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Review Article

# A systematic review of massive transfusion protocol in obstetrics

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ABSTRACT

Post-partum obstetric haemorrhage is a leading cause of mortality among Japanese women, generally treated with haemostatic measures followed by supplementary transfusion. Commonly used in the setting of severe trauma, massive transfusion protocols (MTPs), preparations of red blood cell concentrate (RBC) and fresh frozen plasma (FFP) with additional supplements, have proved effective in decreasing patient mortality following major obstetric bleeding events. Although promising, the optimal configuration of RBC and FFP utilized for obstetric bleeding needs to be verified. Here, we conducted a systematic literature review to define the optimal ratio of RBC to FFP for transfusion therapy during instances of obstetric bleeding. Our analysis extracted four retrospective, observational studies, all demonstrating that an FFP/RBC ratio of $\geq$1 was associated with improved patient outcomes following obstetric haemorrhage. We therefore conclude that, from the standpoint of haemostatic resuscitation, an FFP/RBC ratio of $\geq$1 is a necessary condition for optimal clinical management during MTP administration in the field of obstetrics. Hence, we further propose an optimized MTP strategy to be utilized in the setting of severe obstetric bleeding.



## Introduction

Obstetric bleeding is the leading cause of maternal mortality in Japan [1]. In addition to clinical strategies designed to achieve haemostasis, transfusions are a critical component in the management of severe bleeding events. Currently, a massive transfusion protocol (MTP) is the recommended therapeutic transfusion strategy for the clinical management of severe trauma. Generally utilized following a major bleeding event, an MTP is defined by the administration of fixed proportions of red blood cell concentrate (RBC), fresh frozen plasma (FFP), and platelet concentrates (PC) to the patient. As accessibility to these various blood-derived preparations differs across countries, a diverse array of MTPs exists, supplemented with various adjuncts including cryoprecipitate, fibrinogen concentrate, and recombinant factor VIII. Additionally, it is common for individual institutions to establish in-house ratios for administration of the respective blood-derived preparations.

While these factors make systematic reviews challenging [2–6], previous investigation reported significantly reduced mortality in patients receiving MTPs containing suitable coagulation factor supplements [7]. Although early and sufficient coagulation factor supplementation can improve patient outcomes, tissue injury due to coagulopathy in these patients has already occurred prior to MTP administration [8]. Interestingly, this report further demonstrated that MTPs were significantly more effective when containing an

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FFP/RBC ratio of 1.0 or greater [7]. As the pathology of obstetric bleeding mirrors that of severe trauma, an MTP with FFP/RBC ratios resembling the preparations utilized for trauma may be useful for obstetric bleeding. Therefore, in the present investigation, we have conducted a systematic literature review regarding the ratio of RBC to FFP utilized in transfusion therapies for obstetric bleeding to verify the optimal MTP configuration for obstetric bleeding. We further propose a novel treatment strategy for massive obstetric bleeding.

## Materials and methods

PubMed and MEDLINE online journal databases were queried regarding articles detailing the clinical effectiveness of MTP published from October 31, 2005, to October 31, 2015. Three key phrases were utilized to query these databases: postpartum haemorrhage; obstetric haemorrhage; and massive transfusion. Only articles written in English were selected. All matching articles were independently screened by two experts. For inclusion into analysis, identified manuscripts were required to fulfil the following criteria:

1. The study background, objectives, and subjects of the analysis are clearly defined.
2. Specific transfusion therapy utilized for obstetric-related bleeding is described.
3. Methods for solving the problem at hand are clearly demonstrated in the introduction.
4. Clear demonstrations of specific hypotheses regarding each clinical variable as well as functions for deriving the clinical measurement method from theoretical models.
   None of the presented data contradict the conclusions of the study.
5. Properties, definitions, and sources of reported data are clearly demonstrated.
6. The presented data forms the basis of reliable arguments.
7. Sufficient data are reported to characterize the specific bleeding event.
8. The methods are utilised to sufficiently test the validity of the presented hypotheses.
9. A sufficient discussion of the reported data is proposed.
10. The discussion itself was determined to be valid. Specifically, no logical errors are made when presenting final conclusions.
11. Presented and referenced facts are clearly distinguishable from speculation.

All adopted articles were standardized based on PICO (population, intervention, comparison, outcome) criteria and subsequently evaluated. Further, articles were deemed to be within the field of obstetrics when at least 50% of included patients presented with obstetric diseases.

## Results

Database queries utilizing the 3 key phrases described above yielded a total of 18,899 articles. Interestingly, our search did not identify any systematic reviews, meta-analyses or reports regarding randomized, controlled trials (RCT). Following our criteria-based screening protocol, only four original articles and four guidelines were extracted. Patient outcomes in these original articles included reduced transfusion volume, decreased patient morality rate, and acute lung injury (ALI). Interestingly, our database query returned no reports investigating protocol effectiveness relative to control patient populations. Although no control populations were analysed, the following five retrospective observational studies were identified by our search, all investigating the FFP/RBC ratio (FFP/RBC) in the setting of massive obstetric bleeding (Table 1).

Bonnet et al. analysed the FFP/RBC ratio in 38 cases of maternal death caused by massive obstetric bleeding. Specifically, the authors analysed the temporal administration of both FFP and RBC for patients with postpartum haemorrhage to determine peak transfusion times for both preparations. Interestingly, the report indicated that FFP/RBC rose above 1 at 12 h following haemorrhage onset [9]. Specifically, the FFP:RBC ratio in 4 out of 5 patient groups are less than 1; median FFP:RBC ratio was 0.6 (range 0–2) [9]. Further, the authors reported that blood test results of patients with coagulopathies normalised after the performance of an MTP.

Matsunaga et al. investigated 196 cases of massive obstetric bleeding necessitating aggressive coagulation factor supplementation. The study determined that when the transfusion therapy was performed to meet specific haemostatic targets, the calculated FFP/RBC ratio was 1.3 when converted from whole blood [10].

In a cohort of 181 patients in the United Kingdom, Green et al. analysed the amount of blood products utilized in instances of massive obstetric bleeding requiring transfusion therapy. In the United Kingdom, cryoprecipitate is readily available. Therefore, if cryoprecipitate is considered as five units of FFP, then the amount of FFP utilized in these patients exceeded the amount of RBC administered, essentially shifting the FFP/RBC ratio to values of 1 or greater [11].

Gutierrez et al. defined their MTP protocol as a package consisting of six units of O-negative RBC, four units of plasma (either liquid AB plasma or thawed type-specific plasma), and one apheresis platelet (PLT) unit. Favourable haematologic indices were observed post-resuscitation [12].

Tanaka et al. examined 54 patients (22 suffering mortality) with uterine artery embolization, hysterectomy, and a FFP/RBC transfusion regimen following amniotic fluid embolism complicated by coagulopathy. Interestingly, the FFP/RBC ratio was 1 or greater in transfusions administered to 40.9% of patients (9/22 patients) who died as well as 90.6% of patients (29/32 patients) surviving embolism. This finding was associated with significantly improved rates of post-embolism survival following transfusion with a FFP/RBC ratio $\geq$1 (odds ratio: 28.32; 95% confidence interval: 4.26–188.37). No significant differences were observed with respect to either uterine artery embolization or hysterectomy between the groups [13].

*Four guidelines for obstetric bleeding*

1. American College of Obstetrician and Gynecologists (ACOG) [14,15]

The article entitled “Preventing Maternal Death: 10 Clinical Diamonds” does not describe a specific MTP [9]. However, one of the “Clinical Diamonds” listed, informed by severe trauma treatment strategies, does recommends the generic introduction of an MTP [2,3]. Moreover, when massive transfusions are required this guideline further recommends early and aggressive transfusion at an RBC:FFP:PC ratio of 1:1:1. It concludes that therapy following an MTP may potentially facilitate the resolution of coagulopathies, hypothermia, and acidosis, all conditions that significantly increase the likelihood of patient mortality. Although not definitively proven for obstetric bleeding, similarities between the clinical courses of traumatic and obstetric bleeding lead this guideline to conclude that transfusions following an MTP utilised during traumatic bleeding could be effective in the setting of obstetric bleeding.

**Table 1**
Identified studies detailing massive transfusion protocols during obstetric haemorrhage.

| | Year | Cases | Protocol |
|---|---|---|---|
| Bonnet MP et al. [9] | 2011 | 38 | FFP/RBC ratio exceeds 1 at 12 h following the onset of obstetric haemorrhage. |
| Matsunaga S et al. [10] | 2012 | 196 | Medically necessary FFP/RCC ratio is 1.3 in obstetric haemorrhage. |
| Gutierrez MC et al. [12] | 2012 | 26 | MTP was defined as a combination of 6 units of O-negative RBC, 4 units of FFP (liquid AB plasma or thawed type-specific plasma), and 1 apheresis platelet (PLT) unit. |
| Green L et al. [11] | 2016 | 181 | FFP/RBC ratio $\geq$ 1 required during massive obstetrics haemorrhage. |
| Tanaka H et al. [13] | 2016 | 52 | Transfusion of FFP/RBC ratio $\geq$ 1 reduces mortality during amniotic fluid embolism with coagulopathy. |

FFP; fresh frozen plasma, RBC; red blood cell concentrate, RCC; red cell concentrate, MTP; massive transfusion protocol.

2. The Royal College of Obstetricians and Gynaecologists (RCOG)

The "Green-top Guideline: Blood Transfusion in Obstetrics" recommends 12–15 ml/kg of FFP for every 6 units of RBC [16]. Further, subsequent amounts of FFP should be based primarily on coagulation test results, by referencing prothrombin time (PT) and activated partial thromboplastin time (APTT). The guideline's targets for PT and APTT are 1.5 times normal, and 150 mg/dl or higher for fibrinogen is. It further states that both blood counts as well as coagulation tests (PT, APTT, fibrinogen) should be performed regularly during persistent bleeding. This guideline further recommends administration of cryoprecipitate as two 5-unit sets, while maintaining fibrinogen at a level of 150 mg/dl.

3. The Society of Obstetricians and Gynaecologists of Canada (SOGC)

In 2009, the SCOG published 'Prevention and Treatment of Postpartum Hemorrhage', unfortunately without mention of specific transfusion methods [17]. In fact, this guideline expresses a primarily preventive standpoint. Further, 'Hemostatic Shock', published in 2002 by SOGC, made no mention of any transfusion methods.

4. Japan Association of Obstetricians and Gynecologists (JAOG), Japan Society of Obstetrics and Gynecology (JSOG)

This guideline states that 'Obstetric bleeding can easily convert to disseminated intravascular coagulation (DIC), so fresh frozen plasma should be administered in addition to red cell products'. It further states that 'Pregnant women are susceptible to hypercoagulation and excessive consumption of coagulation factors, which means the coagulation factors that have been consumed need to be supplemented' [18]. Regarding RBC, this guideline provides a formula for calculating haemoglobin (Hb) levels, a measurement expected to increase following RBC administration. For FFP, this guideline recommends that transfusions be administered to achieve a fibrinogen level of 150 mg/dl.

## Discussion

Our systematic review demonstrated that with respect to transfusions for obstetric bleeding, the amount of administered FFP exceeded the amount of RBC utilized. As the mortality rate from massive obstetric bleeding is significantly reduced relative to traumatic bleeding, prospectively investigating the effects of an MTP on patient mortality rate would be extremely challenging. Indeed, our review identified no such articles. Additionally, as the decline in platelet levels is milder in the setting of obstetric haemorrhage compared to traumatic bleeding, no articles make specific mention of platelet ratios when discussing an MTP.

All retrospective studies identified regarding transfusions for obstetric bleeding recommend that the FFP/RBC ratio be $\geq$ 1. From the standpoint of haemostatic resuscitation, these results strongly indicate that this ratio should be a necessary condition for any administered MTP in the field of obstetrics. As different institutions will utilise differing stocks of blood products, each treatment centre should work to establish an MTP configuration where the FFP/RBC ratio is $\geq$ 1 by adjusting the relative ratios of these blood-derived preparations according to product availability. The greatest limitation of this systematic review is all study was performed as a retrospective analysis.

'Haemostatic resuscitation' is an important concept that aims to achieve both local surgical haemostasis as well as reduce coagulopathies. In MOH, massive bleeding reduces blood flow to the uterus. Subsequent tissue hypoperfusion increases the production of thrombomodulin in vascular endothelial cells and promotes the activation of protein C. Protein C activation produces severe coagulopathies by irreversibly inhibiting factor Va and factor VIIIa while simultaneously suppressing plasminogen activator inhibitor-1 [19] and activating the system [8]. These events result in increased production of fibrinogen degradation products, secondarily suppressing uterine contractions. As these events occur in traumatic as well as obstetric bleeding cases, patient condition may rapidly deteriorate when tissue damage occurs concurrent with coagulopathy, making an MTP an important part of achieving haemostatic resuscitation in both pathologies.

Guidelines from several countries further recommend aggressive supplementation of coagulation factors. At present, the target for this, the fibrinogen level, is 100 mg/dl in Japan, relatively low compared to other countries. Indeed, in other developed nations, plasma fibrinogen levels from 150 to 200 mg/dl are recommended [20–24].

Based on previous reviews [25–37], the scientific committee of the Japanese Council for Implementation of Maternal Emergency Life-Saving Systems (J-CIMELS) has developed a new therapeutic strategy to be implemented in the setting of massive obstetric bleeding [38]. Broadly described, this new strategy focuses on 2 points: 1) assessing condition severity and 2) determining the underlying pathology of the obstetric bleeding [38].

Insufficient evidence exists regarding MTP in the setting of obstetric haemorrhage. Although conducting an RCT would be the ideal method to obtain such evidence, the withholding of an MTP from patients with severe obstetric bleeding would be clinically dangerous and, as a result, is ethically impossible. Therefore, the best option is to retrospectively examine greater numbers of patients, such as through large-scale observational studies.

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## Conflicts of interest

None of the authors have any conflicts of interest to declare.

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