

When to Perform Curettage After Uterine Artery Embolization for Cesarean Scar Pregnancy: a Clinical Study

Qiao Wang

West China Second University Hospital of Sichuan University

Hongling Peng

West China Second University Hospital of Sichuan University

Xia Zhao

West China Second University Hospital of Sichuan University

Xiaorong Qi (✉ qixiaorong11@163.com)

West China Second University Hospital of Sichuan University

Research Article

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Abstract

Background: Prophylactic uterine artery embolization (UAE) combined with following curettage was suggested as an effective and minimally invasive treatment strategy for cesarean scar pregnancy (CSP) with high bleeding risk. However, the timing of curettage after UAE remains to be studied. Thus, we aimed to identify the optimal time interval to perform curettage after UAE in patients with CSP.

Methods: We conducted a retrospective cohort study in a large medical center for women and children in southwest China. CSP patients treated by UAE combined with following curettage were included and grouped by the treatment time interval between these two procedures. The clinical outcomes among arms were compared by univariate and multi-variable analysis.

Results: Our study finally included a total of 314 CSP patients who received this combination treatment in our department from January 2014 to December 2019. The median time interval between UAE and curettage was 48 hours with a range of 12-168 hours in all participants. Thirty-two cases (10.2%) experienced intra-operative hemorrhage (blood loss $\geq 200\text{mL}$). Seventeen cases (5.4%) used intrauterine balloon tamponade. Fourteen cases (4.5%) were converted into laparoscopy (or laparotomy). In the cohort study, patients with longer treatment interval had more intra-operative blood loss and higher incidence of complications than those with shorter interval ($P=0.05$). The rate of intra-operative bleeding was 5.0% in patients who received curettage within 24 hours after UAE (Arm 1), in comparison with 19.4% in those who had treatment interval longer than 72 hours (Arm 4). In the multi-variable logistic regression model of bleeding, the treatment interval ≥ 72 hours had an adjusted odds ratio of 3.37 (95% confidence interval: 1.40-8.09).

Conclusion: We suggest that curettage should not be delayed longer than 72 hours after UAE under general conditions.

Background

Cesarean scar pregnancy (CSP) is a late complication of cesarean section (CS), which is defined as an early pregnancy implants in the scar from the prior CS [1]. CSP was considered as a rare type of ectopic pregnancy, but it is occurring more often than before due to the increased CS rate, especially for developing countries [2]. Since the pregnancy sac implants in the scar tissue which is a weakness in the lower segment of uterus, CSP can cause life-threatening conditions such as uncontrollable bleeding, uterine rupture, and maternal mortality [3].

Currently, no optimal treatment of CSP has been recommended [1]. The management should be individualized [4]. According to previous studies, adjuvant uterine artery embolization (UAE) combined with following curettage (including dilatation and curettage or vacuum aspiration) was suggested as an effective and minimally invasive treatment strategy for CSP patients with high bleeding risk [5–7]. Prophylactic UAE can reduce the risk of severe bleeding during curettage by pre-treatment of local methotrexate (MTX) administration and blockage of the main blood supply. The efficacy and safety of

UAE have been evaluated by numerous studies. However, the timing of curettage after UAE remains to be studied. In previously reported studies, the time intervals between UAE and curettage were quite different, ranging from 24 to 72 hours [5–11]. There is no consensus on the optimal time interval to perform curettage after UAE.

We therefore conducted the present clinical study to investigate the relation between clinical outcomes and treatment interval between UAE and curettage in CSP patients, aiming to identify the most appropriate timing to perform curettage after UAE.

Methods

Subjects

This study was approved by the Institutional Review Board of Ethics Committee of West China Second Hospital, Sichuan University, People's Republic of China. We recruited all the patients diagnosed with CSP who received the combination treatment of adjuvant UAE and ultrasound-guided curettage in the Department of Gynecology and Obstetrics of our hospital from January 2014 to December 2019. Signed informed consent forms were obtained from each patient whose clinical data were collected. Since our hospital is one of the largest gynecology and obstetrics medical centers in southwest China, women with difficult and complicated diseases (such as CSP patients) would be transferred to our department.

Diagnosis

The CSP was diagnosed depending on: (1) a history of low-transverse cesarean delivery; (2) a positive blood test of serum beta-human chorionic gonadotrophin (beta-hCG); and (3) ultrasound imaging. Ultrasonographic diagnosis was made by the following criteria [12]: (1) empty uterine cavity and cervical canal; (2) a gestational sac, with or without fetal cardiac activity, located in the anterior portion of the lower uterine segment (the scar of prior CS); and (3) a thin ($\leq 3\text{mm}$) or absent myometrium between the gestational sac and the bladder. We classified the CSP cases into two types depending on ultrasound imaging and magnetic resonance imaging (MRI): (1) type I (endogenic type) with progression toward uterine cavity; or (2) type II (exogenic type) with progression toward the bladder. MRI could assess a cesarean scar defect and identify the trophoblastic layer and the myometrium separately, which guided the decision-making of treatment strategy. Thus, a pelvic MRI was performed for every CSP patient who needed prophylactic UAE treatment, as radiologists required.

Inclusion and exclusion criteria

Our study included CSP patients who met the following criteria: (1) 5–12 weeks of gestation; (2) diagnosis and clarification of CSP confirmed by both transvaginal Doppler ultrasound and MRI [8,13]; (3) receiving UAE within 48 hours after diagnosis; and (4) undergoing ultrasound-guided curettage following the pre-treatment of UAE. We excluded patients: (1) who had ever received failed surgical or medical treatment before transferred to our department; or (2) who had maternal hepatic, renal, or blood system

diseases. The type of gelfoam (with diameters of 1–3.0 mm, Aicon, Hangzhou, China) and dose of MTX (50 mg/m² body surface area) used in UAE were consistent in each case. All procedures of UAE and curettage were performed by specialists in our hospital, following the same protocol.

Study design

This was a retrospective study, designed as a cohort study to evaluate clinical outcomes among four arms which were grouped by the time interval between UAE and curettage. Medical records and clinical data of every patient meeting the inclusion criteria were reviewed. Characteristics extracted as variables in the analysis included maternal age, gravidity, parity, number of prior CS, time interval between last-time CS and present CSP, presence of fetal cardiac activity, level of serum beta-hCG, gestational age, diameters of gestational sac (or CSP mass), thickness of myometrium between the gestational sac and the bladder, ultrasonographic presence of peritrophoblastic blood supply, and the type of CSP. In addition, we also took the recurrence of CSP as one of the variables into the analysis. The primary outcome in our study was intra-operative blood loss. The bleeding volume was measured by weighing of blood captured in the suction device and under-buttocks pad. Other clinical outcomes included the incidence of complications and the total length of hospital stay. Clinical events recorded as complications were: (1) usage of intrauterine balloon tamponade to control the active bleeding during or after curettage; (2) excessive hemorrhage with blood transfusion; (3) persistent CSP; (4) subsequent laparoscopy or laparotomy due to uterine rupture or uncontrollable bleeding; and (5) surgical infection. Statistical reviews between the bleeding group and control group were further conducted to identify risk factors of intra-operative bleeding. The bleeding group included cases with blood loss ≥ 200 mL during curettage. Patients with intra-operative blood loss less than 200 mL were in the control group.

Statistical analysis

The data analysis was conducted by the software of IBM SPSS Statistics 23.0. Data were analyzed by parametrical tests or non-parametrical tests appropriately. Continuous variables were reported as mean \pm standard deviation (SD). Discrete variables were reported as median (interquartile range, IQR). Data with normal distribution were compared by independent-sample *t* tests between two groups. Data with non-normal distribution were compared by rank sum tests between two groups. Categorical variables were reported as number (%), compared by chi-square (χ^2) tests between two groups. Comparison of data among multiple arms were tested by analysis of variance (ANOVA). P value < 0.05 was considered statistically significant. Confounding factors were adjusted in multi-variable analysis. A multi-variable binary logistic regression model was conducted to evaluate the relation between variables and intra-operative bleeding. Odds ratio (OR) and 95% confidence interval (CI) of each variable were calculated to identify the risk factors of bleeding (if both OR and 95% CI $\neq 1$).

Results

Our study finally included a total of 314 CSP patients who were treated in combination of UAE and curettage between January 2014 and December 2019 (Fig. 1). Among them, 46 cases (14.6%) experienced at least one of the following events as complication. Intrauterine balloon was used in 17 cases (5.4%) for active bleeding without uterine rupture. Fourteen cases (4.5%) with active bleeding and uterine rupture were converted into emergency laparoscopy or laparotomy for uterus repair. We found eight persistent CSP cases (2.5%). Five cases (1.6%) required blood transfusion. Only one case (0.3%) underwent hysterectomy because of uncontrollable bleeding.

In all participants, the median treatment interval between the two procedure was 48 hours with a range of 12–168 hours. In the analysis of a cohort study, patients were divided into four arms depending on the time interval between UAE and curettage. The baseline patient characteristics and clinical outcomes of each arm are listed in Table 1. There were no significant differences in the baseline characteristics of patients among different arms ($P>0.05$). However, we found that CSP patients treated with longer treatment interval were likely to have worse clinical outcomes (more intra-operative blood loss, higher rate of complications, and longer hospital stays, with $P<0.05$) than those in the shorter interval arms (Fig. 2). The rate of excessive hemorrhage was 5.0% in patients who received curettage within 24 hours after UAE (Arm 1), in comparison with 19.4% in those who had treatment interval longer than 72 hours (Arm 4).

Thirty-two cases (10.2%) had intra-operative blood loss ≥ 200 mL during curettage. Univariate analysis showed there were significant differences in gestational age, diameter of CSP mass, myometrial thickness, blood supply, type of CSP, as well as treatment interval (the timing of curettage after UAE) between the bleeding group and control group (Table 2). Accordingly, these variables were identified as potential risk factors of hemorrhage in this combination treatment strategy. Multi-variable analysis was further conducted to adjust confounding factors. These candidate risk factors were divided as two-categories variables respectively and analyzed in multi-variable binary logistic regression models of intra-operative bleeding (Table 3). The cut-off of each non-categorical variable was selected depending on the median value in bleeding cases. In the final model, the interval between UAE and curettage >72 hours was identified as one of the four significant risk factors, with an adjusted OR of 3.37 (95% CI: 1.40–8.09, $P = 0.007$). The other three risk factors were myometrial thickness ≤ 0.1 cm (adjusted OR 4.55, 95% CI: 1.73–11.94, $P = 0.002$), maximum diameter of CSP mass ≥ 5 cm (adjusted OR 3.86, 95% CI: 1.53–9.74, $P = 0.004$), and type II CSP (adjusted OR 3.00, 95% CI: 1.25–7.21, $P = 0.014$). In order to discuss about the optimal timing of curettage, we further set different cut-offs of treatment interval in the multi-variable logistic regression. When the variable of treatment interval was divided at the cut-off of 48 hours, the adjusted OR was 2.2 (95% CI: 0.94–4.92, $P = 0.068$). The variable with cut-off at 24 hours had an adjusted OR of 2.1 (95% CI: 0.59–7.77, $P = 0.243$).

Discussion

One of the main challenges in management of CSP is massive bleeding. Uterine artery embolization, which has been widely used in controlling hemorrhage in gynecology and obstetrics, is regarded as a good option of treating CSP with minimal invasion, especially when used as an adjuvant therapy with

other surgical treatment such as curettage. There have been dozens of studies evaluating the efficacy and safety of UAE used in CSP treatment, either as a single therapy or combined with other methods [5–10, 14–19].

However, there is currently no study pointing out the optimal timing to perform surgical treatment after prophylactic UAE. The previously reported study designs were quite different in the treatment interval between UAE and curettage.

During the UAE procedure, MTX was locally injected through the uterine arteries followed by the main stems of uterine arteries blocked by gelfoam particles [20]. MTX works on killing the embryo and trophoblastic cells. The reduce of uterine blood supply by UAE was impermanently, since the gelfoam could be resolved within 7–14 days. Depending on this mechanism, most authors theoretically suggested that curettage should be taken within 24–72 hours after UAE to balance the benefit of onset time and the risk of recanalization [5–11]. Currently, it is only a clinical opinion which still needs reliable clinical evidence. In our hospital, gynecologists performed curettage even within 24 hours or longer than 72 hours after UAE in some cases. The treatment intervals were individualized depending on operation schedules, gynecologists' intentions, or patients' preferences. Thus, we designed the present study to discuss the most appropriate time to perform curettage after UAE.

In this cohort study, we found that patients in the short interval arm were likely to have better clinical outcomes than those in the long interval arms. This result demonstrated that the delay of curettage following UAE might increase the risk of intra-operative bleeding and other complications. Consistently, the result of multi-variable logistic regression indicated that the treatment interval longer than 72 hours after UAE was one of the risk factors of intra-operative bleeding. This increase of bleeding risk by time delay might be explained by the initiating of collateral circulation or tissue edema due to long-time ischemia. The incidence of bleeding was lower in shorter-interval arms, which appeared that treatment interval within 24 hours might be ideal. However, when we adjusted the cut-off of this variable at 24 or 48 hours in the multi-variable analysis, the statistical results showed no significance. Therefore, we could not get a final conclusion about the best timing of curettage after UAE based on this study, but we strongly suggest that curettage should not be delayed longer than 72 hours under general conditions.

Other risk factors identified as risk factors of bleeding in this combination therapy included thinner myometrial thickness, larger diameter of CSP mass, and type II CSP. Since this finding coincides with our previous study [14] and other reports [21, 22], we did not discuss more about these factors. However, the gestational age and peritrophoblastic blood supply which were identified as potential risk factors in the univariate analysis were not included in the result of our final regression model. This result might be explained by: (1) the synergy of gestational age and diameter of gestational sac (adjusted as a confounding factor); (2) the blood supply shown at the time of diagnosis had been successfully blocked by UAE, no longer influencing the clinical outcome in this combination treatment strategy.

There are limitations of our study. Firstly, this is a retrospective and observational research. The interventions were decided depending on the intentions of clinicians and patients with selective bias.

Secondly, the bleeding risk factors in treatment of CSP are multi-factorial and interactive. Our study showed that the influence of treatment interval had significantly clinical and statistical meaning, but it might not be an independent factor. Lastly, even though our sample size is large enough as a study of one single medical center, multi-center randomized controlled trials (RCTs) with more reliable evidence are needed to get a better conclusion.

Conclusions

In combination treatment of adjuvant UAE and following curettage for CSP, patients who have shorter time interval between these two procedures are likely to have lower risk of bleeding than those in the longer interval group. The treatment interval > 72 hours is a significant risk factor of bleeding during curettage. We strongly suggest that curettage should not be delayed longer than 72 hours after UAE under general conditions. However, more clinical trials, such as RCTs, are necessary to get a final conclusion about When to perform curettage after UAE.

List Of Abbreviations

Uterine artery embolization (UAE); Cesarean scar pregnancy (CSP); Cesarean section (CS); Methotrexate (MTX); Beta-human chorionic gonadotrophin (beta-hCG); Magnetic resonance imaging (MRI); Standard deviation (SD); Interquartile range (IQR); Analysis of variance (ANOVA); Odds ratio (OR); Confidence interval (CI); Randomized controlled trials (RCTs).

Declarations

Ethics approval and consent to participate:

The experimental protocol was established, according to the ethical guidelines of Helsinki Declaration and was approved by Medical ethics committee of West China Second Hospital of Sichuan University, No 175. Written informed consent was obtained from individual or guardian participants.

Consent for publication:

Not applicable

Availability of data and materials:

All data generated or analysed during this study are included in this published article.

Competing interests:

we declare that we have read and understood the BMC Group policy on declaration of interests and have no relevant interests to declare.

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Author Contributions:

Qiao Wang and Xiaorong Qi did the study design and prepared the manuscript. Qiao Wang and Hongling Peng did the data collection and statistical analysis. Xia Zhao and Xiaorong Qi revised the manuscript. Final version of this manuscript was approved by all authors.

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Tables

Due to technical limitations, table 1-3 xlsx are only available as a download in the Supplemental Files section.

Figures

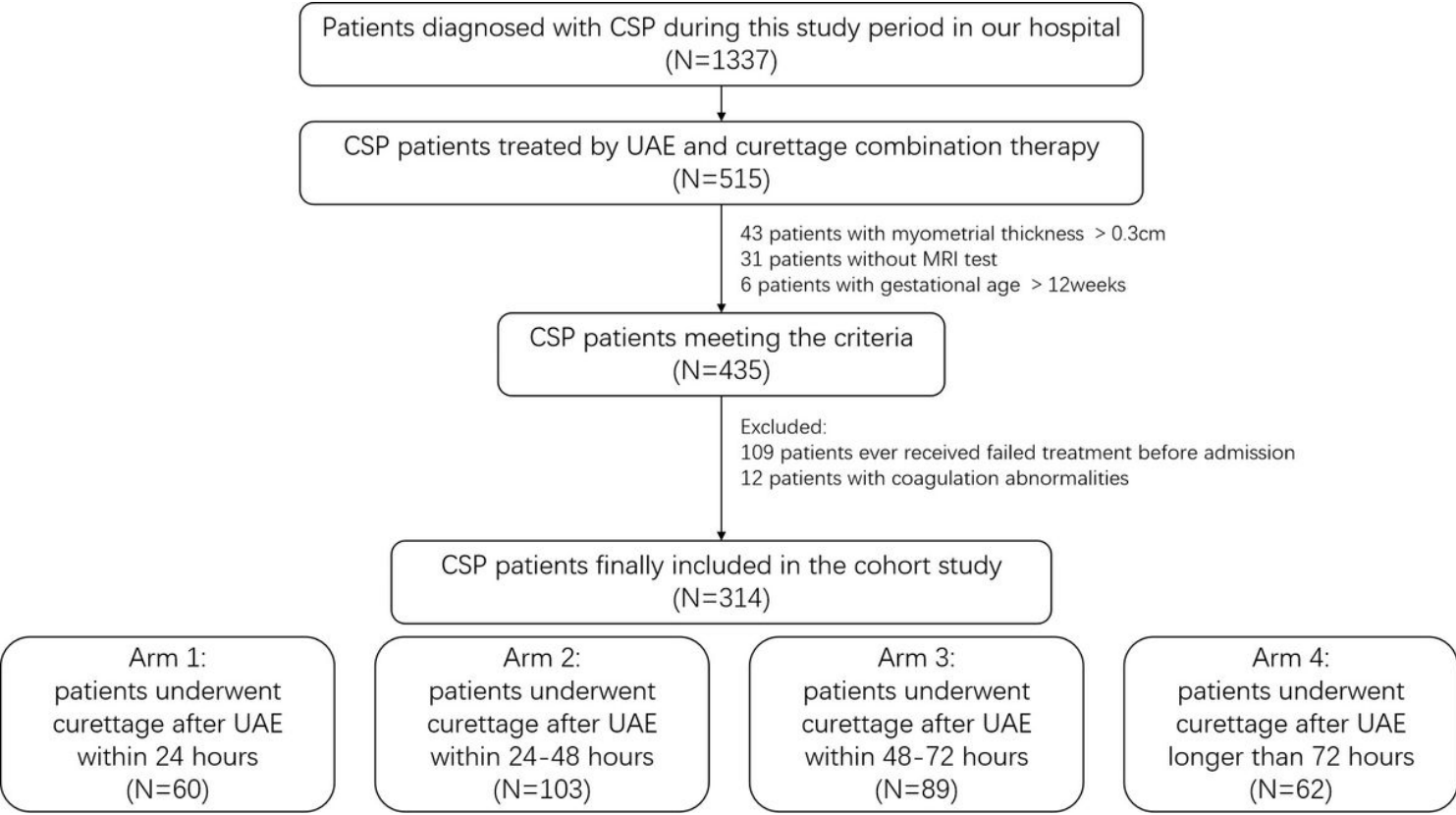


Figure 1

Flow chart of participants. Our study finally included 314 CSP cases who were treated in combination of UAE and curettage. We divided the participants into four arms depending on the time interval between UAE and curettage. CSP= cesarean scar pregnancy. UAE= uterine artery embolization. MRI= magnetic resonance imaging.

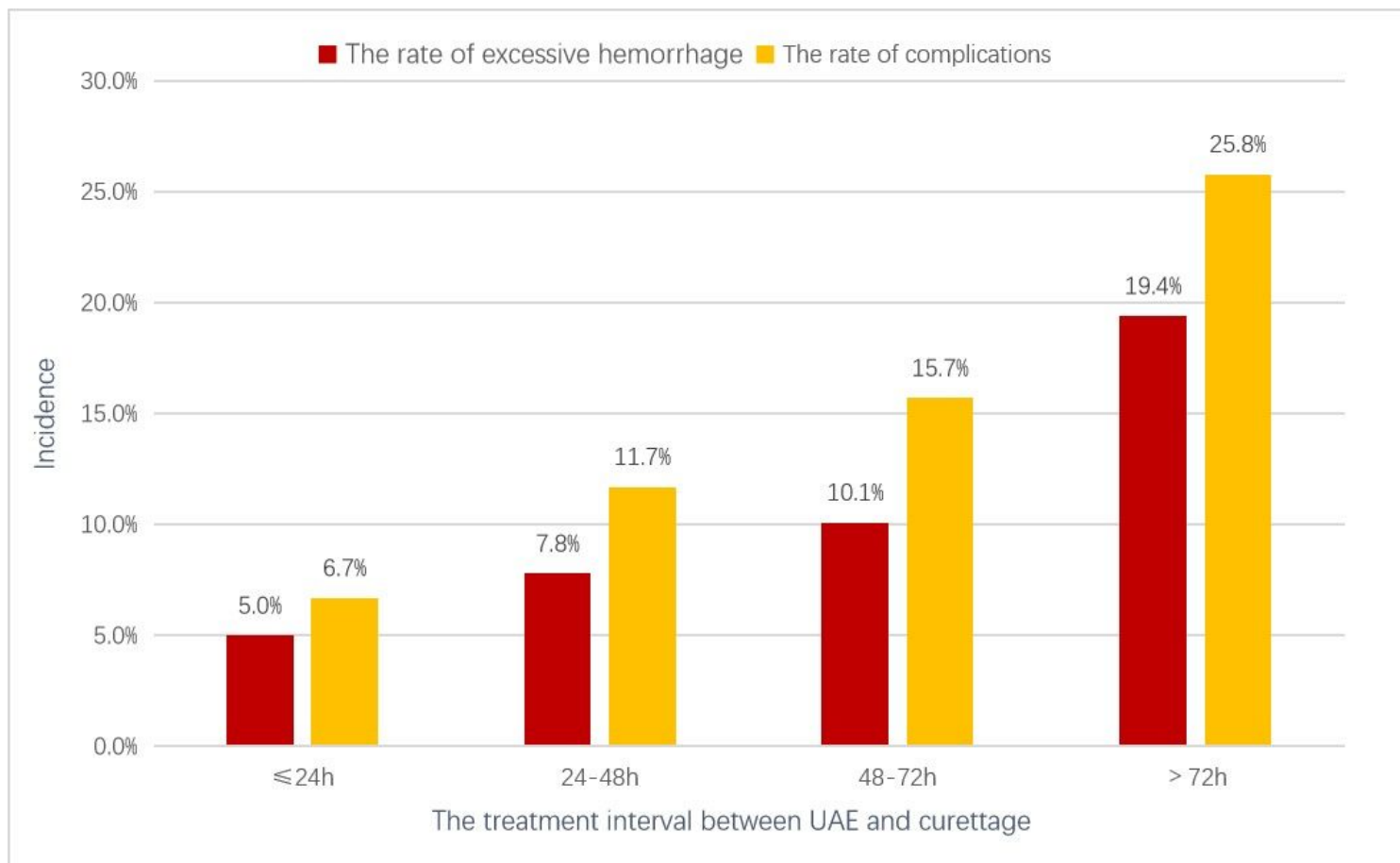


Figure 2

Differences in clinical outcomes of each arm. CSP patients treated with longer time interval between UAE and curettage were likely to have higher rate of excessive hemorrhage and other complications. CSP= cesarean scar pregnancy. UAE= uterine artery embolization.

Supplementary Files

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