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Clinical application of low-dose misoprostol in the induced labor of 16 to 28 weeks pathological pregnancies (a STROBE-compliant article)

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Abstract

Oral mifepristone combined with rivanol lactate (rivanol) is commonly used in second-trimester pregnancy termination. However, rivanol is not suitable to premature rupture of membranes and oligohydramnios because amniocentesis is difficult. Mifepristone combined with misoprostol is suitable for the patients with oligohydramnios. In accordance with the misoprostol dosing recommendations by the International Federation of Gynecology and Obstetrics (FIGO), the incidences of uterine rupture and cervical laceration are relatively high in Chinese pregnant women. The aim of our study was to optimize misoprostol dosing regimen in terms of efficacy and safety in Chinese pregnant women.

We modified the Bishop Score, and then gave patients low-dose misoprostol according to the modified Bishop score. Based on the amniotic fluid volume (AFV) indicated by type-B ultrasonic instrument, the cases with AFV $\leq$2 cm receiving low-dose misoprostol combined with mifepristone and the cases with amniocentesis failure followed by receiving low-dose misoprostol combined with mifepristone were enrolled into study group, and the cases with AFV >2 cm receiving rivanol combined with mifepristone were enrolled into control group. The start time of uterine contractions, time of fetal expulsion, birth process, hospital day, successful induced labor rate, complete induced labor rate, and incomplete induced labor rate were observed and compared between the 2 groups.

There were significant differences in the start time of uterine contractions, time of fetal expulsion, birth process, and hospital day between the control group and the study group (all $P < .05$). The successful induced labor rate, complete induced labor rate, and incomplete induced labor rate were also significantly different between the 2 groups (all $P < .05$).

In the induced labor of 16 to 28 weeks pathological pregnancy, low-dose misoprostol can markedly improve the successful induced labor rate and complete induced labor rate, shorten the birth process and hospital day, and decrease uterine curettage rate and uterine rupture risk. Low-dose misoprostol combined with mifepristone is suitable to the induced labor of 16 to 28 weeks pathological pregnancy in Chinese women.

Abbreviations: AFV = amniotic fluid volume, d = day, FIGO = Federation International of Gynecology and Obstetrics, h = hour, PROM = premature rupture of membranes.

Keywords: bishop score, induced labor, mifepristone, misoprostol

1. Introduction

Pathological pregnancies, such as oligohydramnios, fetal anomaly, dead fetus, and premature rupture of membranes require termination of pregnancy by induced labor. Oral mifepristone combined with rivanol lactate (rivanol) could markedly shorten the start time of uterine contractions and the time of fetal expulsion, and could decrease vaginal bleeding and uterine curettage rate in second-trimester pregnancy termination for scarred uteruses.[1] However, rivanol is not suitable to premature rupture of membranes and oligohydramnios because amniocentesis is difficult. Mifepristone combined with misoprostol is suitable for the patients with oligohydramnios requiring the second-trimester pregnancy termination. However, base on the dosage of misoprostol recommended by Federation International of Gynecology and Obstetrics (FIGO), the incidences of uterine rupture and cervical laceration are relatively high in Chinese pregnant women.[2,3] Si[4] believed that low-dose misoprostol was safer and more economical than large-dose misoprostol. Therefore, the Chinese obstetricians seek to optimize misoprostol dosing to balance the risk of serious adverse event (e.g., uterine rupture) occurrence, while maintaining the labor induction effect. We modified Bishop Score, and then gave patients different low-dose misoprostol according to the modified Bishop score. Our results suggest that rivanol is not the best choice, and risk ratio is similar. This study has important clinical significance for the safe and effective application of misoprostol in second-trimester pregnancy termination for Chinese women.

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2. Materials and methods

All study methods were approved by the Ethics Committee of Hubei Maternal and Child Health Hospital. All the subjects enrolled into the study gave written informed consent to participate.

2.1. Subjects

From January 2017 to June 2017, 185 cases with 16 to 28 weeks gestation that underwent termination of pregnancy due to oligohydramnios, fetal anomaly, dead fetus, and premature rupture of membranes in our hospital were collected. Before induced labor, intrauterine pregnancy, placental attachment position, and incision thickness of scarred uterus were detected by type-B ultrasonic instrument in all patients. And preoperative blood routine, blood type, coagulation time, liver and kidney functions, electrocardiogram were also performed on all patients.

The inclusion criteria included oligohydramnios, fetal anomaly, dead fetus, and premature rupture of membranes with 16 to 28 weeks gestation; no contraindication for using mifepristone, misoprostol, and rivanol; and normal preoperative routine examinations. The exclusion criteria were poor conditions, such as cardio-cerebrovascular disease, severe anemia, abnormal liver and kidney function, and/or active tuberculosis; patients in acute stages of various diseases; patients with generative organ inflammation; patients with genital tract malformation; inevitable abortion with regular contractions; and patients with premature rupture of membrane asking to rescue fetus.

2.2. Grouping

We modified Bishop Score, and then gave patients different low-dose misoprostol according to the modified Bishop score. According to the amniotic fluid volume (AFV) indicated by type-B ultrasonic instrument, the cases with AFV $\leq$2 cm receiving low-dose misoprostol combined with mifepristone and the cases with amniocentesis failure followed by receiving low-dose misoprostol combined with mifepristone were enrolled into study group, and the cases with AFV >2 cm receiving rivanol combined with mifepristone were enrolled into control group. To verify our method, the results of low-dose misoprostol were compared with the results of the most traditional and common rivanol.

2.3. Induced labor

In the control group, oral 50 mg of mifepristone (25 mg per tablet, Hubei Gedian Renfu Pharmaceutical Co., Ltd., Wuhan, China) was given twice a day for 2 days. On the second day after oral mifepristone, under the guidance of type-B ultrasonic instrument, 100 mg of rivanol (Qinghai Pharmaceutical Co., Ltd.) was injected into the amniotic cavity. In the study group, according to the modified Bishop score (Table 1), for the patients with >6 scores, 50 μg of misoprostol (Piramal Healthcare UK Limited, Northumberland, UK) was applied to the posterior vaginal fornix; for the patients with 4 to 6 scores, oral 50 mg of mifepristone twice a day for 1 day followed by applying 100 μg or 200 μg of misoprostol (100 μg of misoprostol for the patients with 24- to 28-week gestation and 200 μg of misoprostol for the patients with <24-week gestation) to the posterior vaginal fornix; for the patients with <4 scores, oral 50 mg of mifepristone twice a day for 2 days followed by applying 100 μg or 200 μg of misoprostol (100 μg of misoprostol for the patients with 24- to 28-week gestation and 200 μg of misoprostol for the patients with <24-week gestation) to the posterior vaginal fornix. If the patients had no regular uterine contractions 6 hours after administration, 100 μg or 200 μg of misoprostol (100 μg of misoprostol for the patients with 24- to 28-week gestation and 200 μg of misoprostol for the patients with <24-week gestation) was again applied to the posterior vaginal fornix. After fetal expulsion, 20 IU of oxytocin was intramuscularly injected in all patients.

Table 1

The modified Bishop rating scale.

Items	Scores				
	0	1	2	3	4
Cervical dilatation, cm	0	0.5–1	1–2	3–4	5–6
Cervical length, cm	>2	1.1–2	0.5–1	<0.5	
Cervical hardness	Hard	Moderate	Soft		
Cervical position	Posterior	Middle	Anterior		

2.4. Outcome measures

The start time of uterine contractions: the duration from the first administration (rivanol or misoprostol) to the first uterine contraction; the time of fetal expulsion: the duration from the first administration (rivanol or misoprostol) to fetal expulsion; birth process: the duration from the first uterine contraction to fetal expulsion; vaginal hemorrhage volume: a total of vaginal hemorrhage from the first uterine contraction to 24 hours after fetal expulsion; and adverse reactions: cervical laceration and adverse drug reactions.

2.5. Evaluation of induced labor

Successful induced labor included complete induced labor and incomplete induced labor. Complete expulsion of fetus and placenta was regarded as complete induced labor. The residues of partial placenta or fetal membrane which required uterine curettage, were regarded as incomplete induced labor. Failed induced labor referred to no regular uterine contractions 72 hours after administration without fetal expulsion.

2.6. Indications of curettage

Any of the following items required uterine curettage: >100 mL of vaginal hemorrhage within 30 minutes after fetal expulsion; no placental expulsion 1 hour after fetal expulsion; >100 mL of vaginal hemorrhage after fetal and placental expulsions; obvious defect of placenta or fetal membranes; and intrauterine residue indicated by type-B ultrasonic instrument 3 to 7 days after induced labor. B-mode ultrasound was performed on the patients with <20-week gestation 3 days after induced labor; while in the patients with >20-week gestation, B-mode ultrasound was performed 7 days after induced labor. Uterine curettage was immediately performed when vaginal hemorrhage was >100 mL within 1 hour after induced labor. If there was intrauterine residue but vaginal hemorrhage was less, uterine curettage was performed on the first day after B-mode ultrasound examination.

2.7. Statistical analysis

Statistical analysis was performed with SAS9.4 software (SAS Company, North Carolina, USA). The data were summarized

Table 2

Comparison of general data between the 2 groups.

Grouping	Age, y	Number of births (n)	Gestational week	Fetal deformity (n)	Uterine-incision delivery (n)	PROM (n)	Dead fetus (n)
Control group	31.20±5.06	1.47±1.03	21.42±4.01	15	29	12	33
Study group	30.82±4.21	1.73±1.25	21.45±4.00	13	31	17	30
$t/z/\chi^2$ values	0.45	–1.0697	–0.2362		1.1924		
P values	.6527*	.2848†	.8132†		.7548‡		

PROM = premature rupture of membranes.
* Independent samples *t* test.
† Wilcoxon rank test.
‡ Chi-square test.

with descriptive statistics. The frequencies of qualitative data were compared with chi-square test across groups. Quantitative data (summarized and mean and standard deviation) were compared between groups with independent samples *t* test (normal distribution) or Wilcoxon rank test (non-normal distribution). Statistical significance was established at $P < .05$.

3. Results

3.1. General data

According to the inclusion and exclusion criteria, a total of 120 cases were enrolled into this study. In this study, 54 cases receiving low-dose misoprostol combined with mifepristone and the 6 cases with amniocentesis failure followed by receiving low-dose misoprostol combined with mifepristone were allocated into the study group (60 cases), and other 60 cases receiving rivanol combined with mifepristone were allocated into control group (60 cases). Their average age was (31.00±4.64) years, average gestational week was (21.43±3.99), and average number of births was (1.6±1.15) times. The general data including age, gestational week, number of births, and scarred uterus were comparable between the 2 groups (all $P > .05$, Table 2).

3.2. Comparison of outcome measures

There were significant differences in the start time of uterine contractions, time of fetal expulsion, birth process, and hospital day between the control group and the study group (all $P < .05$). Vaginal hemorrhage did not show a significant difference between the 2 groups ($P > .05$) (Table 3).

3.3. Induced labor outcome

In the 60 cases of the control group, 29 cases had scarred uterus. Of the 60 cases, 50 cases underwent successful induced labor. In the 50 cases, 10 had complete induced labor and 40 had incomplete induced labor. Fetal and placental expulsions were performed within 24 hours in 6 cases, within 24 to 48 hours in 39 cases, and within 48 to 72 hours in 5 cases. Failed induced labor occurred in 10 cases including premature rupture of membrane in 8 cases, dead fetus in 1 case, and fetal anomaly in 1 case. And then 50 to 200 μg of misoprostol was used to obtain successful induced labor in the 10 cases (Table 4). B-mode ultrasound-guided uterine curettage was performed for incomplete induced labor. In the 60 cases of the study group, 31 cases had scarred uterus. The 60 cases all underwent successful induced labor including 37 with complete induced labor and 23 with incomplete induced labor. In the 15 patients with >6 scores, fetal and placental expulsions were performed within 4 hours after administration of misoprostol. In other 45 patients, fetal and placental expulsions were performed within 4 to 15 hours after administration of misoprostol. Of the 45 cases, fetal and placental expulsions were performed within 4 to 7 hours after the first administration of misoprostol in 38 cases; while in other 7 cases, fetal and placental expulsions were performed after the second administration of misoprostol. The successful induced labor rate, complete induced labor rate, and incomplete induced labor rate were also significantly different between the 2 groups (all $P < .05$) (Table 4).

3.4. Adverse reactions

Nausea and vomiting occurred in 3 cases of the control group and in 2 cases of the study group. All patients had no other adverse reactions such as fever, shivering, vaginal or cervical laceration, and uterine rupture.

4. Discussion

Termination of pregnancy is necessary for 14 to 28-week pathological pregnancies by induced labor. For mid trimester of pregnancy, induced labors include medical induction of labor and

Table 3

Comparison of outcome measures between the 2 groups.

Grouping	Cases (n)	Start time of uterine contraction, h	Time for fetal delivery, h	Birth process, h	Vaginal hemorrhage, mL	Hospital day, d
Control group	60	29.84±9.48	38.18±9.51	8.33±4.59	34.52±9.37	8.56±0.79
Study group	60	1.21±0.51	7.50±2.47	6.29±2.48	32.42±7.39	5.00±0.80
z values	–	9.3693	9.2093	2.1253	1.0720	9.6153
P values	–	<.0001*	<.0001*	.0336*	.2837*	<.0001*

d = day, h = hour.
* Wilcoxon rank test.

Table 4

Comparison of successful induced labor rate, complete induced labor rate, and incomplete induced labor rate between the 2 groups.

Grouping	Cases (n)	Successful cases (n)	Failed cases (n)	Complete induction (n)	Incomplete induction (n)
Control group	60	50	10	10	40
Study group	60	60	0	37	23
Chi-squared values		–		19.3488	
P values		.0013*		<.0001†	

* Fisher exact probability.

† Chi-square test.

surgical induction of labor. The most common medical induction of labor is intraamniotic injection of rivanol.[5] Li[6] reported that 12 cases with mid trimester of pregnancy had uterine rupture and cervical laceration in 5268 cases receiving intraamniotic injection of rivanol.

In this study, the successful induced labor rate of mifepristone combined with rivanol was 83.33% (50/60). In the 10 cases with failed induced labor, 8 cases had premature rupture of membranes. This may be that the injected rivanol flowed out from the ruptured amniotic cavity, and the concentration of rivanol was too low to induce uterine contractions. Mifepristone combined with misoprostol obtained successful induced labor in all patients. Therefore, for the patients with premature rupture of membranes, mifepristone combined with misoprostol should be a better choice for induced labor.

Intraamniotic injection of rivanol is not suitable to oligohydramnios, dead fetus, and premature rupture of membranes. Since mifepristone was synthesized in 1981, mifepristone combined with misoprostol has been used in second-trimester pregnancy termination.[7] Cervical laceration and uterine rupture caused by mifepristone combined with rivanol or mifepristone combined with misoprostol, have been reported, and especially in scarred uteruses. In 66 cases with scarred uteruses, uterine rupture occurred in 3 cases including 1 case caused by mifepristone and 2 cases caused by rivanol.[8] Wang[9] reported that uterine rupture occurred in 6 cases with scarred uteruses during second-trimester pregnancy termination performed using misoprostol. Therefore, obstetricians face a challenge to find an appropriate dosage of misoprostol for carrying out second-trimester pregnancy termination without uterine rupture.

For termination of pregnancy before 28-week gestation, the regimen of single-use misoprostol recommended by FIGO in 2017 is as follows: 400 μg every 3 hours for 13- to 24-week gestation (per vagina, sublingually, buccal mucosa); 400 μg every 4 hours for 25- to 26-week gestation; 200 μg every 4 hours for 27- to 28-week gestation. For dead fetus: 200 μg every 4 to 6 hours in 13- to 24-week gestation; 100 μg every 4 hours in 27- to 28-week gestation. For inevitable abortion: 200 μg every 6 hours in 13- to 26-week gestation.[10] If mifepristone is available, mifepristone combined with misoprostol should be adopted. Pongsatha and Tongsong[11] reported that the clinical effects of induced labor were similar in vaginal misoprostol 600 and 400 μg, but adverse reactions were more severe in 600 μg than in 400 μg. Gao[12] reported that a case with scarred uterus was in 4-month gestation, 400 μg of vaginal misoprostol led to uterine rupture 36 hours after 250 mg of oral mifepristone. Syed et al[13] also reported that vaginal misoprostol led to uterine rupture. Vaginal administration of misoprostol can produce high concentration of misoprostol acid which will last for a long time in pregnant women with higher bioavailability than oral and sublingual administration of misoprostol, reducing the dosage of misoprostol and clinical side effects of misoprostol.[14] Powers et al[15] believed that misoprostol acid might reach the maximum plasma concentration 5 to 9 hours after vaginal misoprostol. The sensitivity to misoprostol varies according to patients' different conditions, it is necessary to find an objective index to determine the dosage of misoprostol.

Bishop score is usually used to predict delivery mode for late pregnancy. We modified the Bishop score. Fetal presentation scoring was deleted from the Bishop score because the fetal head does not enter the pelvis for 16 to 28-week fetus. The degree of cervical canal regression was changed to cervical canal length in the modified Bishop score. The higher the score is, the greater the successful possibility of induced labor is and the smaller the dosage of misoprostol is. In this study, only 50 μg of vaginal misoprostol was used in the patients with Biship score >6, because mature and softer cervix, coupled with softening and expanding effects of misoprostol on the cervix, could achieve fetal expulsion. For the patients with low Bishop score, oral mifepristone was given first, which made cervix mature and shortened, and increased the sensitivity of uterine smooth muscle to prostaglandin, followed by vaginal administration of appropriate low-dose misoprostol.

Misoprostol is absorbed directly through the arteriovenous plexus of uterine artery without requirement of metabolism in the liver. The absorbed misoprostol first promotes cervical softening and dilatation, and then causes uterine smooth muscle contraction when misoprostol reaches the peak value 5 to 9 hours after vaginal administration. High-dose vaginal misoprostol may induce strong uterine smooth muscle contraction. Cervical maturity does not match the uterine smooth muscle contraction, easily leading to vaginal bleeding, cervical laceration, uterine rupture and even amniotic fluid embolism. At the same time, the incidence of side effects such as fever, diarrhea, and shivering is also increased due to high-dose misoprostol. Therefore, under ensuring successful induction of labor, the dose of misoprostol is less as much as possible. In this study, there were no serious side effects such as gastrointestinal reaction, fever, cervical laceration, uterine rupture, or heavy vaginal bleeding because the low-dose misoprostol was directly absorbed by the vagina, and uterine contractions as well as cervical maturity were consistent. Because of individual differences, the patients' absorption and sensitivity to misoprostol were different. Most patients give birth 4 to 7 hours after the first vaginal administration of low-dose misoprostol; but in 7 patients, regular uterine contractions required the second vaginal administration of misoprostol. After the modified Bishop score was used to guide the dosage of misoprostol in this study, although the dosage of misoprostol was small, fetal expulsion was still successful and no severe events such as amniotic fluid embolism, uterine rupture, and cervical laceration occurred even in scarred uterus. Clouqueur et al[16] reported that in order to avoid uterine rupture in the patients with scarred uterus, the dose of misoprostol was increased by no more than 100 μg during cesarean section, which is similar to this study.

4.1. Limitations

In this study, there were some limitations. First, sample size was relatively small, so our result remains to be further confirmed by large sample. Secondly, we failed to observe the influences of misoprostol on menstruation and fertility because the follow-up period was short. We will further collect sample and prolong follow-up period in future studies.

5. Conclusion

Our results suggest that both mifepristone combined with rivanol and mifepristone combined with low-dose misoprostol guided by our modified Bishop score may be used in induced labor for 16 to 28-week pathological pregnancies. However, mifepristone combined with low-dose misoprostol guided by the modified Bishop score is more effective in induced labor, because it can shorten birth process and hospital day, and has better clinical manipuility. The dosage of misoprostol guided by the modified Bishop score is worth spreading.

Author contributions

Conceptualization: Yan Yang.
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