

1Title page

2**Title: The management of caesarean scar pregnancy with or without a combination of**

3**methods prior to hysteroscopy: ovarian reserve trends and patient outcomes**

4**Running title:** The management of caesarean scar pregnancy

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12**Keywords:** Cesarean scar pregnancy; hysteroscopy; Methotrexate; Uterine artery

13embolization

14Abstract

15**Study Objective:** This study compared the efficacy and safety of a combination of
16uterine artery embolization or methotrexate before hysteroscopy in the treatment of
17cesarean scar pregnancy.

18**Methods:** We divided 276 cesarean scar pregnancy patients into three groups. Group
19A underwent direct hysteroscopy; Group B received uterine artery embolization plus
20hysteroscopy; Group C received the systemic administration of methotrexate prior to
21hysteroscopy.

22**Results:** The patients in Group A lost significantly more blood than those in Groups B
23($P < 0.05$). There were no significant differences between the three groups with

24regards to massive hemorrhage and transfusion ($P > 0.05$). None of the patients
25required hysterectomy. Group A was also associated with a significantly shorter
26period of hospitalization, reduced medical costs, and fewer adverse events than either

27Group B or C ($P < 0.05$). Moreover, among women of advanced age (≥ 35 y), the
28levels of serum anti-Mullerian hormone in Group B were significantly lower than

29those of the baseline group ($P < 0.05$), which were significantly lower than those in

30Group A after surgery (4.22 ± 2.35 vs 2.78 ± 1.89 ng/ml, $P < 0.05$).

31Conclusion: Direct hysteroscopy is a reliable treatment option for most early type I
32cesarean scar pregnancy patients with a gestational sac. A combination of
33methotrexate and uterine artery embolization before hysteroscopy in these patients has
34limited remedial effects. uterine artery embolization may reduce ovarian reserve in
35patients aged ≥ 35 y.

36*Keywords:* Cesarean scar pregnancy; hysteroscopy; Methotrexate; Uterine artery
37embolization

38Introduction

39Caesarean scar pregnancy (CSP) is defined as the implantation of an embryo into a
40previous cesarean scar. The incidence of CSP has increased substantially in China
41over recent years [1], coincident with the creation of the two-child policy and the
42development of better ultrasound diagnosis. The mechanisms underlying CSP remain
43unclear and no universal guidelines have been recommended for the treatment of this
44disease. Furthermore, many patients prefer surgical intervention to medical treatment
45because they are reluctant to undergo prolonged period of follow-up. Dilation and
46curettage (D&C) is a simple and effective form of treatment, with low costs, but a
47high risk of complications, such as uterine perforation, massive hemorrhage, and
48retained products of conception [2,3]. Operative hysteroscopy is an alternative form
49of minimally invasive surgery that offers direct visualization, definitive diagnosis, and
50reduces the risk of the products of conception being retained in the caesarean scar.
51Preoperative procedures, including the systemic administration of methotrexate
52(MTX) or uterine artery embolization (UAE), are often added to treatment plans in
53order to reduce the risk of hemorrhage. However, such combination of management
54strategies remain controversial, particularly with respect to side effects, and the
55selection of patients who might benefit from such treatments [4-7]. In order to identify
56the best therapeutic option for CSP patients, we retrospectively analyzed the clinical
57data of 276 CSP patients that received treatment in our institution. Our aim was to
58compare the clinical outcomes, and ovarian reserve, of patients receiving three
59therapeutic strategies: UAE combined with hysteroscopy; systemic MTX combined

60with hysteroscopy, and hysteroscopy alone.

61**Materials and Methods**

62*Patients*

63This study involved the retrospective analysis of CSP patients treated at the Jinhua
64Municipal Central Hospital between January 2013 and December 2018. The protocol
65for treating CSP in our hospital includes the intrauterine or transabdominal approach;
66in this article, we only address the intrauterine approach. The study was approved by
67the hospital's ethics committee. Women with CSP, who underwent hysteroscopic
68management, were enrolled in the study if they were ≤ 10 weeks of gestation, and
69hemodynamically stable without ruptured uteri or severe bleeding. All patients had a
70myometrial thicknesses ≥ 2 mm (type I, endogenic type) [7]. Six doctors (designated
71as an 'Associate Senior' or above) were responsible for all surgeries; this ensured
72consistency between treatment strategies. All eligible women were informed of the
73potential complications, benefits and alternatives of each approach before they were
74assigned into treatment groups, and all patients were willing to select treatment
75procedure by lots. Our protocol for diagnosis was published previously [8]. A
76combination of transabdominal and transvaginal ultrasonography were used to
77diagnose CSP (gestational sac or mass), and assess the lower uterine segment
78myometrial thickness. Under ultrasound examination, a gestational mass was
79characterized by a solid or solid-mixed echo mass surrounded by a rich or poor
80vascular flow in the scar of the uterus [9]. This condition often arises from the
81incomplete abortion of the gestational sac and the persistence of CSP or residual

82pregnancy.

83*Treatment strategies*

84The women were grouped according to the treatment management plan they received:
85Group A (87 patients) underwent direct hysteroscopic surgery, with the patient under
86general anesthesia and the cervix dilated. An operative hysteroscope was used to
87detect a caesarean scar defect (CSD) with an implanted pregnancy, and an electric
88loop, were then used to remove the gestational tissue. Coagulation was then induced
89for hemostasis, oxytocin and Foley catheter preparation for prevention of active
90bleeding. Group B (101) received a combination of UAE, as described previously
91[10]. In brief, the technique included the bilateral selective catheterization of the
92uterine arteries, followed by the injection of gelatin sponge particles into the vessels;
93occlusion of the stem of the uterine artery was then confirmed by subtraction
94angiography. After 24 h, the patients then underwent hysteroscopy. Group C (88
95cases) received systemic intramuscular MTX prior to hysteroscopy; the dose of MTX
96varied (75–300 mg) according to serum β -hCG levels, as described in our previous
97research [11]. Operative hysteroscopy was performed on the day that serum β -hCG
98fell to $<3,000$ IU/l. Adverse effects, including fever, stomatitis, alopecia, pelvic pain,
99an abnormal complete blood count, or abnormal liver/renal function, were recorded. A
100successful outcome was defined as complete recovery with no need for additional
101interventional treatment, and the absence of severe complications. Severe adverse
102events were defined as a ruptured uterus, massive hemorrhage (estimated blood loss
103 $>1,000$ ml), or hysterectomy. We considered for blood transfusion if Hemoglobin

104level below 6g.

105*Hormone measurements*

106Venous blood samples were drawn from all patients before operation and day 3 of the
107menstrual cycle 6 months postoperatively. We then determined the levels of anti-
108mullerian hormone (AMH) and inhibin B (INH B). Blood samples were assayed using
109specific and sensitive assays for AMH [(Ultrasensitive AMH enzyme-linked
110immunosorbent assay (ELISA), Diagnostic Systems Laboratories (DSL), USA; with a
111detection limit of 0.006 ng/ml], and INH B (ELISA, Ansh Labs). The intra-assay and
112inter-assay coefficients of variation ranged from 9.4 % - 7.2 % for AMH, and 5% -
1138% for INH B.

114**Statistical Analysis**

115Data analysis was carried out with the SPSS statistical package (version 17.0).
116Quantitative data were presented as mean \pm standard deviation (\pm SD), frequency and
117percentage; differences among the groups were determined by the paired sample t-test
118and the independent t-test. Numerical count data were expressed as a rate, and the chi-
119squared test was used for inter-group comparison. *P*-values<0.05 were considered to
120be statistically significant.

121**Results**

122The baseline clinical characteristics of the patients in the 3 groups are summarized in
123Table 1. There were no statistically significant differences among the 3 groups with
124respect to age, number of previous cesareans, time interval between last pregnancy
125and CSP, days of gestation, initial serum β -hCG level, or the rates of cases involving

126a gestational mass. In Group A, 81 women were treated successfully, with a clinical
 127success rate of 93.0%. Four patients experienced massive hemorrhage during surgery,
 128and 3 cases needed blood transfusions. Two CSP patients suffered heavy vaginal
 129bleeding two weeks after hysteroscopy; blood transfusion and emergency removal of
 130residual gestational products via laparoscopy was performed in these cases. In Group
 131B, 95 patients were treated successfully; treatment failed in 6 patients due to residual
 132gestational tissue. In Group C, 84 women were treated successfully; 3 patients
 133suffered massive hemorrhage but blood transfusion was not required. Uterine rupture
 134occurred in one patient intraoperatively; the uterine cleft was sutured under
 135laparoscopy immediately. None of the patients, in any group, required hysterectomy.
 136All of the 16 failed cases, across the 3 groups, involved a gestational mass. All cases
 137involving a gestational sac were treated successfully (clinical success rate: 100%).
 138Treatment outcomes are shown in Table 2. The mean intraoperative blood loss in
 139group A was 66.2 ± 43.6 ml; 18 (20.7%) women experienced blood loss exceeding
 140200 ml, including 11 gestational mass case. Patients in Group A incurred more severe
 141blood loss than those in Groups B (66.2 ± 43.6 vs 22.5 ± 13.9 ml, $P < 0.01$) and C
 142(66.2 ± 43.6 vs 38.9 ± 16.7 ml, $P < 0.05$). However, adverse events were relatively
 143common in Group B (38.7% vs 3.4%, $P < 0.01$), and in Group C (17% vs 3.4%, $P <$
 1440.01) than in Group A. In total, 30 women experienced fever ($38 - 39^{\circ}\text{C}$), and 9

145women felt moderate pelvic pain in Group B. Six cases of stomatitis, 6 cases of
 146alopecia, and 3 cases involving abnormal liver function, were associated with MTX
 147treatment in Group C. There were only 3 cases of fever in Group A ($38 - 38.5^{\circ}\text{C}$). All
 148symptoms were resolved conservatively. As expected, the duration of hospital stay
 149was significantly shorter in Group A than in the other two groups, and the medical
 150cost was lowest in Group A. The three groups were similar with respect to operative
 151time, rates of success, the number of massive hemorrhages, the number of blood
 152transfusions, and the time taken for $\beta\text{-hCG}$ to normalize. It is important to note that
 15318.9% women in group B complained of a reduction in their menstrual blood volume
 154(MBV) after surgery, with reductions of one-half to one-third of their previous MBV.
 155These issues were more common in Group B when compared to Group A.
 156Comparisons of hormonal data are given in Table 3. When we further divided each
 157group before and after operation according to age, we found that among the women of
 158advanced age (≥ 35 y), the serum AMH level in Group B decreased to 2.78 ± 1.89 ng/
 159ml after operation; this trend was statistically significant compared to the baseline
 160group ($P < 0.05$), which also showed significantly lower levels of AMH than Group A
 161after surgery (4.22 ± 2.35 vs 2.78 ± 1.89 ng/ml, $P < 0.05$). There were no other
 162significant differences in terms of serum AMH level among the young women (< 35
 163y) in each group, and the median level of serum INH B was similar across all three
 164groups, both before and after surgery.

165Discussion

166China has been characterized by persistently low fertility rates over recent years; this
167phenomenon has arisen due to a variety of social, economic, and policy-related
168factors. Although the two-child policy came into force in January 2016, this will not
169be sufficient to change the decreasing trend in total fertility rate (TFR) [12].
170Furthermore, the high rate of cesarean sections has led to a large number of CSP
171patients in China [13]. The inappropriate management of CSP carries a high risk of
172uncontrollable bleeding, shock, and can eventually result in hysterectomy [14]. In
173order to maintain the fertility of these CSP patients, it is an urgent need to create
174options to manage the treatment of CSP patients in a safer and more effective manner.
175Researchers now advocate individualized courses of precise treatment for CSP that
176are based on specific patient circumstances, and also consider that the combination of
177methods may produce more favorable outcomes [4,5,15].

178MTX is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase, and
179interferes with DNA synthesis, ultimately resulting in trophoblastic cytolysis [15].
180The use of MTX in the conservative treatment of CSP to reduce hemorrhage has been
181investigated previously [16]. Our study also demonstrated that blood loss was lower
182in the combined MTX group (C) when compared with the direct surgical group (A)

183(66.2 ± 43.6 vs 38.9 ± 16.7 ml, $P < 0.05$). However, there were no significant
184differences between the two groups with regards to massive hemorrhage and

transfusion ($P > 0.05$). Our study showed that MTX treatment was associated with a greater number of side effects; all adverse events were graded with a score of 2 according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 and did not need inpatient management. In theory, MTX takes a long time to cause trophoblastic cytolysis because its half-life is short [17]; furthermore, exposure of the trophoblast to MTX is made difficult by the presence of fibrous tissue surrounding the gestational mass. We needed to prolong the period of hospitalization (19.8 ± 6.1 vs 4.7 ± 1.8 days, $P < 0.01$) to wait for surgery as we needed the serum β -hCG to fall to $<3,000$ IU/l. Most patients cannot tolerate such time periods in order to observe a responsive effect. It might be possible to increase the attractiveness of MTX as an adjunctive treatment if we were able to administer the protocol as part of an outpatient service.

Given that the uterine arteries predominantly supply uterine blood, once UAE has been applied to embolize the bilateral uterine artery, it follows that the blood flow around the CSP mass will decrease sharply. However, UAE is associated with a range of complications that cannot be ignored, including uterine adhesions, bladder necrosis, ovarian failure, pyometra, and pulmonary embolization [18]. Although there were no cases of ovarian failure in the present study, 18.9% women in the UAE group complained of a reduction in their MBV, by one-half to one-third of their previous MBV. Because other factor, such as operative hysteroscopy, could promote these issues, UAE cannot be the only underlying mechanism. It is worth noting that UAE

led to a reduction in the serum levels of AMH in women aged ≥ 35 y women in our study (4.39 ± 1.18 vs 2.78 ± 1.89 ng/ml, $P < 0.05$), this trend for reduction was also statistically significant when compared with the levels of AMH in group A after surgery ($P < 0.05$), although the levels of INH B were similar across all three groups before and after operation. AMH and INH B levels are the most widely used markers for ovarian reserve, and AMH is the most reliable marker of ovarian reserve [19]. This suggests that UAE may reduce the ovarian reserve of women aged ≥ 35 y. In a previous study, Timor et al [18] suggested that UAE should be undertaken mostly to rescue patients from life-threatening hemorrhages. We believe that UAE should be used sparingly in those older women who wish to retain their fertility. The hysteroscopic technique is minimally invasive, and helps to clear the gestational tissue with a lower risk of morbidity; as such, this technique enables patients to resume their normal activities within a relatively short time, thus achieving a double effect in the diagnosis and treatment of CSP [20]. In the present study, we performed UAE and MTX preoperative procedures before hysteroscopy, and compared the clinical outcomes of these procedures with hysteroscopy alone. We found that the success rate was similar across the three groups. Although direct hysteroscopy led to a greater blood loss than the combined methods, there were only 5 cases involving a gestational mass that required blood transfusions. In cases type I CSP patients with a gestational sac, direct hysteroscopy appears to be a reliable treatment option that can

226produce satisfying success rates, with lower medical costs, and shorter hospital stays,
227when compared to combined therapies. Moreover, direct hysteroscopy can treat CSD
228and uterine adhesions at the same time; even under ultrasound guidance, D&C cannot
229achieve such results. The gestational mass type, which is characterized by the
230invasion of trophoblastic cells into the CS scar and myometrium, often features
231thinner healthy myometrium and weaker myometrial contractility, with abundant
232blood flow at the site of implantation, leading to the risk of severe hemorrhage during
233surgery. Our study show that UAE and MTX may reduce transfusion in these patients.
234However, the cases about gestational mass type is small, a larger prospective study
235still needs to evaluate this procedure further. Moreover, the bound of the trophoblastic
236tissue within the myometrium remains unclear, retained trophoblastic tissue within the
237CS defect, or uterine perforation, is therefore [inevitable](#). The significance of defining
238the thickness of the local normal myometrium in gestational mass cases by ultrasound
239remains to be determined. Laparoscopy might be more suitable for these patients.
240In summary, the combination treatments of MTX or UAE prior to hysteroscopy in
241early type I CSP patients with a gestational sac has minimal remedial effects and
242incurs additional side effects. Moreover, UAE has a negative impact on ovarian
243reserve in women aged ≥ 35 y. Direct hysteroscopy appears to be the reliable treatment
244option for these patients.

245**Disclosure of interests:** The authors report no conflicts of relevant financial, personal,
246political, intellectual or religious interests.

247**Contribution to authorship:** JP planned this research study. MS carried out this research
248study. MS and LJi acquired data. FT, LJi and MH analyzed and interpreted the data. KZ
249drafted the manuscript and MS revised the manuscript.

250**Details of ethics approval:** The study was approved by the Ethics Committee of Jinhua
251Municipal Central Hospital (ethics approval No.2019-198), the date of approval: 9/10/2019.

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253agency in the public, commercial, or not-for-profit sectors.

254References

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 257 [Obstet](#) 143:172-177.

2582. Table legends

259**Table 1** There were no statistically significant differences among the 3 groups with
 260respect to age, number of previous cesareans, time interval between last CSP, days of
 261gestation, initial serum β -hCG level, or the rates of cases involving a gestational mass.

262**Table 2** Patients in Group A incurred more severe blood loss than those in Groups B
 263and C. and fewer adverse events than either Group B or C. The duration of hospital
 264stay was significantly shorter in Group A than in the other two groups, and the
 265medical cost was lowest in Group A. Women in group B complained of a reduction in
 266their menstrual blood volume (MBV) after surgery, the difference was statistically
 267significant when compared to Group A.

268**Table 3** Among the women of advanced age (≥ 35 y), the serum AMH level in Group
 269B was significantly lower than those in Group A after operation. the trend of decrease
 270was also statistically significant when compared to the baseline group. There were no
 271significant differences in serum AMH level among the other group, and the median
 272level of serum INH B was similar across all three groups before and after operation.