The method for termination of mid-trimester pregnancy with placenta previa
A case study

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Abstract
Background: Prenatal bleeding is very dangerous for pregnant women with placenta previa during termination of pregnancy in the mid-trimester. Traditionally, cesarean section or hysterectomy is used to stop bleeding. This study aims to investigate the method for termination of mid-trimester pregnancy with placenta previa, especially emergency uterine artery embolization (UAE) combined with cervical double balloon (CDB).

Methods: A retrospective study was conducted based on 261 cases of mid-pregnancy termination in our hospital, where 34 cases with placenta previa were set as the observation group, and the remaining 227 cases were set as control group. At first, the termination method of Mifepristone combined with Misoprostol/Ethacridine Lactate was adopted. If the volume of prenatal bleeding was up to 400 mL, emergency uterine artery embolization (UAE) was implemented to stop bleeding, then cervical double balloon (CDB) was used to promote cervical ripening. Receiver operating characteristic (ROC) curves analysis was performed to assess the accuracy in predicting the length of placental edge crossed the cervical os for prenatal bleeding.

Results: The number of gravidity/parities, the rate of cesarean section, the medical cost, the rate of previous cesarean section were all higher in the observation group than in the control group ($P < .05$). The volume of prenatal hemorrhage, postpartum hemorrhage, the rate of puerperal morbidity, emergency UAE rate and ICU rate were higher in the observation group than in the control group ($P < .05$). There were 4 cases showing prenatal hemorrhage up to 400 mL and undergoing emergency UAE + CDB in the observation group, while there were no such cases in the control group ($P < .05$). An optimal cut-off value of 1.7 cm for the length of placental edge crossed the cervical os in diagnosing prenatal hemorrhage demonstrated sensitivity and specificity of 75.0% and 86.7%, respectively (area under the ROC curve, 0.858).

Conclusion: The combined therapy of mifepristone and Misoprostol/Ethacridine Lactate was useful for termination of mid-trimester pregnancy with placenta previa, and attention needs to be attached to prenatal hemorrhage during labor induction. Emergency UAE + CDB is a good combination method to treat prenatal hemorrhage and promote cervical ripening during the induction.

Abbreviations: 95% CI = 95% confidence interval, CDB = cervical double balloon, DIC = disseminated intravascular coagulation, UAE = uterine artery embolization.

Keywords: cervical double balloon, ethacridine lactate, mid-trimester, misoprostol, placenta previa, uterine artery embolization
1. Introduction

Low-positioned placenta can be classified into placenta previa and low-lying placenta.[1–3] The placenta previa is defined as the placenta partially or completely covering the internal os. In contrast, the low-lying placenta is defined as the placenta that is partially implanted in the lower uterine segment with the length from the lower edge of the placenta to the internal cervical os <20 mm. Placenta previa as a major risk factor for prepartum and/or postpartum hemorrhage can lead to morbidity and mortality of pregnant women and neonate. For pregnancy with placenta previa, cesarean delivery is normally needed.[4,5] With the development of prenatal diagnosis technology, an increasing number of fetal anomalies are found during mid-pregnancy by ultrasound, karyotype analysis or microarray.[4,5] If a pregnant woman with placenta previa needs to undergo termination of mid-pregnancy due to severe fetal malformation, stillbirth, the risks of massive hemorrhage, disseminated intravascular coagulation (DIC), hysterec-tomy and other adverse outcomes may be high, or even the safety of maternal life will be threatened.[3]

How to successfully terminate mid-pregnancy combined with placenta previa, reduce the amount of bleeding and protect the reproductive function of pregnant women is a big challenge. Mifepristone combined with Misoprostol and/or Ethacridine Lactate is chosen for the termination of second-trimester pregnancy with/without placental previa.[6,7] Uterine artery embolization (UAE) has been widely used for treating postpartum hemorrhage, cesarean scar pregnancy, placenta accrete spectrum.[6,8,9] Some researchers have made attempts to use prophylactic UAE to prevent hemorrhage during the termination of mid trimester pregnancy with placenta previa,[6] but the problem is that the overuse of UAE may bring more complications such as severe pain after UAE, ovarian failure, irregular menstruation or affected fertility.[6,11–13] In our study, we retrospectively analyzed the pregnant women with placenta previa who underwent termination of mid-pregnancy in our hospital from January 1st, 2019, to December 31th, 2019, and discussed the labor inducing methods used for them.

2. Methods

2.1. Participants and methods

This study was conducted from January 1, 2019, to December 31, 2019 in our hospital, a tertiary-care teaching hospital in Wuhuan city, Hubei province, in the central of China.

2.2. Ethical approval

The study was a retrospective study. The study protocol was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology ([2019] IEC (XM008)), and it was complied with the Helsinki Declaration formulated in 1975 and revisd in 1983. All parturient women requiring termination of pregnancy in this work signed informed consent for therapeutic procedures and for the publication of this paper.

2.3. Data sources

This retrospective study was based on the data from the maternity department of a tertiary-level public hospital in Wuhan city, Hubei province, China, with annual number of newborn babies of around 25,000 in recent 5 years. The delivery data were collected from the hospital information system from January 1, 2019 to December 31, 2019. A total of 295 cases were included in our study, of which 10 cases with incomplete information, 21 cases of spontaneous abortion, and 3 cases of liver/kidney dysfunction using Cervical Double Balloon (CDB) were excluded. Therefore, a total of 261 cases were finally included (accounting for 88.5% of total data). Of finally selected cases, 37 cases were stillbirth, and 224 cases were malformations confirmed by ultrasound or/and chromosomal abnormalities. According to placenta position, patients with placenta previa were collected in the observation group (n = 34), the other patients were enrolled in the control group (n = 227) (Fig. 1).

2.4. Methods of labor induction

2.4.1. Conventional methods of labor induction on admission.

All patients requiring induced labor were managed by the same obstetric group. All selected cases were assessed by 3 experienced obstetricians. The labor inducing procedures were approved by the biological parents of the fetus in the outpatient department. After admission, they were asked to sign the informed consent for induction of labor. The placentas of all cases were routinely examined by transvaginal ultrasound on admission. The labor inducing method was adopted based on gestational weeks. If the gestational age was less than or equal to 16 weeks, Mifepristone (Simian®, Purple Bamboo Pharmaceutical Co., Ltd, Anhui, China) combined with Misoprostol (Purple Bamboo Pharmaceutical Co., Ltd, Anhui, China) was used. Mifepristone was taken orally with a total dose of 300 mg (50 mg, Bid*3d), and then vaginal medication of Misoprostol was carried out at 8AM on the 4th day (100ug, Q6h). If the gestational age was more than 16 weeks, Mifepristone combined with Ethacridine Lactate (Rivanol®, Hefeng Pharmaceutical Co., Ltd, Guangxi, China) was used. After oral administration of Mifepristone with a total dose of 300 mg, Ethacridine Lactate(100mg) was injected into the amniotic cavity under ultrasound guidance.

2.4.2. Special method of labor induction for prenatal bleeding.

As contractions intensify, the use of drugs to induce labor can lead to prenatal bleeding due to placenta previa for some cases. If the volume of prenatal bleeding was up to or equal to 400mL, emergency UAE was implemented first to stop bleeding, and then CDB (Cervical Ripening Balloon; Cook OB/GYN, Spencer IN. USA) was applied immediately. After 24 hours, the CDB was removed, and 0.5%–1.0% oxytocin was used to augment contractions till the delivery of fetus and placenta. Curettage can be conducted when necessary to take out the fetus and placenta under ultrasound guidance just in case of high fever or antepartum bleeding again.

If the cervical condition was still immature after applying Misoprostol/Ethacridine Lactate for 72 hours in the control group, CDB was used to promote cervical ripening. After 24 hours, the CDB was removed, and curettage can be used, when necessary, just in case of high fever or prenatal bleeding.

The cases with CDB were defined as the comprehensive-induction, and the others without CDB were defined as the simple-induction.

If all those methods failed, cesarean section may be conducted to delivery fetus and placenta. CDB[14]: The patient emptied the bladder and took the lithotomy position and disinfected. Then the obstetricians gently inserted the 5F catheter sheath and catheter into the left uterine sound or/and chromosomal abnormalities. According to placenta position, patients with placenta previa were collected in the observation group (n = 34), the other patients were enrolled in the control group (n = 227) (Fig. 1).
artery for arterial subtraction, perfused Gentamicin 80,000 units, and embolized with gelatin sponge. The right uterine artery was cannulated, perfused and embolized too. After the operation, the catheter and sheath were pulled out before applying the local pressure bandage. The right lower limb was immobilized for 6h, and perioperative antibiotics were given to prevent infection.

2.5. Observational indexes

The observational indexes included maternal age, gravidity, parity, body mass index, terminated gestational week, the history of cesarean section, placenta position, method of labor induction, induction time, antenatal hemorrhage, postpartum hemorrhage, curettage, manual removal of placenta, puerperal morbidity, and proportion of ICU cases, impatient days, and hospitalization cost.

2.5.1. The time for labor induction. The time of labor induction time by using Mifepristone combined with Misoprostol was counted from the insertion of the first tablet of Misoprostol to the delivery of fetus and placenta. The time of labor induction by using Mifepristone combined with Ethacridine Lactate was counted from intraamniotic injection of Ethacridine Lactate to delivery of fetal and placenta. The labor induction time for the comprehensive labor induction cases was counted from using Misoprostol or Ethacridine Lactate to the delivery of fetal and placenta.

2.5.2. ICU transfer criteria. The cases with massive hemorrhage during labor induction required intrauterine balloon tamponade, UAE, or suspected sepsis.

2.6. Statistical analysis

Statistical analysis was performed with software SPSS (v.25.0, SPSS Inc, Chicago, IL). The values and variables are reported as the means ± standard deviation, Student t-test was performed to compare the variables in a Gaussian distribution. The chi-square test and Fisher exact test were conducted to evaluate the categorical variables. The Wilcoxon test was carried out to evaluate the difference in a non-Gaussian distribution between the 2 groups. Pearson correlation coefficient was used to find the sensitive indicators for prenatal hemorrhage. Receiver operating characteristic (ROC) curves analysis was performed to assess the predictive accuracy. The difference was considered statistically significant when \( P < .05 \).

3. Result

3.1. The comparison of general information of maternity

The median(min–mix) numbers of gravidity and parity were 3 (1–10) and 0 (0–3) in the observation group, which were higher than those in the control group [2 (1–7), 0 (0–2)] (\( P < 0.05 \)). The rate of previous cesarean section in the observation group was 35.3% (12/34), which was higher than that in the control group.
that in the control group (31.0h, 4.7–86.3h) (P > 0.05). The average amount of postpartum hemorrhage in the observation group was 326.2 mL, which was larger than that in the control group (278.5 mL, P < 0.05), and the rates of prenatal hemorrhage, postpartum hemorrhage, puerperal infection, transferred to ICU in the observation group were 11.8% (4/34), 17.6% (6/34), 50.0% (17/34), 11.8% (4/34), which were higher than those (0% (0/227), 2.2% (5/227), 17.6% (40/227), 0.4% (4/227)) in the control group (P < 0.05). The data are shown in Table 4.

### 3.4. The sensitive indicators for prenatal hemorrhage in the observation group

There were 4 cases undergoing emergency UAE + CDB for prenatal hemorrhage in the observation group. Maternal age, gravidity, parity, gestational age on termination, BMI on admission, prior cesarean section had no relationship with prenatal bleeding (P > 0.05), only the exceeding length of placenta over the internal os was the sensitive indicator for prenatal hemorrhage (P < 0.05). An optimal cut-off value of 1.7 cm for the exceeding length of placenta over the internal os in diagnosing prenatal hemorrhage demonstrated sensitivity and specificity of 75.0% and 86.7%, respectively (area under the ROC curve, 0.858) (P < 0.05), as shown in Table 5 and Fig 2.

### 4. Discussion

At present, the common methods for termination of pregnancy in China include Mifepristone and Misoprostol for the patients with the gestational age less than and equal to 16 weeks, intraamniotic injection of Ethacridine Lactate for those with gestational age over 16 weeks.[16,17] For pregnant women with placenta previa, Mifepristone + Misoprostol and Mifepristone + Ethacridine Lactate are effective and safe methods for termination of mid-trimester pregnancy.[18] As an acceptable method of labor induction, CDB can be safely applied to pregnant women who undergo vaginal delivery with term pregnancy,[19] or to those with history of cesarean section.[20] CDB is also an alternative method for the application of Misoprostol or Ethacridine Lactate in the mid-trimester.[20] In our observation, Mifepristone combined with Misoprostol or Ethacridine Lactate (88.2%, 30/34) are effective methods for termination of mid-trimester pregnancy with placenta previa, and for termination

#### Table 2

Methods of inducing labor in observation group and control group.

| Group          | n  | Mifepristone with Ethacridine Lactate (n) | Mifepristone with Misoprostol (n) | UAE + CDB(n, %) | CDB(n, %) |
|----------------|----|----------------------------------------|----------------------------------|----------------|----------|
| Observation group | 34 | 29                                      | 5                                | 4, 11.8        | 0, 0     |
| Control group   | 227| 203                                     | 24                               | 0, 0.0         | 6, 1.3   |
| p              |    | 0.511                                   | 0.474                            | 0.000          | 0.000    |

CDB = cervical double balloon, UAE = uterine artery embolization.
Chi-square analysis and Fisher exact test were used.

#### Table 1

The comparison of general information of maternity.

| Groups          | Observation group (n = 34) | Control group (n = 227) | U/Z/X² | P    |
|-----------------|---------------------------|-------------------------|--------|------|
| Age (y, X± s)   | 30.4 ± 5.7                | 29.6 ± 4.9              | −0.898 | 0.370|
| Gravidity (Median, min-mix) | 3.1–10                    | 2.1–7                   | −2.171 | 0.030|
| Parity (Median, min-mix) | 0, 0–3                    | 0, 0–2                  | −1.985 | 0.047|
| Previous cesarean section (n, %) | 12, 35.3                  | 45, 19.8               | 4, 14.6 | 0.042|
| Married (n, %)  | 31, 91.2                  | 221, 97.4               | 3, 393 | 0.065|
| Maternity insurance (n, %) | 8, 23.6                   | 63, 27.8                | 0.266  | 0.606|
| Gestational age (week, X± s) | 21.6 ± 3.3                | 22.7 ± 3.3              | 1.654  | 0.099|
| Body mass index (kg/m², X± s) | 23.4 ± 2.8                | 23.0 ± 3.3              | −0.723 | 0.470|
| Hospitalization days (d, X± s) | 8.5 ± 1.9                 | 8.2 ± 1.2               | −1.332 | 0.184|
| Hospitalization expenses (RMB, Median(95%CI)) | 4145.0 (2060.7–24661.0) | 3631.4 (2682.8–11517.8) | 0.024 | 0.042|

T test, Wilcoxon test, Chi-square analysis, and Fisher exact test were used.
of mid-trimester pregnancy with normal placenta (97.4%, 221/227). For the pregnancy with placenta previa, the amount of postpartum hemorrhage, and the rates of prenatal hemorrhage, postpartum hemorrhage, UAE + CDB (8.8%, 4/34) were higher than the pregnancy with normal placenta. Our results are consistent with the results of previous studies.\(^\text{[9,22]}\)

How to prevent and deal with prenatal hemorrhage in the process of termination of mid-trimester with placenta previa? It is safe and effective to conduct prophylactic UAE before curettage in patients with cesarean scar pregnancy.\(^\text{[9]}\) However, whether to use prophylactic UAE for termination of mid-pregnancy with placenta previa remains debated.\(^\text{[6,23]}\) He et al\(^\text{[9]}\) analyzed 85 cases with complete placenta previa for termination of second-trimester pregnancy, in which 20 cases were treated with cesarean delivery, 30 cases with Mifepristone + Ethacridine Lactate combined with prophylactic UAE, and 35 cases with Mifepristone + Ethacridine Lactate. The results showed that the cases undergoing Mifepristone + Ethacridine Lactate combined with prophylactic UAE had the lowest amount of blood loss during induction and labor, and the highest incidence of fever; and there were 13 patients undergoing emergency UAE and 2 patients undergoing cesarean cesarean section in the cases using Mifepristone + Ethacridine Lactate. Wang et al\(^\text{[9]}\) found there were 15 patients with complete placenta previa undergoing mid-trimester pregnancy termination by prophylactic UAE (n = 15) and 10 patients undergoing mid-trimester pregnancy termination without prophylactic UAE (n = 10), between which there were no significant differences in the rate of success abortion, the bleeding volume, induction-abortion time, but the hospital stay was longer, and pyrexia was more common in the cases with prophylactic UAE. So, prophylactic UAE was not recommended for second-trimester abortion with complete placenta previa. Most second-trimester low-positioned placentas have a higher position in the third trimester, without posing any risks.\(^\text{[24,25]}\) Charlotte et al\(^\text{[24]}\) found that only 14% (37/313) still had a placenta previa in the third trimester. Jennifer et al\(^\text{[25]}\) found that the probability of resolution from low-lying placenta or placenta previa in the mid-trimester to normal placenta was inversely proportional to the distance from the internal os: 99.5% (≥10–20 mm), 95.4% (0.1–10 mm), and 72.3% (placenta previa). In our clinical observation, of 34 cases with placental previa, only 4 cases needed emergency UAE to stop bleeding, and 0 case had prenatal bleeding in the control group. At the same time, due to the complications of UAE,\(^\text{[9,11–13]}\) such as severe pain, ovarian failure, irregular menstruation, or impacted fertility, so prophylactic UAE is better choice than emergency UAE after bleeding for high-risk cases. Our study found that the length of placenta over the internal os was a sensitive indicator of prenatal hemorrhage, and the optimal cut-off value for 1.7 cm for the length of placenta over the internal os in diagnosing prenatal hemorrhage demonstrated sensitivity and specificity of 75.0% and 86.7%, respectively, and the internal area was 0.835.

Immature cervical condition is the other risk factor for termination of mid-trimester pregnancy.\(^\text{[20]}\) We should use comprehensive induction methods including CDB to deal with them and try to avoid cesarean section. Patients with placenta previa will show prenatal hemorrhage if there is an immature cervical condition under strong uterine contractions. In our study, the rate of prenatal hemorrhage (40% vs 0%) was higher in the patients with placental previa. After UAE, the uterus was hypoxic, the placenta and fetus remained in the uterus, which may lead to intrauterine infection, fever, and even septicemia. So, CDB was performed to ripen cervix immediately. The combined labor induction method of UAE + CDB is effective in prevention of prenatal hemorrhage and cervical ripening for patients with placenta previa.\(^\text{[10]}\) It is better to set the labor induction time for mid-trimester pregnancy using CDB to 24h.\(^\text{[14]}\) Antenatal hemorrhage occurred in 4 cases with placenta previa when induction, so the combined method of UAE + CDB was adopted, which led to successful delivery of delivered fetus and placenta.

### 5. Conclusion

For the pregnant women with placenta previa in mid-pregnancy, the conventional induction method by using Mifepristone combined with Misoprostol/Ethacridine Lactate may be useful, but the risk of prenatal hemorrhage will be higher. To this end, UAE + CDB maybe a new combined method to deal with antepartum hemorrhage, promote cervical conditional ripening, and allow short labor induction time for pregnant women with placenta previa.

### 5.1. Limitations

First, this study was a retrospective study in which the data were only collected from patients’ medical records. Second, there was only 4 mid-pregnancies with placenta previa undergoing UAE + CDB to deal with prenatal hemorrhage and promote cervical conditional ripening for labor induction.

Last, placenta previa in the second trimester is very common compared to a full-term pregnancy. We found the length of placenta over the internal os was a sensitive indicator of prenatal hemorrhage. In the next step, we will use prophylactic UAE instead of emergency UAE if the length of placenta over the internal os is >1.7 cm.
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