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Conservative management of retained products of conception in the normal placental position: A retrospective observational study

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ABSTRACT

Objectives: To clarify the outcome of retained products of conception (RPOC) without placenta previa.
Study design: This was a retrospective cohort study consisting of 59 patients who abdominally or vaginally gave birth to infants after 14 weeks without placenta previa and had RPOC between April 2006 and December 2018. Patients' background, characteristics, and outcomes were compared between those requiring and not-requiring intervention for RPOC.
Results: Of the 59 patients, pregnancies after assisted reproductive technology accounted for 18 (31%). The ultrasound-measured RPOC length was 4 cm (median) and 39 (66%) showed hypervascularity within RPOC. Interventions were required in 36 patients (61%), with all due to bleeding-related events. Multivariate regression analyses revealed that the interventions were significantly more likely in the following situations: younger than 35 years (aOR: 4.2, 95%CI: 1.1–18.5), RPOC length ≥4 cm (aOR: 8.6, 95% CI: 2.4–39.2), and RPOC hypervascularity (aOR: 4.6, 95%CI: 1.3–18.8). Methotrexate was administered to 8 patients, of whom 4 (50%) required further hemostatic interventions.
Conclusion: In patients with RPOC without previa, 61 and 39% did and did not require hemostatic interventions, respectively. In the latter, a wait-and-see strategy resulted in the resolution of RPOC. Patients with larger RPOC (≥4-cm fragment length) and hypervascularity were significantly more likely to require hemostatic intervention.

Introduction

After both vaginal and abdominal deliveries, obstetricians sometimes encounter retained products of conception (RPOC) in a normal placental position. This condition can be recognized at the time of placental delivery, on macroscopic examination of the delivered placenta, or during postpartum ultrasound examination. The latter is performed as a part of routine postpartum check-up or in the event of postpartum hemorrhage (PPH).

RPOC sometimes require interventions, whereas others spontaneously resolve with a conservative strategy. We are sometimes obliged to answer the difficult question of whether, intervention or a conservative strategy should be adopted, especially when marked bleeding is absent. The present study was an attempt to characterize the clinical features of RPOC, thereby addressing the above-mentioned clinical question. RPOC are also discussed in relation to placenta accreta spectrum (PAS) disorders. In routine practice, we must deal with RPOC without definitely confirming the presence or absence of PAS. Thus, we targeted RPOC without "evident" (clinically or histologically diagnosed) PAS.

Methods

This study was approved by the ethics committee of our institute. We retrieved medical charts of patients who had RPOC in a normal placental position and without placenta previa between April 2006 and December 2018 in our institute, which is one of the largest perinatal centers in Japan, managing approximately 1,000 deliveries annually. Our perinatal management followed the Japanese guidelines [1–3]. The placental position was determined just before delivery using transvaginal and abdominal ultrasound. Cesarean section (CS) or vaginal delivery was decided by attending obstetricians.

We managed placental delivery at vaginal delivery as follows: 1) cord traction with uterine massage, 2) if not delivered, waiting for placental delivery for approximately 30 min, and if still not delivered, 3) manual removal of the placenta. In some cases of second trimester abortion/delivery, placental removal was

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performed by placental forceps instead of manual removal. At CS, the placenta was manually removed soon after infant delivery in spite of the presence or absence of natural placental separation. When the placenta partly remained in utero at CS, we roughly removed as much as possible; however, mandatory thorough removal of the placenta was avoided. In cases of CS, inspection of the uterine cavity was performed after the placental separation with cleaning-up the uterine cavity. Uterotonics (e.g., oxytocin, methylergometrine) were routinely administered. If significant bleeding from the area of the placental separation occurred, an intrauterine balloon (e.g., Bakri balloon) [4], MT-holding [5], uterine compression suture [6], and/or sutures for bleeding surfaces were employed by experienced obstetricians (HT, YB, HS, RU, AO, and SM) at their discretion. Nevertheless, if the bleeding continued, transarterial embolization (TAE) or hysterectomy was employed. Regarding the selection of TAE or hysterectomy, TAE was only employed for patients with: 1) stable vital signs, and 2) a desire to preserve the uterus. Inclusion criteria were that RPOC were detected by transvaginal or transabdominal ultrasound: 1) at delivery associated with difficult placental delivery, 2) on routine check-up on postpartum day 4 or 5, or 3) at the time of secondary PPH. The RPOC findings were as follows: 1) intrauterine high-echoic lesion adjacent to myometrium, 2) hypervascular lesion seen in the uterine cavity. Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) can differentiate RPOC from blood clots and uterine artery pseudoaneurysms, and, thus, we employed CT/MRI to confirm the RPOC diagnosis in some cases.

Placenta previa (PP) frequently accompanies RPOC [7,8]. Previa and non-previa may show different clinical features, and, thus, we also excluded PP in this study. We also excluded the following three evident PAS-related conditions. 1) Ultra-sonographically pre-diagnosed PAS [9], for which we fundamentally performed cesarean hysterectomy without placental removal [10]. The condition was diagnosed as pre-diagnosed PAS based on the previous history and ultrasound findings when a patient had all of the following: history of prior CS (+), anterior-dominant placenta previa, loss of a clear zone, multiple placental lacunae, and uterovesical hypervascularity [9]. However, there were no patients who fulfilled these criteria, and thus the present study population did not involve patients with 1). 2) Focal PAS was suspected at first and uterine-preserving methods (described above) were employed; however, marked PPH, continued necessitating hysterectomy for primary PPH. Three patients met this criterion and thus were excluded. 3) Suspicious PAS at vaginal delivery, in which, at the time of manual placental removal attempt, the separation-cleavage plane was totally absent between the uterine wall and placenta, and thus was considered as clinically diffuse PAS [11]. Two patients met this criterion and thus were excluded. In the present study, histological examinations were not performed and thus such less severe PAS could not be identified and may have been present in this study population. We excluded cases with severe PAS, severe to the extent that PAS was clinically evident and possibly corresponding to diffuse PAS or increta/percreta.

We routinely performed transvaginal ultrasound at 4 days after vaginal delivery and 5 days after CS. In addition, ultrasound was employed in suspected cases of RPOC, if necessary. When the condition was diagnosed as the presence of RPOC, the maximum length of RPOC was ultra-sonographically measured. We also examined the vascularity of RPOC using mainly transvaginal color Doppler ultrasound. Transvaginal ultrasound examinations were performed using a 5–7.5-MHz transducer. With regard to the configuration of the velocity range in color Doppler, it was performed at a maximum of 10–20 cm/s, which was low-velocity. If images could not be obtained by transvaginal ultrasound, transabdominal ultrasound (2.5–5-MHz transducer) was employed instead. RPOC that showed apparent vascular flow detected by color Doppler was defined as hypervascularity (+). In contrast, when the Doppler signal was absent or inconspicuous, we defined it as hypervascularity (−). Hypervascularity +/− was finally determined by two specialists (HT and MO) based on the recorded images. We did not analyze myometrial hypervascularity in this study [12,13]. If symptoms including significant bleeding (secondary PPH), continuous bleeding, or infection were apparent, interventions were considered. The main regimens of intervention were: dilatation and evacuation (D&E), intravenous methotrexate (MTX), and TAE. The timing and regimen of interventions were determined at the experienced obstetricians' discretion. Intravenous MTX had been reported to be an option for RPOC treatment [14–16], and thus MTX was employed for some patients with continuous low-level bleeding until 2012. We did not administer MTX for patients with massive bleeding. Considering side effects [17,18], it was not employed after 2013. TAE was mainly employed for patients with massive bleeding.

From electronic medical records, we retrieved maternal backgrounds (e.g., age, parity, mode of conception, maternal complications) and delivery information such as gestational age, blood loss, and manual placental removal. The Mann-Whitney *U* test and Fisher's exact test (two-tailed) were used to compare RPOC characteristics, maternal backgrounds, and outcomes between intervention (+) vs. (−) associated with RPOC. Parameters significant ($P < 0.15$) on univariate analysis were used for multivariate regression analysis. All analyses were performed using JMP version 10 (SAS Institute, Tokyo, Japan), with $P < 0.05$ considered significant.

Results

Table 1 shows patients' background. Fifty-nine patients (median age: 33, interquartile range: 29–39), were included. Pregnancies after assisted reproductive technology accounted for 18. Approximately three-quarters (46/59) gave birth to infants vaginally. Manual removal of the placenta at vaginal delivery was performed in 17. The median blood loss at delivery was 960 (interquartile range: 600-1,560) mL. Only one patient conspicuously bled (8920 mL) and was complicated with uterine inversion. Transfusion at delivery was performed in 7% (4/59). The 59 patients bled more than those who delivered in this center over a period of 5 years (n = 4,141 between 2010 and 2014, median blood loss in singleton pregnancies 460 mL, $P < 0.001$ (data not shown)). Of 46 vaginal deliveries, placenta removal was required in 22 (48%) patients.

Table 2 shows the characteristics of RPOC. It was recognized due to a difficult placental delivery in 24 patients, secondary PPH in 23, or incidentally on routine ultrasound in 12. RPOC could be diagnosed by ultrasound in all 59 patients. The diagnosis of RPOC was supported by CT and/or MRI in 18 and 14 patients, respectively. There were no patients in whom ultrasound diagnosis and CT/MRI diagnosis were different. The median RPOC length was 4 cm. Hypervascularity was observed in 39 patients (66%).

Table 3 shows interventions performed for RPOC. Interventions were required in 36 patients (61%), in all of whom bleeding-related events prompted us to perform the interventions. The duration between delivery/abortion and the intervention was 22 days (median). Five (8%) patients were transfused because of secondary bleeding associated with RPOC. D&E, TAE, and intravenous MTX were performed in 15, 11, and 8, respectively. No patient required hysterectomy. Apart from this, intravenous antibiotics were needed in 8 (8/59: 14%) due to suspected uterine infection. All 8 patients recovered sorely with the antibiotics.

Table 4 shows a comparison between patients with and without intervention. Patients with intervention compared with without intervention had larger RPOC ($P = 0.002$) and were more likely to

Table 1
Patients' background.

Characteristic	n = 59
Age (years), median (IQR)	33 (29–39)
<30, *n* (%)	17 (29)
30–34, *n* (%)	20 (34)
35–39, *n* (%)	11 (19)
40≤, *n* (%)	11 (19)
Primipara, *n* (%)	8 (14)
History of CS, *n* (%)	5 (8)
History of D&E, *n* (%)	17 (29)
Pregnancy by ART, *n* (%)	18 (31)
Multiple pregnancy, *n* (%)	3 (5)
Abortion*, n (%)	12 (20)
Gestational age at delivery, *n* (%)	
<30 weeks, *n*	2 (3)
30 + 0–33 + 6 weeks, *n*	2 (3)
34 + 0–36 + 6 weeks, *n*	3 (5)
37≤ weeks, *n*	40 (68)
Mode of delivery, *n*(%)	
Vaginal†	46 (78)
CS	13 (22)
Blood loss at delivery** (mL), median	960
IQR	600–1,560
range	20–8,920¶
Hemostatic procedure at delivery‡, *n* (%)	2 (3)
Transfusion at delivery, *n* (%)	4 (7)
Removal of placenta at vaginal delivery, *n* (%)	22 (48: 22/46)
manual	17 (37: 17/46)
placental forceps§	5 (11: 5/46)

*excluded 1 st trimester abortion, †included induced abortion using prostaglandin E1, **included amniotic fluid at CS, precise blood loss values in 6 cases are missing, ‡Intrauterine balloon, uterine compression suture, Matsubara-Takahashi holding the cervix method, or transarterial embolization was employed. ¶Only one patient showed massive bleeing (8,920 mL) and was also complicated with uterine inversion. §Cases are at 19, 20, 21, 23, and 23 gestational weeks, respectively. ART, assisted reproductive technology; CS, cesarean section; D&E, dilatation and evacuation; IQR, interquartile range.

have hypervascular RPOC (P = 0.025). Multivariate regression analyses showed that the following were independent risk factors for requiring intervention: younger than 35 years (aOR: 4.2, 95%CI: 1.1–18.5), RPOC length ≥ 4 cm (aOR: 8.6, 95%CI: 2.4–39.2), and RPOC hypervascularity (aOR: 4.6, 95%CI: 1.3–18.8) (data not shown).

Table 5 shows a comparison between patients with and without term deliveries. Reasons why patients' outcomes were preterm deliveries and abortions (and not term delivery) are listed in Supplementary Table 1. Patients with term deliveries bled more at deliveries (P = 0.038) and needed transfusion more frequently (P = 0.047). The RPOC size and vascularity did not show differences between the two groups. Patients with term deliveries needed

Table 2
Characteristics of RPOC.

	n = 59
Reason for detection, *n* (%)	
difficulty of placental delivery	24 (41)
secondary PPH	23 (39)
incidental detection on routine ultrasound	12 (20)
Concurrent imaging study employed†,*n* (%)	
CT	18 (31)
MRI	14 (24)
RPOC length* (cm), median (IQR)	4.0 (2.6–6.0)
RPOC hypervascularity, *n* (%)	39 (66)
hCG at diagnosis (mIU/mL), median (IQR)	71 (6–301)
Disappearance of RPOC** (day), median (IQR)	70 (34–92)

†Ultrasound was performed in all patients. *maximum length. **length <5 mm, CT, computed tomography; IQR, interquartile range; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; PPH, postpartum hemorrhage; RPOC, retained products of conception.

Table 3
Intervention for RPOC.

Characteristic	n = 59
Intervention required, *n* (%)	36 (61: 36/59)
Trigger event, *n* (%)	
significant bleeding	20 (56: 20/36)
continuous small amount of bleeding	16 (44:16/36)
Duration between delivery/abortion and intervention (days), median (IQR)	22 (6–38)
Transfusion associated with bleeding, *n* (%)	5 (8)
Regimen of intervention, *n* (%)	
D&E	15 (42: 15/36)
TAE	11 (31: 11/36)
intravenous MTX	8 (22: 8/36)
UCS	1 (3: 1/36)
chemical curettage*	1 (3: 1/36)

D&E, dilatation and evacuation; IQR, interquartile range; MTX, methotrexate; RPOC, retained products of conception; TAE, transarterial embolization; UCS: uterine compression suture, *oral progesterone and preparations.

interventions more frequently, but this was not significant (P = 0.163).

Table 6 shows complications of interventions. Complications occurred in 7 patients, being bleeding in all cases, which required additional hemostatic procedures. Of the 7, D&E, TAE, or intravenous MTX was performed as the first intervention in 1, 2, and 4 patients, respectively. Of 8 patients in whom intravenous MTX was administered, 4 (50%) required hemostatic additional treatments, leading to an incidence higher than that in those with D&E (7%) or TAE (18%).

Discussion

This study generated three important findings: 1) Patients with RPOC showed marked bleeding at delivery and often required manual removal of the placenta; 2) Some interventions were required in 61% of patients: younger than 35 years, RPOC length ≥ 4 cm, and RPOC hypervascularity were independent risk factors of interventions; 3) Intravenous MTX more frequently led to the necessity of additional treatments compared with the other interventions.

Patients with RPOC showed marked bleeding at delivery and required manual removal of the placenta, and, thus, difficult delivery preceded RPOC. The median blood loss at delivery was as much as 1 L and the rate of transfusion at delivery was as high as 17%. Manual placental removal was performed in approximately two-fifths of vaginal deliveries. This is consistent with findings from two recent studies [19,20]. Placenta-related complications in the third stage of labor were independent risk factors of RPOC occurrence (OR: 12.5, 95% CI: 9.0–17.3) [19]. Manual placental removal increased the incidence of transfusion among patients with RPOC [20]. Manual removal may indicate that the placenta is difficult to remove. However, looking at it from a different viewpoint, in the present study, the placenta was smoothly delivered in approximately two-thirds of vaginal deliveries. Thus, easy removal of the placenta never guarantees non-occurrence of RPOC: the presence or absence of RPOC should be evaluated in patients with PPH irrespective of whether placental removal was smooth.

A RPOC length ≥ 4 cm and RPOC hypervascularity were independent risk factors of interventions. As a large RPOC may be more difficult to resolve and thus bleeding is more likely to occur, hemostatic interventions are more likely to be required. A previous study in patients with placenta previa also showed the associations of the retained placental degree, i.e., entirely or partially left, and interventions including hysterectomy or TAE [21]. The second factor associated with increased intervention was

hypervascularity of RPOC. The findings of retrospective studies by Kamaya et al., although they mainly targeted placental rest after spontaneous abortions (not after delivery) [22,23], were in line with the present findings: they classified 4 groups by the degree of vascularity of a RPOC using ultrasound; a high vascularity score was a significant predictor of hemostatic surgical interventions (OR:1.77, 95% CI:1.16–2.70). In the present study, hypervascularity was also shown to be an important indicator of additional treatments in patients after preterm or term deliveries. Color Doppler transvaginal ultrasound revealed the hypervascularity of RPOC, and thus this should be performed in suspected cases. Alternatively, this examination may be routinely adopted in postpartum checkups depending on the situation since smooth placental delivery does not guarantee the absence of RPOC.

The size and vascularity of RPOC after term delivery vs. non-term delivery (preterm or abortive) were the same. A previous study showed that RPOC after term deliveries were larger and had less vascularities compared with those after abortions [24]. However, abortions in the first trimester were excluded from our study, which may account for this discrepancy between the two. Additional studies are needed to clarify this issue and outcome.

The placenta left *in situ* strategy in PAS has attracted wide attention. Whether a placenta left *in situ* spontaneously resolves, and if so, what type of placenta is more likely to resolve are currently under discussion. For example, the largest study to date (n = 167) showed that 22% of cases required hysterectomy during a wait-and-see strategy [25]. Whether TAE should be employed is also under discussion [11]. These findings may be helpful when considering the treatment strategy for RPOC; however, placental and uterine characteristics may markedly differ between PAS (+) vs. (−). The present study targeted patients with RPOC without clinically evident PAS. PAS should be finally diagnosed by histological examinations, and thus, the present study population may involve less severe sub-clinical PAS. However, in routine practice without evident histological findings, it is not possible to clinically diagnose the presence or absence of PAS. The present study illustrated the condition of RPOC without clinically evident PAS, which we frequently encounter.

This study had some limitations. First, this was a retrospective analysis and the timing of intervention was based on attending physicians' discretion. Interventions were required in 61% of patients with RPOC; however, of those, 16 patients (44%) required them due to a small amount of bleeding. RPOC of these patients may have been absorbed if we had adopted a wait-and-see strategy. Second, it was not determined why patients younger than 35 years significantly more frequently required interventions. We may have unintentionally intervened earlier to preserve the uterus for subsequent pregnancies in younger patients, or other factors may underlie this phenomenon. Third, we did not follow subsequent pregnancies. The subsequent pregnancy rate following RPOC removal using transcervical resection (TCR) was as high as 69–92% [26]. Some retrospective analyses showed that TCR induced less intrauterine adhesions compared with curettage

Table 4
Univariate analysis among patients with RPOC in the presence or absence of intervention.

	Intervention (+) (n = 36)	Intervention (−) (n = 23)	P-value
Age (years), median (IQR)	32.5 (28-35)	35 (31-40)	0.055
Less than 35 years, *n* (%)	25 (69)	11 (48)	0.111
Pregnancy by ART, *n* (%)	11 (31)	7 (30)	1.000
History of CS	4 (11)	1 (4)	0.639
History of D&E	9 (25)	8 (35)	0.557
2nd trimester delivery/ abortion, *n* (%)	5 (14)	6 (26)	0.310
CS, *n* (%)	7 (19)	6 (26)	0.748
Gestational age at delivery (weeks), median (IQR)	38 (30–40)	37 (22–39)	0.305
Blood loss at delivery (mL), median (IQR)	981 (590–1487)	950 (585–1785)	0.836
Transfusion, n (%)	7 (19)	2 (9)	0.460
Manual removal of placenta, *n* (%)	12 (31)	12 (50)	0.182
RPOC length* (cm), median (IQR)	4.7 (3.8–6.9)	2.9 (2.3–4.9)	0.002
Length ≥ 4 cm, n (%)	25 (71)	7 (30)	0.003
RPOC hypervascularity, *n* (%)	28 (78)	11 (48)	0.025
hCG at diagnosis (mIU/mL), median (IQR)	85 (9–706)	14 (2–288)	0.356
Duration until disappearance of RPOC	69 (34–90)	71 (34–92)	0.579

*RPOC size in one case is missing. ART, assisted reproductive technology; CS, cesarean section; D&E, dilatation and evacuation; IQR, interquartile range; RPOC, retained products of conception.

Table 5
Univariate analysis between patients with and without term deliveries.

	with term (n = 40)	without term** (n = 19)	P-value
Age (years), median (IQR)	32 (28–36)	35 (33–40)	0.008
Pregnancy by ART, *n* (%)	12 (30)	6 (32)	1.000
History of CS	2 (5)	3 (16)	0.316
CS, *n* (%)	8 (20)	5 (26)	0.738
Blood loss at delivery (mL), median (IQR)	1015 (666–1688)	688 (400–1080)	0.038
Transfusion at delivery, *n* (%)	9 (23)	0 (0)	0.047
Manual removal of placenta, *n* (%)	16 (40)	7 (37)	1.000
RPOC length* (cm), median (IQR)	4 (2.9–6.1)	4 (2.6–5.6)	0.366
Length ≥ 4 cm, n (%)	22 (55)	10 (53)	0.757
RPOC hypervascularity, *n* (%)	26 (65)	13 (68)	1.000
Intervention, *n* (%)	27 (68)	9 (47)	0.163
hCG at diagnosis (mIU/mL), median (IQR)	24 (2–281)	74 (22–713)	0.432

*RPOC size in one case is missing. **preterm deliveries and abortions. ART, assisted reproductive technology; CS, cesarean section; IQR, interquartile range; RPOC, retained products of conception.

Table 6
Complications of interventions for RPOC.

Characteristic	n = 7
D&E	
additional treatment (+) due to bleeding	1/15 (7%)
TAE	1
TAE	
additional treatment (+) due to bleeding	2/11 (18%)
second TAE	1
TCR	1
Intravenous MTX, *n* (%)	
additional treatment (+) due to bleeding	4/8 (50%)*
TAE	1
D&E	2
TAE + D&E	1

*significant between D&E and MTX (p = 0.033); D&E, dilatation and evacuation; MTX, methotrexate; RPOC, retained products of conception; TAE, transarterial embolization; TCR, transcervical resection.

[27,28]. However, few studies are available regarding the outcome of pregnancy subsequent to a RPOC after either a wait-and-see strategy or some interventions.

In conclusion, RPOC was more likely to be preceded by manual removal at delivery, and some interventions were required in 61% of patients, especially for those with a RPOC length ≥4 cm and hypervascularity. Thus, we partly answered the clinical question of who should undergo interventions or a wait-and-see strategy: patients with small and non-hypervascularized RPOC may be candidates for a wait-and-see strategy among those with term deliveries. Further prospective studies are needed to validate our results and propose an optimal strategy for this condition. Finally, we wish to add one thing: RPOC diagnosis is not easy in clinical practice, and it can be misdiagnosed as a blood clot, especially early postpartum. The possibility of RPOC should always be borne in mind.

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Ethical approval

All procedures in this study involving human participants were conducted in accordance with the declaration of Helsinki.

Contribution to authorship

Conception and design of this study: Takahashi H, Baba Y

Acquisition of data: Ohhashi M, Baba Y, Nagayama S, Ogoyama M, Suzuki H, Hirashima H, Usui R

Analysis and interpretation: Takahashi H, Ohhashi M, Baba Y, Ohkuchi A

Writing and revising the manuscript: Takahashi H, Ohhashi M, Matsubara S

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Patient anonymity

Preserved.

Institutional review board approval

Obtained.

Appendix A. Supplementary data

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