

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

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30 **Abstract**

31 **Background**

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

37 **Methods**

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

42 **Results**

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

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

58 **Conclusion**

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

61 **Keywords**

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

64 **Background**

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

88 **Methods**

89 **1.Participants and methods**

90 This study was conducted from January 1st, 2017 to March 31th, 2021 in our hospital,
91 a tertiary-care teaching hospital in Wuhan city, Hubei province, in the central of
92 China.

93 **1.1 Ethical approval**

94 The study protocol was a retrospective research, and the study protocol was approved
95 by the Ethics Committee of Maternal and Child Health Hospital of Hubei Province
96 ([2019] IEC (XM008)). All pregnant women requiring termination of pregnancy in
97 our work signed informed consent.

98 **1.2 Data sources**

99 This retrospective research was based on the data collected from the birth center of a
100 tertiary- level public hospital in Wuhan city, Hubei province, China, with annual
101 number of newborn babies of around 30, 000 in recent 3 years. The data were
102 collected from the hospital's information system from January 1st, 2017 to March
103 31th, 2021.

104 **1.3 Inclusion and exclusion criteria**

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

111 **1.4 The methods of labor induction**

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

121 **UAE^[3]**: Patients were placed in the supine position, disinfected and draped in the
122 inguinal area, and then Lidocaine was given for local anesthesia before surgery. The

123 surgeon punctured the right femoral artery according to Seldinger's method, inserted
124 the 5F catheter sheath and catheter into the left uterine artery for arterial subtraction,
125 perfused Gentamicin 80,000 units, and embolized with gelatin sponge. The right
126 uterine artery was cannulated, perfused and embolized as well. After the operation,
127 the catheter and sheath were pulled out before applying the local pressure bandage.
128 The right lower limb was immobilized for 6h, and perioperative antibiotics were
129 given to prevent infection.

130 **CDB^[4]**: The patient emptied the bladder and took the lithotomy position. Then the
131 obstetricians gently placed the speculum into the vagina, disinfected the cervix,
132 inserted the CDB into the cervix till both balloons entered the cervical canal, injected
133 40 mL of normal saline into the “U” balloon, pulled the “V” balloon out of the
134 cervical external orifice and injected 40 mL of normal saline into it. At last, two
135 balloons were added till the volume of both balloons reached 80 mL. If the patient
136 was unbearable for 80 mL of normal saline, then 10-20 mL of normal saline should be
137 drawn out from both balloons. The CDB duration varied between 12 and 24 hours
138 according to the cervical condition.

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

141 **1.5 Observational indexes**

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

150 The induction time of mifepristone combined with misoprostol was counted from the
151 insertion of the first tablet of Misoprostol to the delivery, and the induction time of
152 mifepristone combined with ethacridine lactate was from intra-amniotic injection of

153 ethacridine lactate to delivery. If only oral mifepristone was applied for prenatal
154 bleeding, the induction time was counted 0.

155 **1.6 Statistical analysis**

156 The data analysis was conducted using IBM SPSS Statistics 23.0 software. Data were
157 appropriately analyzed by parametrical tests or non-parametrical test. Continuous
158 variables were reported as the mean \pm standard deviation (SD). Discrete variables were
159 reported as medians (min-mix). Normally distributed data of two groups were
160 compared by paired t tests. Non-normally distributed data were compared by means
161 of paired rank sum test. Categorical variables were reported as numbers (%) and a
162 $p < 0.05$ was considered statistically significant.

163 **Results**

164 A total of 11 patients with CPP were included in this analysis. Prenatal diagnosis of
165 CPP was confirmed by ultrasound for all patients. The average age was 34.2 years
166 old, the average gestational week was 21.6 weeks, the body mass index (BMI) on
167 admission was 23.7 kg/m² and the median gravidity was 3. 5 cases were at older
168 maternal age (≥ 35 years old), 6 cases had previous curettage, 3 cases (3/11) had
169 previous caesarean delivery, and 2 cases underwent myomectomy. The indications of
170 termination in the second trimester included fetal death (5/11), malformations
171 confirmed by ultrasound (3/11), and malformations confirmed by amniocentesis
172 karyotype analysis (3/11). The clinical and obstetric characteristics of the 11 patients
173 are listed in table 1.

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

	Mean/Median or Number	Range or percentage
Age(years) (mean; range)	34.2 \pm 6.6	24-41
Gestation weeks at delivery(weeks)(mean/range)	21.6 \pm 4.5	15 ⁺¹ -27 ⁺⁶
Gravidity(median/range)	3	1-7
Parity(median/range)	1	0-2

BMI on admission(kg/m²) (mean; range)	23.7±2.1	19.5-26.0
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 karyotype analysis	3	27.3

176 All selected patients were treated with medical termination at first. 10 cases of them
177 underwent emergency UAE for prenatal bleeding equal or up to 400 mL. For the
178 reasons of infection or prenatal bleeding, 4 cases (4/10) used curettage to take out
179 fetus and placenta, and 1 case underwent prophylactic UAE after application of
180 mifepristone for suspected placenta percreta by ultrasound, then CDB+curettage were
181 used step by step to promote cervical ripening and take out fetus and placenta. The
182 methods of induction are shown in **Fig 1**. 4 cases exhibited prenatal hemorrhage
183 during oral Mifepristone. Case 1 was the one for which we used we for first time used
184 CDB to ripen cervix after UAE and the duration from UAE to CDB placement was 58
185 h, with septicemia as a result. The average durational of CDB was 13.1 h and the
186 average time of induction was 39.9 h. (**Fig 2**)

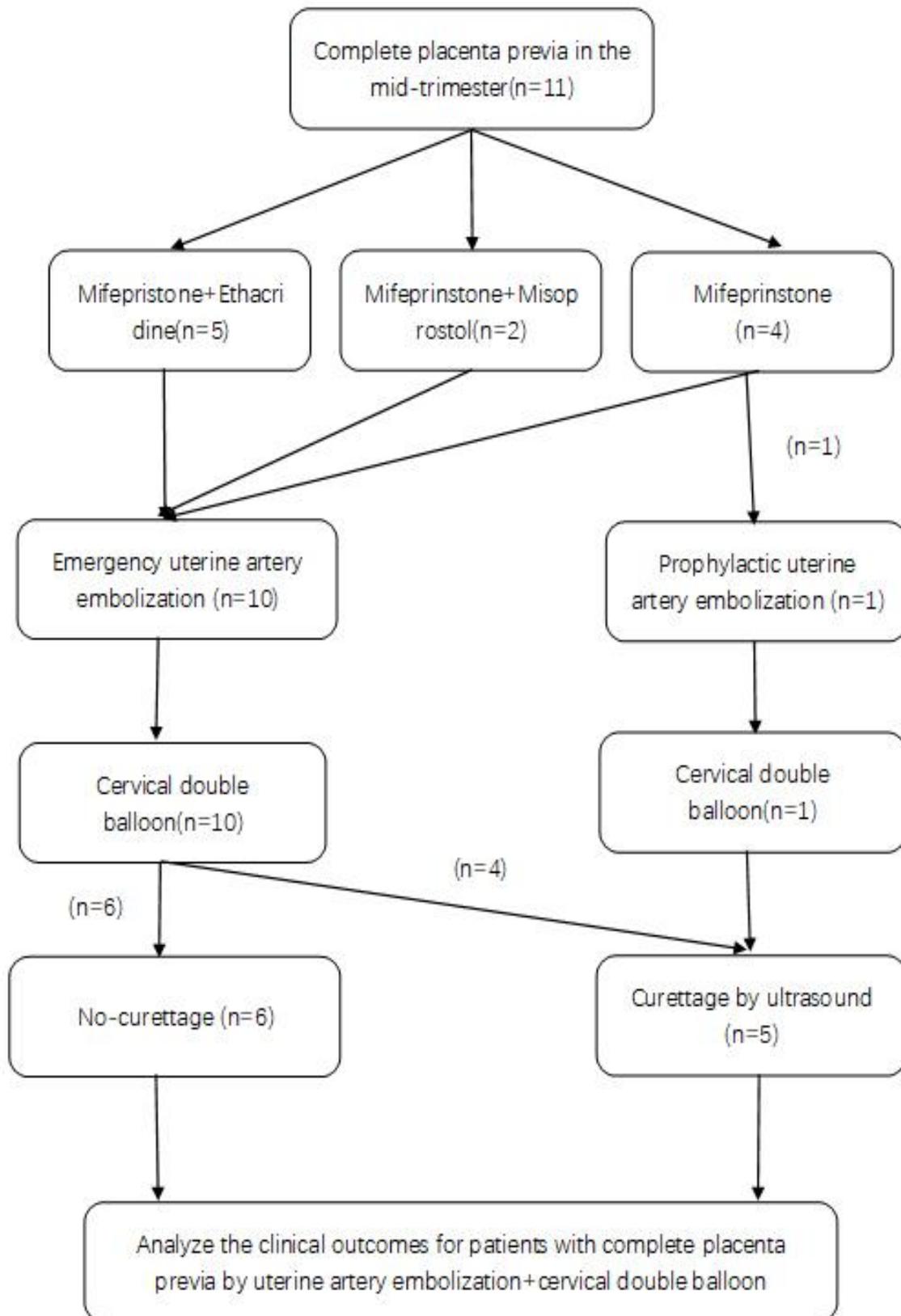


Fig 1. Flowchart demonstrating: The clinical outcomes of terminational pregnancy with complete placenta previa in the mid- trimester

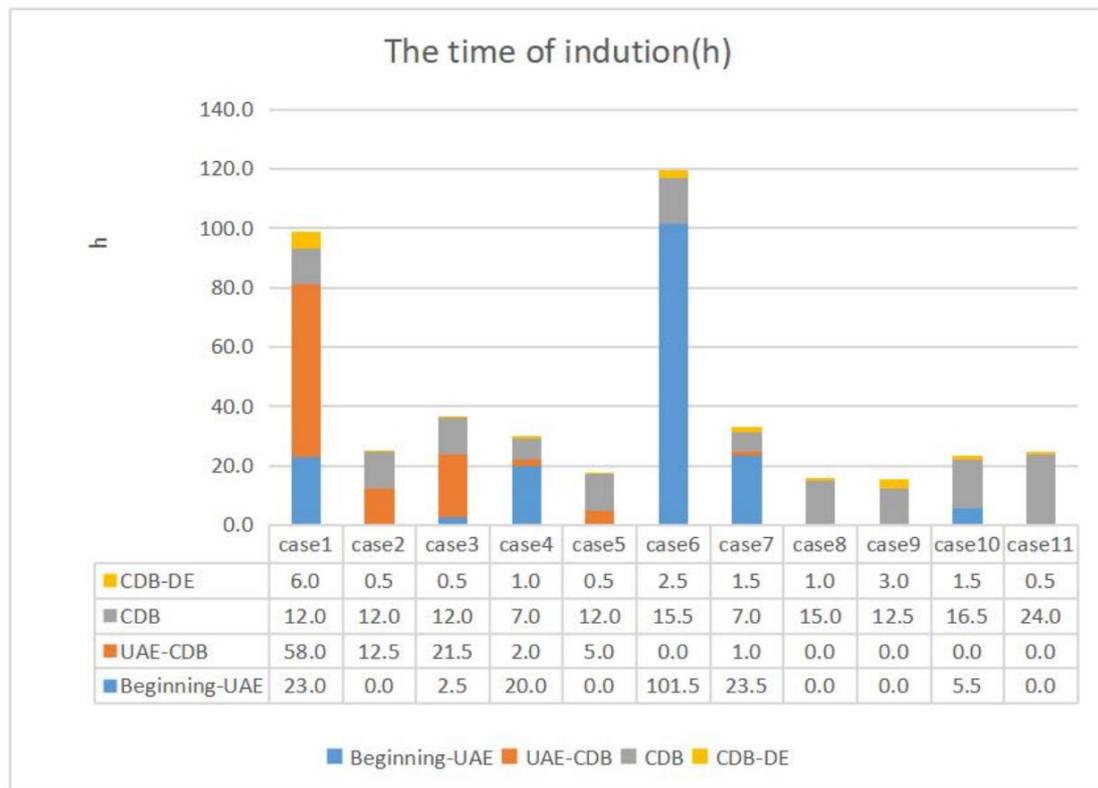


Fig2: The time of induction

188

189 Ultimately, with the application of adjuvant treatment, including UAE and CDB
 190 and/or curettage under ultrasound guidance, the placenta clearance rate reached 100%
 191 and uterus preservation was achieved in all 11 patients.

192 Among the 11 patients with CPP who underwent conservative management, the
 193 complications included prenatal hemorrhaging (10/11), blood transfusion (5/11), fever
 194 (2/11), and septicemia (1/11). (see in Table 2)

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

	n/mean	Percent (%) / Standard deviation / Min-Max
The methods at first		
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	1	9.1
Bleeding volume(mL)		
Prenatal (ml)	450.0	165.8
Intrapartum (ml)	274.5	89.9
Blood transfusion		
n	5	45.5
Red blood cell(u)	1.5	0-4
curettage		
Curettage for fetus and placenta	5	45.5
Curettage for placenta	4	36.4
Resean reblood		
Resean infection		
Infection		
Septicemia	1	
Puerperal infection	2	
MICU	11	
Antibiotics		
Days	4	2-14
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
198 0cm to 1.9cm, the length of cervix was from 3.5 cm to 0.6 cm and the Bishop scores
199 were from 1.5 to 7.3 after CDB , and the changes were statistically significant ($p <$
200 0.05). (see in Table 3)

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

202 **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
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203 *CDB: cervical double balloon*

204 *T-test is used*

205 The blood routine including WBC, HBG, CRP were changed by termination using
 206 medicine+UAE+CDB and/or curettage, the mean WBC was higher on discharge (15.0
 207 $\times 10^9/L$) than on admission ($9.3 \times 10^9/L$), and the median CRP was higher on
 208 discharge (54.3 mg/L) than on admission (1.13 mg/L) ($p < 0.05$). (see in Table 4)

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

	WBC($\times 10^9/L$)	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	-4.440	3.137	-5.712
p	0.002	0.012	0.000

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

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

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

	n/mean	Percent (%) / Standard deviation / Min-Max
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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

223 Discussion

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

235 UAE with minimal invasion has been widely used in the field of gynecology and
236 obstetrics to control hemorrhages, including caesarean scar pregnancy^[10], postpartum
237 hemorrhage^[11] by caesarean delivery or vaginal delivery. Whether or not to use
238 prophylactic UAE for termination in the second trimester for pregnant women with
239 CPP remains debated^[7,10]. Wang Y^[10] et al. investigated 15 patients with CPP who
240 underwent second-trimester pregnancy termination by prophylactic UAE, and found
241 that intra-amniotic injection of 100mg of ethacridine lactate followed by oral

242 administration of mifepristone did not significantly improve outcomes of
243 second-trimester abortion including the rate of abortion, bleeding volume, and
244 induction-to-abortion time. He F et al^[7] found CPP patient in the second trimester
245 treated with ethacridine and mifepristone combined with prophylactic UAE exhibited
246 significantly reduced bleeding amount during induction and lower risk of emergency
247 procedures. Our study found that both emergence UAE (10/11) and prophylactic UAE
248 (1/11) were effective hemostasis measure for prenatal hemorrhage during induction
249 for the CPP patients in the second trimester. Within 60 days of UAE, 90.9% (10/11)
250 had abdominal pain, 18.2% (2/11) had low fever, 36.4% (4/11) had nausea and
251 vomiting, 18.2% (2/11) had buttock pain, and one case showed oligomenorrhea, the
252 complications of UAE were high. Although the etiology of post-uterine artery
253 embolization syndrome remains unclear, uterine tissue ischemia may be the main
254 cause of secondary inflammation^[10]. The prenatal bleeding during labor induction was
255 very rapid, which reached with 400 mL in a short time. In order to reduce
256 complications of UAE and ensure the safety of pregnant women, prophylactic UAE
257 can be adopted to treat high-risk bleeding for pregnant women with CPP combined
258 with placenta accreta spectrum under the guidance of ultrasound and/or magnetic
259 resonance imaging^[12,13].

260 CDB is a good alternative method for inducing women with unfavorable
261 cervix^[14], which has been a commonly used induction for the term pregnancies^[15],
262 prolonged pregnancies^[16], vaginal birth after caesarean section^[17], high risk of uterine
263 hyperstimulation^[18], and oligohydramnios^[19]. CDB used in labor has low risk of
264 hyperstimulation and brings high maternal satisfaction^[20]. According to the
265 guideline^[15], the maximum waiting time for CDB is 12h. If not effective, the CDB
266 will be removed. In our research, We found that 4 patients with CDB lasting for 12
267 hours needed curettage, 6 patients with spontaneous balloon prolapses did not need
268 curettage, and 1 patient with CDB lasting for 24 hours needed curettage. For the
269 unfavorable cervix in the second trimester, we prolonged the waiting time for CDB
270 from 12 h to 24 h in mid-trimester pregnancy, which was beneficial for cervical
271 ripening and reducing the chance of curettage^[21].

272 Curettage combined with Foley balloon is a mature, cheap and easily performed
273 minimally invasive method with a short hospital stay for caesarean scar
274 pregnancy(CSP)^[22]. UAE combined with curettage is also an adjuvant therapy for
275 CSP^[23]. In our study, whether or not to perform curettage was based on cervical
276 condition, bleeding, or infection. There was 1 case undergoing curettage exhibited
277 higher fever, 4 cases suffered from active bleeding under ultrasound guidance.
278 At present, adjuvant therapies based on UAE, CDB, and/or curettage for CPP with
279 prenatal hemorrhage^[24] in the second trimester have been less reported rare reported.
280 Wang Q et al.^[23] observed that if the patients with CSP underwent curettage within 24
281 h after UAE, the risk of intraoperative bleeding was 5.0%. However, such risk was
282 19.4% for those who had a treatment interval longer than 72h. Since ontravascular
283 interventional embolus absorption may result in recanalization within 7-14 days after
284 UAE^[25,26,27], the fetus and placenta should be taken out within 24 h to avoid bleeding
285 and/or infection. Case 1 was the first case undergoing UAE, CDB, and curettage step
286 by step who experienced prenatal high fever(39°C), odor of fetus and placenta, and
287 sepsis,the durational from UAE to delivery (UAE-CDB 58h, CDB 12h,
288 CDB-curettage 6h) was long. After applying UAE for hemostasis, the uterus was
289 ischemia, the placenta in the cervix and fetus remained in the uterus, which may lead
290 to prenatal hemorrhage again. It might be an ideal method to short the time from UAE
291 to delivery. Within 24 hours after UAE, the hemostasis effect was the best, and CDB
292 implantation from the cervix was safe and effective, the Bishop scores could change
293 from 1.5 to 7.3, the average length of cervix was from 3.5cm to 0.6cm, the dilation of
294 cervix was from 0cm to 1.9cm. The mature cervix obtained by CDB provided
295 favorable condition for subsequent treatment and avoided hysterotomy or
296 hysterectomy. The average levels of WBC and CRP were higher, and HBG was lower
297 after delivery for those 11 patients. This further reminded us that we should pay more
298 attention to infection and bleeding during the adjuvant therapy of UAE, CDB and/or
299 curettage for the patients with CPP in the mid-trimester.

300 **Conclusions**

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

304 **Limitations**

305 First, this is a retrospective study, the interventions were determined based on the
306 intentions of obstetrician and patients, so selection bias existed.

307 Second, this report included 11 case with CPP in the second trimester in one big birth
308 center, which was a small sample size. Hence, multicenter randomized controlled
309 trials (RCTs) are needed to provide more reliable evidence of the adjuvant therapy of
310 UAE, CDB and/or curettage step by step.

311 **Abbreviations**

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

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320 **Author's contributions**

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334 **Availability of data and materials**

335 Access to the qualitative data will be given upon request to the corresponding author
336 after taking any necessary precautions to safeguard participants' privacy and
337 confidentiality.

338 **Ethical approval and patient consent**

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

342 **Consent for publication**

343 Not applicable.

344 **Conflicts of interest**

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

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