui ont fréquenté l'Urgence de l'Hôpital Général Juif, Montréal, Canada, entre 2011 et 2013. Seules les femmes ayant reçu une prescription de misoprostol étaient admissibles. En ce qui concerne le premier objectif, les femmes admissibles devaient avoir un âge gestationnel par échographie en dessous de 8 semaines. La principale variable d'intérêt était les semaines d'aménorrhées. En ce qui a trait au deuxième objectif, l'imagerie échographique de toutes les patientes admisses à l'étude devait être accessible à des fins de révision. La principale variable d'intérêt était les mesures échographiques du contenu utérin, incluant : la distance antéropostérieure, la distance longitudinale, la distance transversale et le volume utérin. La régression logistique a été utilisée afin d'évaluer l'effet des variables d'intérêts sur

l'échec du traitement médical, définit par : la nécessité d'une dilatation et curetage (D&C) ou un retour non planifié à l'Urgence (RNPU).

Résultats : Les semaines d'aménorrhées sont reliées à un risque plus accru de D&C, ainsi qu'à un RNPU. Plus précisément, le risque de D&C était de 13.64% pour les femmes à 8 semaines ou moins d'aménorrhées et de 26.32% pour celles au-dessus de 8 semaines, $p < 0.05$. Parmi les mesures échographiques du contenu utérin évaluées dans cette étude, la distance antéropostérieure est fortement reliée à un risque accru de D&C et un RNPU. En effet, les patientes avec une distance antéropostérieure de 15 mm ou plus avaient des rapports de cotes significativement plus élevés, 2.65 (1.31 - 5.36) pour la D&C et 2.59 (1.41 - 4.79) pour le RNPU.

Conclusion : Les variables cliniques, autant que les variables échographiques jouent un rôle important pour prédire l'efficacité du traitement médical des fausses couches spontanées précoces. Plus les semaines d'aménorrhées sont élevées, plus haut est le risque d'échec du traitement médical; indépendamment de l'âge gestationnel mesuré par échographie. De plus, les patientes ayant une mesure de la distance antéropostérieure du contenu utérin sous 15 mm devraient être considérées comme de bonnes candidates pour le traitement médical. Malgré le fait que d'autres études sont nécessaires pour valider ces résultats, les semaines d'aménorrhées, ainsi que la mesure échographique de la distance antéropostérieure, des contenus utérins peuvent être utiles à sélectionner les patientes pouvant recevoir un traitement médical pour une fausse couche au premier trimestre de façon sécuritaire et efficace.

Mots clés : misoprostol; fausse couche spontanée précoce, grossesse du premier trimestre, âge gestationnel, échographie prénatale

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CONTRIBUTION OF AUTHORS

Melissa Lavecchia is the primary author of this thesis under the supervision and guidance of Dr. Haim A. Abenhaim.

Melissa Lavecchia and Dr. Haim A. Abenhaim contributed to the study concept and design.

Melissa Lavecchia contributed to the data collection.

Melissa Lavecchia and Dr. Haim A. Abenhaim contributed to the analysis and interpretation of the data, to the drafting of the manuscript and to the critical revision of the manuscript for important intellectual content.

Dr. Stephanie Klam contributed to the revision of one of the manuscript included in the thesis: "Effect of Uterine Contents Ultrasound Measurements on Medical Management Failure in Women with Early Pregnancy Loss"

The thesis supervisor Dr. Haim A. Abenhaim reviewed and edited initial drafts of the whole thesis.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ß-hCG	Beta Human Chorionic Gonadotropin
CAPD	content anteroposterior distance
CRL	crown rump length
CTD	content transverse distance
CLD	content longitudinal distance
D&C	dilatation and curettage
ED	Emergency Department
GS	gestational sac
hCG	human chorionic gonadotropin
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
OR	odds ratio
p-hCG	plasma Human Chorionic Gonadotropin
PACS	picture archiving and communication system
PO	per os
PV	per vagina
RPOC	retained products of conception
SL	sublingual
SOGC	Society of Obstetricians and Gynecologists of Canada
URED	unplanned return to the Emergency Department
US	ultrasound

CHAPTER 1: INTRODUCTION

Early pregnancy loss is the most common complication of pregnancy affecting 25% of pregnancies[1] and over one million women in North America each year.[2,3] It is both an emotionally and a psychologically difficult experience.[4] Over the last two decades, medical management has slowly started to supersede surgical management.[5,6] In deed, a study evaluating the use of misoprostol in Brazil, Jamaica and the United States found that obstetricians-gynecologists used misoprostol 57% of the time for missed abortions.[7] In Canada, misoprostol is the only medication available for management of first trimester pregnancy loss.[8] Outpatient medical treatment of miscarriage is an attractive option to both physicians and patients. It seemingly decreases hospital stay and hospital costs by avoiding surgery.[8,9] Studies have shown that some women prefer misoprostol because they wish to avoid surgery or because they feel more at ease with completing the process in the privacy of their home.[10]

Surgical management of first trimester pregnancy loss poses risks for certain complications such as anesthesia-related complications, uterine perforation, cervical laceration and infection.[5,8,11,12] However, with advanced technology and awareness of the rare, but potential complications, adverse events from the procedure are nearly inexistent.[8,11-13] In fact, current statistics demonstrate a rate for uterine perforation of < 0.6%.[13] Furthermore, apart from being extremely safe,[5,8,11-14] surgical treatment has a very high success rate and allows for rapid resolution of miscarriage.[5,8,11,12]

Medical management on the other hand, also comprises risks. Some of the adverse events and side effects reported include gastrointestinal upset, delayed evacuation of products of conception, heavy prolonged bleeding and severe pain.[11,12,15]

Although life-threatening complications such as profuse prolonged bleeding are rare, they can lead to hematometra, disseminated intravascular coagulopathy and need for emergency surgical evacuation.[16-18] Failing medical management, meaning requiring emergency dilatation and curettage (D&C), increases maternal morbidity and exposes women to the increased risks of emergency surgery[1].

Research in the area of first trimester adverse outcomes focuses on the prevention and investigation of recurrent pregnancy loss, as well as management of induced abortions. There is a paucity of consistent, reliable information in the literature on the medical management of early pregnancy loss. In fact, there are no North American guidelines for the management of women undergoing miscarriage. Physicians must rely on the Society of Obstetricians and Gynecologists of Canada (SOGC)[12] and the American College of Obstetricians and Gynecologists' (ACOG)[11] guidelines on induced abortion.

Furthermore, ultrasonography plays a central role in early pregnancy assessment units.[19,20] However, once ultrasound (US) information is obtained in a stable patient, nearly all other clinical information is disregarded and all subsequent decision making is based on a few imaging results. Recognizing the paucity of reliable markers to predict medical management failure of early pregnancy loss, this thesis sought to explore potential clinical and sonographic predictors of failure.

CHAPTER 2: LITERATURE REVIEW

The following chapter is divided into four sections. The first describes the pathophysiology and presentation of the various types of early pregnancy losses. The second presents the management options available to women undergoing early pregnancy failure. The third reviews commonly used practice guidelines on patient management. In the final section, studies on clinical and sonographic predictors of failed medical management of earl pregnancy loss are discussed.

2.1 Pathophysiology and presentation of early pregnancy loss

Early pregnancy loss is defined as the spontaneous termination of pregnancy before the 20th week of gestation.[21,22] In medicine, it is interchangeably used with the term abortion, however given then layperson's interpretation suggests the voluntary termination of pregnancy, the terms early pregnancy loss, early pregnancy failure or miscarriage are preferred.[22]

2.1.1 General definition of early pregnancy loss

Early pregnancy loss most commonly occurs within the first 12 weeks of pregnancy and usually involves the death of the embryo or fetus prior to expulsion from the uterine cavity.[21,22] Following fetal death, hemorrhage usually ensures provoking uterine contractions and eventually expulsion of the products of conception.[22]

2.1.2 Incidence

Miscarriage occurs in approximately 12% to 20% of recognized pregnancies.[1] However, by measuring urinary concentrations of human chorionic gonadotropin (hCG), Wilcox et al. found that the actual rate of loss after implantation was 31%.[23] In fact, many women undergo clinically silent miscarriages, whereby the spontaneous abortion is thought to be heavy or late menses.[21,22] Of all women trying to conceive, approximately 75% will experience miscarriage throughout the course of their reproductive life.[24,25]

2.1.3 Causes

Causes of early pregnancy loss can be divided into fetal and maternal factors.[22,26] The most common cause is chromosomal abnormalities in the embryo or fetus affecting 49% of spontaneous abortions.[22,26] Maternal factors associated with early pregnancy loss include age, medical disorders, environmental causes and developmental abnormalities.[22,27] Table 1 describes common causes of early pregnancy loss.

Table 1 – Causes and risk factors associated with early pregnancy loss*	
Fetal factors	**Maternal factors**

- Aneuploidy
- Trauma from invasive intrauterine procedures
- Chorionic villus sampling
- Amniocentesis
- Genetic abnormality
- Structural abnormality
	- Infection
	- Endocrinological disorder
	  o Diabetes mellitus
	  o Thyroid disorders
	  o Polycystic ovarian syndrome
	- Cancer
	- Previous chemotherapy or radiation therapy
	- Obesity
	- Poor nutrition
	- Inherited thrombophilias
	- Immunological factors
	- Uterine structural defects (inherited and acquired)
	- Medications
	- Substance use
	  o Smoking
	  o Illicit drugs
	  o Alcohol
	  o Caffeine
	- Chemical and toxin exposure

*Table adapted from[21,22,26,27]	

2.1.4 Classification of early pregnancy loss

2.1.4.1 Threatened abortion

Threatened abortion involves vaginal bleeding through a closed cervical os.[21,22] Bleeding in the first trimester is highly predictive of subsequent abortion, whereby approximately half of women will loose their pregnancy.[22,26] However, because first trimester bleeding does not always results in pregnancy loss, the diagnosis and management of threatened abortion will not be further discussed.

2.1.4.2 Inevitable abortion

Inevitable abortion occurs when there is vaginal bleeding with cervical os dilatation.[22] Usually the products of conception have not yet been expelled and women may experience uterine contractions.[22,27]

2.1.4.3 Complete abortion

Complete abortion involves the complete expulsion of products of conception, whereby the uterine cavity is empty on US and has a thin endometrial lining.[22,27] It is accompanied by vaginal bleeding and the cervical os is dilated.[22,28]

2.1.4.4 Incomplete abortion

Situations in which products of conception are retained in the uterus or in the cervical os are termed incomplete abortions.[22,28] Most cases result from passage of the embryo or fetus and retention of the entirety or part of the placenta.[22,28] Products of conception can also be found in the cervical canal and vaginal vault. Usually, in a

pregnancy loss before ten weeks gestation, both the fetus and placenta are expelled together resulting in a complete abortion.[22]

2.1.4.5 Missed abortion

A missed abortion involves a nonviable intrauterine pregnancy, which has not been expelled.[22,28] The cervical os remains closed and women do not experience the typical symptoms associated with spontaneous abortion.[22]

2.1.4.6 Anembryonic abortion

An anembryonic pregnancy consists of a pregnancy in which embryonic development failed or arrested early on.[27] It is sometimes termed blighted ovum or empty sac pregnancy.[22,28] It resembles a missed abortion, whereby the cervical canal remains closed and the products of conception are retained in the uterus.[27,28] It is an US diagnosis[27] and is considered by some equivalent to a missed abortion.[29]

2.1.5 Signs and symptoms of early pregnancy loss

Complete and incomplete miscarriages usually present with similar signs and symptoms. Women often experience uterine contractions, pelvic pain and heavy bleeding with passage of tissue.[22,27,28] Inevitable abortions will present with low pelvic pain and occasionally bleeding.[22,27] The products of conception will be retained in the uterus. However, the cervical os will be open, indicating impeding pregnancy loss.[22,27] Missed abortions and anembryonic pregnancies are usually found during first trimester US evaluation, as women typically do not experience any symptoms.[22] Some women with

missed abortion may even notice that their symptoms associated with pregnancy have subsided.[28]

2.1.6 Diagnosis

In a woman with a confirmed pregnancy, ultrasonography is the modality of choice to diagnose early pregnancy failure.[22,26,28] In women with a missed abortion, fetal heart tones will be absent on US.[22,27] Anembryonic pregnancies will present as an empty gestational sac (GS) on US.[22,27] Table 2 summarizes the various US criteria for diagnosing early pregnancy failure in women with suspected arrested pregnancies.

Beta Human Chorionic Gonadotropin (ß-hCG) levels are also sometimes used in conjunction with ultrasonography to confirm the diagnosis.[22,26] In a normal pregnancy, serial ß-hCG levels taken 48 hours apart are expected to rise by at least 53%.[30] Women whose ß-hCG levels decreases by 50% or greater within that same time frame are likely to have an arrested pregnancy.[31] In women with a suspected incomplete abortion, both clinical and US findings are used to make the diagnosis.[27] Transvaginal US will reveal retained products of conception (RPOC) in the uterus in the absence of an embryo or fetus. Women with complete abortions will experience bleeding, but US will show an empty uterus.

Table 2 - Ultrasound criteria for diagnosing arrested pregnancy*			
Diagnosis	**Criteria**[22,31,32]	**Diagnosis confirmation**[31]	**Modality**[22,31-33]
Missed abortion	Absent cardiac activity in an embryo ≥ 7mm crown-rump length	Repeat scan minimum of 7 days later	Transvaginal ultrasound probe
Anembryonic pregnancy	Empty gestational sac (no yolk sac) ≥ 25mm	Repeat scan 7 to 10 days apart	Transvaginal ultrasound probe
* Table adapted from [22,31-33]			

2.2 Management options for early pregnancy loss

There are three possible options for managing women with a diagnosis of missed, anembryonic or incomplete miscarriage: expectant, medical or surgical management.[1,8,22,26,27] It is important to discuss all possible treatment options with patients and allow women to make an informed decision by considering preference, acceptability, risk, time to completion and invasiveness of the treatment method.[21] However, in cases with severe bleeding or evidence of infection or sepsis, patients require immediate surgical treatment.[21,22] In women not requiring immediate management, all three methods are acceptable.[21,22] Furthermore, all three methods are also safe for future pregnancies.[21]

2.2.1 Expectant management

Expectant management is an attractive option as it is noninvasive and consists of waiting for spontaneous passage of the products of conception.[27] While 50% to 70% of women with nonviable pregnancies opt for this method,[21] it has a failure rate of 50%.[22]

Expectant management is acceptable for women with a gestational age up to 14 weeks and works best for incomplete abortions.[8] In women who succeed management, it usually takes up to two weeks before spontaneous miscarriage occurs.[8] Women opting for expectant management can experience significant pain and bleeding[27] and occasionally require emergency D&C as a result.[8,27]

2.2.2 Medical management

The most commonly used medication for the medical management of early pregnancy loss is misoprostol.[8] While mifepristone, another medication for inducing abortion exists and is increasingly used in the United States and Europe,[34] misoprostol is the only medication available to Canadian physicians for the management of miscarriage.[8] Therefore, this section of the review will mainly focus on misoprostol.

2.2.2.1 Mifepristone

Mifepristone is a norethindrone derivative that blocks the action of progesterone.[11,35] It reversibly binds progesterone receptors with greater affinity than progesterone itself, but does not activate the receptor.[11,35] It's mechanism of action in relation to the management of incomplete abortion and arrested pregnancy involves decidual necrosis, cervical softening, increased uterine contractility and increased prostaglandin sensitivity, therefore leading to expulsion of products of conception.[11,35]

2.2.2.2 Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analogue.[8] While it was initially developed for the treatment of peptic ulcers, it is widely used off label for its abortifacient properties.[11] Misoprostol binds myometrial cells to cause strong myometrial contractions leading to expulsion of the products of conception.[36] However, as gestational age increases, the clinical efficacy of misoprostol decreases.[37] Apart from increasing uterine tone and producing regular uterine contractions, misoprostol also induces softening of the cervix.[11,36,38] The medication can be administered by four routes: oral (PO), vaginal (PV), sublingual (SL) or buccal.[38] Upon oral administration, misoprostol undergoes the first-pass effect and serum levels rise and drop rapidly.[21,38] With vaginal, sublingual or buccal administration, plasma serum levels remains higher for a longer period of time and are therefore preferred.[11,21,38] Side effects, which include nausea, vomiting and diarrhea, are more common with oral administration.[21]

While studies have demonstrated the effectiveness of misoprostol in missed, anembryonic and incomplete abortions,[1,21] there is a wide discrepancy in regards to success (i.e. complete evacuation) and failure rates reported in the medical literature.[8,22,39] These inconsistencies may be due to the various inclusion criteria and techniques used.[22] In fact, success rates have been reported to be between 30% and 90%, while failure rates range between 5% and 40%.[8,22,39] Given the serious adverse complications associated with failed medical management, such as excessive heavy bleeding, severe pelvic pain and possible need for emergency D&C,[1] it is crucial to establish the true effectiveness of misoprostol. Although it has been used extensively for the management of early pregnancy loss since the early 2000s,[5] we have yet to establish a standard formulation for

treatment.[8] Misoprostol is currently being administered through several different routes, dosing regimens and frequencies. Most importantly, there is great variability in the recommendations regarding gestational age, as well as by which modality gestational age should be established: menstrual age versus US findings. (See *Guidelines* section below)

2.2.3 Surgical management

Surgical management typically consists of dilatation of the cervix followed by sharp curettage or suction evacuation.[8] Women with an arrested pregnancy up to 14 weeks gestational age can be managed with D&C, whereas failed pregnancies with a higher gestational age require dilatation and evacuation.[1,8] The success rate of surgical treatment is extremely high between 95% and 100%[1,8,22]. While this method leads to rapid resolution, it is an invasive procedure[22] and involves anesthesia, usually conscious sedation and a paracervical block.[8] Surgical management comprises a few, but rare serious operative complications such as uterine perforation, cervical trauma, infection and anesthesia-related complications. However, these complications are extremely rare, occurring in approximately 1% to 2% of women.[8] Moreover, there is no difference in future live birth rates following surgical, medical or expectant management.[8]

2.3 Guidelines on the management of early pregnancy loss

The following guidelines are those most commonly used by practicing physicians to aid in the decision-making process when choosing management options for women with first trimester early pregnancy loss.

2.3.1 National Institute for Health and Care Excellence (NICE) guidelines on miscarriage and ectopic pregnancy[31]

While this guideline also discusses ectopic pregnancy, we will focus our discussion on the management of miscarriage. The NICE *guideline* on miscarriage and ectopic pregnancy which was developed by the National Collaborating Centre for Women's and Children's Health, based at the Royal College of Obstetricians and Gynaecologists, are meant to cover the diagnosis and management of pregnancies up to 12 weeks gestation. In regard to early pregnancy loss, they suggest using US criteria for diagnostic purposes. Ultrasound should be used to identify the location of the pregnancy and viability of the embryo. The guideline also discusses using serum hCG concentration changes over 48 hours to aid in the diagnosis. As for management options and recommendations covered in the guideline, the benefits and risks of all three options, i.e. medical, surgical and expectant; are exposed and compared to one another. However, there are no indications as to the circumstances in which each option is the most effective. In terms of medical treatments for miscarriage, the guideline discusses and compares misoprostol alone, mifepristone alone and a combined regimen of mifepristone plus misoprostol. Furthermore, the various routes of administration are also compared. The suggested regimens for medical treatment, as well as the different surgical options are shown in table 3.

Table 3 - NICE *guideline* on miscarriage and ectopic pregnancy: Management options for early pregnancy loss management*	
Management options	**Indication**
Expectant	< 6 weeks gestation, bleeding but not in pain
Medical Misoprostol 800µg Misoprostol 600µg	 Missed abortion Incomplete abortion
Surgical Manual *vaccum* aspiration under local anesthesia Surgical management in a theatre under general anesthesia	 Where clinically appropriate Where clinically appropriate
*Table adapted form [31]	

While each management option has it's own advantages and disadvantages, it is important to also consider the management and patient characteristics which will lead to a successful outcome. In fact, evidence has shown that the effectiveness of medical management varies depending on gestational age.[11,12,31,40] Furthermore, while surgical management plays an important role in the treatment of women with miscarriage there is a noticeable lack of specification as to when it should be considered. Finally, the guideline states that it covers information for miscarriage up to 12 weeks gestational age; however, there is no mention as to how gestational age should be determined: by menstrual dates or by US; nor is there information as how to treat wide discrepancies between menstrual and US dates.

2.3.2 ACOG's guideline on the Medical Management of First-Trimester Abortion[†11]

While the ACOG has published guidelines for the "Management of recurrent pregnancy loss", guidelines for the general management of early pregnancy loss are inexistent and most physicians rely on the ACOG's revised guidelines on the "Medical

Management of First-Trimester Abortion" published in March 2014 to guide their management of women with first trimester early pregnancy loss. These guidelines explore and compare the various medications that can be used for inducing abortion, as well as surgical options. Contrary to the NICE guidelines, the ACOG's guideline goes into great detail about the different gestational ages at which various regimens for medical management are effective, as well as their overall success rate according to gestational age (See table 4). Moreover, the preferred routes of administration are also discussed. Women tend to prefer the vaginal route because it enables them to complete the abortion process sooner, compared to other routes. Furthermore, while the guideline goes into great detail about which regimen should be used according to gestational age, it does not give a clear indication as to which modality should be used to determine a woman's gestational age. In fact, it is suggested that before medical abortion is performed, gestational age should be confirmed by clinical evaluation or US examination. While the guideline presents evidence that combining menstrual age with US information can be relied upon and will only result in 1.6% of women erroneously receiving medical management, there is no indication as how to treat cases in which there is a wide discrepancy between menstrual and US information.

Table 4 - ACOG's guideline on the Medical Management of First-Trimester Abortion: Evidence-based regimens used for medical abortion*		
Regimens	**Gestational age (weeks)**	**Success rate (%)**
Mifepristone[1] 600mg PO[2] + misoprostol 400µg PO 48 hours later	Up to 7	92
Mifepristone[1] 200mg PO[2] + misoprostol 800µg PV[3], PO[2] or SL[4] 24-48 hours later	Up to 9	95-99
Misoprostol 800µg PV[3] or SL[4] every 3 hours for 3 doses	Up to 9	84-85
[1]Not available in Canada [2]Per os [3]Per vagina [4]Sublingual *Table adapted from [11]		

While the ACOG's guideline for the "Medical Management of First-Trimester Abortion" is somewhat complete and covers some of the patient characteristics that influence success of treatment, these guidelines are intended for the treatment of women undergoing induced abortion of a viable pregnancy and cannot be fully relied upon for the successful management of women undergoing early pregnancy loss. Induced abortion and early pregnancy loss are fundamentally different events. In incomplete, missed or anembryonic abortions, fetal growth can arrest at any time from a few days to a few weeks before the pregnancy loss is recognized; whereas an in an induced abortion the pregnancy is still viable.

2.3.3 SOGC's Induced Abortion Guideline[†12]

While the SOGC has guidelines for the "Ultrasound Evaluation of First Trimester Pregnancy Complications", these guidelines do not cover the different management options once an early pregnancy loss is confirmed. Because the SOGC also lacks

guidelines for the management of early pregnancy loss, similarly to ACOG, physicians must rely on the SOGC's "Induced Abortion" guideline when managing women with miscarriage.

The SOGC's guideline, similarly to those above, discusses the possible medication regimens as well as surgical options available. The guideline states that is it essential to accurately estimate the gestational age of the pregnancy. They suggest determining gestational age by comparing uterine size through bimanual pelvic examination with menstrual dates and using US information when gestational age is questionable. Contrary to the ACOG and the NICE guidelines discussed above, the SOGC recommend medical abortion in women up to ≤ 8 weeks gestational age. Misoprostol 800µg alone can be use through the vaginal route every 24 to 48 hours until abortion occurs for a maximum of three applications. The criteria for surgical management are also rather detailed compared to the guidelines discussed above. Manual *vaccum* aspiration can be performed up to ≤ 10 weeks gestational age, whereas *vaccum* aspiration can be performed up to ≤ 13 weeks. The details, advantages and disadvantages of each method are explored in this guideline. However, as it is the case for the ACOG's guideline on "Medical Management of Frist-Trimester Abortion", we must be cautious when using this guideline in clinical practice given it was developed for the management of induced abortions, rather than first trimester early pregnancy loss.

[†]The use of methotrexate in induced abortion was omitted from the literature review given it is not used for the medical management of early pregnancy loss.

2.4 Studies on clinical and sonographic predictors of failed medical management of earl pregnancy loss

By examining the current guidelines and available literature regarding the medical management of early pregnancy loss, we can notice that the scientific evidence is both inconsistent and conflicting in regard to clinical and imaging criteria for the administration of misoprostol.

2.4.1 Menstrual age as a clinical predictor of failed medical management of early pregnancy loss

While increasing gestational age is widely used as a predictor of failure of medical management, several studies fail to expose the presence of any discrepancies between menstrual age and US age. [40-44]

The maintenance of pregnancy is largely dependent on the presence of progesterone.[45-47] In fact, progesterone regulates uteroplacental blood flow and quiescence, maternal immunotolerance to the fetus, as well as contributing to placental growth and neovascularization.[45,48] However, with an anembryonic pregnancy or when embryonal death ensues, the sustained presence of progesterone contributes to the continuation of the pregnant state, with retention of products of conception within the uterus.[45,46] In fact, following fetal death the placenta remains a living, functioning and growing organ,[45] as fetal death has no immediate effect on progesterone production.[12] Therefore, regardless of fetal death in a missed abortion or a pregnancy being anembryonic, as menstrual age continues to increase, the size of the placenta and volume of the products of conception also continue to increase. When determining age using

ultrasonography, only measurements of the crown-rump length (CRL) and GS are considered.[19,20,32] Because of the increased volume of products of conception, medical management might be more likely to fail as menstrual age increases, regardless of US determined gestational age.

Literature examining the relationship between menstrual gestational age and success of medical management regardless of US age is scarce. Most studies use US determined gestational age and completely disregard menstrual age.[40-43,49-52] To our knowledge there are no studies in the literature acknowledging the effect of disparities between menstrual and US age in association with medical management failure.

Zhang et al. conducted a large randomized trial evaluating the efficacy, safety and acceptability of misoprostol for failed first trimester pregnancy.[52] Their study included 652 women with anembryonic pregnancy, embryonic or fetal death, as well as incomplete or inevitable abortion. Patients were randomized to either receive 800µg of misoprostol PV on day one or three, if expulsion hadn't yet occurred, or undergo *vaccum* aspiration. Treatment failure consisted of need for surgical evacuation on day eight for the misoprostol group and repeat *vaccum* aspiration for the surgical group. Among the misoprostol group, 16% of women failed treatment and required *vaccum* aspiration. Following this trial, a planned secondary analysis, conducted by Creinin et al., sought to identify potential predictors for treatment success in medical management with misoprostol for early pregnancy failure.[51] Among 491 women who received misoprostol during the trial, 485 met inclusion criteria for the secondary analysis. Several clinical and US predictors were evaluated. Gestational age was calculated according to standard US recommendations for diagnosing missed or anembryonic gestations and data regarding

pregnancy length was also collected. Results showed that parity of zero or one and vaginal bleeding within the last 24 hours was predictive of first dose success. Gestational age, US and menstrual, at time of misoprostol administration was not found to be a significant predictor of failure.

This study is one of the largest multicenter trials evaluating misoprostol for failed first trimester pregnancy. While the authors analyzed the effect of over 25 different independent variables, including regularity of periods, age at first menstrual period and menstrual length, they did not investigate the effect of wide disparities between menstrual and US age.

Grønlund et al. conducted a multicenter randomized trial comparing the efficacy of two different medical treatment regimens.[41] Their study compared mifepristone 600 mg orally plus misoprostol 400µg vaginally or misoprostol 400µg vaginally with surgical evacuation in women with missed abortion. Gestational age was estimated using US and the primary outcome was need for surgical evacuation in the medication group and need for re-evacuation in the surgical group. The success rate for mifepristone plus misoprostol, misoprostol and surgical evacuation were 74%, 71% and 96%, respectively. The study's secondary analyses revealed that an initial plasma-hCG (p-hCG) between 2,000 and 20,000 IU/l and a gestational age < 75 days was significant at predicting better response to medical treatment. Of the women with a low p-hCG and a low gestational age only 10% failed medical management compared to 35% of women not satisfying the above criteria.

While this trial seems to suggest a potential association between failed medical management and gestational age, the results surrounding these findings are not clearly

described. In fact, while the authors conclude that combining p-hCG and gestational age is predictive of treatment response, these results fail to distinguish between medication groups. In fact, it appears as if the results presented are a combination of the women who were treated with mifepristone plus misoprostol and women who received misoprostol alone.

2.4.2 Sonographic parameters influencing misoprostol efficacy

It has been well established that an endometrial thickness < 15mm is associated with a higher risk of requiring surgical evacuation following medical management of first trimester pregnancy loss.[53-55] However, no studies have assessed the influence of the measurements of RPOC on management failure. During miscarriage, the embryo or fetus, the GS, as well as blood clots can be present in the uterus. Because pregnancy size can affect miscarriage management,[31] measurements of the RPOC may impact on misoprostol efficacy.

While US is a widely used diagnostic tool in early pregnancy assessment,[19,20,32] there is a paucity of reliable markers to predict medical management failure. While some studies have previously evaluated sonographic predictors of successful medical management,[56-58] to our knowledge, none have assessed the effect of the volume of retained products in the uterus.

Agostini et al. conducted two studies evaluating clinical and US factors influencing efficacy of misoprostol for first trimester pregnancy loss.[56,58] In their first study, they assessed CRL, as well as GS diameter and found no difference between patients who succeed compared to those who failed misoprostol.[56] Their cut-off for

successful medical management was an endometrial thickness of > 15mm, which resulted in a success rate for misoprostol of 65.2%.

Agostini et al.'s second study used US measurements of cervical length as a predictor for misoprostol efficacy.[58] Cervical length was not found to be predictive of medical treatment success. Among other parameters studied, CRL, GS diameter, as well as distance between GS and the "virtual" cervical os (upper limit of the cervical glands) were not significant at predicting misoprostol success. Using the same cut-off for failure as previous, an endometrial thickness > 15mm, the success rate was 64.8%.

Both Agostini et al's studies have several limitations. In fact after receiving one dose of intravaginal misoprostol 800μg, women were scheduled for follow-up evaluation to determine treatment efficacy only 24 hours later.[56,58] Having such a short protocol for re-evaluation of treatment success could have influenced the studies' results. In fact, longer intervals between misoprostol administration and US examination are known to increase success rate.[52]

Odeh et al. conducted a similar study to those of Agostini et al. by which US and clinical factors were evaluated as predictors of medical management failure.[57] Among sonographic predictors, GS volume and CRL were not found to be significant at predicting need for surgical evacuation following medical management.

Finally, Vejborg et al. conducted a retrospective study on 882 patients with first trimester miscarriage.[39] Four hundred and ninety four women underwent surgical evacuation and the 388 women who received medical treatment were classified into four groups according to ultrasonographic biometries: CRL < 6 mm, CRL ≥ 6 mm, GS < 18 mm and GS ≥ 18 mm. The overall success rate for misoprostol was 39.2%. Only CRL < 6

mm was found to have a significantly higher success rate and GS ≥ 18 mm a significantly lower success rate compared to other groups. This study has several limitations. In fact, while most guidelines advise using an intravaginal misoprostol dose of 800µg, [12,31] a dose of 400µg was used, which may explain the very low success rate for medically managed women. Furthermore, the mean menstrual age for the GS ≥ 18 mm group was noticeably higher compared to those of the other three groups.

Table 5 presents a summary of the studies on the association between gestational age and the efficacy of medical management.

Table 5 – Summary of the studies on the association between ultrasound predictors and the efficacy of medical management						
Study	**Objectives**	**Study design**	**Sample size (n)**	**Misoprostol dose**	**Gestational age estimate**	**Findings**
Odeh et al., 2010[57]	To determine whether GS volume measurements as well as CRL and clinical and demographic characteristics (age, number of previous pregnancies, abortions and deliveries) can predict the success rate of medical treatment for early pregnancy failure.	Prospective observational study Women admitted to the department diagnosed with missed abortion or anembryonic pregnancy with CRL below 12 weeks Western Galilee Hospital, Nahariya, Israel	N=81	Misoprostol 800 µg PV Patients were re-evaluated by transvaginal US 12–24 hours later. If intact GS or endometrial lining ≥ 30 mm, a second dose of misoprostol 800 µg PV or surgical evacuation was offered.	US and menstrual	Success rate of misoprostol: 39.5% Effect of gestational age: - No significant difference in menstrual or US age between success and failure groups Parity and previous pregnancies and ß-hCG were significantly higher in the failure group
Agostini et al., 2007[58]	To assess the role of cervical length measurement in predicting successful treatment, by misoprostol administration, of early pregnancy failure.	Prospective observational study Women with early pregnancy failure and ultrasound dating of less than 12 weeks. La Conception Hospital, Marseille, France	N=125	Misoprostol 800µg PV Re-evaluation 24h later	US	Success rate of misoprostol: 64.8% Effect of CRL, GS diameter, cervical length and distance between GS and 'virtual' cervical internal os : - No significant difference between treatment success and treatment failure groups

Vejborg et al., 2007[39]	To assess if a single dose of misoprostol could reduce the number of surgical interventions in early pregnancy failure, and to compare efficacy in different ultrasonographically-defined subgroups.	Retrospective study Women with first trimester miscarriage and missed or anembryonic pregnancy. Hvidovre Hospital in Copenhagen, Denmark	N=882 n=388 misoprostol n=494 surgical evacuation	Misoprostol 400 µg PV Re-evalution 24 h later	US and menstrual	Success rate of misoprostol: 39.2% Effect of gestational age: - Effect of menstrual age not evaluated - Women with CRL < 6mm had significantly higher success rate of 50% compared to CRL ≥ 6mm, 38.8% - Women with GS ≥ 18mm had significantly lower success rate of 26.6% compared to GS < 18 mm, 42.6%
Crenin et al., 2006[51]	To identify potential predictors for treatment success in medical management with misoprostol for early pregnancy failure.	Planned secondary analysis from a multicenter trial (Zhang et al., 2005) Women with an anembryonic gestation, embryonic or fetal death or an incomplete or inevitable abortion who received misoprostol. US (Columbia University, University of Miami, University of Pennsylvania and University of Pittsburgh)	N=485	Day 1: misoprostol 800µg PV Day 3: If expulsion not complete, second dose of misoprostol 800µg PV Day 8: Re-evaluation	US and menstrual	Success rate of misoprostol: - Day 3: 71% - Day 8: 84% Effect of gestational age: - No significant effect of US or menstrual age on success Predictors of 1st dose success: - Vaginal bleeding within the last 24 hours - Parity of 0 or 1 Predictors of overall success: - Lower abdominal pain or vaginal bleeding within the last 24 hours - Rh-negative blood type - Nulliparity

Agostini et al., 2005[56]	To evaluate the clinical and ultrasound factors influencing the efficacy of misoprostol in the treatment of first trimester pregnancy failure.	Prospective observational study Women with early pregnancy failure and ultrasound dating of less than 12 weeks. La Conception Hospital, Marseille, France	N=276	Misoprostol 800µg PV Re-evaluation 24 h later	US and menstrual	Success rate of misoprostol: 65.4% Effect of gestational age: - No significant difference in US and menstrual age between success and failure groups Mean gravidity, parity and vaginal delivery number were significantly higher in the failure group
Zhang et al., 2005[52]	To assessed the efficacy, safety, and acceptability of misoprostol to treat women who have a failed pregnancy in the first trimester.	Multicenter randomized trial Women with an anembryonic gestation, embryonic or fetal death or an incomplete or inevitable abortion. US (Columbia University, University of Miami, University of Pennsylvania and University of Pittsburgh)	N=652 n=491 misoprostol n=161 *vaccum* aspiration	Day 1: misoprostol 800µg PV Day 3: If expulsion not complete, second dose of misoprostol 800µg PV Day 8: Re-evaluation	US	Success rates: - Misoprostol day 3: 71% - Misoprostol day 8: 84% - *Vaccum* aspiration: 97% Unscheduled return visits to the ED: - Misoprostol: 23% - *Vaccum* aspiration:17% (p=0.09) Acceptability of treatments: no difference between groups Effect of gestational age: No significant effect in either treatment group

Grønlund et al., 2002[41]	To compare the efficacy of two different medical treatment regimens: mifepristone 600 mg orally plus misoprostol 400μg vaginally or misoprostol 400μg vaginally with conventional surgical evacuation in women with missed abortion.	Prospective observational study Women with missed or anembryonic pregnancy Gentofte, Herlev and Glostrup, Copenhagen, Denmark	N=176 n=54 mifepristone + misoprostol n=73 misoprostol n=49 surgical treatment	Mifepristone + misoprostol: - Day 1: mifepristone 600 mg PO - Day 3: misoprostol 400μg PV - If no vaginal bleeding within 2 h, additional misoprostol 200μg was given. - The patient was observed for 4 h Misoprostol: - Day 1: Misoprostol 400μg PV - If no vaginal bleeding within 2 h, additional misoprostol 200μg was given. - The patient was observed for 4 h	US	Success rates: - Mifepristone + misoprostol: 74% - Misoprostol: 71% - Surgical evacuation: 96% Effect of gestational age: - No significant effect as a univariate predictor - Women with a p-hCG between 2,000 and 20,000 IU/l and a gestational age < 75 days had a significantly better response to the medical treatment

CHAPTER 3: RATIONALE, OBJECTIVES AND HYPOTHESES

Early pregnancy loss is the most common complication of pregnancy.[2,3,59] While research efforts are particularly geared towards prevention and understanding recurrent pregnancy loss, there are few reliable guidelines focusing on the management of women undergoing first trimester pregnancy loss. In North America, we must rely on the SOGC's and the ACOG's guidelines on induced abortion when managing incomplete, anembryonic or missed abortions.[11,12] While medical management has gained increasing importance as a treatment option, success rates in the literature vary widely and the evidence regarding predictors of failure is conflicting.[50,51,60-62] Although rare, complications such as prolonged heavy bleeding, intense pelvic pain and need for blood transfusion do occur.[8,21] One of the most serious complications of misoprostol is need for emergency D&C.[8,21] Being able to identify which women will most likely fail medical treatment would allow physicians to recommend an elective procedure, which involves less risk and complications compared to emergency surgery. The potential for this research is to improve patient management and to decrease the number women who fail medical treatment of early pregnancy loss.

Therefore the objectives of this thesis are:

1. To assess the effect of menstrual gestational age on the efficacy of misoprostol, in a population of women with a low sonographic gestational age.

2. To assess the value of uterine content ultrasound measurements in predicting medical management failure in women with early pregnancy loss.

CHAPTER 4: EFFECT OF MENSTRUAL AGE ON MEDICAL MANAGEMENT FAILURE IN WOMEN WITH EARLY PREGNANCY LOSS

The following chapter presents the methods and results of objective 1 to assess the effect of menstrual age on the efficacy of misoprostol in women with a low US gestational age. This manuscript has been accepted for publication in the Journal of Obstetrics and Gynecology Canada.

The topic presented in this manuscript will be introduced with some background information. The methods will cover comprehensive information on the study population and statistical methods used. Results are described in detail and a thorough discussion provides critical information as well as study limitations and future implications.

Effect of Menstrual Age on Medical Management Failure in Women with Early Pregnancy Loss

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4.1 Abstract

Objective: Women with gestational age < 8 weeks are considered good candidates for medical management of early pregnancy failure. The purpose of our study was to evaluate the effect of menstrual age on failed medical management among women with early pregnancy loss estimated at < 8 weeks by ultrasound (US).

Methods: We conducted a retrospective cohort study on all women discharged from the Emergency Department (ED) with a diagnosis of early pregnancy failure who were managed with misoprostol and had a gestational age < 8 weeks on US between 2011 and 2013. We used logistic regression to estimate the effect of menstrual age on failed medical management defined as dilatation and curettage (D&C) or unplanned return to the ED (URED).

Results: Among 823 women presenting to the ED with first trimester bleeding, 199 had failed pregnancy < 8 weeks by US and were discharged with misoprostol. Menstrual age was associated with an increased risk of D&C and URED. Specifically, risk of D&C was 11.8% at < 8 weeks, 18.5% at 8-9 weeks, 25.3% at 10-11 weeks and 30.6% at ≥ 12 weeks, $p < 0.05$. As well, risk of URED was 14.7%, at < 8weeks, 27.8% at 8-9weeks, 36.0% at 10-11weeks and 41.7% at ≥ 12 weeks, $p < 0.05$.

Conclusion: Menstrual gestational age is an important predictor of failed medical management of early pregnancy loss that is independent of US estimated gestational age. Menstrual gestational age should be considered when discussing treatment options with women who have an early pregnancy failure.

4.2 Introduction

Early pregnancy failure is the most common complication of pregnancy occurring in roughly 25 % of pregnancies and affecting over one million women in North America each year.[3,24,59,63,64] For some women it is a traumatic experience with devastating social and psychological sequelae.[4] Women may choose outpatient medical management of failed early pregnancy because they believe in it's safety, that it is more natural and private or to avoid surgery altogether.[10] For physicians, it is easy, more convenient than surgery and associated with decreased hospital costs and shorter hospital stays.[9,65,66] Currently, North American guidelines for the management of early pregnancy loss are inexistent and we rely on guidelines for induced abortion, which state that medical management is recommended up to 63 days gestation with ultrasound (US) findings playing an important role in deciding on medical versus surgical management.[11,67-70]

Although women with a failed pregnancy with US dates < 8 weeks are considered ideal candidates for misoprostol and are consistently managed medically, there remains a proportion of women who return to hospital with profuse and prolonged bleeding requiring further evaluation and occasionally additional treatment.[16,68,69] Such treatment failures can lead to prolonged excessive bleeding and possibility hematometra, hemorrhagic shock or disseminated intravascular coagulopathy.[16-18]

While failed early pregnancy is extremely common, it remains difficult to predict the risk of failure of treatment as a function of clinical or US criteria.[56] There is a paucity of evidence concerning the effects of menstrual age on failure of misoprostol. The purpose of our study is to evaluate the effect of menstrual age in failure of medical management of women with US age < 8 weeks.

4.3 Materials and Methods

We performed a retrospective hospital-based cohort study of all women with early pregnancy loss presenting to the Emergency Department (ED) of the Jewish General Hospital, McGill University, Montreal, Quebec, Canada. Using our institution's electronic medical records system, we created a cohort of all women having visited the ED for early pregnancy loss between January 2011 and December 2013. Data were collected on maternal characteristics such as age, parity, previous cesarean, previous abortions, menstrual dates and type of abortion. The inclusion criteria for the study were an ED discharge prescription for medical management and an US diagnosis of arrested pregnancy (missed or anembryonic) < 8 weeks or an incomplete abortion. We excluded all women with US dates ≥ 8 weeks or whose medical charts lacked their US information. Women in our cohort were categorized by menstrual age, which was calculated using information recorded in medical charts. Outcomes of interest were defined as need for dilatation and curettage (D&C) or an unplanned return to the ED (URED).

We estimated that there would be approximately two times more women with menstrual age > 8 weeks as compared to ≤ 8 weeks, assuming a baseline risk of 15 %. Our sample size calculation estimated that we would need 195 patients to demonstrate a two-fold increase in outcome in women with menstrual age > 8 weeks as compared to ≤ 8 weeks with a power of 80 % and alpha of 0.05. Our analysis was carried out in three steps. First, we conducted a descriptive analysis of baseline characteristics of all women in our study cohort, including maternal age, parity previous cesarean, previous abortions, type of abortion and menstrual age. Age was categorized as < 25, 25 to 34, and ≥ 35

years; parity and previous abortions were categorized as 0, 1, ≥ 2; and menstrual age was categorized as ≤ 8 and > 8 weeks, as well as < 8, 8 – 9, 10 – 11 and ≥12 weeks. Second, we examined the relationship between categories of menstrual age and our outcomes of interest; D&C and URED. We used multivariate logistic regression to calculate adjusted odds ratios for need for D&C and URED at different menstrual ages. We used menstrual age ≤ 8 weeks as the reference in our primary regression analysis and < 8 weeks in our secondary analysis. Finally, we performed a Wald test for trend using menstrual age as a continuous variable in the regression model. All models were adjusted for baseline characteristics. A p-value of < 0.05 was considered to be statistically significant.

In keeping with provincial legislation, the use of our institution's electronic medical record system for research purposes was approved by the Jewish General Hospital's Research Ethics Committee.

4.4 Results

During the three-year study period, 270 women with early pregnancy loss received medical management. A total of 199 women with an US diagnosis of early pregnancy failure < 8 weeks or incomplete abortion were identified. Seventy-one women were excluded from the study given the unavailability of their US information. Over the study period, there were a total of 44 D&Cs and 62 UREDs, yielding an overall incidence of 22.1 % for D&C and 31.2% for URED. Analysis of baseline characteristics (Table 1) demonstrated that women were predominantly above the age of 25, had never miscarried in the past and were mainly amenorrhoeic for more than 10 weeks. More women had an

arrested pregnancy of either missed or anembryonic type, than an incomplete abortion and nearly half were nulliparous.

Rates of both D&C and URED were 13.6 % in women with menstrual age ≤ 8 weeks and 26.3 % in women with menstrual age > 8 weeks. Outcomes were significantly worse in women with menstrual age > 8 weeks and increasing menstrual age demonstrated a significant increasing trend for D&C and URED. (Table 2 and Figure 1)

4.5 Discussion

Complications of early pregnancy failure such as failure of misoprostol are an important issue, affecting approximately 25-30% of women.[24,25] Several studies have shown that the effectiveness of misoprostol varies widely and can range from 30% to 90%.[50,51,60-62] In North America, physicians rely greatly on US findings to determine gestational age and decide between medical versus surgical management of failed early pregnancy.[11] Approximately 36% of women with early pregnancy loss or who desire termination of pregnancy receive medical management despite persistently high failure rates.[71] Because prescribing misoprostol for early pregnancy loss < 8 weeks on US is common, it is important to identify which factors influence failure. Our study showed that women with early pregnancy failure of advanced menstrual age tend to require D&C and URED more often than those with lower menstrual age following medical management.

Although medical treatment is well accepted for the management of early pregnancy loss in both hospitals and in the office, several studies support the notion that surgical management has a higher rate of complete evacuation of the uterus.[40,60,72,73] De

Jonge et al. conducted a randomized control trial comparing miscarriage treated surgically versus medically.[60] Surgical management was associated with less pain and vaginal bleeding than medical treatment, as well as fewer daily hospital attendances. Only 3 of 23 patients (13%) were treated successfully with misoprostol compared with 26 of 27 patients (96%) allocated to surgery. The mean gestational age of women treated medically was > 11 weeks and > 13 weeks in those managed surgically. Although these results support our findings of an increasing trend of failure with medical management as menstrual age increases, this high failure rate likely reflects the fact that the women included in the trial had higher gestational ages and did not receive US evaluation of their first trimester pregnancy loss. Unlike our study, they were unable to account for the discrepancies between menstrual and US age. US diagnosis and dating plays an important role when deciding between medical versus surgical treatment and is currently recommended for management of early pregnancy loss and termination of pregnancy.[11,70]

A possible biological explanation for the high failure rate of medical management as menstrual age increases involves the notion that following fetal/embryonic demise, the placenta continues growing due to its self-sustained production of progesterone.[45-47] Women would therefore have a larger uterine size due to the increased volume of the placenta. A study conducted by Hinshaw et al. comparing medical treatment versus surgical management in women with missed and incomplete abortions revealed that in women with small uterine contents, no difference between medical and surgical treatment was found in the rate of complete evacuation.[74] However, women with larger uterine contents had a significantly lower rate of successful medical management when compared to those having undergone surgical treatment.

Since a higher menstrual age may possibly lead to more placental tissue due to continued growth following embryonic/fetal demise, it is expected that patients would be subject to increased bleeding and pain when managed medically.[45-47,60] Johnson et al. conducted a randomized controlled trial evaluating pain and bleeding in miscarriage treated surgically versus medically.[72] Women managed surgically experienced significantly less pain and bleeding than those managed medically. This is because those managed medically experienced uterine contractions. Women who undergo surgical treatment bleed less because a surgical procedure is more thorough and less likely to leave products of conception in the uterus.

Findings from other studies also support the idea of a lower evacuation rate of medical management with increasing menstrual age. Grønlund et al. conducted a multi-center trial comparing the efficacy of medical treatment regimens with surgical evacuation in women with missed abortion.[41] In the medical management group, 29% of women required surgical evacuation after medical treatment. Combining plasma-human Chorionic Gonadotropin (p-hCG) and gestational age revealed a group of women with a low incidence of evacuation. A p-hCG level between 2000 and 20,000 and a gestational age < 75 days was associated with a 25 % lower rate of evacuation compared to women not fulfilling those criteria ($p < 0.05$). Furthermore, they found no difference in the success rates according to US measurements of crown-rump length (CRL) and gestational sac (GS). Although this study supports our findings that women undergoing medical treatment of early pregnancy loss must be carefully selected according to menstrual age regardless of US age, failure of medical management did not include women who required an unplanned return visit to the ED. In Grønlund et al.'s trial,

women who required a second course of medical management were not classified as failed medical treatment, but rather considered as successful cases. In our study, we showed that women with menstrual age > 8 weeks have significantly higher rates of URED visits than women with menstrual age ≤ 8 weeks. URED is an established marker of quality of care whereby when patients return to the ED for an unplanned visit, it is generally assumed that their initial evaluation or treatment was inadequate.[75-77] This also places this category of women at increased risk of encountering adverse events and requiring emergency hospitalization.[77,78] A high rate of unplanned ED return visits impinges on the function of our health care system in part by influencing ED overcrowding leading to decreased quality of care and longer waiting times.[79] As well, URED is also associated with increased ED health care costs.[9]

It is important to balance the risks and benefits of medical management to predict which patients are at higher risk of failing misoprostol and requiring D&C. Our study suggests that, as menstrual age increases, the odds of D&C and URED increase. The choice between elective D&C and misoprostol must be carefully thought out for each woman. Elective curettage includes several benefits, among which are convenient timing and high success rates. Although extremely rare, it is important to keep in mind the associated risks, such as infection, perforation, cervical lacerations, and uterine adhesions.[44,65] Misoprostol, on the other hand, is also associated with certain benefits such as safety and efficacy without mechanical dilatation. However, it is equally accompanied by several adverse events, such as diarrhea (most common), nausea, vomiting, pain, cramping, fever, chills and prolonged persistent bleeding in 1% to 10% of women.[80-82] The most important complication of misoprostol is of course need for

surgical evacuation and URED.[80-82] Although our study was limited in terms of identifying all causes of failed medical management, a report by Ashok et al. evaluating over 2,000 consecutive cases of early medical treatment of abortion described several severe complications of medical management.[83] These included need for unplanned surgical evacuation, hemostatic uterine evacuation, heavy bleeding requiring oxytocins, blood transfusions, need for surgical evacuation due to heavy bleeding, pain and significant side effects of prostaglandin. Moreover, a systematic review of the Cochrane database on the medical treatment of incomplete miscarriage by Neilson revealed similar complications of medical management.[84]

Our study demonstrated relatively high overall rates of D&C and URED of 22.1% and 31.2%, respectively. A meta-analysis by Sotiriadis et al. analyzed the relative benefits and harms of different management options for first trimester pregnancy failure.[44] Randomized or quasi-randomized controlled trials that allocated women with first trimester missed or incomplete abortion to various surgical or conservative management options were included in their review. Similarly to our findings, women who underwent surgical management had significantly higher rates of complete evacuation of the uterus than those medically managed (risk difference 32.8 %, NNT = 3). Cases with incomplete abortion indicated that medical management had two-thirds the chance to induce complete evacuation compared with surgical management. Data from studies that evaluated outcome at 48 hours or more after allocation also showed that medical management had a worse success rate than surgical management. While this possibly explains why so many women in our study returned to the ED for an unplanned

visit after their initial evaluation, Sotiriadis et al.'s meta-analysis does not specify which studies used US versus menstrual dating.

There are several limitations to our study. First, given our study was based in a tertiary hospital center; our patient population is not representative of general office based practice, but rather reflective of more severe cases. Women with milder symptoms may have presented to their physician's office and received medical management for early pregnancy loss. These women might be of lower menstrual age and more likely to succeed treatment with a single course of misoprostol and not be included in our cohort.

An additional limitation in our study revolves around missing information concerning dose, route and frequency of misoprostol among different patient groups. It has been shown in several studies that dose, route and frequency of misoprostol play an important role in success of medical management.[49,50,60,61] While we are uncertain of the regimens used in our study, they are likely those proposed by the Society of Obstetricians and Gynecologists of Canada's (SOGC) Guidelines for Induced Abortion, which our staff is familiar with.[12,42,43,81,82] Another limitation is whether or not the medications prescribed were actually taken. This could have resulted in the inclusion of patients who underwent expectant management rather than medical management in our analysis. However, this issue reflects the true effectiveness of medical management, allowing us to observe the real-life clinical context in which misoprostol is used in EDs for the treatment of first trimester failed pregnancy. We therefore consider our study to be a true reflection of outcome when women are treated for early pregnancy loss in EDs of tertiary level centers comparable to ours.

It is important to note that in Canada, misoprostol is the only drug available for medical management, as mifepristone has not yet been approved by Health Canada. In the United States, the FDA has approved a highly effective regimen of mifepristone, a progesterone receptor antagonist, followed 48 hours later by a prostaglandin analog, usually misoprostol.[11] This regimen has been shown to have higher success rates when compared to misoprostol alone.[11] This may explain our study's high rates of D&C and URED when compared to American based studies evaluating the effectiveness of mifepristone and misoprostol combined for the management of early pregnancy failure.[85-87]

4.6 Conclusion

Despite improvement in management of first trimester bleeding, failed medical treatment remains high among women with early pregnancy loss. Although sonography plays an important role in deciding between medical versus surgical management of early pregnancy failure, it is crucial to consider menstrual age in spite of early US dating as it has an important impact on treatment failure. In view of our results, we conclude that increasing menstrual age is a fundamental contributor to poor outcomes in medically managed women with early pregnancy failure. We therefore advocate that women with early pregnancy loss and advanced menstrual dates despite US date < 8 weeks, should be counseled towards opting for elective curettage rather than outpatient self-administration of misoprostol.

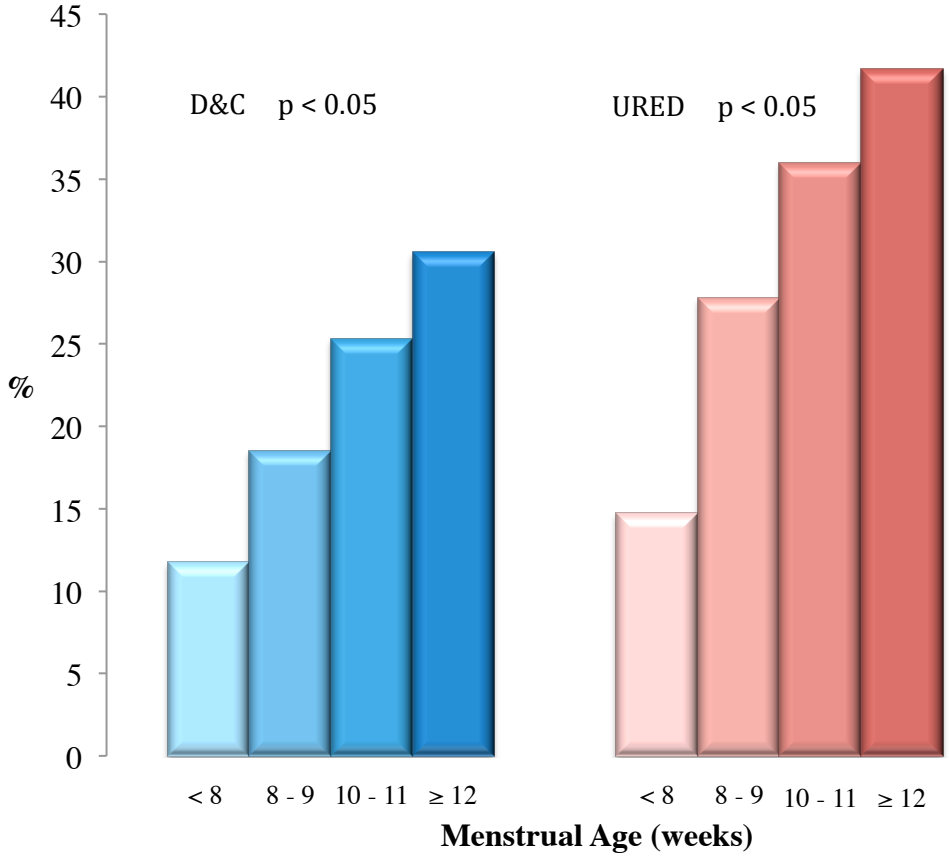
4.7 Tables and Figures

Table 1 - Baseline Characteristics for Women with Early Pregnancy Failure Discharged with Medical Management	
Characteristics	**N=199 (%)**
Age (years)	
< 25	18 (9.05)
25 - 34	94 (47.24)
> 35	87 (43.72)
Parity	
0	84 (42.21)
1	65 (32.66)
≥ 2	50 (25.13)
Previous Cesarean	24 (12.06)
Previous Abortions	
0	106 (53.27)
1	57 (28.64)
≥ 2	36 (18.09)
Abortion Type	
Incomplete	78 (39.20)
Missed	66 (33.17)
Anembryonic	55 (27.64)
Menstrual Age (weeks)	
≤ 8	66 (33.17)
> 8	133 (66.83)

Table 2 – Multivariate Analysis[1] of D&C and URED for Menstrual Age (weeks)				
	%	**Adjusted OR (95% CI)**	***P*-value**	**Test for trend (*P*-value)**
D&C	22.11			
Primary Analysis				
≤ 8	13.64	1.00		
> 8	26.32	2.25 (1.00* - 5.07)	< 0.05	
Secondary Analysis				
< 8	11.77	1.00		
8 - 9	18.52	1.73 (0.49 - 6.04)	NS	
10 - 11	25.33	2.55 (0.79 - 8.29)	NS	
≥ 12	30.56	3.28 (0.92 - 11.69)	NS	
Trend				1.46 (< 0.05)
URED	31.16			
Primary Analysis				
≤ 8	13.64	1.00		
> 8	26.32	2.40 (1.17 - 4.90)	< 0.05	
Secondary Analysis				
< 8	14.71	1.00		
8 - 9	27.78	2.32 (0.75 - 7.16)	NS	
10 - 11	36.00	3.37 (1.15 - 9.88)	< 0.05	
≥ 12	41.67	3.98 (1.24 - 12.76)	< 0.05	
Trend				1.52 (< 0.05)

D&C: Dilatation and Curettage
URED: Unplanned Return to Emergency Department
*Does not cross 1.00
[1]Data adjusted for age, parity, previous abortions and previous cesarean as continuous variables

Figure 1: Trend Analysis of Menstrual Age (Weeks) on Outcomes of Interest



D&C: Dilatation and curettage

URED: Unplanned return to the Emergency Department

CHAPTER 5: EFFECT OF UTERINE CONTENT ULTRASOUND MEASUREMENTS ON MEDICAL MANAGEMENT FAILURE IN WOMEN WITH EARLY PREGNANCY LOSS

The following chapter presents the methods and results of objective 2 to assess the value of uterine content US measurements in predicting medical management failure in women with early pregnancy loss. This manuscript is under review in the Journal of Obstetrics and Gynecology Canada.

The following topic will be introduced with some background information. The methods will cover comprehensive information on the study population and statistical methods used. Results are described in detail and a thorough discussion provides critical information as well as study limitations and future implications.

Effect of Uterine Content Ultrasound Measurements on Medical Management Failure in Women with Early Pregnancy Loss

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5.1 Abstract

Objective: Medical management is commonly used among women with early pregnancy failure. The purpose of our study was to evaluate uterine content ultrasound (US) measurements in predicting medical management failure of early pregnancy loss.

Methods: We conducted a retrospective cohort study in a university-affiliated hospital center on all women discharged from the Emergency Department (ED) with a diagnosis of early pregnancy failure who were managed medically with misoprostol between 2011 and 2013. Only women with US images available for review were included in our study. All images were reviewed and the following uterine content measurements, excluding endometrial lining, were measured: content anteroposterior distance (CAPD), content longitudinal distance, content transverse distance and volume. Logistic regression analysis was used to identify measurements independently associated with subsequent need for dilatation and curettage (D&C) and unplanned return to the ED (URED).

Results: Among 823 women presenting to the ED with first trimester bleeding, 227 met inclusion criteria. Of all measurements evaluated, CAPD was found to be independently associated with D&C and URED. When using a CAPD cutoff of 15 mm, women were more likely to require D&C, 2.65 (1.31-5.36), $p < 0.01$ and to have an URED, 2.59 (1.41-4.79), $p < 0.01$. In women with a CAPD below 15 mm, 87.1% had successful medical management of early pregnancy loss and 80.0% did not require an URED.

Conclusion: Although there is a need for further validation, patients identified as having a CAPD below 15 mm should be considered good candidates for successful medical management.

5.2 Introduction

Early pregnancy failure is the most common complication of pregnancy affecting 1 in 4 women in their lifetime.[24,59,63] According to the Centers for Disease Control and Statistics Canada, over one million women in North America suffer from early pregnancy loss or undergo termination of pregnancy each year.[3,64] While management remains mostly surgical, the use of medical treatment is also well established and has been steadily increasing, passing from 3.4% in 2001 to 17.2% in 2010.[11,88] Although there is an abundance of research comparing medical and surgical management of early pregnancy loss, the optimal treatment remains controversial.[86,89] In North America, ultrasonography plays an important role in the evaluation of early pregnancy complications.[19,90,91] While ultrasonography remains the most accurate modality for determining gestational age and plays an inherent role when opting for medical treatment, there is paucity in reliable parameters predictive of medical management failure in women with early pregnancy failure.[56,58,90] Although rare, life-threatening complications of failed medical management include persistent prolonged bleeding, which may lead to hemorrhagic shock, placenta accreta, hematometra and disseminated intravascular coagulopathy.[16-18,68,69] Recognizing the deleterious effects of failed medical management and the limited evidence available on predictors of outcome, we sought to evaluate the association of uterine content ultrasound (US) measurements with failure of misoprostol. [56]

5.3 Materials and Methods

Our study is a secondary analysis of previously collected data for a retrospective hospital-based cohort study of all women with early pregnancy loss presenting to the

Emergency Department (ED) of the Jewish General Hospital, McGill University, Montreal, Quebec, Canada. Using our hospital's electronic medical records system, we created a cohort of all patients having visited the ED for early pregnancy loss between January 2011 and December 2013. The inclusion criterion for the study was an ED discharge prescription for medical management. We excluded women whose medical charts lacked their US report images. Our exposure of interest was defined as uterine content US measurements, which were obtained from our institution's picture archiving and communication system (PACS). With regards to uterine content US parameters, we collected measurements for content transverse distance (CTD), content longitudinal distance (CLD) and content anteroposterior distance (CAPD), defined as the longest diameter in each plane, excluding the endometrial lining. (Figure 1) Uterine content volume was calculated from measurements obtained by the geometrical formula for a prolate ellipsoid:

$$\text{Volume} = 4/3 \times \pi \times \text{CAPD} / 2 \times \text{CTD} / 2 \times \text{CLD} / 2.$$

Outcomes of interest were defined as need for dilatation and curettage (D&C) or an unplanned return to the ED (URED). Our analysis was carried out in three steps. First, we conducted a descriptive analysis of baseline characteristics of all women in our study cohort, including maternal age, parity, previous cesarean, previous abortions, type of abortion and menstrual age. Age was categorized as < 25, 25 to 34, and ≥ 35 years; parity and previous abortions were categorized as 0, 1, ≥ 2; and menstrual age was categorized as < 8, 8 – 9, 10 – 11 and ≥ 12 weeks. Second, we used Mann-Whitney U test for the bivariate statistical analysis to identify differences between outcomes according to median US measurements. We also performed multivariate analyses on all uterine

content US measurements to isolate predictive parameters for failed medical management. Only significant values were included in the multivariate logistic regression model, which was used to calculate adjusted odds ratios for need for D&C and URED. We adjusted our model for baseline characteristics. A p-value of < 0.05 was considered to be statistically significant.

In keeping with provincial legislation, the use of our institution's electronic medical record system for research purposes was approved by the Jewish General Hospital's Research Ethics Committee.

5.4 Results

During the three-year study period 270 women with early pregnancy loss were identified as having received medical management. A total of 227 women with US images available on PACS were included in our cohort. Over the study period, there were a total of 45 D&Cs and 68 UREDs, yielding an overall incidence of 19.82% for D&C and 29.96% for URED. Analysis of baseline characteristics demonstrated that women were predominantly above the age of 25, had never miscarried in the past and were on average amenorrhoeic for more than 10 weeks (Table 1). More women had an arrested pregnancy of either missed or anembryonic type, than an incomplete abortion and nearly half were nulliparous.

We observed a significant difference in median CAPD measurements for both D&C and URED, as well as a significant difference in median measurements of CLD and uterine content volume for URED. Of all measurements, CAPD was found to be independently associated with D&C and URED (Table 2). When using an CAPD cutoff

of 15 mm, women were more likely to require D&C, 2.65 (1.31 - 5.36), $p < 0.01$ and to have an URED, 2.59 (1.41 - 4.79), $p < 0.01$ (Table 3). Of all patients included in our study, 57.3% had a CAPD below 15 mm. Of these women, 87.1% had successful medical management of early pregnancy loss and 80.0% did not require an URED.

5.5 Discussion

Complications such as failure of misoprostol can affect up to 30% of women undergoing medical management of early pregnancy loss.[92] The objective of our study was to identify predictors of failed medical management based on a function of uterine content US measurements. Our hospital-based cohort study demonstrated that a CAPD above 15 mm is an independent risk factor for need for D&C and URED following medical management of early pregnancy loss.

In North America, many rely on guidelines for the management of induced abortion when treating women with early pregnancy failure, as such guidelines have not yet been established. The American College of Obstetrics and Gynecology currently recommends the use of medical management up to 63 days gestation.[11] With regards to examining women with suspected complications of early pregnancy, ultrasonography has become the accepted standard of care and is critical for accurate diagnosis.[11,90,91,93] Various US measurements have already been studied in an attempt to predict medical management outcome.[56-58] Agostini et al. conducted an observational prospective study evaluating the influence of clinical and US characteristics on the efficacy of misoprostol treatment of early pregnancy failure.[58] Among their exposures of interest, crown-rump length (CRL), gestational sac (GS) diameter, cervical length and distance between the GS

and the internal cervical os, none were associated with a significant difference between the treatment success and treatment failure groups. Their study defined failure as an endometrial thickness of >15 mm following misoprostol administration. Results showed that of all patients with endometrial thickness < 15 mm, none required surgical intervention and none had complications of medical management. Using this cutoff for failure, they obtained a success rate for misoprostol of 64.8%. Odeh et al. conducted a similar study evaluating ultrasonographic measurements of GS volume and CRL as a function of predicting successful medical management.[57] They found a much lower success rate for misoprostol of 39.5%, which may be explained by their cutoff for failure of an endometrial thickness of > 30 mm. In their study, GS volume and CRL were not found to predict success of medical management. Although both studies used endometrial thickness cutoffs to define failure, neither evaluated the significance of uterine content US measurements, including retained products of conception (RPOC) while excluding the endometrial lining. To the best of our knowledge, this is the first study evaluating the association between failure of medical management and CAPD. Basic scientific research proposes the notion that following fetal demise, the placenta continues growing due to its self-sustained production of progesterone.[45-47] This concept may explain why Agostini et al.[58] and Odeh et al.'s[57] uterine ultrasonographic measurement analyses were unsuccessful in predicting medical management success. It is expected that if the placental volume continues to increase compared to GS size and CRL following arrest in pregnancy, omitting measurements of RPOC will influence the significance of such factors in predicting successful medical management.

In Canada, misoprostol is the only drug available for medical management of early pregnancy loss whereas in the United States, a highly effective regimen of mifepristone, a progesterone receptor antagonist, followed 48 hours later by a prostaglandin analog, usually misoprostol, is currently considered the optimal treatment.[11] When compared to misoprostol alone, mifepristone combined with misoprostol has been show to be more effective and may explain why our study reports higher rates of D&C and URED when compared to American studies.[11,85-87] Moreover, if we were to apply medical management only to patients with a CAPD < 15 mm, in order to avoid URED and delayed emergency D&Cs, this would significantly increase the number of patients requiring surgical management. If more effective medical treatments, such as mifepristone, were available to us, this might not be an issue.

Several limitations arise from the use of a database created from a single hospital center's electronic medical records system. First, we were unable to collect information concerning dose, route and frequency of misoprostol on all. These factors have been widely studied and are proven to affect success rates of medical management.[49,50,60,61] While we were unable to obtain sufficient information concerning the regimen of misoprostol used, our staff follows the Society of Obstetricians and Gynecologists of Canada's Guideline on Induced Abortion.[12] These guidelines suggest using 800mg of intravaginal misoprostol every 24 or 48 hours (days 1–5) with a maximum of three applications.[12] Another limitation involves patient selection. Because our study was based in a tertiary teaching hospital; our patient population is reflective of more severe cases. Women at lower risk of failing medical management may be more likely to present to their physician's outpatient office and succeed with treatment consisting of a single

course of medication. Because the patient population of our institution does not reflect a general office based practice, women in our cohort may have been at higher baseline risk for failure. Another limitation involves patient compliance with medical advice. As we have no way of ascertaining whether or not patients actually took the prescribed medication, this could have resulted in the inclusion of patients who underwent expectant management rather than medical management, thus potentially overestimating the incidence of failed medical treatment. While this issue prevents us from measuring the efficacy of misoprostol, it reflects the true effectiveness and allows us to observe real life outcomes when used in an uncontrolled setting. We therefore consider our study to be a true reflection of outcome when women are treated for early pregnancy loss in EDs of tertiary level centers comparable to ours.

5.6 Conclusion

In conclusion, our extensive evaluation of uterine US content measurements associated with need for D&C and URED following medical management for early pregnancy loss has enabled us to identify a CAPD cutoff of 15 mm as a new predictor for poor outcome. While the use of ultrasonography for the evaluation of suspected early pregnancy complication has become standard of care, there remains a paucity of reliable markers to identify potential treatment failures. Although there is a need for further validation, using a CAPD cutoff of 15 mm in a hospital-based population of women with early pregnancy failure may be helpful in selecting patients that can safely be managed medically.

5.7 Tables and Figures

Table 1 - Baseline Characteristics for Women with Early Pregnancy Loss Having Undergone US Evaluation	
Characteristics	**N=227 (%)**
Age (years)	
< 25	23 (10.13)
25 - 34	103 (45.37)
> 35	101 (44.49)
Parity	
0	98 (43.17)
1	70 (30.84)
≥ 2	59 (25.99)
Previous Cesarean	30 (13.22)
Aborta	
0	123 (54.19)
1	64 (28.19)
≥ 2	40 (17.62)
Abortion Type	
Incomplete	78 (34.36)
Missed	86 (37.89)
Anembryonic	63 (27.75)
Menstrual Age (weeks)	
< 8	35 (15.42)
8 - 9	56 (40.09)
10 - 11	84 (37.00)
≥ 12	52 (22.91)
US: Ultrasound	

Table 2 – Uterine Content Ultrasound Measurements with Successful and Failed Medical Management for Early Pregnancy Loss

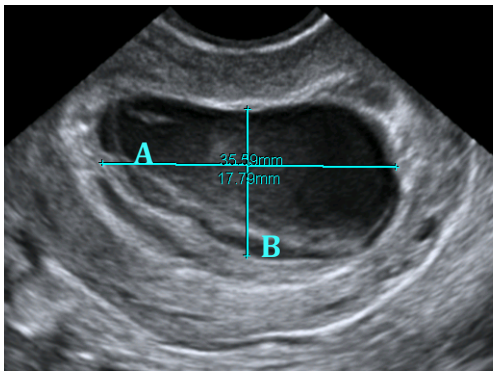
Sonographic measurements	**Treatment outcome**		**Mann-Whitney Test**	**Regression Model**
Median (95 % CI)	**D&C** *(n = 45)*	**No D&C** *(n = 182)*	**P-value**	Adjusted P-value[1]
CTD	16.0 (7.9-22.5)	11.6 (4.8-19.5)	NS	NS
CLD	23.2 (17.3-36.2)	20.3 (9.9-29.6)	NS	NS
CAPD	18.4 (9.8-30.8)	11.4 (5.4-18.4)	< 0.01	< 0.05
Volume (mm^3)	4318.7 (700.3-8630.4)	1642.63 (187.7-4624.5)	NS	NS
	URED *(n = 68)*	**No URED** *(n = 159)*		
CTD	16.2 (8.2-22.5)	11.4 (4.6-18.3)	NS	NS
CLD	25.0 (13.7-37.2)	19.8 (9.4-26.8)	< 0.05	NS
CAPD	17.6 (9.3-26.8)	10.1 (5.4-18.0)	< 0.01	0.08
Volume	3849.8 (5216.6-11399.2)	1209.3 (2642.54-5377.6)	< 0.01	NS

D&C: Dilatation & Curettage
URED: Unplanned Return to the Emergency Department
SD: Standard deviation
CTD: Content transverse distance
CLD: Content longitudinal distance
CAPD: Content anteroposterior distance
[1]Data adjusted for CTD, CLD, CAPD and content volume as continuous variables

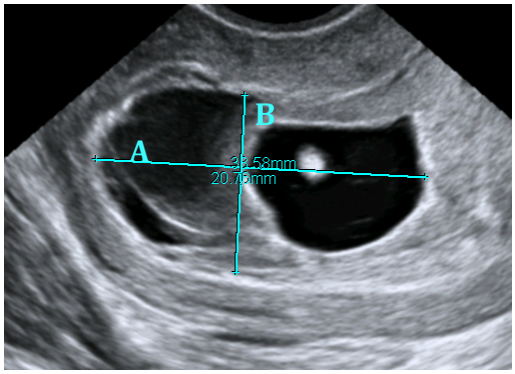
Table 3 – Multivariate Analysis[1] of CAPD and Outcome				
	CAPD < 15 130 (57.3%)	**CAPD ≥ 15** 97 (42.7%)	**Adjusted OR** **(95% CI)**	***P*-value**
D&C	17 (13.1)	26 (29.2)	2.65 (1.31 - 5.36)	< 0.01
URED	27 (20.8)	41 (42.7)	2.59 (1.41 - 4.79)	< 0.01

CAPD: Content anteroposterior Distance
D&C: Dilatation and Curettage
URED: Unplanned Return to Emergency Department
[1] Data adjusted for age, parity, previous abortion, menstrual age in weeks and previous cesarean as continuous variables

Figure 1 – Transvaginal Ultrasonography showing Uterine Cavity Content Measurements



A: Content transverse distance (CTD)
B: Content anteroposterior distance (CAPD)



A: Content longitudinal distance (CLD)
B: Content anteroposterior distance (CAPD)

CHAPTER 6: GENERAL DISCUSSION

The results provided in this thesis reveal new predictors of failed medical management of early pregnancy loss.

6.1 Findings and summary for the effect of menstrual age on misoprostol efficacy for early pregnancy loss

In the first objective, menstrual age > 8 weeks was found to be significantly associated with increased odds of need for D&C and URED. To our knowledge this is the first study directly evaluating the effect of menstrual age on failed medical management. While the efficacy of misoprostol has been vastly studied over the last decade,[84,94] no studies have taken into account the disparities between menstrual and US gestational ages. Two Cochrane reviews have aimed at comparing the different treatment options for both incomplete and missed abortions.[84,94]

In 2013, The Cochrane Collaboration published a review evaluating randomized controlled trials comparing medical treatment with expectant care or surgery in women with incomplete abortions < 13 weeks' gestation.[84] A total of 20 trials were included. Their primary outcomes were complete miscarriage, need for surgical evacuation and death or serious complications. The conclusions of this review indicated that there was no significant different between surgical, medical and expectant management for women with incomplete abortion at < 13 weeks, except that elective surgical intervention seemed to reduce the adverse effects associated with misoprostol. In the analysis of their results, the effect of increasing gestational age on the efficacy of treatment was overlooked.

In 2006, The Cochrane Collaboration published a review evaluating clinical trials that assessed the effectiveness and safety of different medical treatments for the termination of missed abortions and anembryonic pregnancies up to 24 weeks' gestation.[94] Their primary outcomes included complete miscarriage and death or serious complications. The review included 24 studies, 19 of which included women < 14 weeks' gestation. While the authors conclude that misoprostol is a potential alternative to surgical and expectant management, the results presented do not distinguish between first and second trimester missed abortion outcomes. Moreover, gestational age was solely calculated by means of sonography and menstrual age was not taken into account in any of the studies. While US provides the best estimate of gestational age,[52] our study demonstrated that menstrual age > 8 weeks is significantly associated with increased odds of need for D&C and URED. Moreover, our secondary analysis demonstrated a significantly increasing trend for both D&C and URED as menstrual age increases.

First trimester pregnancy loss is a common event for which women receive medical management.[5,6] Considering the devastating effects failed misoprostol can have on women and their families,[4,16-18,69] it is essential to identify additional factors predicting which patients will most likely require subsequent care. These women could therefore be counseled towards surgical management and avoid the potential serious adverse effects of failed misoprostol. While few studies evaluate the effect of gestational age on the efficacy of misoprostol for early pregnancy loss, studies that do include this variable consistently focus on US gestational age.[41,51,52] Though it would be unreasonable to ignore sonographic measurements prior to treating a miscarriage, other parameters such as menstrual age should also be considered in the equation.

Recent studies incorporating US gestational age as an independent predictor for medical management failure in early pregnancy loss did not find a significant association.[41,51,52] Therefore, guidelines on the management of first trimester miscarriage do not use a cut-off gestation for the use of misoprostol.[31,95] As long as the pregnancy is in the first trimester, misoprostol can be used [31,95]. In contrast with guidelines on the management of miscarriage, guidelines for induced abortion use noticeably lower cut-offs for gestational age at which medical treatment can safely be used.[11,12] In fact, when the pregnancy is viable, the Society of Obstetricians and Gynecologists of Canada (SOGC) recommends limiting misoprostol treatment to women with a gestational age ≤ 8 weeks[12] and the ACOG recommends misoprostol up to ≤ 9 weeks.[11] The rationale behind these cut-off values is that the failure rates increase as gestational age increases.[11,12] Considering a missed abortion can go unnoticed for several weeks, the difference between the estimated menstrual and US age can be quite extreme, whereas the difference in dates of an induced abortion is more likely to be less important. Following this reasoning, a missed abortion with large disparities between sonographic and menstrual age may be more likely to fail misoprostol. Although, the fetus and GS arrest in development and cease growing in a missed or anembryonic abortion, the sustained presence of progesterone allows the placenta to continue increasing in size. [11,12,45,46] This may therefore contribute to heavier bleeding, pain and subsequent need for emergency surgical evacuation. While further studies are needed to better quantify the effect of menstrual age on misoprostol failure, our study demonstrated that in women with US age < 8 weeks, increasing menstrual age is an independent predictor of need for D&C and URED following misoprostol treatment.

6.2 Findings and summary for the effect of sonographic measurements of uterine cavity contents on misoprostol efficacy for early pregnancy loss

In the second objective, US measurement of the uterine CAPD was found to be a significant independent risk factor for D&C and URED following medical management of first trimester miscarriage.

While US is generally used in cases of suspected first trimester pregnancy loss,[20,32] there is paucity of reliable markers guiding physicians and patients towards the best management option.[56,58] Our study evaluated several US uterine cavity content biometries in the hopes of identifying factors predicting which women will fail or succeed medical management. CAPD ≥ 15mm was found to have an odds ratio of 2.65 (1.31-5.36) for D&C and 2.59 (1.41-4.79) for URED when compared to women with a CAPD < 15mm.

While evidence suggests an association with CRL and successful medical termination of first trimester pregnancy,[11,12] few studies have directly assessed the association between US biometries and the efficacy of misoprostol for early pregnancy loss. Parameters that have been previously studied include CRL, GS diameter, GS volume, cervical length and distance between the GS and the 'virtual' cervical os (upper limit of the cervical glands).[39,56-58] While cervical length, GS volume and distance between the GS and the 'virtual' cervical os have been shown to have no significant association with the efficacy of medical management,[56-58] the evidence regarding CRL and GS diameter is inconsistent.[39,56-58] In fact, Agostini et al.'s two studies in 2005 and 2007, as well as Odeh et al.'s study in 2010 evaluating the influence of ultrasound factors on the efficacy of misoprostol in first-trimester pregnancy failure found that success was

independent of CRL and GS diameter.[56-58] In Agostini et al.'s study in 2005, only parity was significantly smaller in the successful medical management group, however, this difference was minimal.[56] Vejborg et al.'s study also evaluated the efficacy of misoprostol according to *ultrasonopgrahic* measures.[39] They found that CRL < 6 mm was predictive of a higher success rate compared to CRL ≥ 6 mm and GS measurements.

Because our study sought to identify sonographic predictors of misoprostol efficacy applicable to all types of early pregnancy losses, we opted to measure uterine cavity contents. In women with a CAPD < 15 mm, 87.1% did not require a D&C and 80.0% did not return to the ED for an unplanned visit. While further studies are needed evaluating ultrasonographic factors influencing efficacy of misoprostol, CAPD can be used to identify patients who are more likely to undergo successful misoprostol treatment.

6.3 Strengths and limitations

Both studies have many methodology strengths. In fact, several clinical and ultrasonographic parameters were collected, including age, parity, gravida, aborta, history of previous cesarean, type of abortion, menstrual age, transvaginal ultrasonographic biometries to estimate gestational age (CRL and GS), uterine cavity content US measurements (CAPD, CTD and CLD) and outcomes such as need for D&C and URED. Unfortunately, we were unable to ascertain if all patients included in the study actually took the intended treatment. However, this allowed us to observe the true effectiveness of misoprostol in real life circumstances when used in uncontrolled settings.

Both studies also have limitations. The dose, route and frequency of administration of misoprostol are known to influence efficacy.[49,61] However, we were unable to obtain such information for a large number of patients. Given the ED staff and obstetrician-gynecologists at the institution where the study took place are known to follow the SOGC's guideline on induced abortion,[12] we assumed patients received 800μg of intravaginal misoprostol with a maximum of three applications. Furthermore, because the study involved women with early pregnancy loss visiting the ED of a tertiary hospital center, our patient population may be reflective of more severe cases. Women visiting their family physician or community clinic may have a lower risk of misoprostol failure.

Additional prospective studies are now required to validate the effect of menstrual age and the effect of uterine cavity content measurements on the efficacy of misoprostol for early pregnancy loss that has been demonstrated in this thesis.

CHAPTER 7: CONCLUSION

Early pregnancy loss is the most common complication of pregnancy and is increasingly being treated with medical management.[5-7] Identifying reliable predictors for successful misoprostol treatment is essential towards efforts for decreasing maternal morbidity. Although ultrasonography has become standard of care for women with suspected miscarriage,[11,32] there is paucity of reliable markers to predict successful medical management.[56-58] Our study demonstrated that an US measurement of uterine CAPD ≥ 15 mm is significantly associated with increased odds of need for both D&C and URED. Clinicians should also be aware that women with a high menstrual age regardless of an US age < 8 weeks are more likely to require surgical evacuation following medical management. Although there is need for further validation, these clinical and *sonogrpahic* factors may help physicians identify which women can safely undergo misoprostol treatment for early pregnancy loss.

CHAPTER 8: FUTURE RESEARCH DIRECTIONS

While there are clear North American guidelines for the management of induced abortion,[11,12] there is need for additional research in the area of missed and incomplete abortion care. Well-designed randomized controlled trials are necessary to validate the effect of menstrual age and uterine cavity content US measurements, as well as potentially identify other predictors of misoprostol success. Furthermore, mifepristone, an antiprogesterone medication approved for the termination of pregnancy by the United States Food and Drug Administration since 2000, is known to be a safe and effective regimen for evacuating the uterus.[96] While both retrospective and prospective studies have evaluated the combined regimen of mifepristone plus misoprostol for the management of first trimester pregnancy loss, the results are conflicting.[40,97-100] Additional well-designed randomized controlled trials are needed to clarify the value of adding mifepristone to our current medical treatment protocol for miscarriage.

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CHAPTER 7: APPENDIX

7.1 Jewish General Hospital Research Ethics Office Approval

Hôpital général juif
Jewish General Hospital

BUREAU D'ÉTHIQUE DE LA RECHERCHE
RESEARCH ETHICS OFFICE

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January 15, 2014

Dr. Haim Abenhaim
Obstetrics and Gynaecology
Jewish General Hospital

SUBJET: **Retrospective Chart Review CR14-04** *entitled* "Risk Factors for emergency curettage following failed medical management of missed or incomplete abortions"

Dear Dr. Abenhaim,

Subsequent to the receipt and review of the above-mentioned project, please be advised that your request for permission to review 400-500 medical charts at the Jewish General Hospital as part of your clinical research project is granted.

It is our understanding that the purpose of this chart review is to identify the risk factors for emergency curettage in patients who failed medical treatment for missed of incomplete abortions. This retrospective chart review will be done by Melissa Lavecchia. The data collected will be anonymous and kept in a password protected computer in H-412 for a period of 5 years. No contact will be made with patients at any time during this retrospective chart review.

For your information the above-mentioned protocol will be presented for corroborative approval at the next meeting of the Committee, February 14, 2014.

This approval is for the period of one year at which point you must request permission once again. Please contact Ms. Louise Tanguay, Director at the Medical Records Department of the Jewish General Hospital to arrange for consulting charts. She may be contacted at (514) 340-8222, ext. 8202.

Sincerely,

Vasiliki Bessy Bitzas, N, PhD(C), CHPCN(C)
Chair, Research Ethics Committee

Joseph Portnoy, MD
Director of Professional Services

VBB/kb

CC: Ms. Louise Tanguay, Tel: 514-340-8222, ext. 8202
Director of Medical Records, Room C-110

Carmen Tapia – DPS A-142