A Retrospective Study on the Clinical Effect of Uterine Artery Embolization Combined with Cervical Double Balloon for Patients with Complete Placenta Previa Undergoing Pregnancy Termination in the Second Trimester

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Research Article

Keywords: uterine artery embolization (UAE), complete placenta previa (CPP), second trimester, termination of pregnancy, cervical double balloon (CDB)

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A retrospective study on the clinical effect of uterine artery embolization combined with cervical double balloon for patients with complete placenta previa undergoing pregnancy termination in the second trimester

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Abstract

Pregnancy termination in the second trimester is a complex and delicate situation for patients with complete placenta previa (CPP), which has less been reported. The objective of this research was to investigate and evaluate the clinical effect of uterine artery embolization (UAE) combined with cervical double balloon (CDB) for patients with CPP.

Methods

We conducted a retrospective study based on a large medical center. The medical records of patients who were diagnosed with CPP and treated UAE combined with CDB for termination in the second trimester in our hospital from January 2017 and March 2021 were retrospectively reviewed. The clinical outcomes were analyzed.

Results

A total of 11 patients with CPP were included in this study. Prenatal diagnosis of CPP was realized by trans-vaginal ultrasound. The average age was 34.2 years old, and the gestational week was 21.6 weeks. Of the selected patients, 3 cases (3/11) had previous caesarean delivery, 5 cases were at older maternal age (≥35 years old), 10 cases underwent emergency UAE for prenatal bleeding equal or up to 400 mL and 1 case underwent prophylactic UAE for placenta percreta, and all cases underwent CDB to promote cervical ripening. It was worth noting that 5 cases (5/11) of selected patients underwent curettage to take out fetus and placenta.

The uterus preservation was achieved in all 11 patients. The complications associated with conservative management included prenatal hemorrhaging (10/11), blood transfusion (5/11), fever (2/11), and septicemia (1/11). The mean dilation of cervix was from 0cm to 1.9cm, the length of cervix was from 3.5cm to 0.6cm and the Bishop scores were from 1.5 to 7.3 after using CDB, the changes of cervical conditions were statistically significant (p<0.05). The levels of WBC and CRP were higher after termination with medicine+UAE+CDB and/or curettage.
Conclusion

The adjuvant therapy of UAE, CDB, and curettage step by step is a preferred choice for patients with CPP who underwent pregnancy termination in the second trimester.

Keywords

uterine artery embolization (UAE), complete placenta previa (CPP), second trimester, termination of pregnancy, cervical double balloon (CDB)
Complete placenta previa (CPP) hinders the normal delivery channel of cervix, causing severe bleeding and other complications, and even death \(^1\). The etiology of CPP is currently unclear. Placental migration, maternal age, pregnancy times, history of caesarean section, uterine cavity operation, abortion, and assisted reproductive technology are risks for CPP \(^1\). With the release of universal two-child policy, more elder women with a history of caesarean section choose to have pregnancy again \(^2\), and they are more prone to fetal death, malformation and CPP in the second trimester of pregnancy. In clinical practice, the proportion of pregnancy termination in the second trimester with CPP is also increasing. However, there are limited data on pregnancy termination in the second trimester for patients with CPP in the literature. Mifepristone combined with ethacridine lactate or misoprostol are medicine methods for induction in the second trimester for pregnant women with CPP in China. Therefore, it is very important to find a suitable induction method for patients with CPP. To deal with prenatal bleeding during medicine induction, emergency or prophylactic uterine artery embolization (UAE) can be used. However, after UAE, with the recanalization of uterine blood vessels, a high risk of prenatal hemorrhage is resulted. Cervical double balloon (CDB) is a good method for inducing women with an unfavorable because of low risk of hyper-stimulation and high maternal satisfaction. Using CDB to promote cervical ripening during the best hemostatic effect after UAE may be a good idea. With the aim of investigating the optimal management strategies, we analyzed 11 patients with CPP who underwent pregnancy termination in the second trimester from January 2017 and March 2021 in our birth center.

**Methods**

1. **Participants and methods**

This study was conducted from January 1st, 2017 to March 31th, 2021 in our hospital, a tertiary-care teaching hospital in Wuhan city, Hubei province, in the central of China.
1.1 Ethical approval
The study protocol was a retrospective research, and the study protocol was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province ([2019] IEC (XM008)). All pregnant women requiring termination of pregnancy in our work signed informed consent.

1.2 Data sources
This retrospective research was based on the data collected from the birth center of a tertiary-level public hospital in Wuhan city, Hubei province, China, with annual number of newborn babies of around 30,000 in recent 3 years. The data were collected from the hospital’s information system from January 1st, 2017 to March 31th, 2021.

1.3 Inclusion and exclusion criteria
Inclusion criteria included: (1) Gestation of weeks: from 14+0 w to 27+6 w. (2) the placenta completely covers the internal cervix by trans-vaginal ultrasound. (3) UAE, CDB and/or step-by-step curettage. (4) Delivery in our birth center. Exclusion criteria included: (1) Gestation of weeks: less than 14+0 w or more than 27+6 w. (2) the placenta was normal or the edge of the placenta reached the cervix or partially covered the internal cervix. (3) single usage of UAE or CDB.

1.4 The methods of labor induction
The placentas of all cases were routinely examined by trans-vaginal ultrasound after admission. At first, if the gestational weeks was less than or equal to 16 weeks, oral mifepristone (50mg, Bid*3d) combined with vaginal misoprostol was applied (100ug, Q6h). If the gestational weeks was more than 16 weeks, oral mifepristone (50mg, Bid*3d) combined with ethacridine lactate (100mg) was injected into the amniotic cavity under ultrasound guidance. After those induction methods, if the volume of prenatal bleeding was up to or equal to 400 mL, emergency UAE was implemented first to stop bleeding, and then CDB was applied and finally the curettage was used step by step based on the cervical condition, bleeding or infection indexes.

UAE[^3]: Patients were placed in the supine position, disinfected and draped in the inguinal area, and then Lidocaine was given for local anesthesia before surgery. The
surgeon punctured the right femoral artery according to Seldinger's method, inserted the 5F catheter sheath and catheter into the left uterine artery for arterial subtraction, perfused Gentamicin 80,000 units, and embolized with gelatin sponge. The right uterine artery was cannulated, perfused and embolized as well. After the operation, the catheter and sheath were pulled out before applying the local pressure bandage. The right lower limb was immobilized for 6 hours, and perioperative antibiotics were given to prevent infection.

**CDB[^1]:** The patient emptied the bladder and took the lithotomy position. Then the obstetricians gently placed the speculum into the vagina, disinfected the cervix, inserted the CDB into the cervix till both balloons entered the cervical canal, injected 40 mL of normal saline into the “U” balloon, pulled the “V” balloon out of the cervical external orifice and injected 40 mL of normal saline into it. At last, two balloons were added till the volume of both balloons reached 80 mL. If the patient was unbearable for 80 mL of normal saline, then 10-20 mL of normal saline should be drawn out from both balloons. The CDB duration varied between 12 and 24 hours according to the cervical condition.

All UAE, CDB and curettage procedures were performed by specialists in our hospital following the same protocol.

### 1.5 Observational indexes

The observation indexes included maternal age, gravidity, parity, body mass index, terminated gestational week, the history of caesarean section, placenta position, the reasons for induction, method of labor induction, induction time (the time from the beginning to UAE, the time from UAE to CDB, the time from CDB to curettage), antenatal bleeding, postpartum hemorrhage, curettage, manual removal of placenta, puerperal morbidity, and impatient days, the blood routine including white blood cell(WBC), Hemoglobin(HBG), C-reactive protein(CRP) on admission and after delivery.

The induction time of mifepristone combined with misoprostol was counted from the insertion of the first tablet of Misoprostol to the delivery, and the induction time of mifepristone combined with ethacridine lactate was from intra-amniotic injection of...
ethacridine lactate to delivery. If only oral mifepristone was applied for prenatal bleeding, the induction time was counted 0.

1.6 Statistical analysis

The data analysis was conducted using IBM SPSS Statistics 23.0 software. Data were appropriately analyzed by parametrical tests or non-parametrical test. Continuous variables were reported as the mean ±standard deviation (SD). Discrete variables were reported as medians (min-mix). Normally distributed data of two groups were compared by paired t tests. Non-normally distributed data were compared by means of paired rank sum test. Categorical variables were reported as numbers (%) and a p<0.05 was considered statistically significant.

Results

A total of 11 patients with CPP were included in this analysis. Prenatal diagnosis of CPP was confirmed by ultrasound for all patients. The average age was 34.2 years old, the average gestational week was 21.6 weeks, the body mass index( BMI) on admission was 23.7 kg/m$^2$ and the median gravidity was 3. 5 cases were at older maternal age (≥35 years old), 6 cases had previous curettage, 3 cases (3/11) had previous caesarean delivery, and 2 cases underwent myomectomy. The indications of termination in the second trimester included fetal death (5/11), malformations confirmed by ultrasound (3/11), and malformations confirmed by amniocentesis karyotype analysis (3/11). The clinical and obstetric characteristics of the 11 patients are listed in table 1.

**Table 1. Characteristics of the 11 patients of complete placenta previa in the second trimester**

|                      | Mean/Median or Number | Range or percentage |
|----------------------|-----------------------|---------------------|
| Age(years) (mean; range) | 34.2 ±6.6             | 24-41               |
| Gestation weeks at delivery(weeks)(mean/range) | 21.6±4.5             | 15$^{+1}$-27$^{+6}$ |
| Gravidity(median/range) | 3                    | 1-7                 |
| Parity(median/range)   | 1                    | 0-2                 |
| BMI on admission(kg/m2) | 23.7±2.1 | 19.5-26.0 |
|------------------------|----------|----------|
| (mean; range)          |          |          |

**Risk factors(n)(percent)**
- Older maternal age (≥35 years old) 5 45.5
- Previous curettage 6 54.5
- Previous cesarean delivery 3 27.3
- Myomectomy 2 18.2

**Indications of termination**
- Fetal death 5 45.5
- Malformations confirmed by ultrasound 3 27.3
- Malformations confirmed by amniocentesis and karyotype analysis 3 27.3

All selected patients were treated with medical termination at first. 10 cases of them underwent emergency UAE for prenatal bleeding equal or up to 400 mL. For the reasons of infection or prenatal bleeding, 4 cases (4/10) used curettage to take out fetus and placenta, and 1 case underwent prophylactic UAE after application of mifepristone for suspected placenta percreta by ultrasound, then CDB+curettage were used step by step to promote cervical ripening and take out fetus and placenta. The methods of induction are shown in Fig 1. 4 cases exhibited prenatal hemorrhage during oral Mifepristone. Case 1 was the one for which we used we first time used CDB to ripen cervix after UAE and the duration from UAE to CDB placement was 58 h, with septicemia as a result. The average durational of CDB was 13.1 h and the average time of induction was 39.9 h. (Fig 2)
Fig 1. Flowchart demonstrating: The clinical outcomes of terminational pregnancy with complete placenta previa in the mid-trimester
Ultimately, with the application of adjuvant treatment, including UAE and CDB and/or curettage under ultrasound guidance, the placenta clearance rate reached 100% and uterus preservation was achieved in all 11 patients.

Among the 11 patients with CPP who underwent conservative management, the complications included prenatal hemorrhaging (10/11), blood transfusion (5/11), fever (2/11), and septicemia (1/11).  

(see in Table 2)

Table 2. The Methods and complications of termination of pregnancy with complete placenta previa in the second trimester

| The methods at first               | n/mean | Percent (%)/Standard deviation/Min-Max |
|------------------------------------|--------|----------------------------------------|
| Mifepristone + Ethacridine         | 2      | 18.2                                   |
| Mifepristone + Misoprostol         | 4      | 36.4                                   |
| Mifepristone                       | 5      | 45.5                                   |
| UAE                                |        |                                        |
| Emergency UAE                      | 10     | 90.9                                   |
Prophylactic UAE
Postoperative complications within 60 days after UAE abdominal pain, low fever, nausea and vomiting, and buttock pain\textsuperscript{71,47,39,36}

| Bleeding volume(mL) | Prenatal (ml) | Intrapartum (ml) |
|---------------------|---------------|------------------|
|                     | 450.0         | 165.8            |
|                     | 274.5         | 89.9             |

| Blood transfusion | n | Red blood cell (u) |
|-------------------|---|-------------------|
|                   | 5 | 45.5              |
|                   | 1.5 | 0-4               |

| Curettage         | Curettage for fetus and placenta | 5 | 45.5 |
|                   | Curettage for placenta | 4 | 36.4 |

| Resean reblood    | 5 |
| Resean infection  | 45.5 |

| Infection | Septicemia | 1 |
|           | Puerperal infection | 2 |

| MICU | 11 |

| Antibiotics | Days | 4-14 |
|-------------|------|------|
|             | Caftezole sodium+ornidazole | 8 |
|             | Ampicillin sodium+ornidazole | 1 |
|             | Benzylpenicillin | 2 |

| Length of hospitalization(d)(mean/range) | 8.5±2.9 | 5-16 |

197 The cervical conditions were ripened by CDB, the mean dilation of cervix was from 0cm to 1.9cm, the length of cervix was from 3.5 cm to 0.6 cm and the Bishop scores were from 1.5 to 7.3 after CDB, and the changes were statistically significant ($p<0.05$). (see in Table 3)

**Table 3. Bishop scores before CDB placement and after CDB removed**

|                   | Before CDB placement | After CDB removed | t      | p      |
|-------------------|----------------------|-------------------|--------|--------|
| Bishop scores     | 1.5±0.7              | 7.3±0.9           | -15.156| 0.000  |
| Length of cervix(cm) | 3.5±0.6            | 0.6±0.4           | 11.737 | 0.000  |
Dilation of cervix (cm) 0 1.9±0.6 10.844 0.000

CDB: cervical double balloon

T-test is used

The blood routine including WBC, HBG, CRP were changed by termination using medicine+UAE+CDB and/or curettage, the mean WBC was higher on discharge (15.0×10⁹/L) than on admission (9.3×10⁹/L), and the median CRP was higher on discharge (54.3 mg/L) than on admission (1.13 mg/L) (p<0.05). (see in Table 4)

Table 4. The WBC, HBG, and CRP of the 11 patients between the period of admission and discharge

| WBC(×10⁹/L) | HBG(g/L) | CRP (mg/L) |
|-------------|----------|------------|
| On admission | 9.3±1.6  | 121.2±14.1 | 1.13(0.5-2.8) |
| On discharge | 15.0±4.4 | 106.0±10.6 | 54.3(34.8-93.4) |

| t/z | p     |
|-----|-------|
| -4.440 | 0.002 |
| 3.137 | 0.012 |
| -5.712 | 0.000 |

No one had delayed hysterectomy due to massive vaginal bleeding or uterine necrosis or sepsis. The 11 cases had stable haemodynamic condition.

Of those 11 cases, 10 cases had abdominal pain, 2 cases had low fever, 4 cases had nausea and vomiting and 2 cases had buttock pain within 60 days of UAE. After delivery, the average bleeding time was 6.6 d and volume were 49.6 mL. Their menstruation was recurred within 3 months after delivery, and one of them described lower menstrual volume and other 10 cases were normal. The beta-human chorionic gonadotropin (β-hCG) were normal within 2 months after delivery. 4 cases had spontaneous pregnancy and birth, 1 case had spontaneous abortion in the early trimester and 4 cases had no fertility requirement again. (see in Table 5)

Table 5. The fellow-up of 11 cases with complete placenta previa in the second trimester

| n/mean | Percent (%)/Standard deviation/Min-Max |
|                          | UAE                      |          |          |
|--------------------------|--------------------------|----------|----------|
| Abdominal pain           | 10                       | 90.9     |          |
| Low fever                | 2                        | 18.2     |          |
| Nausea and vomiting     | 4                        | 36.4     |          |
| Buttock pain             | 2                        | 18.2     |          |
| **Bleeding after delivery** |                          |          |          |
| Lasting time (d)         | 6.6±2.2                  | 3-10     |          |
| Volume (ml)              | 49.6±9.2                 | 30-70    |          |
| **Menstruation after delivery** |                        |          |          |
| Recurrence (d)           | 49.6±9.2                 | 35-65    |          |
| Normal                   | 10                       | 90.9     |          |
| **Beta-hCG from delivery to normal** |                  |          |          |
|                          | 20.4±5.8                 | 14-28    |          |

|                          | late fertility            |          |          |
| Spontaneous pregnancy and birth | 4                        | 36.4     |          |
| Abortion in the early trimester | 1                        | 9.1      |          |
| No fertility requirements     | 4                        | 36.4     |          |

**Discussion**

One of the main challenges in management of the second-trimester pregnancy termination for women with CPP is prenatal massive vaginal bleeding from placenta located in the cervical os with an unfavorable cervix. In some cases, total or subtotal hysterectomy\(^5,6\) is needed to stop those life-threatening bleeding. Mifepristone combined with ethacridine lactate/misoprostol is common method used in the second-trimester pregnancy termination in China especially for those CPP patients\(^7\), and those methods of drugs are effective and safe\(^8,9\). How to deal with the prenatal bleeding during induction for CPP patients with unfavorable cervix in the second trimester is the focus of current clinical work. In our study, we found the average prenatal bleeding volume reached 400mL quickly and blood transfusion was needed urgently(RBC, 0-4u).

UAE with minimal invasion has been widely used in the field of gynecology and obstetrics to control hemorrhages, including caesarean scar pregnancy\(^10\), postpartum hemorrhage\(^11\) by caesarean delivery or vaginal delivery. Whether or not to use prophylactic UAE for termination in the second trimester for pregnant women with CPP remains debated\(^7,10\). Wang Y\(^10\) et al. investigated 15 patients with CPP who underwent second-trimester pregnancy termination by prophylactic UAE, and found that intra-amniotic injection of 100mg of ethacridine lactate followed by oral
administration of mifepristone did not significantly improve outcomes of second-trimester abortion including the rate of abortion, bleeding volume, and induction-to-abortion time. He F et al[7] found CPP patient in the second trimester treated with ethacridine and mifepristone combined with prophylactic UAE exhibited significantly reduced bleeding amount during induction and lower risk of emergency procedures. Our study found that both emergence UAE (10/11) and prophylactic UAE (1/11) were effective hemostasis measure for prenatal hemorrhage during induction for the CPP patients in the second trimester. Within 60 days of UAE, 90.9% (10/11) had abdominal pain, 18.2% (2/11) had low fever, 36.4% (4/11) had nausea and vomiting, 18.2% (2/11) had buttock pain, and one case showed oligomenorrhea, the complications of UAE were high. Although the etiology of post-uterine artery embolization syndrome remains unclear, uterine tissue ischemia may be the main cause of secondary inflammation[10]. The prenatal bleeding during labor induction was very rapid, which reached with 400 mL in a short time. In order to reduce complications of UAE and ensure the safety of pregnant women, prophylactic UAE can be adopted to treat high-risk bleeding for pregnant women with CPP combined with placenta accreta spectrum under the guidance of ultrasound and/or magnetic resonance imaging[12,13].

CDB is a good alternative method for inducing women with unfavorable cervix[14], which has been a commonly used induction for the term pregnancies[15], prolonged pregnancies[16], vaginal birth after caesarean section[17], high risk of uterine hyperstimulation[18], and oligohydramnios[19]. CDB used in labor has low risk of hyperstimulation and brings high maternal satisfaction[20]. According to the guideline[15], the maximum waiting time for CDB is 12h. If not effective, the CDB will be removed. In our research, We found that 4 patients with CDB lasting for 12 hours needed curettage, 6 patients with spontaneous balloon prolapses did not need curettage, and 1 patient with CDB lasting for 24 hours needed curettage. For the unfavorable cervix in the second trimester, we prolonged the waiting time for CDB from 12 h to 24 h in mid-trimester pregnancy, which was beneficial for cervical ripening and reducing the chance of curettage[21].
Curettage combined with Foley balloon is a mature, cheap and easily performed minimally invasive method with a short hospital stay for caesarean scar pregnancy (CSP) [22]. UAE combined with curettage is also an adjuvant therapy for CSP [23]. In our study, whether or not to perform curettage was based on cervical condition, bleeding, or infection. There was 1 case undergoing curettage exhibited higher fever, 4 cases suffered from active bleeding under ultrasound guidance.

At present, adjuvant therapies based on UAE, CDB, and/or curettage for CPP with prenatal hemorrhage [24] in the second trimester have been less reported rare reported. Wang Q et al. [23] observed that if the patients with CSP underwent curettage within 24 h after UAE, the risk of intraoperative bleeding was 5.0%. However, such risk was 19.4% for those who had a treatment interval longer than 72h. Since ontravascular interventional embolus absorption may result in recanalization within 7-14 days after UAE [25, 26, 27], the fetus and placenta should be taken out within 24 h to avoid bleeding and/or infection. Case 1 was the first case undergoing UAE, CDB, and curettage step by step who experienced prenatal high fever (39 °C), odor of fetus and placenta, and sepsis, the duration from UAE to delivery (UAE-CDB 58h, CDB 12h, CDB-curettage 6h) was long. After applying UAE for hemostasis, the uterus was ischemia, the placenta in the cervix and fetus remained in the uterus, which may lead to prenatal hemorrhage again. It might be an ideal method to short the time from UAE to delivery. Within 24 hours after UAE, the hemostasis effect was the best, and CDB implantation from the cervix was safe and effective, the Bishop scores could change from 1.5 to 7.3, the average length of cervix was from 3.5cm to 0.6cm, the dilation of cervix was from 0cm to 1.9cm. The mature cervix obtained by CDB provided favorable condition for subsequent treatment and avoided hysterotomy or hysterectomy. The average levels of WBC and CRP were higher, and HBG was lower after delivery for those 11 patients. This further reminded us that we should pay more attention to infection and bleeding during the adjuvant therapy of UAE, CDB and/or curettage for the patients with CPP in the mid-trimester.
Conclusions

Our preliminary results suggest that the adjuvant therapy of UAE, CDB, and/curettage step by step is a preferred choice for patients with CPP who underwent pregnancy termination in the second trimester.

Limitations

First, this is a retrospective study, the interventions were determined based on the intentions of obstetrician and patients, so selection bias existed. Second, this report included 11 case with CPP in the second trimester in one big birth center, which was a small sample size. Hence, multicenter randomized controlled trials (RCTs) are needed to provide more reliable evidence of the adjuvant therapy of UAE, CDB and/or curettage step by step.

Abbreviations

UAE: uterine artery embolization; CPP: complete placenta previa; CDB: cervical double balloon; WBC: white blood cell; HGB: Hemoglobin; CRP: C-reactive protein; β-hCG: beta-human chorionic gonadotropin; CSP: caesarean scar pregnancy; BMI: Body mass index; RCTs: randomized controlled trials

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Author’s contributions

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Availability of data and materials
Access to the qualitative data will be given upon request to the corresponding author after taking any necessary precautions to safeguard participants’ privacy and confidentiality.

Ethical approval and patient consent
The study protocol was approved by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province. All included women signed written informed consent for therapeutic procedures and also for the publication of those reports.

Consent for publication
Not applicable.

Conflicts of interest
The author has no conflict of interest regarding the publication of this paper.

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