
Correlation between various epidemiological, biochemical and biophysical factors and successful induction of abortion by Misoprostol among women with first trimester missed abortion

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Study design; prospective

Method: A total of 33 patients with first trimester missed abortion were enrolled in this study. Their age, body mass index, serum fibrinogen, platelets count and cervical lengths were taken. All the patients were given Misoprostol vaginally 800 microgram daily for 5 days. Dilatation and curettage was done if induction fails after 5 days.

Results: there was significant association between response to Misoprostol and age, body mass index, baseline platelet count as well as parity. Odd ratio was 0.53, 0.44, 1.03 and 10, respectively. No significant association was found with maternal hemoglobin level.

Conclusion: use of calculated cut off values may help to predict women who will respond to Misoprostol for those with first trimester missed abortion.

Keywords:

Introduction

The introduction of Mifepristone into clinical practice by the French scientist for medical induction of abortion in 1993 was considered as a revolutionary turn point in the gynecological practice^[1].

However mifepristone which work as progesterone antagonist was not proved to be effective in missed abortion^[2]. This poor response is mediated by low levels of serum estrogen which is present in missed abortion, an important prerequisite to the action of mifepristone^[3].

Few years later with the start of the new millennium prostaglandins analogues E1 or Misoprostol was introduced as medical inducer of abortion^[4]. Unlike Mifepristone, prostaglandins works on the uterine muscle irrespective of the estrogen levels in the blood^[1,2].

However, unlike the dramatic response of estrogen primed uterus to the administration of Mifepristone, Misoprostol has a higher failure rate than Mifepristone for induction of abortion, and not uncommonly women require surgical evacuation of dead fetus in the form of dilatation and curettage^[5].

The aim of this study is to correlation success of abortion induction by Misoprostol with cervical length, baseline serum levels of human chorionic gonadotropin, platelets count, fibrinogen levels, coagulation profile and epidemiological factors, among women with missed abortion.

1-The study was conducted In Al-Yermouk Teaching Hospital between November 2008 and December 2009. During this period a total of 67 patient with missed abortion were attended our outpatient clinic. Unfortunately lot of the patient could not have access to the vaginal ultrasound scan or the hormonal changes, which were prerequisite to enter our analysis. As much as 33

patients who met the criteria were collected and enrolled into this study. For all the women taken into this study, their verbal consent was taken.

2-Patient selection was based on taking them all from the outpatient clinic in AL-Yermouk teaching hospital. All patients who were enrolled were in the first trimester bellow 12 weeks gestation, as to grade failure in the form of need for surgical evacuation later by surgical curettage. For all the patients double ultrasound scan was taken, sometimes 1 week apart to confirm fetal death. The basic outpatient data that were taken included age, parity and body mass index. Hemoglobin level, serum fibrinogen, platelets count as well as coagulation screen for prothrombin and partial thromboplastin time was taken also. All patients enrolled in the study were also sent for cervical length by vaginal ultrasound in centimeters, and all done by the same ultrasonographer. Hormonal assessment for baseline human chorionic gonadotropin or hCG was assessed also by our hospital lab facility. After completing the investigations and after admission to the hospital they were scheduled to receive 200 microgram Misoprostol tablet, every 6 hours in the posterior fornix, which was supervised by a registrar doctor. Should abortion occur, the case is further managed by the resident doctor in call? Failure to achieve induction was defined as failure to abort after 5 days course. And for those patients failed to abort, they were scheduled to have dilation and curettage at day 6 after admission. A pint of cross matched blood was prepared for all the patients and given if necessary. At the end of the study a total 20 patients were collected for the responder group (N=20) who had complete abortion, versus 13 patients who needed surgical evacuation (N=13). All patients in either group were put on prophylactic antibiotic after abortion irrespective of the mode, to prevent pelvic infection.

3-Statistical analysis was conducted to the variable mentioned above. Continuous data were expressed as mean and standard deviation while categorical data as number and percent. To calculate the adjusted odd ratios for the different variables among responders, a logistic regression module was constructed with calculation of the 95 confidence intervals. For those variables found to be significant, the cut off values were calculated by constructing Receiver Operator Characteristic curve or ROC analysis. P values less than 0.05 were considered as significant

Results:

In table number 1 the overall epidemiological, biochemical, hematological and hormonal characteristics are presented and compared among the responder versus failed groups. Women that achieved successful abortion were significantly younger than non responder; 25.25 versus 28.15 years. Odd ratio is 0.53 with P value less than 0.0001. Body mass index which is a reflection of obesity and fat deposition was significantly lower among responder group; 25.75 versus 28.76, with odd ratio equal to 0.44. It is interesting that neither hemoglobin levels nor prothrombin and partial thromboplastin time were found to be significant

among the two groups. However serum fibrinogen and platelets count were significantly different among the two groups. Odd ratio for the fibrinogen serum level was 1.04 with P value equal 0.01. While odd ratio for platelets count at admission was 1.035 with p value equal 0.005. The baseline serum hCG was different statistically among women who responded to misoprostol than non responder group with odd ratio equal to 1.11 and p value 0.003. The baseline cervical length as assessed by vaginal ultrasound scan was significantly shorter for the responder group with odd ratio equal to 0.26 with p value equal to 0.01. Finally women who responded to misoprostol have higher incidence of parity than non responder despite they were younger in age. The odd ratio was 10 with p value equal 0.005. None of patients in this study who responded to Misoprostol required surgical evacuation or blood transfusion.

In order to clarify the exact cut off value for the significant parameters found in table number 1, ROC curve analysis was done to predict the various cut off values for them. In table number 2 the various cut off values with their sensitivities and specificities are given.

Table number 1 which shows the epidemiological characteristics for both study groups

characteristics	Responder (N=20)	Non Responder (N= 13)	Odd Ratio	95 % Confidence interval	P Value
Age (Years)	25.2500+2.0487	28.1541 +4.0731	0.5346	0.3450 to 0.8284	P < 0.0001
BMI	25.7500+1.6504	28.7692+2.2043	0.4421	0.2601 to 0.7512	0.002547
Hemoglobin level	10.9500+0.6048	10.6923+0.6304	2.0632	0.6108 to 6.9691	0.2435
Serum platelets/cubic mm	312.7000+74.2167	199.9231+40.4958	1.0356	1.0104 to 1.0615	0.005396
PT (seconds)*	13.0500+0.9445	13.0769+0.8623	0.9662	0.4390 to 2.1268	0.9320
PTT (seconds)*	36.6500+1.5652	36.6923+1.6525	0.9826	0.6263 to 1.5414	0.9390
Cervical length (millimeters)	23.5000+1.7014	28.4615+1.1983	0.2637	0.0933 to 0.7454	0.01193
Serum HCG [(IU)* 1000]	61.4500+6.3202	37.6154+7.8160	1.1109	1.0361 to 1.1912	0.003101
Serum Fibrinogen (mg/dl)	346.5000+32.0518	206.5385+42.1300	1.0441	1.0092 to 1.0802	0.01293
Parous women (N %)	15 (75 %)	3 (23.07 %)	10.0000	1.9401 to 51.5442	P = 0.0059
Nulli Parous Women	5 (25 %)	10 (76.93 %)	0.1000	0.019 to 0.515	P= 0.0059

* PT; Prothrombin Time, PTT; Partial Thromboplastin Time

Table number 2 which shows the various cut off values for the significant parameters in this study

factor	Cut off value	Sensitivity	95% CI	Specificity	95% CI
Age (years)	<=28 *	90.00	68.3 - 98.5	84.62	54.5 - 97.6
Body mass Index	<=27 *	85.00	62.1 - 96.6	92.31	63.9 - 98.7
Serum platelets/cubic mm	>210 *	95.00	75.1 - 99.2	76.92	46.2 - 94.7
Cervical length (millimeters)	<=29 *	95.00	75.1 - 99.2	76.92	46.2 - 94.7
Serum HCG [(IU)* 1000]	>50 *	65.00	40.8 - 84.5	100.00	75.1 - 100.0
Serum Fibrinogen (mg/dl)	>199 *	100.00	83.0 - 100.0	76.92	46.2 - 94.7

Summarize to say from table number 2 that the women who are likely to achieve successful

termination of missed abortion by misoprostol should have one or more of the followings; age less

than or equal 28 years, BMI less than or equal 27, serum platelet count more than 210 per cubic milliliter, cervical length equal or less than 29 millimeter, baseline hCG more than 50,000 IU/ ml and finally serum fibrinogen more than 199 mg/ dl. In addition parous women are more likely to have successful induction of abortion than nulliparous women. The highest sensitivity was for serum fibrinogen 100 %, while the lowest was for serum hCG 65%.

Discussion:

It does without saying that achieving medical abortion represents a giant leap in the history of gynecological practice. Dilatation and curettage which is one of the oldest procedures and one of the most frequently practiced operations is still risky in a small subset of patients. Possible complications include hemorrhage, pelvic inflammatory disease and perforation of the uterus.

The rate of uterine perforation in dilatation and curettage is highest among women with missed abortion Cameron et al ^[6]. However as mentioned in the introduction of this paper, neither mifepristone nor Misoprostol work as perfect abortifacient among women with missed abortion as in inducing abortion for alive fetus, El-Rafaey *et al*, Peyron et al ^[2,3]. Low levels of estrogen associated with missed abortion reduce the uterine sensitivity to both oxytocin receptors as well as to prostaglandin receptor through direct effect on their chemical configuration, Creinin *et al* ^[7].

This hypothesis may explain some of the results which have been obtained in this study.

According to our data in the results, women who have responded to Misoprostol have higher serum fibrinogen and platelets count, which in turn they depend indirectly on the estrogen levels circulating in the blood. Once missed abortion occurs, the placenta die also and the fraction of circulating estrogen contributed by the placenta is removed. In addition, release of tissue thromboplastin occurs continuously from the dead placenta leading ultimately to depletion of the clotting factors, fibrinogen and platelets levels.

Ironically the coagulation screen for prothrombin time as well as for partial thromboplastin time was found to be no significant in both groups in our study, which suggest that they didn't pass to the frank state disseminated intravascular coagulation associated with fetal demise. It has been found in this study that women with missed abortion had significantly shorter cervix than non responders. Despite that this finding is also reached by other researchers like Hausknecht et al ^[8], it really difficult to be interpreted clinically. It is quit unclear whether this short cervix is associated with sub clinical uterine contractions prior to admission for expelling the dead fetus, or present de novo. Creinin et al ^[9] has suggested in his

study that women with short cervix de novo may have better response to induction of abortion by misoprostol. Body mass index which represent the fatty mass was found in this study to be associated significantly to induction of abortion. Lean women responded better to Misoprostol than over weight and obese women. Despite that fatty tissue is well known to be metabolically active; unfortunately we couldn't find a genuine article from the different sources in the web which link between BMI and better response to Misoprostol. However it is well known that women with obesity are more liable to become over due and post term in normal pregnancy, Koopersmith et al ^[10]. Yet, it is unlikely that normal labor physiology can be directly extrapolated to first trimester abortion. In the same context age factor which has been found to be associated in significant manner with better response to Misoprostol may be ruled by factors other than pregnancy itself. This factor is consistent with results obtained by Bugalho et al ^[11]. In his study both age factor in the form of younger women as well as women with high parity responded better to first trimester abortion induced by Misoprostol.

Finally the significant association of better response of pregnant women with high baseline hCG levels to Misoprostol may explained by direct relation to the period of fetal death.

The longer fetal death period, the less estrogen and hCG levels in the blood, which means that the uterus become less sensitive to the effect of oxytocic drugs.

Conclusion:

In our small study we have found that age, baseline hCG levels, serum fibrinogen and platelets count as well as age and body mass index can be a reliable predictor to uterine response for vaginally administered Misoprostol among women with missed abortion. However further trials are needed to confirm the results so far obtained in our study.

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