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Original Article

Effect of vaginal pH on the efficacy of vaginal misoprostol for induction of mid trimester abortion

Obstetrics and Gynecology

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ABSTRACT

Background: Missed abortion occurs when the deceased result of conception remains in the uterus beyond 20 weeks of gestation. Misoprostol, a prostaglandin analogue, is often employed for medical purposes.

Objective: The aim of this study is to investigate whether change in the acidity of the vagina affects the pharmacokinetics of the misoprostol and, therefore, its efficacy for mid-trimester abortion induction

Methodology: The study is a prospective study conducted on a cohort of 81 pregnant women (gestational age 14-26 weeks and failed abortion) at the obstetric department of Al-Zahra university hospitals in the interval from August2021 till February 2022 they were followed up for 24 hours.

Results: Induction abortion intervals were substantially longer in group with pH ≥ (5) than in group with pH < (5) (22.33± 2.29 hrs. vs. 11.80± 1.63 hrs. p<0.001). Group pH ≥ (5) showed an increased prevalence of fever and intense abdominal pain compared to group < (5) (p<0.001 & 0.007 respectively).

Conclusion: Misoprostol used vaginally for inducing of mid-trimester abortion is more effective when vaginal acidity is increased as it was more effective in group pH < (5).

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Keywords: Acetic acid, misoprostol, second trimestric pregnancy termination, vaginal pH.

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INTRODUCTION

Missed abortion occurs when the deceased result of pregnancy remains in the uterus beyond 20 weeks of pregnancy [1]. One in every five births ends in abortion [2]. Abortion may result in both medical and psychological suffering, such as heavy hemorrhage and infections, as well as anxiety, despair, and post-traumatic stress disorders [3].

Fetal death occurring between 13 and 26 weeks is defined as early second trimester loss. It accounts for about 2-3%of pregnancies. However, it holds a higher level of complication when compared to 1st trimesteric loss, which usually accounts for 20% of pregnancies [4] Embryonic or fetal death, cervix closure and no or only little vaginal hemorrhage are all signs of missed abortion in the second trimester. A non-viable embryo or fetus may be seen on ultrasound [5].

Misoprostol, a prostaglandin analogue, is often used to produce myometrial contractions and help in the evacuation of gestation tissue in the medical treatment of miscarriage [6]. However, misoprostol is not always successful, and 15–40% of women need a further misoprostol dosage, lengthening the treatment period [2]. Misoprostol pills are thought to liquefy better in acidic media due to their anti-progestin action. Some studies advocate moistening misoprostol with acetic acid and placing it in the vaginal canal. In this respect, different results have been published, with some studies indicating no substantial changes [7]. The aim of this study is to explore how vaginal pH influenced the effectiveness of misoprostol for the induction of mid-trimester abortion.

PATIENT AND METHODS

A Prospective randomized controlled trial was conducted on 81 pregnant women (with gestational age 14-26 weeks and failed abortion as a reason for mid-trimester abortion initiation) they were followed up for 24 hours. The study was carried out at the Obstetrics and Gynecology department, Al-Zahraa University Hospital, and Kafr El

Zayat General Hospital between August2021 and February 2022.

Inclusion criteria: (i) Singleton gestation at 14–26 weeks of pregnancy (based on last menstrual cycle or prior ultrasounds), gestational age computed from the first day of the last menstrual cycle or recorded 1st trimester ultrasound and prenatal care. (ii)apparently normal, closed cervix with no engorgement on physical exam, (iii) no uterine activity, and (iv) no disseminated intravascular coagulopathy (DIC) as illustrated by regular partial thromboplastin time (PTT) and serum fibrinogen ratios.

Exclusion criteria: The existence of bloody discharge, vaginal hemorrhage, ruptured membranes, or suspicion of septic abortion, extreme polyhydramnios or an underlying clinical disorder, such as high blood pressure or diabetes mellitus, the existence of cervical cerclage or previous cervical trauma (cauterization, lacerations, or cerclage, earlier failed attempt to terminate the existing gestation, contraindication to clinical abortion, such as placenta previa or a recognized damaged uterus owing to past uterine perforation or surgery, such as a cesarean delivery or myomectomy, contraindications to take prostaglandin equivalents as history of asthma and coagulopathy or women on anticoagulants.

Ethical consideration: The study procedure was approved by the Ethics and Research Committee of Al Azhar University, Faculty of Medicine for Girls. Before being included in the research, the study's objective and value as well as the procedures that were started were described to all participants in a written informed consent form.
All participants were subjected to a detailed history taking such as; personal history as age, residency, level of education, and working status, menstrual history, obstetric history as gravidity and parity, etc, also, medical, surgical, or obstetric difficulties in initial or late gestation, as well as family history were taken.

General physical examination: Vital signs especially blood pressure and BMI.

Obstetric examination: Abdominal examination: to estimate the fundal level, vaginal examination to ensure that the cervix is closed without vaginal bleeding.

2D trans-abdominal ultrasound was done to confirm the presence of missed abortion, and to ensure the gestational age as well as to exclude cases with any of the exclusion criteria. Laboratory investigations: (full blood test, renal and hepatic functions) were performed on a regular basis, coagulation profile, blood type and antibody status were checked and Rh immune globulin given if indicated. Measurement of vaginal pH: it was determined using a dipstick test on admission, and two groups were generated: Group (A): Pregnant women with vaginal pH < 5 (n = 41) and Group (B): pregnant women with vag. pH ≥5 (n =40). All women were given 200 mg of intra vaginal misoprostol tablets every 4 hours for a total of 5 doses in 24 hours. If the patient did not have enough contractility, the same schedule was reapplied for the next 24 hours, and if no reaction was obtained, the treatment was termed a failure.

Follow up: All patients were clinically observed for 24 hours, with vital signs, time of commencement of discomfort, vaginal bleeding, and time of ejection of fetus product, and for the misoprostol side effects as nausea, vomiting, diarrhea, fever, and chills. Narcotic analgesics such as Nalbuphine hydrochloride (Nalufin; 20 mg/ ampoule) was given by intramuscular injection for marked pain. Vaginal ultrasound was done to confirm complete abortion. Dilatation and curettage was done for cases having incomplete abortion.

Measured Outcomes: The most important outcome indicators were: Inducement -to-abortion interval (described as the period between the administration of misoprostol and the ejection of the products of conception) and complete abortion (described as ejection of the product of conception between 12- 24 hours). Secondary outcome measures: The need for curettage, the need for and the dose for analgesia. Nausea, vomiting, diarrhea, and fever (described as a single temperature measurement over 37.3°C) are all negative impacts of misoprostol.

Statistical analysis
Sample size: Epi Info STATCALC was used to calculate the sample size by considering the following assumptions. Study design is a prospective randomized controlled trial, 95% confidence level, the correlation between vaginal acidity and high effect of misoprostol for induction of abortion is 70 with a margin of error 5% and power 80% taking in consideration the dropout due to complicated abortion which requires ICU admission. So, in the present study, we recruited 81 women in total. All statistical tests done by SPSS version 20, quantitative variables tested for normality by Kolmogrov-Smirnov test. An independent t test was employed for comparing of the binary groups with normally distributed data, and a Mann-Whitney test was utilized for comparing of groups with none normally distributed data, these quantitative data were presented as (mean, ± standard deviation, range and median). When comparing qualitative data, the Chi-square test was performed. A Spearman's correlation test was also done. P value < 0.05 was used to determine statistical significance.

RESULTS

In the present study, no significant differences were observed between the 2 groups regarding age, BMI, gestational age, number of pregnancies and interval from last pregnancy. There was statistical significance

between the 2 groups regarding number of deliveries (p 0.023) (table 1). All abortion process characteristics were significantly higher in group (B) compared with group A regarding the need for analgesia, induction abortion interval, total misoprostol does number and amount of pethidine used ($p < 0.05$) (table 2). Regarding complications of the abortion process, there was no significant difference between the 2 groups regarding vomiting and diarrhea. Group B showed a higher significant incidence of fever and marked abdominal pain compared to group A (table 3). There was significant positive correlation between inducement-abortion interval with number of deliveries ($r = 0.609$, $p < 0.05$) and pregnancies ($r = 0.617$, $p < 0.05$). Also, induction-abortion interval showed significant positive correlation with the amount of pethidine used ($r = 0.918$, $p < 0.05$) and total number of misoprostol used ($r = 0.943$, $p < 0.05$). (table 4 and figure 1, 2).

Table (1): Demographic and clinical characteristics of the studied groups

Variables	Group A (pH<5) (n = 41) Mean± SD	Group B (pH≥5) (n = 40) Mean± SD	Stat. test	P-value
Age (years)	26.20± 3.38	25.65± 3.48	t= 0.721	0.473
BMI (Kg/m2)	29.52± 1.66	30.19± 2.12	t=1.58	0.119
Gestational Age (weeks)	19.98± 2.34	20.43± 1.97	t=0.9352	0.353
Number of pregnancies	2.22± 0.88	2.70± 1.34	t= 1.9101	0.06
Number of deliveries	1.34± 0.73	1.87± 1.26	t= 2.3234	0.023*
Interval from last pregnancy (m)	28.24± 7.99	27.23± 8.88	t=0.538	0.592

SD= standard deviation, t: t=Student t test, BMI: Body mass index, m: month, *: Significant P value (≤0.05)

Table (2): Comparison between the studied groups according to abortion process characteristics

Abortion process characteristics	Group A (pH<5) (n = 41) Mean± SD	Group B (pH≥5) (n = 40) Mean± SD	Stat. test	p-value
Need for analgesia (no., %) - Negative - Positive	 15 (36.6%) 26 (63.4%)	 1 (2.5%) 39 (97.5%)	X^2= 14.84	<0.05*
Induction abortion interval (hrs.) [Media (IQR)]	12.0 (10.7-12.9)	22.5 (20.78-23.88)	$Z_{MWU=}$ 7.77	<0.05*
Total misoprostol Doses number [Media (IQR)]	2.0 (1.47-2.05)	4.0 (3.84-4.52)	$Z_{MWU=}$ 8.19	<0.05*
Amount of pethidine used(mg) [Media (IQR)]	91.0 (78.9-97.4)	126.0 (117.3-142.29)	$Z_{MWU=}$ 9.63	<0.05*

IQR: inter quartile range, ZMWU: Mann-Whitney test, X^2: Chi-square test, *: Significant P value (≤0.05)

Table (3): Comparison between the studied groups regarding complications of the abortion process

Complications	Group A (pH<5) (n = 41) no. (%)	Group B (pH≥5) (n = 40) no. (%)	Stat. test	p-value
Vomiting - Negative - Positive	 270(65.9) 14 (34.1)	 30 (75.0) 10 (25.0)	X^2= 0.812	0.367
Diarrhea - Negative - Positive	 38 (92.7) 3 (7.3)	 38 (95.0) 2 (5.0)	X^2=0.188	0.665
Fever - Negative - Positive	 31 (75.6) 10 (24.4)	 14 (35.0) 26 (65.0)	X^2=13.52	<0.05*
Marked abdominal pain - Negative - Positive	 34 (82.9) 7 (17.1)	 22 (55.0) 18 (45.0)	X^2=7.40	<0.05*

*: Significant P value (≤0.05)

Table (4): Correlation between induction abortion interval and different parameter

Variables	Induction abortion interval	
	r	p- value
Age	-0.087	0.439
GA (W)	0.094	0.404
BMI	0.098	0.383
Number of pregnancies	0.617	0.001*
Number of deliveries	0.609	0.001*
Interval from last pregnancy (m)	-0.119	0.291
Total number of Doses	0.943	0.001*
Amount of pethidine used (mg)	0.918	0.001*

BMI: Body mass index, GA: Gestational age, *: Significant P value (≤0.05)

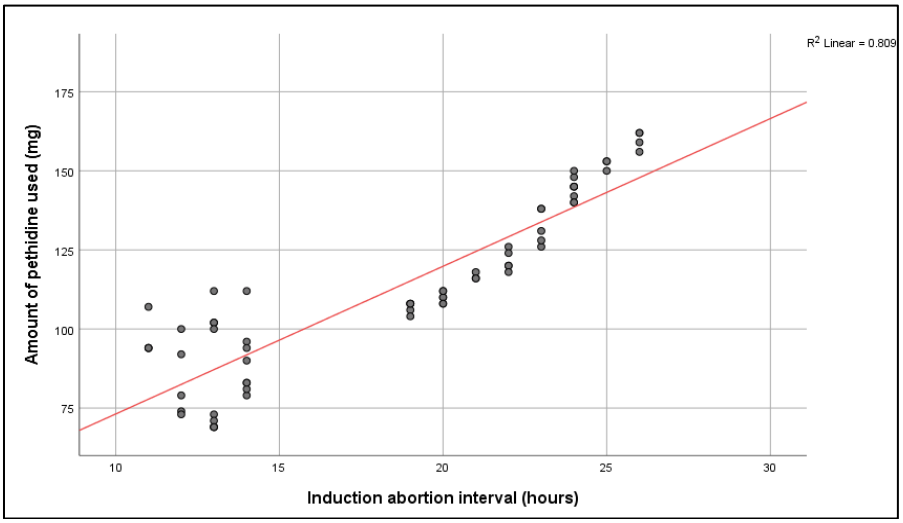

Figure (1): Scatter plot showing positive correlation between induction- abortion interval and the amount of pethidine used

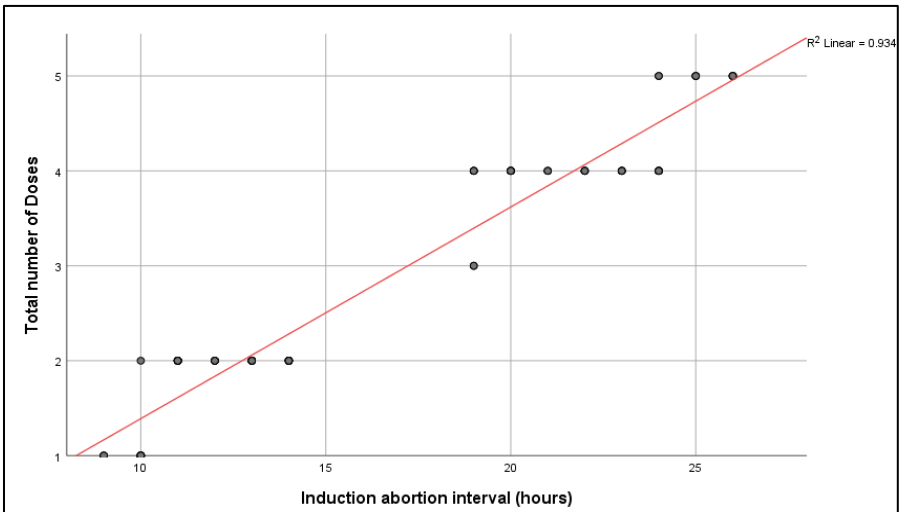

Figure (2): Scatter plot showing positive correlation between induction- abortion interval and total number of misoprostol used

DISCUSSION

Numerous procedures have been offered in this respect, and there is a global trend toward non-surgical approaches rather than surgery for ending gestation in the second trimester [8]. When compared to surgery, medical abortion reduces adverse reactions such as hemorrhage and infections, as well as patient worry [9].

The current research was conducted to test how vaginal pH affected the efficiency of misoprostol in inducing midtrimester abortion. A total of 81 pregnant females were enrolled in the study, all of them were identified with a missed mid-trimester abortion. They were divided into Group (A): Pregnant women with vag. pH < 5 (n = 41) and Group (B): pregnant women with vaginal pH ≥5 (n =40).

The present study found no significant differences between the 2 groups in demographic or clinical data except for number of deliveries.

The current study revealed that misoprostol was more effective in women with a lower vaginal pH (<5) than those with a greater vaginal pH as evidenced by a shorter induction-abortion time and a higher abortion rate within 24 hours. The induction-abortion interval was significantly lower in group A (median of 12 hours) compared to group B (median of 22.5 hours). Also, a reduced incidence of fever or severe abdominal pain and consequently a reduced analgesic dose were significantly lower in group A than group B. In terms of the incidence rate of vomiting and diarrhea, there were non-significant differences between the two groups. Vomiting and diarrhea (34.1% & 7.3% respectively) were higher in patients of group (A) versus (25.0% & 5.0% respectively) in group (B). The effectiveness of misoprostol given intravaginally for cervical ripening and labor initiation has previously been studied in connection to vaginal pH. Furthermore, low vaginal pH was associated with a reduced total dose and number of misoprostol dosages. A significant lower total number of doses were observed in group A (median of 2 doses) compared to group B (median of 4 doses) with a p-Value of 0.001.Hydrating of the misoprostol tablets with acetic acid 5% in our research increased the rate of success abortion. The results of the present study detected significant positive correlation between induction abortion interval and number of deliveries, pregnancies, the amount of pethidine used and total number of misoprostol used. These findings were in line with Maboud et al. [10], their research was done on 110 women with a gestation of 14-26 weeks who were eligible for inducing abortion.

The patients were divided into two groups: A (pH <5) and B (pH≥ 5) and they were given 200 micrograms of vaginal misoprostol hydrated with acetic acid every four hours in each. The findings demonstrated a relationship among vaginal pH and the time it takes to administer misoprostol for abortion, which was substantially shorter in group A than in group B. Furthermore, in group A, the rate of complete abortion was 100%, whereas in group B, it was 63.8%. Also, Behrooz et al. [11] in their research compared 100 women with a failed abortion as a sign of abortion inducement with 100 women with a gestation of 14-26 weeks. The vaginal pH was determined on admission, and the patients were divided into two groups: (A) those with a pH < 5 (n= 66), and (B) those with a pH ≥ 5 (n= 34). Intravaginal misoprostol pills were given to all of the women, hydrated with 3 ml of 3% acetic acid. A total of 5 dosages of 200 g were given every 4 hours for a total of 5 doses in 24 hours. The study found a positive relationship between the pH of the vagina and the time of induction abortion. In addition they stated that use of misoprostol in women with pH <5 has accompanied with the shortest and the most disposal rates compared with women with amount of pH≥ 5 (P< 0.001). On the contrary, Najafian et al. [12] compared the effectiveness of 800µg vaginal misoprostol after soaking alkaline pH vagina with three pieces of cotton soaked in 3ml of 3% acetic acid to 800µg vaginal misoprostol alone for legal pregnancy termination before 12 weeks' gestation in 100 instances. The overall abortion rate was 14%, which was the same in both groups. The average duration between induction and abortion was 19±14 hours. In this study they used multiple vaginal misoprostol doses with dosing interval 12 hours for 48 hours. The mean dose of the used misoprostol was 1640±738.4µg. Despite this higher dose, yet the complete abortion rate (14%) was less than our reported result. This difference may be due to they did not soak misoprostol tablets as what happened in our study; instead, they changed the pH of vagina. Similarly, other researchers who administered misoprostol 50 mg/4 h for a maximum of three doses in 103 women until either spontaneous ruptured of the membranes or active labor happened found that all women with a vaginal pH < 5 entered the active phase of labor compared to 87 % in patients with a vaginal pH ≥ 5, also, 59.6% and 23.3 % of women with a vaginal pH of 5 delivered within 12 hours, respectively [13].

Another two investigations, however, indicated that the drug's effectiveness was unrelated to the existence of a vaginal pH of less than 5 [14].

Despite the fact that another recent research revealed no relation between weeks of gestation and the induction-to-abortion delay, Nulliparous women were more likely to fail to abortion with vaginal misoprostol, especially those with progressed pregnancy [15] . Surprisingly, only in multiparous women did we found a substantial positive connection between gestation age and the induction-to-abortion interval. This discrepancy is difficult to explain, however it seems that a longer induction-to-abortion gap is connected with increasing gestation age.

CONCLUSION

Despite moistening misoprostol tablets with acetic acid to aid disintegration, variations in effectiveness in causing mid-trimester abortion were still shown to be linked to vaginal pH, according to the current research. This indicates that the influence of vaginal pH on the efficacy of misoprostol given vaginally may go beyond influencing the drug's pharmacokinetics. The mechanism of the increasing impact of a low vaginal pH on the efficiency of vaginal misoprostol requires further research.

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الملخص العربي

تأثير الأس الهيدروجيني المهبلي على فعالية الميزوبروستول المهبلي لتحريض الإجهاض في منتصف الثلث الأخير من الحمل

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ملخص البحث:

المقدمة: يحدث الإجهاض المفقود عندما تبقى نتيجة الحمل المتوفاة في الرحم بعد 20 أسبوعًا من الحمل. غالبًا ما يستخدم الميسوبروستول ، وهو نظير البروستاغلاندين ، للأغراض الطبية.

الهدف: الهدف من هذه الدراسة هو التحقق مما إذا كان التغيير في حموضة المهبل يؤثر على الحرائك الدوائية للميزوبروستول ، وبالتالي فعاليته في تحريض الإجهاض في منتصف الأشهر الثلاثة. الموضوعات والطرق: الدراسة عبارة عن دراسة استباقية أجريت على مجموعة من 81 امرأة حامل (عمر الحمل 14-26 أسبوعًا والإجهاض الفاشل) في قسم التوليد بمستشفيات جامعة الزهراء في الفترة من أغسطس 2021 حتى فبراير 2022 تمت متابعتهن. لمدة 24 ساعة.

النتائج: كانت فترات الإجهاض التعريفي أطول بكثير في درجة الحموضة المجموعة ≤ 5 عنها في درجة الحموضة للمجموعة >5 (22.33 ± 2.29 ساعة. مقابل 11.80 ± 1.63 ساعة). أظهرت مجموعة الأس الهيدروجيني > 5 زيادة انتشار الحمى وآلام البطن الشديدة مقارنة بالمجموعة < 5.

الاستنتاجات: استخدام الميزوبروستول عن طريق المهبل للحث على الإجهاض في منتصف الثلث يكون أكثر فعالية عندما تزداد حموضة المهبل لأنه كان أكثر فاعلية في مجموعة الأس الهيدروجيني < 5.

الكلمات المفتاحية: حمض الخليك، الميزوبروستول، إنهاء الحمل في الثلث الثاني من الحمل، درجة الحموضة المهبلية.

الباحث الرئيسي

الاسم: منى محمد إبراهيم ابو حسين، قسم النسا والولادة، كلية طب بنات، القاهرة، جامعة الازهر، جمهورية مصر العربية.

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