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Factors related to successful medication management with mifepristone and misoprostol in missed miscarriage: a retrospective case-control study

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Abstract

Background Treatment with mifepristone in combination with misoprostol may be a safe and less expensive option compared with surgical management in missed miscarriage, but the efficacy of medication management varies in clinical practice. This study aims to identify the risk factors related to successful medical management using mifepristone and misoprostol for missed miscarriage.

Methods We carried out a retrospective case-control study in the First Affiliated Hospital with Nanjing Medical University from January 1, 2023 to December 31, 2023. Patients were recruited into this study if they were aged 16 years and older, diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 13 weeks of pregnancy (by last menstrual period), and chose to have medication management. Women who failed to spontaneously pass the gestational sac within 24 h of the oral misoprostol dose were included in the case group, while women who had complete gestational sac expulsion within 24 h of the oral misoprostol dose were defined as controls. The baseline characteristics of the patients were collected in the electronic medical record system and the meteorological data were obtained from the Nanjing Meteorological Observation Centre. Logistic regression analysis was used to identify the risk factors which affected medication management efficacy.

Results A total of 163 patients met inclusion criteria, including 60 patients in the case group and 103 patients in the control group. Our results showed that the history of gravidity, history of parity, history of miscarriage, history of caesarean section, prior uterine surgery, and the use of supplemental vaginal misoprostol could be potential risk

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factors, while the remaining variables showed no significant differences between the two groups. The univariable logistic regression model demonstrated that the risk of unsuccessful medication management was increased 3.67-fold in patients who had been pregnant more than 3 times (95% CI: 1.66, 8.08; $p=0.001$); increased 2.29-fold in parous women (95% CI: 1.13, 4.62; $p=0.021$); and increased 2.09-fold in patients who had previous miscarriages (95% CI: 1.10, 4.00; $p=0.026$). Additionally, prior uterine surgery was related to the outcomes of medication management (OR: 2.94; 95% CI: 1.46, 5.93; $p=0.003$), especially caesarean section (OR: 2.09; 95% CI: 1.13, 4.62; $p=0.021$). Interestingly, the repeated vaginal administration of misoprostol was not associated with an increased success rate (OR: 3.65; 95% CI: 1.76, 7.56; $p=0.001$). Moreover, we evaluated the effect of meteorological factors on which the exposure of 4 days average visibility emerged as a statistically significant risk factor (OR: 1.13, 95% CI: 1.01, 1.27; $p=0.036$). Multivariable logistic regression model showed that the history of parity, prior uterine surgery, use of supplemental vaginal misoprostol and 4 days average visibility were still independently associated with the outcomes of medication management, while the gestational age by ultrasound was no longer related.

Conclusions The missed miscarriage patients who are parous or have uterine surgery history may suffer from a higher risk of unsuccessful medication management. The exposure to reduced visibility had a significant influence on the efficacy of mifepristone and misoprostol, while the supplementary administration of vaginal misoprostol could not increase the chance of successful miscarriage management.

Keywords Missed miscarriage, Mifepristone, Misoprostol, Meteorological factors

Introduction

Early pregnancy loss (EPL), also known as miscarriage or spontaneous abortion, is defined as a nonviable, intrauterine pregnancy at less than 13 weeks of gestation, which occurs in about 1 of 3 pregnancies and affects approximately 1 million pregnant individuals each year in the US [1, 2]. Missed miscarriage is a particular type of EPL, referring to embryonic or fetal death with the retained intrauterine products of conception that fail to be discharged naturally [3]. There are three management options for patients with missed miscarriage who do not have vaginal bleeding or signs of infection, including expectant management, medication management and procedural or surgical management [1, 4]. The first-line treatment for missed miscarriage is expectant management. However, if expectant management is not successful or not acceptable to the woman, medication management is preferred. It is reported that mifepristone and misoprostol in combination were more effective than misoprostol alone in achieving completion of missed miscarriage, and this combination reduced the number of women who need surgical intervention after failed medication management [5–7].

Medication management is the preferred option for many missed miscarriage women, which is recommended in international clinical guidelines [4]. Patients for whom medication management is not successful will commonly undergo subsequent procedural management, such as uterine aspiration. Moreover, many women prefer surgical evacuation to expectant or medication treatment because it provides more immediate completion of the process with less follow-up [2, 8]. To reduce the physical, psychological, economic, and time costs for missed miscarriage patients, individualized management should be provided regarding different risk factors affecting the efficacy of medication management.

Pregnancy raises the vulnerability of women to climate change and increases the risk of adverse pregnancy outcomes [9–11]. However, the exact mechanism remains unclear. Animal and cell experiments have shown that meteorological factors may affect the sensitivity of prostaglandins [12, 13], but more powerful evidence is lacking. In addition to investigating the role of clinical factors on the outcomes of medication management in missed miscarriage, we also took meteorological factors into account. We hope that patients experiencing missed miscarriage have access to personalized treatment.

Methods

Study population

We conducted a retrospective case-control study according to STROBE guidelines in PICO format. During the period from January 1, 2023 to December 31, 2023, we gathered data on patients who were aged 16 years and older and had been diagnosed with a missed miscarriage by pelvic ultrasound scan within the first 13 weeks of pregnancy (by last menstrual period) following International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes: O02.1 (missed abortion), and these patients chose to have medication management of miscarriage at the First Affiliated Hospital with Nanjing Medical University. The diagnostic criteria for missed miscarriage were determined by trained ultrasonographers in early pregnancy units in accordance with international diagnostic criteria when a non - viable pregnancy with a gestational sac was identified on an ultrasound scan [14]. This study was approved

by the Ethics Committee of The First Affiliated Hospital with Nanjing Medical University (2024-SR-651).

Exposures

All patients received standardized mifepristone plus misoprostol treatment according to the drug instructions during the hospitalization. However, women who had already passed the gestational sac before misoprostol or presented with hemorrhage, hemodynamic instability, or signs of infection should be excluded. All patients were administered mifepristone orally at a dosage of 50 mg twice daily for three days. Subsequently, on the fourth day, they were administered a single oral dose of misoprostol 600 μg. After receiving oral misoprostol, if a patient experienced no or minimal bleeding and did not pass the gestational sac, a single 600 μg dose of vaginal misoprostol was administered (4 h apart). If a patient had already expelled the gestational sac within 4 h of taking the oral misoprostol dose, the scheduled 600 μg vaginal dose of misoprostol could be omitted. The study ultimately included 163 patients.

Outcomes and groups

Women who failed to pass the complete gestational sac within 24 h of oral misoprostol dose were included in the case group. The 24 h was chosen in line with previous studies and the stipulated baseline rate of completion [15, 16]. This outcome could be assessed before the participant was discharged from the hospital. If there is still no vaginal bleeding after 24 h of misoprostol treatment, further individualized treatment is needed, and surgical treatment could be considered to reduce physical, psychological, time and health-care systems costs [17]. On the contrary, women who had complete gestational sac expulsion (herein defined as successful abortion) within 24 h of the oral misoprostol dose were defined as controls.

The baseline characteristics of the patients were collected such as age, height, weight, body mass index (BMI), blood group, the use of progesterone in early pregnancy, method of conception (spontaneous, in vitro fertilization and assisted by ovulation induction drugs without in vitro fertilization), gestational age by last menstrual period, gestational age by ultrasound, history of gravidity, history of parity, history of miscarriage, history of caesarean section, uterine anomalies (myomas, septate), prior uterine surgery (caesarean section, myomectomy, hysteroscopy surgery, aspiration or curettage), and use of supplemental vaginal misoprostol. In our study, all methods were carried out in accordance with the relevant guidelines and regulations.

Meteorological data

The daily data of meteorological factors during the study period were obtained from Nanjing Meteorological Observation Centre, including daily maximum pressure (kPa), daily minimum pressure (kPa), daily average pressure (kPa), 4 days average pressure (kPa), daily maximum temperature (℃), daily minimum temperature (℃), daily average temperature (℃), 4 days average temperature (℃), daily relative humidity (%), 4 days average humidity (%), daily minimum visibility (km), 4 days average visibility (km), daily precipitation (mm), daily evaporation (mm), daily maximum wind speed (0.1 m/s), daily extreme wind speed (0.1 m/s), and sunshine duration (h). In general, for each patient in this study, the exposure levels of meteorological factors were matched to the day on which misoprostol was used and the average levels during four days when standardized mifepristone plus misoprostol was received.

Statistical analysis

The study's binary outcome variable was whether the gestational sac spontaneously passed within 24 h of misoprostol dose. Categorical data are expressed as percentages [n (%)], while continuous data are expressed as median + IQR or mean ± standard deviation. The data for the case and control groups were analyzed using the t-test or Mann-Whitney U test for continuous variables and the chi-square test for categorical variables, respectively. Logistic regression analysis was used to identify the risk factors which affected medication management efficacy. Initially, all factors were tested in an univariable logistic regression model. Then the model was built by Backward Stepwise Regression using Likelihood Ratio (LR) Test and all factors were further analyzed by multivariable analysis, while collinear factors were manually deleted. The statistical analyses were conducted utilizing SPSS version 27 (IBM Corp., Armonk, NY, USA) and R version 4.4.2 (The R Foundation for Statistical Computing), with P values below 0.05 deemed significant.

Results

General characteristics

A total of 254 patients were obtained from the First Affiliated Hospital with Nanjing Medical University. During the 4 days' standardized mifepristone plus misoprostol treatment according to the drug instruction, 87 patients spontaneously expelled the gestational sac before taking misoprostol and 4 patients presented with hemorrhage and hemodynamic instability, which were excluded. Finally, 163 patients were enrolled in this study, including 103 patients in the control group, who completed gestational sac expulsion within 24 h of the misoprostol dose, and 60 patients who failed in the case group (Fig. 1).

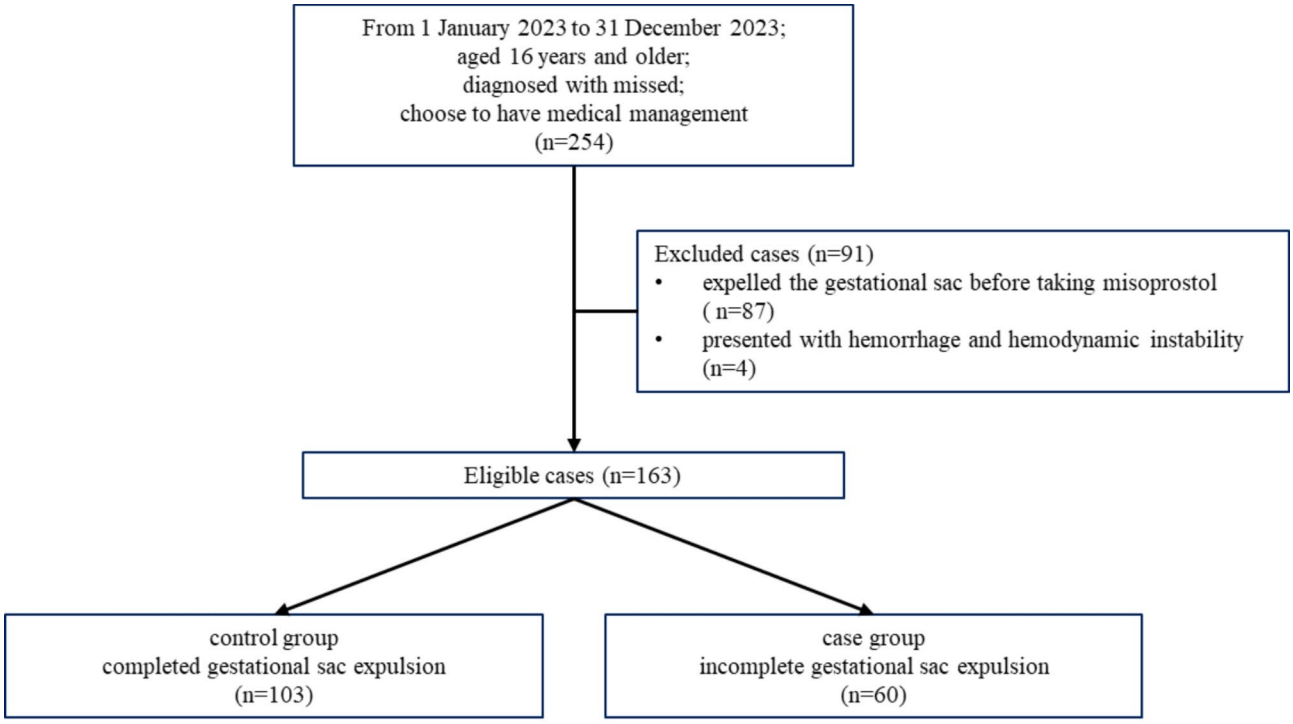

Fig. 1 Flow chart for patient selection

The clinical characteristics of patients in the control group and the case group are shown in Table 1. Apart from the history of gravidity, history of parity, history of miscarriage, history of caesarean section, prior uterine surgery, and the use of supplemental vaginal misoprostol, the remaining variables between the control and the case group showed no significant differences. About 45.0% of women in the case group and 18.4% in the control group had been pregnant more than three times; about 38.3% of women in the case group and 21.4% in the control group had previous deliveries; about 60.0% of women in the case group and 41.7% in the control group had previous miscarriages, and all differences mentioned above were statistically significant ($p < 0.05$). The proportion of prior uterine surgery was higher in the case group than in the control group (75% vs. 50%, $p = 0.003$), especially the history of caesarean section, which was more common in the case group (38.3% vs. 21.4%, $p = 0.016$). The case and control groups exhibited a significant difference in terms of a further dose of misoprostol (55.0% vs. 27.2%, $p < 0.001$), which indicated that the use of misoprostol vaginally as a supplement could not increase the efficacy of miscarriage management.

Meteorological characteristics

Table 2 showed the distribution of meteorological factors exposure in the control group and case group. For meteorological variables, there were no significant differences observed. These variables include the exposure level on a single day on which misoprostol was used and the average levels during the four days when standardized mifepristone plus misoprostol was received.

Screening for the risk factors

The relationship between clinical factors and the outcomes of mifepristone plus misoprostol for missed miscarriage was explored in the univariable logistic regression model. The history of gravidity, history of parity, history of miscarriage, history of caesarean section, prior uterine surgery, and use of supplemental vaginal misoprostol had a significant influence on the success of medication management (Table 3). We found that the risk of unsuccessful treatment was increased 3.67-fold in patients who had been pregnant more than 3 times (95% CI: 1.66, 8.08; $p = 0.001$); increased 2.29-fold in parous women (95% CI: 1.13, 4.62; $p = 0.021$); and increased 2.09-fold in patients who had previous miscarriages (95% CI: 1.10, 4.00; $p = 0.026$). Our results showed a positive correlation between prior uterine surgery and the outcomes of medication management (OR: 2.94; 95% CI: 1.46, 5.93; $p = 0.003$), especially caesarean section (OR: 2.09; 95% CI: 1.13, 4.62; $p = 0.021$). Moreover, the further dosage of misoprostol by vaginal was not associated with increased success (OR: 3.65; 95% CI: 1.76, 7.56; $p = 0.001$).

Similarly, the univariable logistic regression model was used to screen for meteorological risk factors (Table 4). Our results indicated that the exposure of 4 days average

Table 1 Clinical characteristics of all patients in the control group and case group
Continuous variables are described as the mean ± standard deviation, categorical variables are expressed as numbers and percentages. * indicates significant result.

Variable	Control group (n=103)	Case group (n=60)	p-value
Age (years)	31.92 ± 4.43	33.33 ± 5.60	0.077
Height (centimeter)	163.02 ± 4.56	162.00 ± 5.00	0.186
Weight (kilogram)	59.71 8..34	59.74 9.30	0.643
Body mass index (kg/m2)	22.46 3.03	22.76 3.32	0.623
Gestational age by last menstrual period (days)	68.83 ± 8.16	70.50 ± 8.30	0.213
Gestational age by ultrasound (days)	55.93 ± 7.63	55.42 ± 8.37	0.249
History of gravidity (Numbers)			0.001*
1	49 (47.6%)	19 (31.7%)	
2	35 (34.0%)	14 (23.3%)	
≥3	19 (18.4%)	27 (45.0%)	
History of parity(Numbers)			0.016*
0	81 (78.6%)	37 (61.7%)	
≥1	22 (21.4%)	23 (38.3%)	
History of miscarriage(Numbers)			0.018*
0	60 (58.3%)	24 (40.0%)	
≥1	43 (41.7%)	36 (60.0%)	
History of caesarean section(Numbers)			0.016*
0	81 (78.6%)	37 (61.7%)	
≥1	22 (21.4%)	23 (38.3%)	
Blood group (n,%)			0.313
A	30 (29.1%)	25 (41.7%)	
B	21 (20.4%)	7 (11.7%)	
O	41 (39.8%)	22 (36.7%)	
AB	11 (10.7%)	6 (10.0%)	
Use of progesterone in early pregnancy (n,%)			0.871
Yes	51 (49.5%)	31 (51.7%)	
No	52 (50.5%)	29 (48.3%)	
Method of conception (n,%)			0.707
spontaneous	57 (55.3%)	31 (51.7%)	
ovulation induction	4 (3.9%)	4 (6.7%)	
in vitro fertilization	42 (40.8%)	25 (41.7%)	
Uterine anomalies (n,%)			0.716
null	77 (74.8%)	44 (73.3%)	
myomas	22 (21.4%)	15 (25.0%)	
septate	4 (3.9%)	1 (1.7%)	
Prior uterine surgery (n,%)			0.003*
Yes	52 (50.5%)	45 (75.0%)	
No	51 (49.5%)	15 (25%)	
Use of supplemental vaginal misoprostol (n, %)			<0.001*
Yes	28 (27.2%)	33 (55.0%)	
No	75 (72.8%)	27 (45.0%)	

Table 2 Exposure levels of meteorological factors during medication management
Meteorological factors are described as the median and interquartile range (IQR)

Meteorological variables	Control group (n=103)		Case group (n=60)		p-value
	median	IQR	median	IQR	
Daily maximum pressure(kPa)	101.02	1.81	101.14	2.02	0.846
Daily minimum pressure(kPa)	100.63	1.33	100.67	1.64	0.776
Daily average pressure(kPa)	100.86	1.57	100.87	1.73	0.758
4 days average pressure (kPa)	100.87	1.67	101.04	1.76	0.806
Daily maximum temperature (°C)	23.90	19.50	24.00	18.55	0.792
Daily minimum temperature (°C)	13.50	19.90	14.95	20.48	0.804
Daily average temperature (°C)	17.15	19.30	19.50	19.35	0.787
4 days average temperature (°C)	18.99	20.50	19.79	20.37	0.832
Daily relative humidity (%)	47.00	31.00	47.00	29.75	0.867
4 days average humidity (%)	48.00	28.00	45.13	31.25	0.665
Daily minimum visibility (km)	3.56	3.41	4.41	2.72	0.179
4 days average visibility (km)	4.33	3.77	6.46	5.54	0.059
Daily precipitation (mm)	0.00	1.50	0.00	1.63	0.645
Daily evaporation (mm)	2.80	2.50	2.50	2.15	0.526
Daily maximum wind speed (0.1m/s)	39.00	16.00	39.00	19.50	0.557
Daily extreme wind speed (0.1m/s)	68.00	32.00	68.00	33.00	0.586
Sunshine duration (h)	6.40	7.40	5.15	8.43	0.553

visibility emerged as a statistically significant risk factor (OR:1.13; 95% CI:1.01, 1.27; $p = 0.036$).

We further explored the risk factors for the efficacy of medication management by multivariable logistic regression model. After Backward Stepwise Regression using Likelihood Ratio (LR) Test, these variables including gestational age by ultrasound, history of parity, prior uterine surgery, use of supplemental vaginal misoprostol and 4 days average visibility were incorporated into the same model (Table 5). The history of parity, prior uterine surgery, use of supplemental vaginal misoprostol and 4 days average visibility were still independently associated with the outcomes of medication management, while the gestational age by ultrasound was no longer related.

Discussion

Missed miscarriage is a common form of early pregnancy loss and previous studies reported that the success rates of mifepristone plus misoprostol treatment varied widely between 83% and 93.3% [7, 18–20]. The differences in results may depend on doses and routes of administration, repeated or single-dose treatment and some clinical factors, such as vaginal bleeding, blood type, history of parity [21] and uterine size [7]. However, studies investigating factors that affect the outcome of medical treatment for missed miscarriage have not been well established.

In our study, the increased numbers of gravidity, parity, and abortion decreased the chance of successful

Table 3 The clinical risk factors associated with the efficacy of medication management
* indicates significant result

Variable	Univariable	
	OR (95% CI)	p-value
Age (years)	1.06 (0.99, 1.14)	0.080
Height (centimeter)	0.96 (0.89, 1.02)	0.186
Weight (kilogram)	1.00 (0.96, 1.04)	0.981
Body mass index (kg/m2)	1.03 (0.93, 1.14)	0.558
Gestational age by last menstrual period (days)	1.03 (0.99, 1.07)	0.213
Gestational age by ultrasound (days)	1.02 (0.98, 1.07)	0.249
History of gravidity (Numbers)		0.002*
1	1	
2	1.03 (0.46, 2.33)	0.940
≥3	3.67 (1.66, 8.08)	0.001*
History of parity (Numbers)	2.29 (1.13, 4.62)	0.021*
History of miscarriage (Numbers)	2.09 (1.10, 4.00)	0.026*
History of caesarean section (Numbers)	2.29 (1.13, 4.62)	0.021*
Blood group		0.322
A	1	
B	0.40 (0.15, 1.10)	0.074
O	0.64 (0.31, 1.35)	0.245
AB	0.66 (0.21, 2.02)	0.461
Use of progesterone in early pregnancy	1.09 (0.58, 2.06)	0.791
Method of conception		0.710
spontaneous	1	
ovulation induction	1.84 (0.43, 7.86)	0.411
in vitro fertilization	1.09 (0.57, 2.12)	0.789
Uterine anomalies		0.669
null	1	
myomas	1.19 (0.56, 2.54)	0.646
septate	0.44 (0.05, 4.04)	0.466
Prior uterine surgery	2.94 (1.46, 5.93)	0.003*
Use of supplemental vaginal misoprostol	3.27 (1.68, 6.39)	<0.001*

Table 4 The meteorological risk factors associated with the efficacy of medication management
* indicates significant result

Meteorological variables	Univariable	
	OR (95% CI)	p-value
Daily maximum pressure(kPa)	1.04 (0.77, 1.40)	0.800
Daily minimum pressure(kPa)	1.05 (0.76, 1.44)	0.780
Daily average pressure(kPa)	1.04 (0.77, 1.42)	0.789
4 days average pressure (kPa)	1.00 (0.73, 1.36)	0.998
Daily maximum temperature (℃)	1.0 (0.97, 1.03)	0.944
Daily minimum temperature (℃)	1.00 (0.97, 1.03)	0.845
Daily average temperature (℃)	1.00 (0.97, 1.03)	0.893
4 days average temperature (℃)	1.00 (0.97, 1.04)	0.835
Daily relative humidity (%)	1.00 (0.99, 1.02)	0.763
4 days average humidity (%)	1.00 (0.98, 1.02)	0.668
Daily minimum visibility (km)	1.01 (0.93, 1.09)	0.894
4 days average visibility (km)	1.13 (1.01, 1.27)	0.036*
Daily precipitation (mm)	1.00 (0.98, 1.02)	0.925
Daily evaporation (mm)	0.98 (0.84, 1.14)	0.801
Daily maximum wind speed (0.1m/s)	0.99 (0.97, 1.02)	0.559
Daily extreme wind speed (0.1m/s)	1.00 (0.98, 1.01)	0.626
Sunshine duration (h)	0.97 (0.90, 1.05)	0.454

medication management. The prior uterine surgery had a significant influence on the success of the mifepristone plus misoprostol treatment (Tables 1 and 3). Studies have reported that treatment with mifepristone could convert the inactive early pregnant uterus to an active organ and increase the sensitivity of the myometrium to prostaglandin [22]. A systematic review, including 7,858 women who underwent emergency peripartum hysterectomy, showed that 87% of them were multiparous [23]. Hence, we suspect that previous pregnancies could negatively affect the efficiency of uterine contractions. However, more research is needed to confirm that. Interestingly, a further dose of misoprostol could not increase the chance of successful miscarriage management, which indicated that the efficacy of mifepristone and misoprostol in cases of missed miscarriage may be more closely associated with factors beyond the drug dosage.

Climate change poses a major risk to reproductive health, which is especially pronounced among pregnant women [24]. Many studies have reported that meteorological factors were associated with miscarriage, preterm birth and complications of pregnancy [25–28], but the mechanisms were not clear. Our results showed that the 4 days average visibility during medication management had a significant influence on the success of the mifepristone plus misoprostol treatment (Tables 2 and 4).

Table 5 Multivariable logistic regression models
* indicates significant result

Variable	Multivariable	
	OR (95% CI)	p-value
Gestational age by ultrasound (days)	1.04 (0.99, 1.09)	0.072
History of parity (Numbers)	2.52 (1.16, 5.46)	0.019*
Prior uterine surgery	2.42 (1.14, 5.15)	0.022*
Use of supplemental vaginal misoprostol	3.53 (1.69, 7.38)	0.001*
4 days average visibility (km)	1.14 (1.01, 1.30)	0.038*

Visibility is related to airborne particulate matter (PM), which is a pollutant of concern [29, 30]. Animal experiments indicated that particulate matter exposure induces adverse effects on uterus [31, 32], while some clinical studies also demonstrated that particulate matter exposure raises the risks of unfavorable birth outcomes and pregnancy complications [33, 34]. Based on a consistent dose and administration of mifepristone and misoprostol for missed miscarriage patients, our study implied that the sensitivity of progesterone and prostaglandins may be affected by particulate matter in uterus.

Health care providers should fully communicate with patients about treatment options for missed miscarriage with a keen sense of what the patient strongly desires [2, 4]. It is highly likely that the duration of treatment may be most important for women, especially when the option is a vacuum aspiration that could be performed in a relatively short period of time. Hence, one of the primary problems is the definition of success for medical treatment. Currently, there are no clear international, evidence - based recommendations regarding the time frame for assessment and the optimal diagnostic tools to be utilized. Although many prior studies defined the outcome as failure to spontaneously pass the gestational sac within 7 days to 30 days [5, 19, 21], more than 90% of patients pass the complete gestational sac within 24 h after oral misoprostol dose. The criterion in our studies was failure to spontaneously pass the gestational sac within 24 h of misoprostol dose, which was chosen in line with previous studies and the stipulated baseline rate of completion [16, 35, 36], and this outcome could be assessed before the participant was discharged from the hospital.

This study also has several limitations. Firstly, although some factors were incorporated into our model, more potential factors were not included, which could influence the efficacy of medication management, such as socioeconomic status, the inter pregnancy interval, dietary practices and smoking or alcohol consumption, which are potential co-variates. These factors were outside the scope of the present study but warrant further investigation. Secondly, it is a retrospective case-control design. While this approach offers convenience, it may introduce certain biases. The sample size may lead to unrepresentative results, although the sample sizes of the control group ($n = 103$) and the case group ($n = 60$) achieve 96.445% power to detect an odds ratio of the group proportions of 3.5. Additionally, our model lacks external validation. Thirdly, this study was confined to the region of Nanjing, which may affect the extrapolation of the results. Fourthly, similar to other studies, we could not obtain individual exposure data but used average data from fixed meteorological monitoring stations for our analysis. Finally, we did not explore the lagged effects of meteorological factors.

The patients experiencing missed miscarriage could suffer from physical damage, such as excessive bleeding and infection, and psychological harm, including anxiety, depression, and post-traumatic stress disorder [17]. As risk factors increase, optimising medication management is important, and it must be tailored to the needs of the individual it serves. We hope that more studies will be designed to analyze the effectiveness and acceptability of different medical regimens for patients with various risk factors and our findings could have potential benefits for the update of clinical guidelines in the future.

Conclusions

This retrospective study demonstrates that the missed miscarriage patients who are parous or have had uterine surgery previously may suffer from a higher risk of unsuccessful medication management. The exposure to

reduced visibility had a significant influence on the efficacy of mifepristone and misoprostol, while supplementary administration of vaginal misoprostol could not increase the chance of successful miscarriage management. In order to provide further validation, future studies should consider conducting multicenter prospective trials with larger sample sizes.

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Author contributions
H. W and Y. H drafted the proposal and composed the main manuscript text. G. G and J. Z participated in the collection of the clinical data. X. Y collected the meteorological data. R. T, D. P, and J. W analyzed the data. J. L reviewed the evidence and prepared the tables. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
In compliance with the Declaration of Helsinki, this study received ethical approval from the Ethics Committee of The First Affiliated Hospital with Nanjing Medical University (2024-SR-651). Data used in this retrospective analysis were de-identified upon extraction from the electronic health records database to ensure confidentiality. This retrospective observational study was deemed exempt by the Ethics Committee, which waived the need for consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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