

Spontaneous resolution of retained products of conception in late pregnancy: retrospective cohort study

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November 11, 2022

Abstract

Objective: The aim of this study was to analyse the surgical and conservative management of RPOC after 34 weeks of gestation and to elucidate its natural course. **Design:** Retrospective cohort study **Setting:** Study in a single center **Population:** Patients diagnosed RPOC at Kindai university from January 2013 to March 2022 **Methods:** Clinical data from patients' electronic medical records was reviewed retrospectively. **Main outcome measures:** The onset of heavy bleeding, date of RPOC disappearance, and serial changes of serum hCG. **Results:** 19 of 41 cases of RPOC diagnosed after 34 weeks of gestation had the retained placenta manually removed within 24 hours of delivery; nine cases had no emergent symptoms before placental removal; and five and three cases experienced heavy bleeding during and after placental removal, respectively. Six out of 22 cases with RPOC managed conservatively had heavy bleeding for no determinable reason. Six cases experienced heavy bleeding during the placental extraction trial. These events occurred within 60 days of delivery. RPOC disappeared spontaneously in 17 cases (77%), with a median time of 130 days. Serum human chorionic gonadotropin of the 14 patients who did not undergo UAE, fell below the measurable threshold at a median of 67 days postpartum, with a half-life of 4.7 days. **Conclusion:** RPOC in late pregnancy can cause heavy bleeding and infection, but these events do not occur after 60 days postpartum, and spontaneous resolution of RPOC is possible. Conservative management may be an option in the treatment protocols for RPOC.

Introduction

Delay in placental delivery may cause heavy bleeding in late pregnancy. Therefore, it is recommended that obstetric providers use uterotonic agents immediately after delivering the foetus and deliver the placenta by controlled cord traction¹). Retained products of conception (RPOC), in which placental tissue remains in the uterus after delivery, occur in about 1% of pregnant women and causes severe postpartum haemorrhage^{2,3}). The National Institute for Health and Clinical Excellence (NICE) and the World Health Organization (WHO) recommend that obstetric providers perform manual removal of the placenta (MROP) if it is not expelled within 30 minutes to 1 hour after the baby is delivered⁴). However, MROP may increase the risk of hysterectomy and death due to heavy bleeding. Additionally, the placenta often remains partly after MROP⁵). If conservative management is chosen immediately after deliver, or RPOC occurs after MROP, there is a risk of subsequent massive haemorrhage or infection⁶⁻⁹). Therefore, some studies suggest that RPOC should be removed by transcervical resection (TCR) to avoid bleeding and infection during conservative management^{10,11}). However, surgical RPOC removal also carries a high risk of massive bleeding¹²).

Recently, several Japanese facilities have reported that RPOC spontaneously disappeared without surgical management^{13,14}). However, evidence for the conservative management of RPOC, especially after term delivery, is lacking, and there are no criteria to determine which cases can achieve spontaneous resolution^{15,16}). It is also unclear when major bleeding or infection occurs and how long it will take for RPOC to be absorbed spontaneously.

Our hospital is the only university hospital in the South Osaka district, and most patients with RPOC in this area are referred to our hospital. We have treated many cases with RPOC conservatively until they spontaneously disappear. This study aimed to analyse the clinical course of RPOC after 34 weeks of gestation and to elucidate its natural history. The results of this study show that conservative management should be incorporated into the standard treatment for RPOC.

Materials and Methods

Patients

This study included patients who delivered after 34 weeks of gestation and were managed for RPOC at Kindai University Hospital from January 2013 to March 2022. Participants were divided into two groups: those who underwent MROP within 24 hours of delivery and those who were managed conservatively without MROP. Patients with RPOC who delivered before 20 weeks of gestation and did not undergo uterine artery embolization (UAE) were also included to evaluate serial changes in serum human chorionic gonadotropin (hCG) levels. This study was approved by the ethical review board of Kindai University (Approval number: R04-166).

Endpoint

Clinical data from patients' electronic medical records was reviewed retrospectively. The following variables were investigated: gestational weeks and mode of delivery, RPOC diameter at diagnosis, blood flow in RPOC, bleeding, infection, UAE, MROP, TCR, dilatation and curettage (D&C), hysterectomy, blood transfusion, the onset of heavy bleeding, date of RPOC disappearance, and serum hCG levels. We defined "heavy bleeding" as bleeding accompanied by a change in vital signs; "moderate bleeding" as normal menstrual blood loss; and "light bleeding" as minor blood loss. Spontaneous resolution was defined as RPOC disappearance without removal of the placenta which confirmed by ultrasound or hysteroscopy.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA). Fisher's exact test and Mann-Whitney *U* test were used to compare continuous variables; $p < 0.05$ was considered statistically significant.

Results

There were 41 cases with RPOC delivered after 34 weeks of gestation with no deaths or hysterectomies. Our institution manages RPOC cases conservatively with informed consent unless there are no signs of placental delivery or urgent conditions such as heavy bleeding. If patients request, we perform MROP within 24 hours of delivery. The placenta was manually removed in 19 cases within 24 hours of delivery. The remaining 22 cases were managed conservatively, without MROP.

19 cases with MROP within 24 hours of delivery

All 19 cases were delivered vaginally, with a median (range) of 39.9 (34.7-41.1) weeks of gestation at delivery. The indications for MROP were haemorrhage in nine cases and infection in one case. MROP was performed at the patient's request without any urgent symptoms in the remaining nine cases. Fifteen of the 19 cases experienced heavy bleeding (Figure 1A). Nine of the 15 patients had heavy bleeding before MROP (Cases 1-9), and all required blood transfusion. Six of the nine cases who underwent MROP without bleeding experienced heavy bleeding during the procedure (cases 10-15), five of them required blood transfusion.

One of the nine cases with heavy bleeding before MROP and four asymptomatic patients had RPOC after MROP. Two cases (Cases 11 and 12) experienced heavy bleeding again, and one case (Case 12) had infection. RPOC spontaneously resolved in all cases within a median of 82 days. Only one of the 14 cases in which the retained placenta was completely removed by MROP had heavy bleeding the day after MROP underwent UAE (Case 14). The remaining 13 cases had neither bleeding nor infection.

22 cases with conservative management

Three cases were delivered via caesarean section. The median RPOC diameter was 46 mm, with five cases exceeding 100 mm (Figure 1B). Seventeen cases had blood flow in RPOC on contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), or Doppler ultrasound (Figure S1). Three cases had no blood flow, and two were not evaluable.

12 cases experienced heavy bleeding and nine cases required haemostasis through UAE. Six of the 12 cases had unprovoked bleeding. The remaining six cases experienced heavy bleeding during placental removal trial. In five cases, pulling on the detached placenta caused major bleeding. Dilatation and curettage (D&C) in one case led to heavy bleeding. Three cases underwent UAE, and three required blood transfusion. Even though the contrast-enhanced MRI did not show any blood flow, case 31 had heavy bleeding due to placental traction.

Three of the 22 cases had infection, all of which were cured with antibiotics. Case 20 underwent MROP on postpartum day 7 and showed signs of infection on postpartum day 15. Eight cases had no complications, such as bleeding or infection, and three of them were delivered via caesarean section. RPOC resolved spontaneously in 17 of 22 cases (77%) without surgical intervention, and the median time from delivery to resolution was 130 days. There was no difference between heavy ($n=12$) and light ($n=9$) bleeding cases in terms of RPOC diameter at diagnosis, blood flow on CT or MRI, and the time from delivery to resolution of RPOC (Table S1).

Regarding the timing, heavy bleeding occurred within 60 days postpartum. Blood transfusion was required within 60 days postpartum, and UAE required within 30 days postpartum. Infection occurred within 30 days postpartum (Figures 2A-D). Heavy bleeding, UAE, blood transfusion, and infection occurred within 40, 40, 20, and 30 days postpartum, respectively, in 16 cases, excluding six patients with haemorrhage in placental removal trial (Figures 2E-H). RPOC disappeared in approximately half of the cases at 100 days postpartum, and in 80% after 1 year postpartum. RPOC resolved spontaneously except in all except five cases, in which it was surgically removed (Figure 3).

Serial changes in serum hCG

Finally, we examined the transition in serum hCG levels in cases with conservative management. Of the 16 cases in which serum hCG was measured, the median time from delivery to serum hCG level below the measurable threshold was 67 (23-113) days. Next, we investigated the changes in serum hCG levels in cases in which serum hCG was examined at least twice before falling below the measurable threshold. In seven cases that delivered after 34 weeks of gestation but did not undergo UAE, the median half-life of serum hCG was 4.7 (2.3-7.5) days (Figure 4A).

Serum hCG levels decreased rapidly after UAE in three patients (Figure 4B). Among the cases who delivered before 20 weeks of gestation and did not undergo UAE, the median half-life of serum hCG was 7.4 (3.8-39.1) days (Figure 4C, 4D). None of the cases delivered after 34 weeks of gestation had a hCG half-life of > 10 days, whereas three cases delivered before 20 weeks of gestation had a half-life of >10 days (Figure 4D).

Discussion

If the placenta does not separate from the uterus after delivery, the NICE and the WHO guidelines recommend that the placenta should be removed manually within 30 minutes to 1 hours after delivery with a set-up to deal with heavy bleeding. If bleeding does not stop, UAE or hysterectomy is required⁴. In Europe and the United States, deliveries are centralized in regional general hospitals. This allows obstetrical providers to perform MROP under anaesthesia, which is performed by anaesthesiologists. In Japan, on the other hand, private clinics handle half of all deliveries, and high-risk cases are transported to advanced medical facilities. As a result, many cases with RPOC have been referred to our hospital. In this study, 41 cases of RPOC delivered after 34 weeks of gestation were successfully treated without hysterectomy or death. The strengths of this retrospective study are as follows: (i) The research period was relatively short (10 years), and the participants were treated consistently. (ii) The clinical characteristics of the participants were homogeneous and were limited to cases delivered after 34 weeks of gestation. (iii) The detailed clinical course of surgical

removal and spontaneous disappearance of RPOC was clarified in all cases.

In this study, 15 of 19 cases with MROP within 24 hours of delivery experienced heavy bleeding during the procedure or the following day. A Japanese multicentre retrospective study demonstrated that the incidence of bleeding of 1000 ml or more at delivery was significantly higher in 41.1% of the women who underwent MROP than in 4.1% of those who did not¹⁷⁾. The cause of heavy bleeding during or after MROP is considered to be that uterine contraction cannot prevent damage to large blood vessel, which occurs after MROP when decidua formation is insufficient or absent¹⁸⁾. In one study, seven of 37 MROP cases were reported to have undergone hysterectomy due to massive bleeding, and those cases were pathologically diagnosed with placenta accreta and no decidua formation¹⁹⁾. Interestingly, in the current study, when MROP was performed on patients with no bleeding or other emergencies, heavy bleeding and partially retained placenta were frequently observed both intraoperatively and postoperatively (Figure 1A). This result suggests that MROP immediately after delivery should be avoided in cases of retained placenta without bleeding because of extensive decidual defect and placental adhesion.

Of the 22 RPOC cases managed conservatively, six cases experienced spontaneous heavy bleeding. Previous studies reported that the RPOC diameters [?] 4 - 4.4 cm^{6,8)} or blood flow in RPOC^{7,21)} had been associated with heavy bleeding during conservative management of RPOC. However, these studies differ from the present study in several respects. First, these studies included cases before 20 weeks' gestation^{6-8, 21)}. Although the size of RPOC is smaller, trophoblast cell viability is higher in early and mid-pregnancy than in late pregnancy²⁰⁾. Furthermore, these studies included cases in which the placenta was manually removed within 24 hours after delivery^{6,8)}. Therefore, the results of previous studies were based on a heterogenous population and may have had various biases. In the present study, there was no correlation between heavy bleeding and RPOC size or blood flow (Table S1). Further research is needed to determine the relationship between RPOC size, blood flow, and heavy bleeding.

The median time for conservatively treated RPOC to develop massive bleeding is reported to be 22-42 days, with a maximum of 38-43 days^{6,8)}. In this study, no events such as heavy bleeding, blood transfusion, UAE, or infection, were observed after 60 days during conservative management (Figure 2). This result may help patients understand when the risk of bleeding decreases during conservative management. There were six cases in which placental removal was attempted despite the absence of heavy bleeding (Figure 1B). None of the cases resulted in the removal of the placenta, and afterwards, the placenta spontaneously disappeared. Therefore, if conservative management does not cause bleeding or infection, placental removal should be avoided and spontaneous resolution can be expected. In this study, the rate of RPOC disappearance during conservative management was approximately 50% at 100 days and 80% at 1 year (Figure 3). In previous studies, the time to spontaneous disappearance of RPOC ranged from 48 to 84 days^{6,7,22,23)}, which was shorter than that in the present study, likely due to the small size of RPOC in early to mid-pregnancy. This study is the first to demonstrate the time until spontaneous resolution of RPOC in late pregnancy. More research is needed to determine whether these data can be validated under the same conditions.

The half-life of serum hCG after intramuscular injection of hCG is 30-32 hours in the absence of hCG-producing tissues in the body²⁴⁾. The longer half-life indicates that hCG-producing trophoblast cells do exist, but gradually undergo apoptosis. In RPOC cases delivered at before 22 weeks of gestation, serum hCG has been reported to be below the measurable threshold at 67 (6-183) days postpartum, and no cases experienced heavy bleeding afterwards²²⁾. The present study also showed that heavy bleeding did not occur when serum hCG levels fell below the measurable threshold. Therefore, it is important to measure serum hCG levels over time to assess the risk of heavy bleeding. We previously reported an average serum hCG half-life of 5.2 days in five cases of RPOC²⁵⁾, similar to the average of 4.7 days in this study (Figure 4A). Interestingly, in three cases, serum hCG levels decreased rapidly after UAE (Figure 4B), suggesting that acute interception of uteroplacental blood flow causes sudden death of trophoblast cells. There were cases of RPOC after 20 weeks' gestation in which the half-life of hCG exceeded 10 days (Figure 4D), but there were no such cases after 34 weeks. The molecular mechanisms of apoptosis in post-partum trophoblast cells may differ between early and mid-term and late pregnancy. Methotrexate is effective in treating ectopic pregnancy

and RPOC during early pregnancy^{26,27}). Methotrexate has also been used for RPOC in late pregnancy⁹), but its effectiveness has yet to be proven. The effect of methotrexate on RPOC in late pregnancy should be confirmed by measuring serum hCG half-life and comparing it with the data obtained in this study.

Conclusion

RPOC in late pregnancy can cause heavy bleeding and infection, but these events do not occur after 60 days postpartum, and spontaneous resolution of RPOC is possible. A limitation of this study is that it was a retrospective study with a small number of cases. A multicentre prospective study is necessary to establish a standard treatment strategy that includes conservative management of RPOC.

Acknowledgement: We thank the women who participated in this study.

Disclosure of Interests: The authors declare no conflict of interest.

Contribution to Authorship: Conceptualization, R.F., K.K. and N.M.; methodology, R.M., K.K. and N.M.; validation, R.F., K.K. and N.M.; formal analysis, R.F., K.K. and N.M.; investigation, R.F., K.K.; data curation, R.F., K.K.; writing—original draft preparation, R.F.; writing—review and editing, R.F., K.K., K.M., R.S., Y.Y. and N.M.; visualization, R.F.; supervision, N.M.; project administration, N.M. All authors have read and agreed to the published version of the manuscript.

Ethics Approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Kindai University (protocol code R04-166).

Funding: This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 21K16813).

Informed Consent Statement: Opt-out consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author.

Figure/Table Caption List

Figure 1A.

Clinical courses of 19 cases with placental removal within 24 hours after delivery

The numbers in “Size and blood flow of RPOC” indicate the size of RPOC (mm).

The numbers in “After” and “Disappearance of RPOC” indicate the duration from delivery to the onset of the events (days).

RPOC, retained products of conception

Figure 1B.

Clinical courses of 22 cases with conservative management.

The number in “Size and blood flow of RPOC” indicate the RPOC size (mm).

The number in “Events” and “Disappearance of RPOC” indicate the duration from delivery to the onset of event (days).

RPOC, retained products of conception

Figure 2.

The cumulative incidence rate of events in RPOC cases with conservative management

The horizontal and vertical axes represent the duration from delivery to the onset of the events (days) and the incidence rate (%), respectively.

Cumulative incidence rates of heavy bleeding (A), blood transfusion (B), UAE (C), and infection (D) in 22 cases with conservative management of RPOC.

Cumulative incidence rates of heavy bleeding (E), blood transfusion (F), UAE (G), and infection (H) in 16 cases without placental extraction trial during conservative management, excluding five cases with placental traction and one with D&C

RPOC, retained products of conception; UAE, uterine artery embolization; D&C, dilatation and curettage
Figure 3.

The cumulative rate of placental resolution in RPOC cases with conservative management

The horizontal and vertical axes indicate the duration from delivery to resolution (days) and the cumulative incidence rate (%), respectively. Arrows and arrow head indicate the timing of MROP and TCR, respectively.

RPOC, retained products of conception; MROP, manual removal of the placenta; TCR, transcervical resection

Figure 4.

Serial changes in serum hCG

The horizontal and vertical axes indicate the duration from delivery to the measurement date (days) and the serum hCG level (IU/L), respectively.

(A)(B) RPOC cases delivered after 34 weeks of gestation

(A) Cases without UAE.

(B) Cases with UAE. Arrows show the date on which UAE was performed.

(C)(D) RPOC cases delivered at less than 20 weeks of gestation and did not undergo UAE

(C) Cases with serum hCG half-life of less than 10 days

(D) Cases with serum hCG half-life of more than 10 days

RPOC, retained products of conception; UAE, uterine artery embolization; hCG, human chorionic gonadotropin

Figure S1.

Representative images of RPOC cases with conservative management

(A) Case 23: Contrast-enhanced CT with heavy bleeding showed strongly contrast-enhanced RPOC in the arterial phase (postpartum day 10). Arrows show RPOC.

(B)-(F) case 37: Serial changes in contrast-enhanced MRI during conservative management

(B) Sagittal T2WI showed an RPOC in the uterus. The RPOC size was 72 x 42 x 49 mm (postpartum day 3).

(C) Sagittal contrast T1WI demonstrated strongly contrasted RPOC (postpartum day 3).

(D) Sagittal T2WI showed RPOC in the uterus, whose size became smaller. The RPOC size was 22 x 17 x 15 mm (postpartum day 22).

(E) Sagittal contrast T1WI still demonstrated strongly contrasted RPOC (postpartum day 22).

(F) MRI did not detect RPOC (postpartum day 64). Ultrasound showed RPOC of 8 mm on postpartum day 87. On postpartum day 102, hysteroscopy showed that the RPOC was 10 mm, and on postpartum day 201, it was finally confirmed that the RPOC had disappeared.

CT, computed tomography; RPOC, retained products of conception; MRI, magnetic resonance imaging; T2WI, T2-weighted imaging

Table S1.

Univariate analysis between RPOC with heavy bleeding and light bleeding during conservative management

RPOC, retained products of conception

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