Original Article

A Comparative Study to Assess the Efficacy and Safety of Prostaglandin-E1 Analogue (Misoprostol) Given Oral Vs Vaginal in the Management of First Trimester Missed Abortion

Neelam Roshan[1], Najma Bibi[2], Maria Ghafoor[3], Fauzia Anbreen[4], Dil Ruba[5]

[1,5]Medical Officer, [2,3]Assistant Professor,[4]Professor
[1,5]Women and children Hospital, MTI, Dera Ismail Khan, Khyber Pakhtunkhwa
[2-4]Department of Obstetrics & Gynecology, Gomal Medical College, MTI, Dera Ismail Khan, Khyber Pakhtunkhwa

Correspondence: *Dr. Najma Bibi*
Assistant Professor, Department of Obstetrics & Gynecology
Gomal Medical College, MTI, Dera Ismail Khan, Khyber Pakhtunkhwa
Email: doctornajmafarhat@gmail.com

Abstract

Objectives: The objectives of the study were to compare the efficacy and safety of oral and vaginal misoprostol among the patients with missed abortion.

Methodology: A Randomized Controlled study was conducted in the Department of Obstetrics and Gynecology, Gomal Medical College, Dera Ismail Khan. The current study was conducted for a period of 6 months commencing from 5th March 2021 to 5th September 2021. A total of 106 patients with the diagnosis of missed miscarriage were enrolled in the study after ethical approval and obtaining informed consent. In group A, patients were given 50 mL of water with 400µg of oral misoprostol as a single dose. In group B, patients received 400µg of misoprostol 4 hourly vaginally up to a maximum of five doses. Efficacy, safety, and comparison of gestational ages were noted in both groups.

Results: Out of a total, 106 Subjects The efficacy was observed in 39 (73.6%) patients of group A as compared to n=48 (90.6%) patients in group B (P= 0.022) while Safety was observed in 42 (79.2%) patients in group A as compared to n=52 (98.1%) patients in group B (P= 0.002). The mean gestational age was 15.528±2.26 weeks in Group A and 15.509±2.15 weeks in Group B, highlighting the later detection of missed miscarriage. The safety was compared in both groups the comparison showed 68.0% in group A, while 91.7% in group B with a gestational age of 15-20 weeks. While the gestational age less than 15 weeks showed 786% safety in group A, and 89.7% in group B with a p-value of 0.25.

Conclusion: Misoprostol has been widely used in gynecology and obstetrics for multiple indications. Our study showed that the misoprostol vaginal route is more efficacious than the oral route in missed abortion among pregnant women. The medication abortion and missed abortions are well managed by the misoprostol alone is effective, and safer. To enable the access of essential health services to the patients is the basic need of developing countries like Pakistan.

Keywords: Missed abortion, Misoprostol, Oral, Vaginal, Efficacy, safety

Cite this article as: Roshan N, bibi N, Ghafoor M, Ambreen F, Ruba D. Comparative Study to Assess the Efficacy and Safety of Prostaglandin-E1 Analogue (Misoprostol) Given Oral Vs Vaginal in the Management of First Trimester Missed Abortion. 2023; 13(3):261-266.

Introduction

A miscarriage is defined by the World Health Organization [WHO] as “the premature loss of a fetus up to 20 weeks of pregnancy and weighing up to 500 g”. Almost 20% of all pregnancies may occur and 80% of them occur during the first 12 weeks of gestational age.[1] The prevalence of miscarriages is high, even miscarriages occur when some patients do not know they are pregnant. In a study conducted to detect the daily hormones monitoring and the rate of miscarriages among pregnant women found that the rate of miscarriage is 31%.[2] The management of miscarriages gives the patients different choices, the surgical management, the dilation and curettage (D& Cs) and Dilation and evacuation (D&Es), and medical management of miscarriage. The medical abortion management is the most common choice among

Authorship Contribution: [1,4]Substantial contributions to the conception or design of the work, acquisition, [5]analysis, or interpretation of data for the work, [2]Drafting the work or revising it critically for important intellectual content, [1-5]Final approval of the version to be published, [1,3]Active participation in methodology.

Funding Source: none
Conflict of Interest: none

Received: Mar 15, 2023
Accepted: Aug 11, 2023

majority of the women. However, this also depends upon the gestational age and the most preferred option in the early first trimester.[3] The non-surgical management is usually done using misoprostol alone or combined with mifepristone and methotrexate.[4] However, the unavailability of mifepristone and the high cost of drugs make misoprostol an acceptable alternative for the medical management of missed abortion, and postpartum hemorrhage.

The misoprostol is a synthetic drug prostaglandin analogue E1 medication marketed to prevent the gastrointestinal damage caused by nonsteroidal anti-inflammatory drugs (NSAIDs). However, misoprostol has been used in various conditions including the medical management of abortions, inducing labor, Cervical ripening required before the surgical procedure, Removal of retained products of conception, and treating postpartum hemorrhages.[5] The post-medication effects include the uterine contraction, GI disturbance including the vomiting, Diarrhea, GI discomfort, chills, and fever however these effects are dose dependents. Although the misoprostol is a drug approved by Food and Drug administration for such indication in earlier 2002, the use of misoprostol was removed from the label and was added in an absolute contraindication in the pregnancy. The misoprostol was listed in the model list of essential drugs EDL list published in April 2013 by World Health Organization (WHO) having a potential use in missed abortions and post-partum hemorrhage and due to its low cost making it a drug of choice in inducing labor.[6]

The misoprostol could be administered oral route buccal/sublingual or per vaginal (PV), while the doses ranged from 100 micrograms to 800 micrograms.[6] A study showed that efficacy of oral misoprostol was 83% effective, with mild nausea and vomiting in few patients in missed abortion.[7] The misoprostol has been discussed in immense numbers of researches the majority of studies presented that the efficacy of vaginal misoprostol is more in percentage %, with mild nausea, Diarrhea, and other self-limiting symptoms.[8] A comparison of three different routes of administration through the vaginal route is comparatively safer and comparatively more effective than the oral route with fewer side effects. In order, the buccal/sublingual route is more effective due to its maximum absorption but is associated with more side effects than either oral or vaginal administration. “A single dose of 800 micrograms of misoprostol by vaginal or oral for missed abortion was recommended by National Institute for Health and Care Excellence [NICE].[9]”

However, some studies reported converse opinion, by pointing out that a lower dose or different routes of misoprostol may be equally effective. Hence, the present study is planned to compare the efficacy and safety of oral and vaginal misoprostol in missed abortion.[10] The maternal age is considered as an important indicator considering the risk and chances of miscarriages. The risk of early trimester miscarriages are 20-23 times greater in the pregnant women with age 30 years[5] and above compared to the age 20-30 which has shown a slight less in the percentages of miscarriages. In previous studies, the results have been compared at different doses thus leaving the conflict behind regarding the oral and vaginal route of administration. The current study was designed to assess the effects of misoprostol alone in women with missed miscarriages and to compare the efficacy through different routes of administration among women to assure the fact of medical management of abortions and miscarriages.

Methodology

A Randomized Controlled study was conducted in the Department of Obstetrics and Gynecology, Gomal Medical College, Dera Ismail Khan for the period of 6 months from 5th March 2021 to 5th September 2021. The Sample size was calculated with a confidence interval of 95%. An expected efficacy of oral misoprostol of 74%.[12] and Expected efficacy of vaginal misoprostol of 92%[12] One-sided hypothesis test for two proportions. n= 106. The Total sample size was divided into two groups. 53 sample size for the Oral group (Group A) while 53 sample size for the vaginal group (Group B).

The Sampling technique used for the study was non-probability consecutive sampling. The participants were female, in the age range 18-35 years with Gestational age ≤ 20 weeks on last month periods LMP with Diagnosis of missed miscarriage on ultrasonography. Closed cervix on bimanual pelvic examination was included in the study, however, the patients with intrauterine devices, bleeding disorders, and complicated pregnancies were excluded from the study. After obtaining the Ethical approval from the ethical committee of the hospital, the patients for this study were recruited from the OPDs or emergency ward at the Department of Obstetrics and Gynecology, Gomal Medical College, Dera Ismail Khan. The Basic demographics like age, gestational age, parity, and weight (on the weighing machine) were recorded in a questionnaire format. patients were divided into two groups. The total sample size was divided into two

groups. 53 sample size for the Oral group (Group A) while 53 sample size for the vaginal group (Group B). In group A, patients were given 50 mL of water with 400µg of oral misoprostol as a single dose. In group B, patients received 400µg of misoprostol 4 hourly vaginally up to a maximum of five doses. Oxytocin infusion was given when expulsion did not start in spite of uterine activity and cervical dilatation to expedite the expulsion process.

All the procedure was performed under the supervision of a consultant gynecologist with 3 years of fellowship experience. A transvaginal ultrasonography examination was performed, after 48 hours by a consultant gynecologist with three years of fellowship experience, efficacy was recorded in both groups. Later on, the Data was entered and analyzed using SPSS version 20. Mean ±SD was presented for quantitative variables like age, gestational age, and weight. Frequency and percentages were computed for qualitative variables like parity, efficacy, and safety were compared in both groups, the sample t test was applied to compare the means and findings of two different groups and significance values p ≤0.05 was considered significant. The Stratification was done with regard to age, gestational, parity, and weight to see the effect of these variables on efficacy and safety.

Results

The age range in this study was 18 to 35 years with a mean age of 27.018±2.09 years, mean gestational age of 15.528±2.26 weeks and mean weight was 66.905±4.10 Kg in Group A, and mean age of 26.358±2.35 years, mean gestational age 15.509±2.15 weeks and mean weight was 67.132±4.44 kg in Group B as shown in Table I.

Table I: Demographic details of Patients in Both groups.

Demographic Details, Safety, and efficacy in groups		Group A n=53 Mean± SD	Group B Mean± SD	
Age (years)		27.018±2.09	26.358±2.35	
Gestational age (weeks)		15.528±2.26	15.509±2.15	
Weight (Kg)		66.905±4.10	67.132±4.44	
Efficacy	Yes	39 (73.6%)	34 (64.1%)	(P=0.022)
	No	14 (26.4%)	19 (35.9%)	
Safety	Yes	42 (79.2%)	52 (98.1%)	(P= 0.002)
	No	11 (20.8%)	1 (1.9%)	

The mean gestational age was 15.528±2.26 weeks in Group A and 15.509±2.15 weeks in Group B, highlighting the later detection of missed miscarriage. The mean weight in group A was noticed as 66.905±4.10 while in group B the weight was noticed as.67.132±4.44 Efficacy was observed in 73.6% patients in Group A as compared to 26.4% of patients. The 64.1% showed efficacy however rest of patients i.e., 35.9% were un responsive to efficacy in Group B (P= 0.022) The safety was compared in both groups the comparison showed 79.2% in Group A, and 98.1% in group B. as shown in Table I

The safety was measured in terms of fewer side effects, no intense bleeding, requiring inpatient care, and other complications. Safety and efficacy with respect to age was observed in 39(79.6%) patients in group A as compared to 46 (93.9%) patients in group B (P= 0.037), however, 20.4% of patients showed no safety towards the drug and few of symptoms were observed. out of total patients more than the age of 30 years (n=04) showed safety 50% of patients (n=2) while all patients showed negative response (p=0.103)

The stratification of efficacy was noted with respect to the gestational, out of 25 patients with gestational age of 15-20 weeks the 68% of efficacy was noted in group A, and 91.7% in group B with p-value of 0.039. The patients showed 73.6% efficacious response in group A, and 89.2% in group B, with the value of P showing 0.251. (Table II)

Table II: Safety & Efficacy with Respect to Gestational Age & Stratification

Groups	Yes	No	P-Value
Age 18-30 years (n=49)			
A	39(79.6%)	10(20.4%)	0.037
B	46(93.9%)	3(6.1%)	
For Age >30 years (n=04)			
A	0(0%)	4(100%)	0.103
B	2(50%)	2(50%)	
Stratification of efficacy with respect to gestational age (15-20 Weeks) (n=25)			
A	17(68%)	8(32%)	0.039
B	22(91.7%)	2(8.3%)	
Gestational age <15 weeks (n=28)			
A	22(78.6%)	6(21.4%)	0.251
B	25(89.2%)	3(10.8%)	

The Parity (0-2) was noticed in the both groups showing the clear results or 77.10% in group-A, and Group A showed no response in 22.90%, the no response was observed in group-A 80% of patients showed response to parity scale (>2) the safety and efficacy was compared in 2 groups of gestational ages i.e., <15 weeks and 15-20 weeks the majority of patients showed safety and comparative lesser side effects, the group A showed 76% of safety in patients with gestational age 15-20

weeks, while group A of gestational age <15 weeks showed safety of 82.10% as mentioned in figure no. 1.

values of patients was observed showing minimum of 50% reduction was considered as success rate of misoprostol.

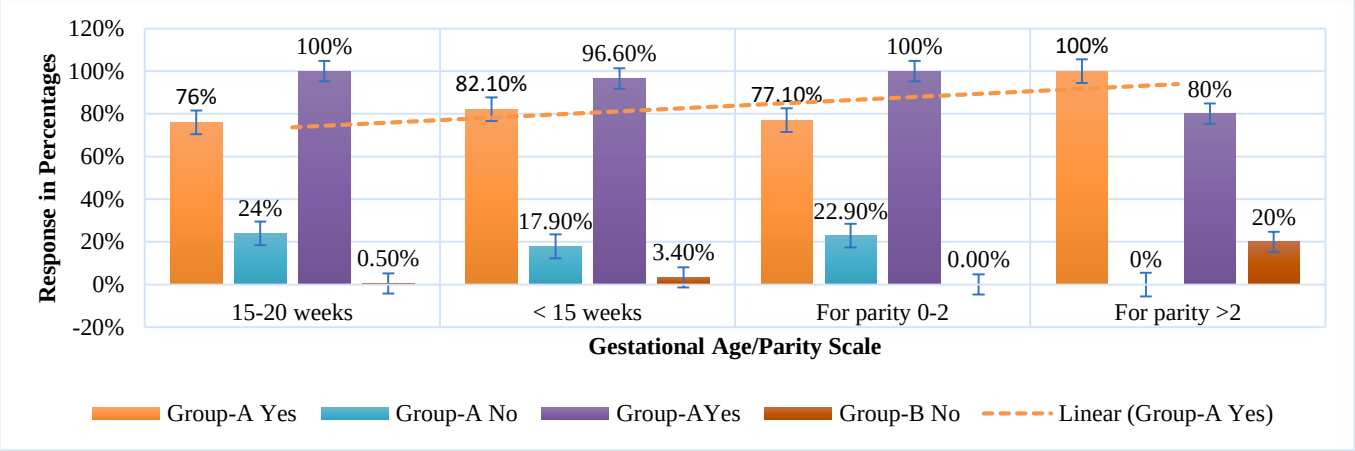

Figure 1. Stratification of safety with respect to Gestational Age & parity in both groups.

The Gastrointestinal side-effects were observed in one group post oral administration of misoprostol showing the incidence of vomiting 36% of cases of nausea among 20% of patients were observed with GI complication most common was diarrhea.

The post drugs effects were managed by the anti-emetics and ant-amebic/antidiarrheal drugs in oral group. Out of total 106 patients the vaginal route of administration showed diarrhea in majority of patients 76.1% however the rest of patients 23.9% had no gastrointestinal associated problems that is associated with the natural response intestine to the use of drug (Misoprostol) itself the study has shown that frequency of nausea was 20% with oral misoprostol and 10% with vaginal misoprostol, vomiting was 16% versus 6%, diarrhea 28% versus 6%, shivering 28% versus 32%, fever 12% versus 36%.Few of patients showing more than 1 effects were also found, the nausea with severe diarrhea and shivering due to the intense abdominal cramps were commonly seen. The complete evacuation was noticed within 48 hours of administration of drug. The transvaginal USG was performed to check the results of misoprostol among women. The percentages of patients showing the complete abortions within 48 hours of administration of misoprostol was observed higher in the group B, as compared to Group A. The serum concentration levels of BHCG were checked continuously showing the rapid decline, over the periods of time (measure in 48 intervals) which shows the decrease chances retained product of conception (RPOCs) and thick endometrium requiring of surgical procedure. The baseline comparison to the current

Discussion

In this study the differential findings and assessment of multiple factors associated with the administration of misoprostol may be secondary to the Pharmacokinetic profile of misoprostol given orally and through vaginal route. However, an extensive clarification on patient's age and gestational ages are one of the major factor in efficacy of misoprostol. In the present study, the patient's age range was observed between 18 to 35 years with a mean age of 27.018±2.09 years which was compared with similar studies conducted on misoprostol showing the similar results the mean difference of 2.1 ±2 was observed which supports the finding of our study.[11]

The early gestational age is one of the major factor in the medical management of abortion, to assess the differential factors the mean gestational age were assessed, and observed that 15.528±2.26 weeks, and the mean weight of women was 66.905±4.10 Kg the patient's age was assessed and compared to the other study conducted on misoprostol showed that women in the study were younger which deferred from the studies conducted in the European and American research studies showing similar results supporting the medical management of missed abortions with misoprostol alone[11] which is a clear indication that early ages conception is prevalent in the country. In our study, efficacy was defined as complete evacuation after 48 hours of misoprostol administration assessed on transvaginal USG The increased success rate of the drug found in the literature supports the use of misoprostol without increasing the healthcare cost in healthcare facilities.

Efficacy was observed among 73.6% of patients in group A as compared to 48 (90.6%) patients in group B (P= 0.022), misoprostol has been proven to be effective in the non-surgical methods of abortions and expulsion of retained products of conceptions (RPOCs) representing the higher efficacy in vaginal route of administration the results are supported by the study on a fact that vaginal route of administration shown the clear results on minimal RPOCs.[12] The small uterus sac or less gestational age supports the safety and efficacy of misoprostol as assessed in previous studies the lesser gestational age showed higher success rates with misoprostol.[13]

Our study found that the efficacy of oral misoprostol was 74% as compared to 92% with vaginal misoprostol in missed abortion are aligned with the study.[13] The success rate of misoprostol use could be due to the various attributes of the drug, considering the small doses, the defined dose schedules, or easy management of drugs side the PGE2 analogs in combination with the misoprostol and mifepristone was observed in only few studies, however the signal use of misoprostol was found easy and more effective and favored.

The efficacy was found totally dose-dependent and a number of doses take repeatedly. The dose intervals play an important role in the use of misoprostol, and an increase in the numbers of doses was found recommended to increase the cumulative effect of the drug.[14] An increased Periods after the last dose of misoprostol has been considered normal due to its prolonged effects. The objective parameters showed a remarkable safety and efficacious use of misoprostol in most of the cases.

In the findings of our study the gestational age was assessed by analyzing the beta HCG levels of patients, which shows a continuous increase in early trimesters however if the serum shows a rapid decline in the beta HCG which confirms the evacuation of the Fetus[15] Safety was observed in 42 (79.2%) patients in group A as compared to 52 (98.1%) patients in group B (P= 0.002). A study has shown that the efficacy of vaginal misoprostol was 36%, while nausea was seen in 0% of patients and vomiting 0% in missed abortion.[15]

The use of Misoprostol is considered controversial due to its potential post-effects and painful results, in some cases, the uterine contraction is not observed effectively depending on the gestational age which restricts the use of misoprostol[12]. The potential limitation of the study was observing the patient's response toward the use of misoprostol through the vaginal route of administration. The study also suggests the observation of the effects of misoprostol in a larger number of participants at different gestational ages.

In our study the most common side effect of misoprostol observed was diarrhea, which is considered the natural response of the drug itself, and an increased level of PGs, which usually subsides itself despite the continuation of the therapy.[16-17] A study has shown response to misoprostol effects, nausea was mentioned among 20% with oral misoprostol and 10% with vaginal misoprostol, vomiting was 16% versus 6%, diarrhea 28% versus 6%, shivering at 28% versus 32%, fever 12% versus 36% supporting the findings of our study showing the similar pattern of post drugs effects.[18]

The lesser side effects associated with the use of drugs could promote the use of misoprostol orally for which the majority of the studies focusing on it[19-20] Maximum women in Group A showed menstruation restoration within 30 to 45 days post-abortion which supports the results of studies conducted in the western countries. [21-23] However, we recommend conducting further studies on a larger group of patients to detect the exceptional effects of drugs and to validate the current findings.

Conclusion

The administration of misoprostol as a practical alternative in the management of medical abortion and missed or incomplete abortion. The drug showed efficacy in various cases along with the safety as compared to the conventional surgical evacuation in the patients with missed abortion considering the patient's acceptability, acceptable post-drug effects/side-effects. The vaginal route of administration is more efficacious yet the time of expulsion varies from patient to patient, when offered by the well-trained medical staff or Gynae-clinicians who can manage the excessive bleeding occurring in few cases, for which the hospitalization is recommended to manage the condition.

Acknowledgement

The authors would like to acknowledge the Medical Affairs department of Getz Pharma for their technical support and assistance in Data Analysis.

References

1. Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE

early pregnancy special interest group. Hum Reprod. 2015;30(3):495–8.
2. Al-Dughaishi T, Al-Jabri MMH, Al-Haddabi AH, Gowri V. Trends of patients' preferences in the management of first and early second trimester pregnancy loss towards the choice of medical or surgical termination of pregnancy in a tertiary care center in Oman. J Reprod Infertil. 2019;20(1):52–6.
3. Guarino A, Di Benedetto L, Assorgi C, Rocca A, Caserta D. Conservative and timely treatment in retained products of conception: a case report of placenta accreta ritention. Int J Clin Exp Pathol. 2015;8(10):13625–9.
4. Abubeker FA, Lavelanet A, Rodriguez, M I, & Kim, C. Medical termination for pregnancy in early first trimester (≤ 63 days) using combination of mifepristone and misoprostol or misoprostol alone: a systematic review. BMC women's health.2020; 20, 1-17.
5. Kapp N, Eckersberge E, Lavelanet A, & Rodriguez, MI. Medical abortion in the late first trimester: a systematic review. Contraception.2019; 99(2): 77-86.
6. Gattás DSMB, da Silva Junior JR, Souza ASR, Feitosa FE, de Amorim MMR. Misoprostol administered sublingually at a dose of 12.5 µg versus vaginally at a dose of 25 µg for the induction of full-term labor: a randomized controlled trial protocol. Reprod Health. 2018;15(1):65.
7. Nwafor JI, Agwu, UM, Egbuji, CC, & Ekwedigwe KC. Misoprostol versus manual vacuum aspiration for treatment of first-trimester incomplete miscarriage in a low-resource setting: A randomized controlled trial. Nigerian Journal of Clinical Practice.2020; 23(5), 638-646.
8. Allamehp Z., Goharian M & Eslamian M. Effect of misoprostol with and without letrozole on the induction of abortion for women with first-trimester missed abortion. International Journal of Gynecology & Obstetrics.2020; 151(2): 214-218.
9. Ibiyemi KF, Ijaiya MA, Adesina KT. Randomised trial of oral misoprostol versus manual vacuum aspiration for the treatment of incomplete abortionat a Nigerian tertiary hospital. Sultan Qaboos Univ Med J. 2019;19(1):e38–e43.
10. Dehbashi Z, Moosazadeh M, Afshari M. Comparison between sublingual and vaginal route of misoprostol in management of first trimester miscarriage missing. Mater Sociomed. 2016;28(4):271–3.
11. Young DC, Delaney T, Armson, BA., & Fanning C. Oral misoprostol, low dose vaginal misoprostol, and vaginal dinoprostone for labor induction: Randomized controlled trial. PLoS One.2020; 15(1); e0227245.
12. Nautiyal D, Mukherjee K, Perhar I, Banerjee N. Comparative study of misoprostol in first and second trimester abortions by oral, sublingual, and vaginal routes. J Obstet Gynaecol India. 2015;65(4):246-50.
13. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A comparative study to evaluate the efficacy of vaginal vs oral prostaglandin E1 analogue (misoprostol) in management of first trimester missed abortion. J Clin Diagn Res. 2016;10(5):QC14-QC18.
14. Bettencourt-Silva B., Rego, MT, Miranda C, Cunha AI, Brás, F, Lopes-Guerra, C & Furtado, J. M. The role of mifepristone on first trimester miscarriage treatment–A double-blind randomized controlled trial–MiFirsT. European Journal of Obstetrics & Gynecology and Reproductive Biology.2023; 289, 145-151.
15. Zhang J, Zhou K, Shan D, & Luo X. (2022). Medical methods for first trimester abortion. Cochrane Database of Systematic Reviews, (5).
16. Chau OS, Law TS, Ng K, Li, TC & Chung, J. P. Five-year retrospective review of ultrasound-guided manual vacuum aspiration for first-trimester miscarriage. Hong Kong medical journal= Xianggang yi xue za zhi, 29(3), 233-239.
17. Jin H, Zhang, M, Yang X, Liu J, Muhetaer M, Chen Y, & Liu X. (2023). Comparison of misoprostol and manual vacuum aspiration in treating first-trimester incomplete miscarriage: a systematic review and meta-analysis of randomized controlled trials.
18. wAl-Memar, M, Bobdiwala, S, Fourie H, Mannino R, Lee YS, Smith A, & MacIntyre, D. A. The association between vaginal bacterial composition and miscarriage: a nested case–control study. BJOG: An International Journal of Obstetrics & Gynaecology.2020; 127(2), 264-274.
19. Ali MK, Emam S M, Abdel-Aleem, MA, & Sobh AM. Misoprostol versus expectant management in women with incomplete first-trimester miscarriage after failed primary misoprostol treatment: A randomized clinical trial. International Journal of Gynecology & Obstetrics..2021; 154(3): 558-564.
20. Olpin JD, Heilbrun M. Imaging of Mullerian duct anomalies. Clin Obstet Gynecol. 2009;52:40–56.
21. Acharya A., Prabhu A, Negi S, Sharma K, Dwivedi R. Spontaneous miscarriage/abortion in the first trimester and expectant management–a meta-analysis approach. Menopause Review/ Przegląd Menopauzalny.2023; 22(1).
22. Wilkowska-Trojniel M, Zdrodowska-Stefanow B, OstaszewskaPuchalska I, Redžko S, Przepieść J, Zdrodowski M. The influence of Chlamydia trachomatis infection on spontaneous abortions. Adv Med Sci. 2009;54:86–9
23. un Nisa S, un Nisa S., Athar, M., Zulfiqar N, Malik BA, & Hira, M. Manual Vacuum Aspiration vs Vaginal Misoprostol for the Management of First-Trimester Incomplete Miscarriage in term of complete abortion. Pakistan Journal of Medical & Health Sciences.2023; 17(04): 205-205.
24. Raymond, E. G., Harrison, M. S., & Weaver, M. A. Efficacy of misoprostol alone for first-trimester medical abortion: a systematic review. *Obstetrics and gynecology*.2019; *133*(1), 137.