Original paper

Predicting the efficacy of vaginal misoprostol in the management of early pregnancy failures: A signal center study

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Abstract

Introduction: Early pregnancy loss is a situation commonly experienced by pregnant women. Management includes expectant, medical and surgical evacuation. Medical management is effective and relatively safe option and involves use of vaginal misoprostol which was recently approved to use in Sri Lanka. Proper patient selection for the medical management will improve the success rate.

Objectives: Aim is to develop a predictive model using different factors to determine the efficacy of vaginal misoprostol in medical management of early pregnancy losses.

Method: This was a single center retrospective descriptive study and was carried out in Teaching Hospital, Mahamodara, Galle. Eligibility criteria was medically managed early pregnancies (<12 weeks of gestation) adherent to Health Ministry guidelines. Data was retrieved using bed head tickets and was entered to data retrieval sheet. Orange Statistics 3.26, a leading free and open-source software was used for the development, testing and validation of predictive model. One hundred thirty four cases, approximately 80% of total (5% precision level), were randomly selected using randomization to train, build, score and evaluate predictive models. The remaining 20% of the cases were used once to validate each model.

Results: 167 women were recruited for the analysis. Overall success rate of vaginal misoprostol was 62.3%. Majority of women (76.6%) didn't have significant adverse effects for misoprostol. Out of the twenty clinical and radiological parameters, only the presence of vaginal bleeding weakly associated with the success of medical management. Other factors were not statistically significant enough to develop a predictive model.

Conclusion: Management of early pregnancy losses with misoprostol was relatively safe and successful in majority of patients. However, it was unable to develop a predictive model with selected factors in this study, except presence of per vaginal bleeding prior to treatment yield high info gain.

Key words: early pregnancy failures, misoprostol in miscarriages, predicting efficacy.

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Background

Early pregnancy failure is defined as loss of the pregnancy within first 12 weeks[1]. Abnormal early pregnancy is a situation commonly experienced by pregnant women. Pregnancy loss or miscarriages is an abnormality which is faced by one in four women during her life time[2]. Chromosomal abnormalities are causative in approximately 50% of spontaneous miscarriages[3].

Miscarriages cause significant physical, psychological and social issues to a woman. Women are at increased risk for significant depression and anxiety for up to one year after spontaneous miscarriages[3]. Adverse effects like infections and bleeding may lead to hospital admission and even life threatening outcomes to a pregnant woman.

As early pregnancy losses causing significant impact on women's life during reproductive age, management plays a main role to overcome the physical, mental and social issues related to it. There are three options for management of early pregnancy losses: expectant, medical and surgical management. Each method has its own merits and demerits.

Expectant management is best matched for the women had incomplete miscarriage and who are hemodynamically stable and without any feature suggestive of infection as it can be managed as an out patient[4]. It is the first line recommendation by NICE guidelines if patient is hemodynamically stable as this method is natural and not associated with the side effects related to surgery or medications. But it takes more time to recover and recovery period may interfere with the woman's daily activities[5].

Suction evacuation is the standard management for more than 50 years which is a procedure performed in an operating theater under general anaesthesia. This is the best option for hemodynamically unstable patients. The main advantage of this is rapid recovery. But it is associated with anaesthesia related complications, uterine perforation, cervical injuries, heavy bleeding, localized pelvic infections and needing of repeated surgical evacuation[6].

With the development of drugs in last few years, medical community began to question whether immediate evacuation by surgical intervention is truly necessary for most cases in early pregnancy failure[7-9].

As several pharmacologic agents, capable of inducing abortion, have become available in the last 20 years, medical termination of pregnancy is now well recognized as an effective treatment option. It was thus a logical progression to use these drugs in the management of miscarriage[4].

Several pharmacological agents are being used for the medical management of miscarriages including mifepristone and misoprostol. Misoprostol takes a significant place in medical management of its various characteristic features. Thus this prostaglandin E1 analog (15-deoxy-16-hydroxy-16-methyl PGE1) has generated attention over the past few decades in regimens for early pregnancy failure. However, now this drug is widely used in Obstetrics and Gynaecology for the medical management of miscarriages, cervical ripening before instrumentation, induction of labour, and prevention and treatment of post-partum haemorrhage due to uterine atony[10].

When considering the pharmacological properties of the misoprostol, it is easily absorbed from oral, sublingual, vaginal and rectal routes. It metabolized to form misoprostol acid in the liver. It causes cervical ripening, uterine contraction and gastric acid secretion reduction by acting on prostaglandin receptors. The misoprostol act on gravid, non-gravid and menopaused uterus and not generally used concomitantly with oxytocin because of the possibility of uterine rupture. Its common side effects include nausea, vomiting, diarrhea, cramps and fever[11-13]. The pharmacodynamics and pharmacokinetics properties are varied according to the root of administration.

After gaining the license misoprostol in 2016, is widely used in Sri Lanka for various indications in Obstetrics and Gynaecology according to the circular issued by the Ministry of Health[10].

The drug should be used with caution in patients with asthma, cervicitis, vaginitis, hypertension or hypotension, anemia, jaundice, diabetes, or epilepsy. They should not be used in patients with acute pelvic inflammatory disease, drug hypersensitivity, or an active renal, hepatic, or cardiovascular disorder. Even though it is considered as a safe drug, it can be associated with life threatening side effects with in advent use. Recognized life threatening side effects are uterine rupture and malignant hyperthemia[10].

So the selection of best candidates for the medical management with misoprostol is very important. Other

than above fact, selection of best candidates for the medical management with misoprostol will increase the success rate, reduce the duration of hospital stay, increase the patients acceptability, unnecessary surgical interventions and its related side effects, expenses of health of the country which is very beneficial to low and middle income countries. To achieve the maximum efficacy and safety profile of misoprostol, it is best to develop a predictive model.

Predictive modeling, also called predictive analytics, is a mathematical process using software package that seeks to predict future events or outcomes by analyzing patterns that are likely to forecast future results. Predictive modeling helps to improve patient centered care based on specific predetermined factors and contributes to the creation of the most effective treatment plans tailored for individual patients.

Materials and methods

This single center retrospective study was carried out at Teaching Hospital, Mahamodara, Galle (THMG). The study was designed to develop a predictive model using selected factors to determine the efficacy of vaginal misoprostol in medical management of early pregnancy losses. Ethical approval was obtained from Ethical Review Committee of Faculty of Medicine, University of Ruhuna (reference number 2019/P/023) and administrative clearance was granted by the Director, THMG for the record room assess and use the misoprostol registry.

Women who had an embryonic gestation or embryonic/fetal demise which were diagnosed according to the NICE recommendations were eligible for inclusion. The Diagnosis of miscarriage was ultrasound based and defined according to the guideline published by the NICE (ectopic pregnancy and miscarriage diagnosis and initial management) in 2019[5].

Embryonic miscarriage is diagnosed with two criteria.

1. If the crown-rump length is less than 7.0 mm with a transvaginal ultrasound scan and there is no visible heartbeat, perform a second scan a minimum of 7 days after the first before making a diagnosis.
2. If the crown-rump length is 7.0 mm or more with a transvaginal ultrasound scan and there is no visible heartbeat with a second opinion on the viability of the pregnancy.

Anembbyonic miscarriage is diagnosed with two criteria.

1. If the mean gestational sac diameter is less than 25.0 mm with a transvaginal ultrasound scan and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis.
2. If the mean gestational sac diameter is 25.0 mm or more using a transvaginal ultrasound scan and there is no visible fetal pole with the a second opinion on the viability of the pregnancy.

Endometrial thickness measured using TVS in mid sagittal plane, less than 15 mm was considered as a successful medical management[14].

The study population was the patients with first-trimester pregnancy losses with less than 13 weeks of menstrual gestational age (which correspond up to 90 days) who were medically managed with misoprostol according to the Ministry of Health protocol[10] (1600 micrograms of vaginal misoprostol, in two divided doses, 3 hours apart and reassessed after 24 hours). All consecutive women with first trimester miscarriages managed medically using misoprostol were selected for the study. Cases were identified using misoprostol register, those who were managed during the period of 1st of January 2017 to 30th of September 2019. Women who were managed with misoprostol who did not comply with the existing protocol, uncertain menstrual dates and significant amount of missing data were excluded after recruitment. Sample size was calculated using G*Power Software, Version 3.1.9.4. The input parameters were 8 as the number of predictors, 0.99 as the power ($1 - \beta$ error) and 0.001 as the α error probability. Data were retrieved by a trained Data Collecting Officer (DCO) who was a BSc degree holder with adequate knowledge with BHT entry.

DCO was trained with enhancing her knowledge on management of miscarriage for the proper collection of necessary data. First 10 sets of data were collected under supervision of main researcher and subsequently collected data was observed by the research team on daily basis for the quality assurance. Data collection was done using a pre-tested and validated data retrieval sheet which consisted of three parts. Part A of the data retrieval sheet consisted of baseline and basic demographic data. Part B contained the details of past

obstetrics and gynaecological history and details of the current pregnancy. Part C contained clinical details and radiological findings of the current pregnancy.

Orange Statistics 3.26, leading free and open-source software for predictive modelling, which was commonly used for data visualization, machine learning and data mining and predictive modelling, was used for the development, testing and validation of predictive models[15]. One hundred thirty-four cases, approximately 80% of total, were randomly selected using randomization to train, build, score and evaluate predictive models. The remaining 20% of the cases were used once to validate each model. Success of medical management with misoprostol treatment was used as the target variable for the predictive model development. Twenty features were used as predictors for the development of predictive model. Sampling type for predictive modelling learners was stratified 10-fold Cross validation. Eleven different learners were used and each learner was scored and ranked on five different characteristics. This was done using Orange Data Mining 3.24.

An ROC curve (receiver operating characteristic curve) was a graph showing the performance of a classification model at all classification thresholds. This curve plotted two parameters: True Positive Rate (TPR) and False Positive Rate (FPR). An ROC curve plotted TPR vs. FPR at different classification thresholds. Lowering the classification threshold classified more items as positive, thus increasing both False Positives and True Positives. Each learner was scored using the area under curve (AUC) and classification accuracy (CA) to evaluate the accuracy or the predictive model. The principal component analysis was performed using Orange data mining software.

Results

The recruitment of the study group is outlined in Figure 1. The total number of bed head tickets (BHT) selected for the analysis was 167 out of 208. Basic characteristics of the study sample is depicted in Table 1. The mean age of the participants is 31 years (SD 5.2) with range of 31 to 40 years. The majority (90%) of the subjects were Singhalese. Median parity of participants were 2 with the range of 1 to 6. Representation of primigravida in the study sample was 32.3% (n=54). Vast majority (80%) of women had delivered their babies vaginally.

Clinical and ultrasonic features of the index pregnancy is summarized in Table 2. Average period of gestation was 10 weeks with the range of 4 to 12 weeks. Mean interval between diagnosis of miscarriage and initiation of treatment was 1.19 days with the range of 1 to 4 days. Ultrasonic features of mean gestational sac size and crown rump length were 4.05 and 3.28 in cm respectively.

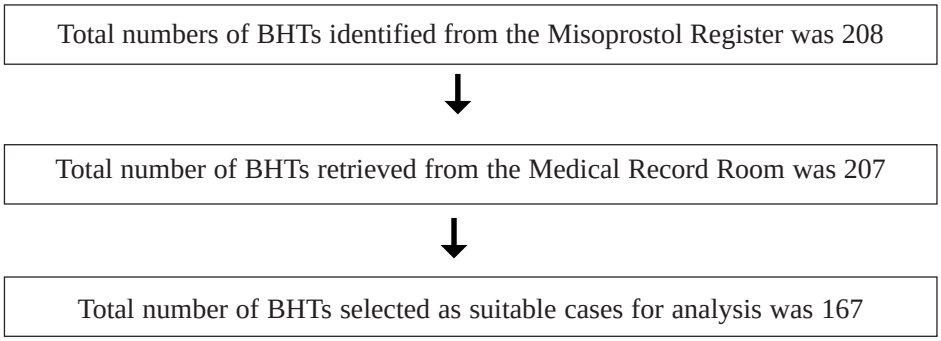

Figure 1. **Recruitment of participants.**

Table 1. Socio-demographic characteristics

Variables	Mean +/- SD	Range	N (%)
Age	31 (5.2)	31 - 40	167 (100)
Ethnicity			
Sinhala	-	-	151 (90.4)
Muslim	-	-	15 (9.0)
Tamil	-	-	1 (0.6)
Obstetric history	Median		
Parity	2	1 - 6	167 (100)
No. of children	2	0 - 4	167 (100)
MOD			
VD			135 (80.9)
CS			32 (19.1)

Table 2. Clinical and ultrasonic features of index pregnancy

Variables	Mean (+/-SD)	Range	Missing
Period of gestation (weeks)	10 (+/- 1.6)	4-12	0
Gestational sac size (cm)	4.05 (+/-1.41)	1.2-7.0	0
Crown rump length (cm)	3.28 (+/-1.7)	0.4-6.7	0
Interval between diagnosis and initiation of management (days)	1.19 (+/-0.5)	1-4	1

Clinical and ultrasonographic success of medical management of miscarriages were reported in 103 women out of 167. Therefore overall success rate was 66.3%.

Overall side effects rate of pervaginal misoprostol for the management of miscarriage was approximately 16% (Table 3). Most commonly occurring unwanted effects were nausea/vomiting and fever with the approximately in one out of 10 women affected. There were no major side effects reported during study period such as malignant hyperthermia and uterine rupture.

Table 3. Side effect profile

Side Effect	%	n
Fever	8.4	14
Nausea /Vomiting	9.0	15
Abdominal cramps	1.2	2
Overall side effects	16.8	28

Table 4. Predictive modelling scores

Feature	Info. gain	Gain ratio	Gini
Age	0.014	0.007	0.009
POG	0.012	0.006	0.008
CRL	0.010	0.005	0.006
Blood group	0.038	0.020	nan
Interval (diagnosis to treatment)	0.0152	0.021	0.010
Presence of bleeding (PV)	0.042	0.064	0.028

Principle component analysis was carried out using selected clinical and ultrosonographic variables. Out of the features studied, Table 4 listed the features that mattered most for the outcome even though they didn't have predictive significance and statistical significance for the outcome. Above predictors cannot be used to develop a predictive model with statistically significant accuracy level. However, presence of pervaginal bleeding at the time of treatment had higher info, gain (0.042) out of other features.

Discussion

Our initial experience in Sri Lanka, the success rate of the misoprostol in the management of miscarriage has improved from 54%[16] to 62% in the current study in the same setting. There is wide variation of the success rate reported elsewhere in the world from 54% to 84%[16-17]. This may be due to different factors in other facilities such as different dosage protocols, usage of mifepristone before the misoprostol, ethnic variations, time given for the action of drugs and duration of the gestation at the initiation of medical management etc. Further more, current study showed that suboptimal success rate in local setting when comparison of other regions. It is high time to conduct more research to find out possible factors to improve success rate of misoprostol in the country.

Current study found 8% of side effects rate among the participants. However, more serious forms of unwanted effects such as malignant hyperthermia and uterine rupture or bleeding necessitating blood transfusion were not reported. Adherence to the guidelines issued by the Ministry of Health could have led to minimal side effects noted in Sri Lankan setting. As the first time in Sri Lanka, we tried to develop a predictive model for most common indication for the use of misoprostol in gynaecological practice. Unfortunately, the study could not predict with significant accuracy any of the features used in this study as the highest predictive value. But there were seven variables out of twenty which had some significant predicting value even though not statistically significant enough to use for a development of predictive model.

ELkholi and Hefeda worked on identifying the potential predictors of the successful medical management of first trimester miscarriage[18] in a prospective observational study and found that active vaginal bleeding and/or localized abdominal colic in the 24 hours preceding misoprostol administration, as potential predictors of the success of medical management with misoprostol. But according to the Aubert Agostini and his co-workers[19], parity was the only predictor for the successful medical management. Melissa Lavecchia[20] carried out two retrospective observational studies which found that increased gestational age is associated with failed medical management.

But these studies failed to find such clinically and statistically significant predictor. This may be due to heterogenisity of those studies with the sample size, protocol of misoprostol, ethnicity difference, time given for the action of the drug and study methodology.

There were few studies which were designed to find predictors with different biochemical and molecular markers. Sahar M et al carried out a study regarding endometrial thickness and serum beta hCG as predictors of the effectiveness of oral misoprostol in

early pregnancy failure, had shown association between high hCG values and failed medical management[21]. Involvement of other pregnancy related hormonal assays (ex- serum progesterone) and other serum markers (ex- pregnancy associated plasma protein-A, soluble FMS like tyrosine kinase) may have given a better predictive value if we studied with an adequate sample, as previously carried out studies gave favourable results[21]. Even though if we had found a predictive significance with such markers, the ultimate use in clinical practice was doubtful as these hormonal assays and serum marker assays were expensive.

References

1. Royal College of Obstetricians and Gynaecologists. The management of early pregnancy loss. Green-top Guideline No. 25. London (UK): RCOG; 2006. https://www.rcog.org.uk › guidelines › gtg25. Retrieved on 22.03.2021
2. Warburton D, Fraser FC. Spontaneous abortion risks in man: data from reproductive histories collected in a medical genetics unit. Am J Hum Genet. 1964; 16(1): 1-25.
3. Graiebel CP, Halvorsen J, Golemon TB, Day AA. Management of spontaneous abortion: American Family Physician, 2005; 72(7): 1243-50.
4. Edmonds DK. Dewhurst's Textbook of Obstetrics and Gynaecology. 2007; 7: 94-9.
5. Ectopic pregnancy and miscarriage, NICE guideline No. 126: 2019 https://www.nice.org.uk › guidance, retrieved on 22.03.2021
6. Royal College of Obstetricians and Gynaecologists. Consent advice No 10. June 2010. London (UK): RCOG; 2010. https://stratog.rcog.org.uk › files › CA10-15072010 Retrieved on 22.03.2021
7. Macrow P, Elistein M. Managing miscarriage medically. BMJ. doi:10.1136/bmj.306.Index_1993_Jun.3
8. Ballagh SA, Harris HA, Demasio K. Is curettage needed for uncomplicated incomplete spontaneous abortion? Am J Obstet Gynecol. 1998; 179(7298): 1279-82.
9. Jurkovic D, Ross JA, Nicolaides KH. Expectant management of missed miscarriage. Br J Obstet Gynaecol. 1998; 105(6): 670-1.
10. Sri Lanka College of Obstetricians and Gynaecologists. Position Statement : 11th July 2014 available at http://www.slcog.lk/img/docs/SLCOG%20-%20Misoprostol%20Position-%2011.07.2014-1%20-%20changed%20(1).pdf and https://www.msd.gov.lk/circulars/circulars/P49662015.pdf
11. Bennett PN, Brown MJ. Clinical Pharmacology 2003; 629-30.
12. Craig CR, Stizel RE. Modern pharmacology with clinical applications,1997: 716-21.
13. Tang O S, Gemzell-Danielsson K, Ho P C (2007). Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. International Journal of Gynecology and Obstetrics 2007: 99 Suppl 2, 160-7.
14. Nielsen S, Hahlin M, Oden A. Using a logistic model to identify women with first trimester spontaneous abortion suitable for expectant management. Br J Obstet Gynaecol 1996; 103(12): 1230-5.
15. Demsar J et al (2013) Orange: Data Mining Toolbox in Python. Journal of Machine Learning Research 2013; 14(Aug): 2349-53.
16. Liyanage PLGC, Dassanayaka DLW, Ponnamperuma T. Effectiveness of Misoprostol in the management of miscarriages in patients admitted to Teaching Hospital Mahamodara. Sri Lanka Journal of Obstetrics and Gynaecology. Abstract book, 40th Annual Academic Sessions of SLCOG, 2018; 79-80.
17. Zhang J. A Comparison of Medical Management with Misoprostol and Surgical Management for Early Pregnancy Failure. The New England Journal of Medicine 2005; 353(8): 761-9.
18. ELkholi DGE, Hefeda MM. Potential predictors for successful misoprostol treatment for early pregnancy failure: Clinical and color Doppler imaging study; Middle East Fertility Society Journal 2015; 20(4): 144-53.
19. Agostini A, Ronda I, Capelle M, Romain F, Bretelle F, Blanc B. Influence of clinical and ultrasound factors on the efficacy of misoprostol in first trimester pregnancy failure. Fertility and sterility; 2005; 84(4); 1030-32.
20. Lavecchia M. Predictors of failed medical management in women with early pregnancy loss; Department of Medicine, Division of Experimental Medicine, McGill University Montreal, Quebec, Canada, 2015. https://escholarship.mcgill.ca › concern › theses retrieved on 22.03.2021
21. Robledo C, Zhang J, Troendle J, Barnhart K, Cerinin MD, Westhoff C, Huang X, Fredrick M. Clinical indicators for success of Misoprostol treatment after early pregnancy failure. International Journal of Gynaecology and Obstetrics 2007; 99(1): 46-51.