Manual removal of the placenta and postpartum hemorrhage: A multicenter retrospective study

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Short running title

Manual removal of placenta and PPH

Abstract

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Aim: In postpartum women, retained placenta is diagnosed in the absence of signs of placental separation and expulsion, and requires manual removal of the placenta (MROP). MROP may lead to massive hemorrhage, hemodynamic instability, and the need for emergency interventions including blood transfusion, interventional radiology, and hysterectomy. In this study, we aimed to identify the risk factors for retained placenta requiring MROP after vaginal delivery and postpartum hemorrhage (PPH) following MROP.

Methods: A multicenter retrospective study was performed using data from women who

delivered at term between 2010 and 2018 at 13 facilities in Japan. Of 36,454 eligible women, 112 women who required MROP were identified. Multivariate logistic regression analyses were conducted to evaluate the risk factors for both retained placenta and PPH.

Results: A history of abortion, assisted reproductive technology (ART), instrumental delivery, and delivery of small-for-gestational-age infant were independent risk factors for MROP (adjusted odds ratios [95% confidence intervals]: 1.93 [1.28–2.92], 8.41 [5.43–13.05], 1.80 [1.14–2.82], and 4.32 [1.97–9.48], respectively). ART was identified as an independent risk factor for PPH (adjusted odds ratio [95% confidence interval]: 6.67 [2.42–18.36]) in patients who underwent MROP.

Conclusions: ART pregnancies significantly increased the risk of retained placenta requiring MROP and PPH. Our results suggest that clinicians need consider patient transfer to a higher-level facility and preparation of sufficient blood products before initiating MROP in cases of ART pregnancies. Our study may assist in identifying high-risk women for PPH before MROP and in guiding treatment decisions, especially in facilities without a blood bank.

Keywords

Assisted reproductive technology, postpartum hemorrhage, pregnancy, retained placenta,

third stage of labor

Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal deaths, and its prevention and management are current pressing issues in perinatal medicine worldwide.[1] In most cases of PPH, maternal deaths are preventable with appropriate management and timely intervention such as the administration of a uterotonic agent, fluid resuscitation, and maternal transfer to a higher-level facility.[2] Nevertheless, PPH is responsible for approximately one in four maternal deaths.[3] A previous report from Japan reported that obstetric hemorrhage accounted for more than 20% of direct maternal deaths until 2014; however, obstetric hemorrhage-related maternal deaths have decreased in more recent years.[4] This recent trend may be explained by a combination of improved education (e.g., lectures specifically on maternal emergencies and the development of guidelines) and training (e.g., for obstetricians, anesthesiologists, midwives, and nurses in life-saving procedures).[5]

Active management of the third stage of labor for the prevention of PPH is recommended in many countries.[6-8] This includes routine administration of a prophylactic uterotonic agent immediately after birth of the infant and controlled cord

traction to expedite delivery of the placenta. Retained placenta is diagnosed if no signs of placental separation and expulsion are observed even after active management has been conducted for a certain period.[9] Retained placenta is considered to be compositely attributed to uterine atony, abnormal placentation, and trapped placenta.[9, 10] Manual removal of the placenta (MROP) is an option for treating retained placenta, while taking into consideration the balance between the risk of PPH due to a prolonged third stage of labor and the likelihood of spontaneous delivery of the placenta.[10-12]

Massive hemorrhage can unexpectedly occur after MROP, leading to hemodynamic instability and requiring interventions such as blood transfusion, uterine tamponade, interventional radiology (e.g., uterine arterial embolization), and surgical interventions (e.g., hysterectomy). Previous studies have demonstrated that MROP results in PPH (blood loss of ≥1,000 mL) in approximately 38%–86% of cases but occurs in only 5.0%–6.6% of cases not involving MROP.[13-15] Although MROP is recognized as a risk factor for PPH, the risk factors for PPH associated with MROP are not well established.[12]

In this multicenter retrospective study, we sought to determine the risk factors for retained placenta requiring MROP after vaginal delivery and investigate the characteristics of women who develop PPH following MROP. Our findings may assist

91 physicians in identifying women at high risk for PPH before initiating MROP. This
92 study is of clinical importance, especially for obstetric caregivers in maternity care
93 facilities without blood banks.
94
95 ***Methods***
96 We conducted a multicenter retrospective study at 13 facilities located in Aichi and Gifu
97 Prefectures in Japan using clinical data from women who delivered at a gestational age
98 of ≥22 weeks between 2010 and 2018. Clinical data on maternal and neonatal
99 characteristics were retrospectively collected from medical charts at each facility and
100 cumulated for further analysis. The ethics committee of Nagoya University approved the
101 study protocol (ethical approval number: 2015–0415), and the Kishokai Medical
102 Corporation Executive Committee approved the study protocol and the use of clinical
103 data (ethical approval number: 2016–009). Waiver of informed consent was approved by
104 the review board because all data were anonymized and retrospectively collected from
105 existing medical records. We applied the opt-out method of obtaining consent to give
106 patients an opportunity to refuse to use their data by posting study information on a
107 website or by displaying posters in each facility; women who refused to use their data
108 were excluded from the study.

A total of 47,981 women who delivered at gestational age ≥22 weeks were eligible for this study. Among the participating 13 facilities, 12 care for low-risk pregnancies and one cares for high-risk pregnancies. Exclusion criteria were defined as multiple pregnancies, preterm birth (<37 weeks gestational age), major congenital and chromosomal abnormalities, stillbirth, cesarean section or unknown delivery mode, and incomplete medical records regarding blood loss at delivery.

Blood loss was quantified using the gravimetric method at three different time points (delivery of the placenta, 1 h postpartum, and 2 h postpartum), and total blood loss was defined as the total amount of blood loss at the three time points. The specific gravity of blood was defined as 1.0, so that blood loss evaluated using the gravimetric method (g) is equivalent to the volumetric measurement of blood loss (mL). Total blood loss did not include amniotic fluid. PPH was defined as a cumulative blood loss of ≥1,000 mL within 2 h postpartum.[6] Active management of the third stage of labor and basic management of PPH (e.g., use of additional uterotonics, fluid resuscitation with isotonic crystalloids, tranexamic acid, and intrauterine balloon tamponade) are standardized throughout the participating facilities, according to the guidelines provided by the Association of Japan Obstetrics and Gynecology.[7] However, details of management and

treatment can differ slightly among facilities and physicians.

Retained placenta was defined as the condition in which signs of placental separation and expulsion were not observed despite active management of the third stage of labor, and the diagnosis was based on the clinical judgment of the physician. Timing of MROP, location (operating room or delivery room), and anesthesia methods were not defined in this study.

Maternal and neonatal demographic and clinical information was collected, including maternal age, gestational age at delivery, parity, history of abortion, body mass index (BMI) before pregnancy, assisted reproductive technology (ART), hypertensive disorders of pregnancy, gestational diabetes mellitus, labor induction, instrumental delivery, duration of the third stage of labor, total blood loss, blood transfusion, infant birth weight, infant sex, and whether the infant was small or large for gestational age. Small-for-gestational-age was defined as birth weight and height below the 10^{th} percentile for gestational age, and large-for-gestational-age was defined as birth weight and height above the 90^{th} percentile for gestational age according to sex-specific Japanese neonatal anthropometric chart in 2000.[16] ART was defined as infertility treatment with assisted reproductive technology such as in vitro fertilization and intracytoplasmic sperm injection; infertility treatment without ART, such as ovulation induction and artificial

insemination, were excluded.

Statistical analysis

Statistical analyses were performed using SPSS version 27 (SPSS Inc., Chicago, IL, USA). To compare baseline maternal and neonatal characteristics, we used the unpaired Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables according to whether the distribution was normal or skewed. The distribution was evaluated using the Shapiro-Wilk test. Adjusted odds ratio (OR) with 95% confidence interval (CI) were evaluated using logistic regression models after adjustment for covariates. Covariates in the multivariate analyses were selected based on literature review. Statistical significance was defined as a *P*-value <0.05.

Results

A total of 47,981 women delivered at 13 facilities between 2010 and 2018. Of these, 11,527 women were excluded, leaving 36,454 women eligible for this retrospective study (Figure 1). During the study period, 112 women who had undergone MROP (MROP group) were identified by medical chart review. Baseline maternal and neonatal

characteristics between the MROP (n=112) and non-MROP (n=36,342) groups are presented in Table 1. Women in the MROP group were significantly older than those in the non-MROP group and were more likely to have a history of abortion, conceived by ART, undergone labor induction, instrumental delivery, hypertensive disorders of pregnancy, and delivered small-for-gestational-age infants. Women in the non-MROP group were more likely to have parity ≥2. The duration of the third stage of labor in the MROP group was longer than that in the non-MROP group (median [interquartile range]: 21 [16–38], 4 [3–6], $P<0.01$, respectively). The total blood loss and prevalence of PPH (≥1,000 mL) were significantly higher in the MROP group than in the non-MROP group (1,106 ± 882 mL and 374 ± 298 mL, $P<0.01$; 41.1% and 4.1%, $P<0.01$, respectively) (Table 1).

Univariate and multivariate logistic regression analyses were performed to identify the independent risk factors for MROP (Table 2). Multivariate analysis was adjusted for nine covariates, namely, maternal age ≥35 years, parity ≥2, history of abortion, ART, hypertensive disorders of pregnancy, labor induction, instrumental delivery, small-for-gestational-age infants, and large-for-gestational-age infants, which revealed that a history of abortion, use of ART, instrumental delivery, and delivery of small-for-gestational-age infant were independent risk factors for MROP (adjusted OR

[95% CI]: 1.93 [1.28–2.92], 8.41 [5.43–13.05], 1.80 [1.14–2.82], and 4.32 [1.97–9.48], respectively) (Table 2).

Of the 112 women who underwent MROP, 46 (41.1%) experienced PPH (MROP-PPH group) and 66 did not experience PPH (MROP-non-PPH group). The maternal and neonatal characteristics of women in the MROP-PPH and MROP-non-PPH groups are presented in Table 3. Women in the MROP-PPH group were significantly older than those in the MROP-non-PPH group and were more likely to have conceived by ART and to have undergone labor induction. The duration of the third stage of labor in the MROP-PPH group was significantly longer than that in the MROP-non-PPH group (median [interquartile range]: 26 [16–50], 19 [15–32], P=0.04).

Univariate and multivariate logistic analyses were performed to identify the independent risk factors for PPH among women who had undergone MROP (Table 4). Multivariate analysis was adjusted for nine covariates, namely, maternal age ≥35 years, history of abortion, pre-pregnancy BMI ≥25 kg/m^2, use of ART, hypertensive disorders of pregnancy, labor induction, instrumental delivery, duration of the third stage of labor, and large-for-gestational-age infant, which revealed that the use of ART was an independent risk factor for PPH (adjusted OR [95% CI]: 6.67 [2.42–18.36]). In addition, each 10-min increase in the duration of the third stage of labor was significantly

associated with an increased risk of PPH (adjusted OR [95% CI]: 1.22 [1.04–1.42]).

An additional analysis was performed to determine the effect of ART on blood loss at delivery according to the presence or absence of MROP (Table 5). Among the 112 women who underwent MROP, 44 (39.3%) conceived with ART and 68 (66.7%) conceived spontaneously. In the ART group, 30 women (68.2%) experienced PPH, compared to 16 (23.5%) in the non-ART group. Among the 44 women who conceived with ART and also underwent MROP, 9 (20.5%) required blood transfusion. The difference in blood loss between women with and without MROP in ART pregnancies was approximately 900 mL, whereas that in non-ART pregnancies was approximately 380 mL, indicating that the effect of ART on blood loss was greater in the MROP group than in the non-MROP group.

Discussion

In this multicenter retrospective study, we sought to identify the risk factors for retained placenta requiring MROP after vaginal delivery and for PPH in patients who underwent MROP. Although the risk factors for MROP have been well described, the factors associated with PPH following MROP have been poorly documented. Our findings provide evidence that ART pregnancies have a greater than 8-fold increased odds of

retained placenta and 6-fold increased odds of PPH following MROP compared with spontaneous pregnancies. Given the rapid growth in infertility technology and an increase in the use of ART, our findings may assist physicians in identifying women at high risk for PPH before attempting MROP and may be useful for obstetric caregivers, especially those working in birth centers and maternity care facilities without a blood bank. In Japan, approximately 40%–50% of all deliveries are performed at maternity care facilities without a blood bank.[17] Our findings support considering transfer to a higher-level facility and preparation of sufficient blood products before attempting MROP in women who conceived through ART.

The prevalence of MROP is approximately 0.3%–3% of all deliveries; thus, cases requiring MROP are relatively common in obstetric clinical practice.[18] There is some consensus regarding risk factors for retained placenta after vaginal delivery: a history of retained placenta, preterm delivery, labor induction, use of ergometrine and oxytocin, a history of uterine surgery (e.g., cesarean section and myomectomy), miscarriage or curettage, uterine abnormality, velamentous cord insertion, maternal age >35 years, and delivery of small-for-gestational-age infants.[9, 10, 12, 13, 19] In the present study, the use of ART, delivery of small-for-gestational-age infant, history of abortion, and instrumental delivery were identified as independent risk factors for MROP, which is

consistent with the findings of previous studies. Although ART has been recognized as a risk factor for placenta accreta and retained products of conception,[20-22] few studies have demonstrated that ART is an independent risk factor for retained placenta requiring MROP.[10]

Currently, approximately 6% of all pregnancies in Japan, which is 5-fold more than 20 years ago, are conceived using ART,[23] indicating the possibility that cases of retained placenta requiring MROP will increase. While the underlying mechanism for the increased risk of retained placenta with ART remains unclear, ART may contribute to abnormal placentation and uterine atony, thus inhibiting the phases of separation of the placenta (e.g., latent, contraction, detachment, and expulsion).[24] Considering the increased risk of retained placenta in women with placental-related complications of pregnancy, such as preeclampsia, recurrent miscarriages, and fetal growth restriction, an early stage of abnormal placentation (e.g., poor trophoblast uterine invasion, impaired transformation of the uterine spiral arteries) attributed to ART may play an important role in adherent placenta and placenta accrete.

Although little documented evidence exists regarding the risk factors for PPH following MROP, we found that ART and a prolonged third stage of labor were independent risk factors for PPH in this group. An earlier study demonstrated an

association between a prolonged third stage of labor (>30 minutes) and PPH following MROP,[25] but did not include multivariate analysis. This finding is consistent with our study showing that a 10-min increase in the duration of the third stage of labor showed a significant association with PPH. This is expected because a prolonged third stage of labor leads to increased blood loss at delivery.[26]

ART is a well-known risk factor for PPH.[27, 28] However, the mechanism underlying the association between ART and PPH remains unclear. Several possible mechanisms have been proposed. First, women who require ART to conceive may already have a potential risk for PPH (e.g., history of endometriosis and obesity). Second, the ART procedure (fresh or frozen embryo transfer, cycle regimens for embryo transfer, and levels of estradiol, progesterone, and human chorionic gonadotropin) may alter the endometrial environment and function, interfering with the early stage of placentation.[20, 29, 30] Third, ART may alter epigenetics and gene expression in the placenta, thus affecting the separation or expulsion of the placenta.[31, 32] Finally, immunological mechanisms may contribute to PPH based on the observation that women who conceived using oocyte donation have an increased risk for PPH compared with women who conceived using autologous ART.[33, 34]

The strengths of our study were the large sample size and the use of clinical data

obtained from 13 facilities, improving the generalizability and objectivity of our results. To our knowledge, no reports have addressed the risk factors for PPH following MROP using multivariate regression analysis. In addition, we performed an additional analysis of blood loss stratified by the presence and absence of ART pregnancy and MROP.

This study also has some limitations. First, information on the type of retained placenta (trapped placenta, placenta adherens, or placenta accreta) was not available for our analysis. According to a large prospective report on cases of retained placenta that did not require hysterectomy, trapped placenta, placenta adherens, and placenta accreta accounted for 13%, 81%, and 6% of cases, respectively.[10] The type of retained placenta may affect the amount of MROP-related blood loss. Information on cause of infertility and details regarding ART (e.g., fresh or frozen embryo transfer and cycle regimens for embryo transfer) were also not available. These factors may affect the development of retained placenta and PPH.[20, 35, 36] Our database also did not include details regarding the surgical methods of abortion (curettage or manual vacuum aspiration). In addition, we excluded most women with a history of uterine surgery because these women delivered by cesarean section. Thus, we did not examine whether a history of uterine surgery, such as transcervical resection, is a risk factor for retained placenta. Finally, the time interval after delivery for the diagnosis of retained placenta is not absolutely defined, although it

is variably defined as a period of 18–60 min,[19] and there is no clear consensus regarding the standard and optimal timing for attempting MROP in cases of retained placenta, which varies to some extent depending on the country, hospital, and physician. Thus, the time interval between delivery and initiation of MROP may differ significantly between cases. We found that each 10-min increase in the duration of the third stage of labor was significantly associated with an increased risk of PPH in patients who underwent MROP. This indicates that in deciding to initiate MROP, the balance between the risk of PPH owing to a prolonged third stage of labor and the likelihood of spontaneous delivery of the placenta should be considered.

In conclusion, our study demonstrated that women who conceived using ART have a significantly increased risk of retained placenta which may require MROP, as well as an increased incidence of PPH and blood transfusion when undergoing MROP. Transfer to a higher-level facility and preparation of sufficient blood products before attempting MROP should be considered for these patients.

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Figure legends

Figure 1. Study flow diagram. Among 47,981 women who delivered at 13 facilities between 2010 and 2018, 36,454 women were eligible for this study after excluding 11,527 women. Among these women, 112 underwent manual removal of the placenta during the study period.