Article type : Ordinary Papers

Haematological features, transfusion management and outcomes of massive obstetric haemorrhage: findings from the Australian and New Zealand Massive Transfusion Registry

Masa Lasica,^{1,2,7,9} Rosemary L Sparrow,¹ Mark Tacey,¹ Wendy E Pollock,^{3,6,8} Erica M Wood,^{1,4}
Zoe K McQuilten,^{1,5}

on behalf of the members of the Australian and New Zealand Massive Transfusion Steering Committee

¹ Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

² Australian Red Cross Blood Service, Melbourne, Australia

³ Maternal Critical Care, Melbourne, Australia

⁴ Department of Haematology, Monash Health, Melbourne, Australia

⁵ Australia and New Zealand Intensive Care Research Centre (ANZIC-RC), Melbourne, Australia

⁶ School of Nursing and Midwifery, La Trobe University, Melbourne, Australia

⁷ Department of Haematology, Eastern Health, Melbourne, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/BJH.16524](https://doi.org/10.1111/BJH.16524)

⁸ Department of Nursing, The University of Melbourne, Australia

⁹ Department of Haematology, St Vincent's Hospital, Melbourne, Australia

Correspondence:

A/Prof Zoe McQuilten

School of Public Health and Preventive Medicine

Monash University

553 St Kilda Road, Melbourne, Australia 3004

E-mail: zoe.mcquilten@monash.edu

Declaration of interests: None to declare

Running title: Massive obstetric haemorrhage transfusion practice

Funding: The ANZ-MTR has received funding from the National Health and Medical Research Council (Australia), National Blood Authority (Australia), Victorian Government Department of Health and Human Services, Australian Red Cross Blood Service, New Zealand Blood Service, CSL Behring, St John of God Health Care and Monash University.

Abstract word count: 200

Manuscript word count: 2,997

Number of references: 35

Number of Tables: 6

Number of Figures: 2

Supplemental tables: 2

Summary

Massive obstetric haemorrhage (MOH) is a leading cause of maternal morbidity and mortality world-wide. Using the Australian and New Zealand Massive Transfusion Registry, we performed a bi-national cohort study of MOH defined as bleeding at ≥ 20 weeks' gestation or postpartum requiring ≥ 5 red blood cells (RBC) units within 4h. Between 2008 and 2015, we identified 249 cases of MOH cases from 19 sites. Predominant causes of MOH were uterine atony (22%), placenta praevia (20%) and obstetric trauma (19%). Intensive care unit admission and/or hysterectomy occurred in 44% and 29% of cases, respectively. There were 3 deaths. Hypofibrinogenaemia ($< 2\text{g/L}$) occurred in 52% of cases in the first 24h after massive transfusion commenced; of these cases, 74% received cryoprecipitate. Median values of other haemostatic tests were within accepted limits. Plasma, platelets or cryoprecipitate were transfused in 88%, 66% and 57% of cases, respectively. By multivariate regression, transfusion of ≥ 6 RBC units before the first cryoprecipitate (odds ratio [OR] 3.5, 95%CI: 1.7-7.2), placenta praevia (OR 7.2, 95%CI: 2.0-26.4) and emergency caesarean section (OR 4.9, 95%CI: 2.0-11.7) were independently associated with increased risk of hysterectomy. These findings confirm MOH as a major cause of maternal morbidity and mortality and indicate areas for practice improvement.

Keywords: obstetric haemorrhage, massive transfusion, coagulopathy, fibrinogen

Introduction

Definitions of severe postpartum haemorrhage (PPH)/massive obstetric haemorrhage (MOH) range from estimated blood loss of ≥ 1500 mL, transfusion of ≥ 5 red blood cells (RBC) units, or any treatment for coagulopathy (McIntock & James, 2011). In developed countries, MOH-related maternal mortality has markedly declined over the past several decades;

however, the incidence of MOH is rising globally, including in Australia and New Zealand (Flood *et al*, 2018; Lawton *et al* 2019, Geller *et al*, 2019). Failure to effectively manage MOH can cause maternal death as well as significant morbidity, including hypovolaemic shock, multi-organ failure and, in severe cases, emergency hysterectomy (Green *et al*, 2016a).

Transfusion support is a key part of the management of MOH. Inefficacious administration of non-RBC components (fresh frozen plasma [FFP] and platelets) to treat MOH is associated with increased risk of dilutional coagulopathy (Gillissen *et al* 2018a; McDonnell & Browning, 2018). In many hospitals, management of MOH is now structured with massive transfusion protocols (MTPs) including early intervention and use of fixed ratios of non-RBC:RBC components; however, protocols vary (Thomasson *et al*, 2019). Some hospitals use a single MTP for all causes of critical bleeding, commonly based on resuscitation strategies for trauma-related bleeding. Others have tailored MTPs for specific causes of bleeding, such as obstetric haemorrhage (Shields *et al*, 2015; Butwick & Goodnough, 2015).

Pregnancy is associated with natural changes towards a hypercoagulable state, with decreased levels of anticoagulant factors and significantly increased levels of procoagulant factors, including von Willebrand Factor (vWF), factor VIII and fibrinogen (McNamara & Mallaiah, 2019). Plasma fibrinogen almost doubles in concentration to 4-7 g/L compared to the non-pregnant adult. Evidence suggests that relative hypofibrinogenaemia of <2 g/L early in the course of obstetric haemorrhage is associated with higher risk of progression to MOH with increased morbidity and mortality (Charbit *et al*, 2007; Cortet *et al*, 2012; Gillissen *et al*, 2018b). Adding to the complexity, results of standard laboratory-based haemostatic tests (i.e. activated partial thromboplastin time [APTT] and international normalised ratio [INR]) are often not reflective of haemostatic changes during MOH, and may remain within normal limits despite significant dilutional and consumptive coagulopathy *in situ* (de Lloyd *et al*, 2011; Green *et al*, 2016b). Fibrinogen replacement and/or other concentrated forms of plasma coagulation factors may not always be included in MTPs, and may only be prescribed when bleeding or coagulopathy has worsened (Matasunga *et al*, 2019). What constitutes optimal transfusion management of MOH remains uncertain.

To gain better insight into transfusion management practice and clinical outcomes of MOH, we performed a bi-national, multi-centre, cohort study of MOH cases captured in the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR) (Oldroyd *et al*, 2016).

The ANZ-MTR is a dataset of comprehensive hospital electronic records of patients with critical bleeding, due to any cause, who required massive transfusion (MT), defined as ≥ 5 RBC units within any 4h period during hospital admission.

Methods

Study setting and population

This study had approval from the Human Research Ethics Committees of Monash University and participating hospitals. The study population included MOH cases that occurred between 2008 and 2015 at 19 sites (14 Australian and 5 New Zealand) captured in the ANZ-MTR; most sites contributed data for cases that occurred from 2011/2012 onwards. The ANZ-MTR's inclusion criteria are patients aged ≥ 18 years who received ≥ 5 RBC units within any 4h period during hospital admission for any cause of critical bleeding (Oldroyd *et al*, 2016). Primary cause of bleeding (obstetric versus non-obstetric) was determined using diagnostic and procedure coding data provided by the hospitals, classified according to the International Statistical Classification of Disease and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) (National Centre for Classification in Health, 2013).

Our case definition of MOH was MT events, as defined by the ANZ-MTR, with obstetric primary cause of bleeding that occurred postpartum or at ≥ 20 weeks' gestation antepartum. The ICD-10-AM diagnostic coding data were used to classify the specific causes of MOH, as previously described (Mhyre *et al*, 2013). In patients with more than one cause of obstetric bleeding coded, we used a hierarchy to assign a primary cause based on the likelihood of the different diagnoses being the primary cause of MOH.

Data collection

In addition to ICD-10-AM and procedure coding data, patient demographics, co-morbidities, laboratory test results, blood components issued, admission/discharge information, ICU admission, requirement for mechanical ventilation were obtained from the ANZ-MTR.

Statistical analysis

The number of blood components issued within 4h and 24h of MT commencement, and ratios of non-RBC:RBC components were determined from the transfusion records.

Laboratory test results closest to the time after MT commenced represented the starting value; the highest or lowest result in the 24h period after MT commenced defined the most abnormal value. Duration of MT was defined as the time interval between issue of the first RBC unit at MT commencement and issue of the last RBC unit in which no further RBC units were issued for ≥ 24 h thereafter.

Outcomes included in-hospital mortality, ICU length of stay (LOS), requirement for mechanical ventilation, hysterectomy, other surgical interventions, and organ failure.

Categorical variables and outcomes are presented as counts and frequencies, with Chi-squared or Fisher's Exact tests used to assess statistically significant differences between variables. Continuous variables are presented as median and interquartile range (IQR), with Mann-Whitney rank-sum tests used to compare across groups. Multivariate logistic regression was used to determine the impact of selected factors on the likelihood of hysterectomy or ICU admission. Statistical significance was defined as $P < 0.01$. Analyses were performed using Stata, version 14.0 (StataCorp, College Station, Texas, USA).

Results

During the study period, of the 5692 MT cases in the ANZ-MTR, 319 (5.6%) were classified as obstetric-gynaecological haemorrhage. Of these, 249 (78%) met the study definition of MOH (Figure 1). Excluded cases ($n=70$, 22%) were haemorrhage due to complications in the first or early second trimester ($n=60$), or primary cause of bleeding due to non-obstetric aetiology ($n=10$). Uterine atony/abnormal forces of labour (22%), placenta praevia (20%) and obstetric trauma (19%) were the predominant primary causes of MOH; specific cause was unavailable for 48 cases (19%) (Figure 1). Hospital details are shown in Figure 1 inset box.

Baseline characteristics

Patient baseline characteristics, by cause of MOH, are shown in Table I. Median age was 34 years; 44% of patients were ≥ 35 years. Modes of delivery were vaginal (46%) or caesarean section (emergency 35%; elective 19%). MOH occurred after-hours in 62% of cases; MT commenced at a median time [IQR] of 13h [5.4-28.5] after hospital admission.

Haematological parameters

Figure 2 shows the levels of haematological parameters at the closest time-point after the start of MT and the most abnormal values in the 24h period after MT commenced, by cause of MOH. As expected, median starting haemoglobin (Hb) was low (<95 g/L) in all MOH cohorts as blood specimens were taken after MT commenced; median nadir Hb levels in the following 24 h further declined by 5 to 14 g/L for all MOH cohorts. Median starting platelet count was $>100 \times 10^9$ /L for all MOH cohorts and remained $>75 \times 10^9$ /L in the 24h after MT commenced. Similarly, median APTT and INR values remained at clinically acceptable levels (i.e. <1.5 -fold above upper normal limit) in the 24h after MT commenced for all MOH cohorts. Median starting and nadir fibrinogen levels for all MOH cohorts were markedly lower than the level considered normal for pregnancy (≤ 4 g/L), ranging from median starting fibrinogen levels of 1.9 to 2.7 g/L and nadir fibrinogen levels of 1.9 to 2.2 g/L.

Transfusion management

Table II summarises the transfusion management in the first 4h after MT commenced, by cause of MOH. There were no significant differences in transfusion management between the MOH cohorts. As per our MT definition, all patients received ≥ 5 RBC units; 88% also received FFP, 66% received platelets and 57% received cryoprecipitate.

Median [IQR] number of RBC units transfused before the first transfusion of FFP, platelets, or cryoprecipitate, was 4 [2-6], 6 [4-8] and 6 [4-8] RBC units, respectively. A <1 h time-interval between transfusion of the first RBC unit and first FFP, platelet, or cryoprecipitate unit occurred in 63%, 45% and 42% of cases, respectively. Median [IQR] FFP:RBC ratio at 4h and 24h after MT commenced was 0.6 [0.3-0.8] at both time-points.

Abnormal haemostatic parameters and transfusion

Low fibrinogen levels of <2 g/L occurred in 40% of patients early in the course of the MT and increased to 52% within the first 24h of MT commencement. In comparison, $<20\%$ of

patients had clinically abnormal platelet counts, APTT or INR values in the 24h period after MT commenced (Table III).

For MOH cases with abnormal starting APTT or INR, or low platelet count $<50 \times 10^9/L$, transfusion of the appropriate non-RBC components occurred for 95% and 83% of cases, respectively, with a time-lag after MT commencement of $<1h$. Of the cases with low starting fibrinogen ($<2 g/L$), only 71% received cryoprecipitate, and had a longer time-lag to transfusion of cryoprecipitate after MT commenced, median [IQR] 1.2h [0.5-2.5] (Table III); of these, only 24% received ≥ 6 units of cryoprecipitate in the 24h after MT commenced.

Outcomes and complications

Median [IQR] duration of MOH was 2.5h [1.0-13.6]. MT of ≥ 10 RBC units within 24h occurred for 31% of all cases, ranging from 21% of uterine atony cases to 43% of placenta praevia cases. Median [IQR] hospital LOS following MOH was 143h [96-190], while 44% of cases were admitted to ICU with median [IQR] ICU LOS of 24h [15-38]. Hysterectomy was performed in 29% of all cases and 65% of placenta praevia cases (Table IV). Other documented complications included respiratory failure needing mechanical ventilatory support (14%), shock (4%), other surgical interventions (4%), acute kidney injury (2%) and amniotic fluid embolism (2%).

There were three in-hospital MOH-related maternal deaths. All three cases received large numbers of RBC units, between 14 and 33 units in the first 4h after MT commenced. Two deaths occurred within 4h of MT commencement; the third death was a complex, high-risk case further complicated by an amniotic fluid embolism.

Predictors of hysterectomy and/or ICU admission

Results for univariate analyses of a range of factors tested for association with the risk of hysterectomy or ICU admission are shown in Supplementary Tables S1 and S2, respectively, available on-line. Factors considered included maternal age, type of hospital, mode of delivery, after-hours admission, specific cause of MOH, haemostatic parameters, transfusion management and duration of MT.

Multivariate regression analysis identified that emergency caesarean section (OR 4.9, 95%CI: 2.0-11.7, $P < 0.001$), placenta praevia (OR 7.2, 95%CI: 2.0–26.4, $P = 0.003$) and transfusion of

≥6 RBC units before the first cryoprecipitate unit (OR 3.5, 95%CI: 1.7-7.2, $P=0.001$) were independently associated with hysterectomy. There were no significant differences between the hysterectomy and no-hysterectomy cases in regard to the starting value of any of the haemostatic parameters or other factors considered (Table V).

Cases admitted to the ICU ($n=110$, 44%) required longer transfusion support (median 6.3h [1.9-29.7] vs 1.6h [0.5-13.9] no-ICU admission cases, $P<0.001$), had a higher median starting APTT and INR values ($P<0.001$ for both), received ≥6 RBC units before the first cryoprecipitate unit (48% vs 27% no-ICU admission cases, $P<0.001$), and before the first platelet transfusion (45% vs 28% no-ICU admission cases, $P<0.001$). Other considered factors were deemed not significantly different for cases admitted/not admitted to ICU. By multivariate regression analysis, transfusion of ≥6 RBC units before the first cryoprecipitate unit (OR 2.5, 95%CI: 1.3-5, $P=0.007$) and before the first platelet unit (OR 3.0, 95%CI: 1.4-6.6, $P=0.006$) were independently associated with ICU admission (Table VI).

Discussion

This bi-national study is one of the largest reported analyses of massive haemorrhage and transfusion management in the obstetric setting. Over half of the women gave birth by caesarean section and 44% were ≥35 years of age. The most common causes of MOH were uterine atony (22%), placenta praevia (20%) and obstetric trauma (19%). Delayed transfusion of cryoprecipitate until after transfusion of ≥6 RBC units was independently associated with necessity for hysterectomy or ICU admission. Placenta praevia and emergency caesarean section were also independently associated with hysterectomy. Almost two-thirds of MOHs occurred outside usual working hours, emphasising the importance of adequate blood bank inventory, staffing levels and expertise at all times.

Our MOH cohort consisted of cases that occurred between 2008 and 2015, which pre-dates the significant advances in management of severe obstetric haemorrhage gained in recent years, including increased use of anti-fibrinolytic tranexamic acid (TXA), point-of-care viscoelastic blood tests, such as ROTEM, and growing awareness that standardised “one-

size-fits-all” MTPs may not be helpful [Weeks, 2019; McNamara & Mallaiah, 2019]. Nevertheless, our findings support timely fibrinogen replacement as a key strategy in effective transfusion management of MOH.

It is notable that 40% of our MOH cohort had a starting fibrinogen level below the recommended fibrinogen replacement trigger of 2 g/L for MOH (National Blood Authority, 2015). Approximately 30% of these cases did not receive cryoprecipitate. In Australia and New Zealand, cryoprecipitate is the standard product for fibrinogen replacement. It contains concentrated levels of pro-coagulant factors that are naturally raised in pregnancy, including fibrinogen, vWF and factor VIII (Callum *et al*, 2009; Novak *et al*, 2018). In some developed countries, a purer lyophilised fibrinogen concentrate product is more widely used. Unlike cryoprecipitate, it does not require thawing prior to use which may have the advantage of more timely access in the setting of critical bleeding (Novak *et al*, 2018). Two recent randomised controlled trials (RCTs) of fibrinogen concentrate did not find benefit in the obstetric haemorrhage setting (Wikkelsø *et al*, 2015; Collins *et al*, 2017). However, of the combined 304 PPH cases, only 12 cases (4%) had a starting fibrinogen level <2 g/L; 48% also received TXA. Both RCTs were limited by the inability to consent women with catastrophic, massive haemorrhage, who may be more likely to have rapid-onset hypofibrinogenaemia, as exemplified by our MOH cohort. No RCTs have been performed that directly compare the efficacy of cryoprecipitate versus fibrinogen concentrate in MOH; however, a small retrospective study of 34 major obstetric haemorrhage cases, all with plasma fibrinogen of <2 g/L, reported equivalent efficacy to correct hypofibrinogenaemia (Ahmed *et al*, 2012).

In our cohort, despite only a minority of cases having abnormal APTT, INR or platelet counts during the 24h-period after MT, 88% of cases received FFP and 66% received platelets in the first 4h after MT commenced. These observations may reflect the use of empiric blood component ratios in the setting of long turn-around times of laboratory-based coagulation test results. The median FFP:RBC transfusion ratio was 0.6 at both 4h and 24h time-points after MT commenced. This was lower compared to the 1:1 ratio specified in many hospital MTPs in use around the time-period of our cohort and similar to some MOH-specific MTPs (Shields *et al*, 2015; Butwick & Goodnough, 2015). Blood haemostatic indices (APTT, INR, fibrinogen and platelet count) in the early stages of MT were not independently predictive of subsequent hysterectomy or ICU admission. Other studies have also reported that APTT,

INR and platelet counts often remain within acceptable limits during MOH and that formulaic-directed transfusion of FFP or platelets is not warranted in a majority of cases (Collins *et al*, 2019).

Our study has several strengths. As one of the largest MOH cohorts described, it also included a significant proportion of cases with hypofibrinogenaemia of <2 g/L, likely representing cases with higher risk for severe MOH-related morbidities and mortality. Cases were systematically identified through hospital information systems without reliance on clinical notes, using previously validated processes (Oldroyd *et al*, 2016). Cases were treated at 19 hospitals across Australia and New Zealand, increasing the generalisability of our findings.

However, our study has limitations, including the observational design. MOH cases that required emergency transfer between hospitals during the MT episode may not have been captured. The range of hospital types was heavily weighted towards large city-based, referral hospitals. Determination of cause of MOH relied on ICD-10 diagnostic coding, which, although previously used by others for this purpose (Mhyre *et al*, 2013), is dependent on correct coding by hospital medical coders and careful interpretation of the clinical context. We were unable to determine the specific cause of MOH in 20% of cases (n=48) due to insufficient diagnostic coding information. Furthermore, the primary cause of bleeding, as entered into the registry, may not have accounted for the multi-factorial aetiology of MOH. In subjects with more than one possible cause entered, we assigned a primary cause according to the likelihood of the different diagnoses listed being the primary cause of MOH. We recognise that this approach may not reflect the complex interplay of different factors in MOH, but is an inherent weakness of registry-based data collection. Adding to the complexity is variation in the agreed definition between a risk factor and cause of MOH (for example, uterine rupture) (Schaap *et al*, 2019; NSW Government, 2017; Vandenberghe *et al*, 2019). Data were not obtained on total blood loss or total bleeding duration. Instead, time-points of the first and last blood components issued were used to estimate MOH duration, which was based on a validation study demonstrating concordance between transfusion laboratory information and clinical records (McQuilten *et al*, 2011). Test results from point-of-care viscoelastic analysers, such as ROTEM, not linked to the laboratory information systems, were unavailable. Anecdotally, the use of such devices in the obstetric setting was

uncommon at the treating hospitals during the time-course of this study. Information on some relevant baseline risk factors for obstetric haemorrhage including obesity, prior obstetric haemorrhage and presence of fibroids were not available. While complete data on transfused blood components issued from the hospital transfusion laboratories were collected, use of other haemostatic agents and/or fluid replacement solutions stored elsewhere in the hospitals were not captured in the ANZ-MTR dataset. Similarly, data on use of TXA was not captured. In light of the recent data on role of TXA in MOH (WOMAN Trial Collaborators, 2017; Brenner *et al*, 2019), several obstetric specialist groups have updated their guidelines for management of obstetric haemorrhage to include TXA as an early intervention (O'Brien *et al*, 2018; Collins *et al*, 2019; Matsunaga *et al*, 2019). Future MOH studies should examine the use of TXA and effect on transfusion requirements and patient outcomes.

In conclusion, MOH resulted in maternal mortality and significant morbidity, including hysterectomy that was associated with emergency caesarean section, placenta praevia and later administration of cryoprecipitate. Areas for practice improvement include timely fibrinogen replacement. The association between hysterectomy and later fibrinogen replacement requires confirmation in prospective studies, and warrants investigation whether earlier and/or larger dosing improves outcomes.

Acknowledgements

We thank all hospital staff involved in providing data and ANZ-MTR colleagues, Mrs Helen Haysom, Dr Cameron Wellard, Dr Nic Saadah and Robyn Sutherland. Our thanks to ANZ-MTR Steering Committee for their leadership.

Author contributions

Study design: ML, ZM, EM, WP. Data collection and analyses: ML, RS, MT, ZM. First draft: ML. Draft revisions and final version approval: All.

References

Ahmed, S., Harrity, C., Johnson, S., Varadkar, S., McMorrow, S., Fanning, R., Flynn, C.M., O'Riordan, J.M. & Byrne, B.M. (2012) The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage--an observational study. *Transfusion Medicine*, **22**, 344-349.

Brenner, A., Ker, K., Shakur-Still, H. & Roberts, I. (2019) Tranexamic acid for post-partum haemorrhage: what, who and when. *Best Practice & Research Clinical Obstetrics and Gynaecology*, **61**, 66-74.

Butwick, A.J. & Goodnough, L.T. (2015) Transfusion and coagulation management in major obstetric hemorrhage. *Current Opinion in Anaesthesiology*, **28**, 275-284.

Cahill, A.G., Beigi, R., Heine, R.P., Silver, R.M., Wax, J.R. on behalf of Society of Gynecologic Oncology, American College of Obstetricians and Gynecologists and Society of Maternal-Fetal Medicine. (2018) Placenta accreta spectrum. *American Journal of Obstetrics and Gynecology*, **219**, B2-B16.

Callum, J.L., Karkouti, K. & Lin, Y. (2009) Cryoprecipitate: the current state of knowledge. *Transfusion Medicine Reviews*, **23**, 177-188.

Charbit, B., Mandelbrot, L., Samain, E., Baron, G., Haddaoui, B., Keita, H., Sibony, O., Mahieu-Caputo, D., Hurtaud-Roux, M.F., Huisse, M.G., Denninger, M.H., de Prost, D. & PPH Study Group. (2007) The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *Journal of Thrombosis and Haemostasis*, **5**, 266-273.

Collins, P.W., Cannings-John, R., Bruynseels, D., Mallaiah, S., Dick, J., Elton, C., Weeks, A.D., Sanders, J., Aawar, N., Townson, J., Hood, K., Hall, J.E., Collis, R.E., on behalf of the OBS2 study team. (2017) Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial. *British Journal of Anaesthesia*, **119**, 411-421.

Collins, P.W., Bell, S.F., de Lloyd, L. & Collis, R.E. (2019) Management of postpartum haemorrhage: from research into practice, a narrative review of the literature and the Cardiff experience. *International Journal of Obstetric Anesthesia*, **37**, 106-117.

Cortet, M., Deneux-Tharaux, C., Dupont, C., Colin, C., Rudigoz, R.C., Bouvier-Colle, M.H. & Huissoud, C. (2012) Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *British Journal of Anaesthesia*, **108**, 984-989.

de Lloyd, L., Bovington, R., Kaye, A., Collis, R.E., Rayment, R., Sanders, J., Rees, A. & Collins, P.W. (2011) Standard haemostatic tests following major obstetric haemorrhage. *International Journal of Obstetric Anesthesia*, **20**, 135-141.

Flood, M.M., Pollock, W.E., McDonald, S.J. & Davey, M.A. (2018) Monitoring postpartum haemorrhage in Australia: Opportunities to improve reporting. *Women and Birth*, **31**, 89-95.

Geller, S.E., Koch, A.R., Garland, C.E., MacDonald, E.J., Storey, F. & Lawton, B. (2018) A global view of severe maternal morbidity: moving beyond maternal mortality. *Reproductive Health*, **15**(Suppl 1), e98.

Gillissen, A., van den Akker, T., Caram-Deelder, C., Henriquez, D.D.C.A., Bloemenkamp, K.W.M., van Roosmalen, J.J.M., Eikenboom, J., van der Bom, J.G. & TeMpOH-1 study group. (2018a) Association between fluid management and dilutional coagulopathy in severe postpartum haemorrhage: a nationwide retrospective cohort study. *BMC Pregnancy and Childbirth*, **18**, e398.

Gillissen, A., van den Akker, T., Caram-Deelder, C., Henriquez, D.D.C.A., Bloemenkamp, K.W.M., de Maat, M.P.M., van Roosmalen, J.J.M., Zwart, J.J., Eikenboom, J., van der Bom, J.G. & TeMpOH-1 Study Group. (2018b) Coagulation parameters during the course of severe postpartum hemorrhage: a nationwide retrospective cohort study. *Blood Advances*, **2**, 2433-2442.

Green, L., Knight, M., Seeney, F.M., Hopkinson, C., Collins, P.W., Collis, R.E., Simpson, N., Weeks, A. & Stanworth, S.S. (2016a) The epidemiology and outcomes of women with postpartum haemorrhage requiring massive transfusion with eight or more units of red cells: a national cross-sectional study. *British Journal of Obstetrics and Gynaecology*, **123**, 2164-2170.

Green, L., Knight, M., Seeney, F., Hopkinson, C., Collins, P.W., Collis, R.E., Simpson, N.A., Weeks, A. & Stanworth, S.J. (2016b) The haematological features and transfusion management of women who required massive transfusion for major obstetric haemorrhage in the UK: a population based study. *British Journal of Haematology*, **172**, 616-624.

Lawton, B.A., MacDonald, E.J., Stanley, J., Daniells, K. & Geller, S.E. (2019) Preventability review of severe maternal morbidity. *Acta Obstetrica et Gynecologica Scandinavica*, **98**, 515-522.

Matsunaga, S., Takai, Y. & Seki, H. (2019) Fibrinogen for the management of critical obstetric hemorrhage. *Journal of Obstetrics and Gynaecology Research*, **45**, 13-21.

McDonnell, N.J. & Browning, R. (2018) How to replace fibrinogen in postpartum haemorrhage situations? (Hint: Don't use FFP!). *International Journal of Obstetric Anesthesia*, **33**, 4-7.

McIntock, C. & James, A.H. (2011) Obstetric hemorrhage. *Journal of Thrombosis and Haemostasis*, **9**, 1441-1451.

McNamara, H. & Mallaiah, S. (2019) Managing coagulopathy following PPH. *Best Practice & Research Clinical Obstetrics and Gynaecology*, **61**, 106-120.

McQuilten, Z.K., Schembri N., Polizzotto, M.N., Akers, C., Wills. M., Cole-Sinclair, M.F., Whitehead, S., Wood, E.M. & Phillips, L.E. (2011) Hospital blood bank information systems accurately reflect patient transfusion: results of a validation study. *Transfusion*, **51**, 943-948.

Mhyre, J.M., Shilkrut, A., Kuklina, E.V., Callaghan, W.M., Creanga, A.A., Kaminsky, S. & Bateman, B.T. (2013) Massive blood transfusion during hospitalization for delivery in New York State, 1998-2007. *Obstetrics and Gynecology*, **122**, 1288-1294.

National Blood Authority (NBA) (2015). Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity. NBA, Canberra, Australia. <https://www.blood.gov.au/pbm-module-5>.

National Centre for Classification in Health. (2013) International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM), the Australian Classification of Health Interventions (ACHI) and the Australian Coding Standards (ASC) NCCH, Sydney, 8th Edition.

Novak, A., Stanworth, S.J. & Curry, N. (2018) Do we still need cryoprecipitate? Cryoprecipitate and fibrinogen concentrate as treatments for major hemorrhage - how do they compare? *Expert Review of Hematology*, **11**, 351-360.

NSW Government. (2017) Maternity – prevention, detection, escalation and management of postpartum haemorrhage (PPH). Document No. GL2017_018. Available at https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2017_018.pdf

O'Brien, K.L., Shainker, S.A. & Lockhart, E.L. (2018) Transfusion management of obstetric hemorrhage. *Transfusion Medicine Reviews*, **32**, 249-255.

Oldroyd, J.C., Venardos, K.M., Aoki, N.J., Zatta, A.J., McQuilten, Z.K., Phillips, L.E., Andrianopoulos, N., Copper, D.J., Cameron, P.A., Isbister, J.P. & Wood, E.M. (2016) Improving outcomes for hospital patients with critical bleeding requiring massive transfusion: the Australian and New Zealand Massive Transfusion Registry study methodology. *BMC Research Notes*, **9**, e457.

Schaap, T., Bloemenkamp, K., Deneux-Tharaux, C., Knight, M., Langhoff-Roos, J., Sullivan, E., van den Akker, T. on behalf of INOSS. (2019) Defining definitions: a Delphi study to develop a core outcome set for conditions of severe maternal morbidity. *BJOG*, **126**, 394-401.

Shields, L.E., Wiesner, S., Fulton, J. & Pelletreau, B. (2015) Comprehensive maternal hemorrhage protocols reduce the use of blood products and improve patient safety. *American Journal of Obstetrics and Gynecology*, **212**, 272-280.

Thomasson, R.R., Yazer, M.H., Gorham, J.D., Dunbar, N.M. & MTP Use Study Investigators, on behalf of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative. (2019) International assessment of massive transfusion protocol contents and indications for activation. *Transfusion*, **59**, 1637-1643.

Vandenbergh, G., Bloemenkamp, K., Berlage, S., Colmorn, L., Deneux-Tharaux, C., Gissler, M., Knight, M., Langhoff-Roos, J., Lindqvist, P.G., Oberaigner, W., Van Roosmalen, J., Zwart, J., Roelens, K., on behalf of INOSS. (2019) The International Network of Obstetric Survey Systems study of uterine rupture: a descriptive multi-country population-based study. *BJOG*, **126**, 370-381.

Weeks, AD. (2019) Recent advances in understanding the enduring and deadly complication of postpartum haemorrhage. *Best Practice & Research Clinical Obstetrics and Gynaecology*, **61**, 1-2.

Wikkelsø, A.J., Edwards, H.M., Afshari, A., Stensballe, J., Langhoff-Roos, J., Albrechtsen, C., Ekelund, K., Hanke, G., Secher, E.L., Sharif, H.F., Pedersen, L.M., Troelstrup, A., Lauenborg, J., Mitchell, A.U., Fuhrmann, L., Svare, J., Madsen, M.G., Bødker, B., Møller, A.M. & FIB-PPH trial group. (2015) Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. *British Journal of Anaesthesia*, **114**, 623-633.

WOMAN Trial Collaborators. (2017) Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage

(WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet*, **389**(10084), 2105e16.

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Table I. Characteristics of the MOH cohort, by cause of bleeding categories

Factor*	Total cohort	Cause of MOH					
		Uterine atony	Placenta praevia	Obstetric trauma	Placenta accreta spectrum [≠]	Other causes [^]	Unspecified cause
Patient cohort, n	249	56	51	48	24	22	48
Age, years; median [IQR]	34 [30-37]	32 [29-37]	36 [32-39]	33 [28-36]	33 [30-36]	33 [29-37]	35 [31-39]
Pre-existing co-morbidities							
Tobacco use	42 (17%)	7 (13%)	10 (20%)	5 (10%)	3 (13%)	9 (41%)	8 (17%)
Diabetes mellitus	33 (13%)	6 (11%)	6 (12%)	7 (15%)	2 (8%)	4 (18%)	8 (17%)
Maternal age ≥35 years	109 (44%)	22 (39%)	29 (57%)	16 (33%)	8 (33%)	9 (41%)	25 (52%)
Mode of delivery							
Vaginal	114 (46%)	28 (50%)	2 (4%)	40 (83%)	9 (38%)	6 (27%)	29 (60%)
Elective caesarean section	48 (19%)	5 (9%)	21 (41%)	2 (4%)	7 (29%)	3 (14%)	10 (21%)
Emergency caesarean section	87 (35%)	23 (41%)	28 (55%)	6 (13%)	8 (33%)	13 (59%)	9 (19%)
Gestation age							
20-25 weeks	7 (3%)	1 (2%)	2 (4%)	1 (2%)	0	1 (5%)	2 (4%)
26-33 weeks	30 (12%)	1 (2%)	17 (33%)	1 (2%)	8 (33%)	3 (14%)	0
34-36 weeks	34 (14%)	5 (9%)	13 (25%)	4 (8%)	5 (21%)	4 (18%)	3 (6%)
37-41 weeks	161 (65%)	39 (70%)	19 (37%)	40 (83%)	10 (42%)	12 (55%)	41 (85%)

≥42 weeks	17 (7%)	10 (18%)	0	2 (4%)	1 (4%)	2 (9%)	2 (4%)
Birth type (other than single-live birth)							
Multiple births	18 (7%)	5 (9%)	4 (8%)	3 (6%)	1 (4%)	3 (14%)	2 (4%)
Stillbirth	8 (3%)	0	0	1 (2%)	2 (8%)	4 (18%)	1 (2%)
Timing of MOH							
After hours#	154 (62%)	34 (61%)	24 (47%)	36 (75%)	16 (67%)	16 (73%)	28 (58%)
MT start relative to admission time, h; median	13	14.4	19.3	12.7	6.3	9.6	10.1
[IQR]	[5.4-28.5]	[7.4-28.9]	[5.3-134.6]	[6.1-20.8]	[2.5-64.8]	[2.1-27.8]	[3.7-22.2]

* Data are shown as n (% of in-group total) unless otherwise indicated

After hours admission, defined as weekends, public holidays and between 6pm and 8am on weekdays

IQR, interquartile ratio; MOH, massive obstetric haemorrhage; MT, massive transfusion

≠Placenta accreta spectrum includes placenta accrete, placenta increta and placenta percreta (Cahill et al, 2018)

^ Other possible causes included uterine rupture and other placenta causes such as retained placenta and premature placental separation.

Table II. Transfusion management in the first 4 hours following start of massive transfusion, by cause of MOH*

Blood component transfused	Total Cohort	Cause of MOH					p-value
		Uterine atony	Placenta praevia	Obstetric trauma	Placenta accreta spectrum≠	Other causes^	Unspecified cause

Patient cohort, n	249	56	51	48	24	22	48	
RBC units								0.06
5	48 (19%)	19 (34%)	4 (8%)	11 (23%)	4 (17%)	2 (9%)	8 (17%)	
6-9	136 (55%)	29 (52%)	30 (59%)	24 (50%)	13 (54%)	13 (59%)	27 (56%)	
≥10	65 (26%)	8 (14%)	17 (33%)	13 (27%)	7 (29%)	7 (32%)	13 (27%)	
Median [IQR]	7 [6-10]	6 [5-8]	7 [6-10]	6.5 [6-10]	7 [6-10]	8 [6-10]	7 [6-10]	0.09
Platelet units								0.4
not given	84 (34%)	21 (37%)	13 (25%)	15 (31%)	12 (50%)	5 (23%)	18 (38%)	
1-2	146 (59%)	34 (61%)	32 (63%)	32 (67%)	10 (42%)	12 (54%)	26 (54%)	
3-8	19 (8%)	1 (2%)	6 (12%)	1 (2%)	2 (8%)	5 (23%)	4 (8%)	
Median [IQR]	1 [0-2]	1 [0-1]	1 [0-2]	1 [0-1]	0.5 [0-2]	1 [1-2]	1 [0-1]	0.3
FFP units								0.9
not given	29 (12%)	6 (11%)	4 (8%)	8 (17%)	4 (17%)	3 (14%)	4 (8%)	
1-5	136 (54%)	35 (63%)	26 (51%)	26 (54%)	12 (50%)	11 (50%)	26 (54%)	
≥6	84 (34%)	15 (27%)	21 (41%)	14 (29%)	8 (33%)	8 (36%)	18 (38%)	
Median [IQR]	4 [2-6]	4 [2-6]	4 [3-6]	4 [2-7]	4 [2-6.5]	4 [3-6]	4 [2-6]	0.6
Cryoprecipitate units								0.6
not given	107 (43%)	29 (52%)	20 (39%)	19 (40%)	11 (46%)	9 (41%)	19 (40%)	
1-5	37 (15%)	6 (11%)	12 (23%)	12 (25%)	0 (0%)	2 (9%)	5 (10%)	
6-10	75 (30%)	15 (26%)	16 (32%)	14 (29%)	7 (29%)	7 (32%)	16 (33%)	
>10	30 (12%)	6 (11%)	3 (6%)	3 (6%)	6 (25%)	4 (18%)	8 (17%)	

Median [IQR]	4 [0-9]	0 [0-10]	4 [0-6]	4 [0-6.5]	6 [0-10.5]	5.5 [0-9]	5.5 [0-8.5]	0.8
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* data are shown as n (% of in-group total) unless otherwise indicated

≠Placenta accreta spectrum includes placenta accrete, placenta increta and placenta percreta (Cahill et al, 2018)

^ Other possible causes included uterine rupture and other placenta causes such as retained placenta and premature placental separation.

Table III. Transfusion management in MOH cases with abnormal haemostatic parameters at MT commencement or during the 24 h following

Factor	Haemostatic parameter, by first test specimen and most abnormal in 24 h following MT commencement							
	Fibrinogen level		Platelet count		APTT		INR	
	<2 g/L		<50 x 10 ⁹ /L		>57 sec		>1.5	
	Starting	24-h nadir	Starting	24-h nadir	Starting	24-h highest	Starting	24-h highest
Patients with test results available, n	207	211	229	230	222	225	172	173
Patients with abnormal results, n (%)*	83 (40%)	109 (52%)	12 (5%)	37 (16%)	19 (9%)	29 (13%)	22 (13%)	31 (18%)
Patients with abnormal test results	59 (71%)	81 (74%)	10 (83%)	32 (86%)	18 (95%)	27 (93%)	21 (95%)	30 (97%)

and transfused [#] , n (% abnormal group)								
Time to appropriate blood product, h;	1.2	1.7	0.0	1.2	0.7	0.2	0.6	0.2
median [IQR]	[0.5 - 2.5]	[0.8 - 2.9]	[0 - 0.9]	[0.1 - 1.5]	[0.2 - 1.5]	[0 - 1.4]	[0.1 - 1.5]	[0 - 1.4]

* % values are relative to the corresponding 'Patient with test results available' data

[#] 'transfused' means patient given appropriate blood product to treat abnormal haemostatic factor

Table IV. Outcomes following MOH, by cause of bleeding categories

Outcome*	Total cohort	Cause of bleeding category					
		Uterine atony	Placenta praevia	Obstetric trauma	Placenta accreta spectrum [≠]	Other causes [^]	Unspecified cause
Patient cohort, n	249	56	51	48	24	22	48
Duration of MOH, h; median [IQR]	2.5 [1.0-13.6]	2.8 [0.8-16.7]	3.2 [1.0-13.0]	2.5 [1.0-20.5]	3.3 [1.4-15.3]	2.1 [1.1-4.8]	1.8 [0.7-10.8]

≥10 RBC units within 24 h post-MT start	78 (31%)	12 (21%)	22 (43%)	14 (29%)	8 (33%)	9 (41%)	13 (27%)
ICU admission	110 (44%)	25 (45%)	24 (47%)	21 (44%)	13 (54%)	5 (23%)	22 (46%)
ICU length of stay, h; median	24	25	21	22	22	33	32
[IQR]	[15-38]	[14-38]	[11-27]	[16-32]	[16-39]	[25-81]	[22-49]
Mechanical ventilation	36 (14%)	9 (16%)	8 (16%)	5 (10%)	6 (25%)	2 (9%)	7 (15%)
Post-MOH hysterectomy	72 (29%)	9 (16%)	33 (65%)	6 (12%)	9 (38%)	5 (23%)	10 (21%)
Post-MOH hospital length of stay, h; median	143	124	163	140	143	169	118
[IQR]	[96-190]	[90-181]	[127-200]	[111-177]	[100-228]	[79-202]	[76-175]

* data are shown as n (% of in-group total) unless otherwise indicated

≠Placenta accreta spectrum includes placenta accrete, placenta increta and placenta percreta (Cahill et al, 2018)

^ Other possible causes included uterine rupture and other placenta causes such as retained placenta and premature placental separation.

Table V. Multivariate regression of factors associated with hysterectomy due to MOH

Factor	Hysterectomy		OR	95% CI	P value
	No n (%)	Yes n (%)			
MOH cases, n (% of total n, 249)	177 (71%)	72 (29%)			
Mode of delivery					
Vaginal	102 (58%)	13 (18%)	1 (ref)	-	-
Elective caesarean section	27 (15%)	20 (28%)	2.0	0.7-5.4	0.19
Emergency caesarean section	48 (27%)	39 (54%)	4.9	2.0-11.7	<0.001
Cause of MOH					
Obstetric trauma	42 (24%)	6 (8%)	1 (ref)	-	-
Placenta praevia	18 (10%)	33 (46%)	7.2	2.0-26.4	0.003
Placenta accreta spectrum [‡]	15 (8%)	9 (12.5%)	2.2	0.6-8.7	0.26
Uterine atony	47 (27%)	9 (12.5%)	1.0	0.3-3.4	0.99
Other causes [^]	17 (10%)	5 (7%)	0.9	0.2-4.1	0.90
Unspecified	38 (21%)	10 (14%)	1.7	0.5-6.1	0.40
Number of RBC units before first cryoprecipitate unit					
Cryoprecipitate not given	90 (51%)	24 (34%)	1 (ref)	-	-
≤5 RBCs before first cryoprecipitate	38 (21%)	6 (8%)	0.4	0.1-1.1	0.08
≥6 RBCs before first cryoprecipitate	49 (28%)	42 (58%)	3.5	1.7-7.2	0.001

[‡]Placenta accreta spectrum includes placenta accrete, placenta increta and placenta percreta (Cahill et al, 2018)

[^] Other possible causes included uterine rupture and other placenta causes such as retained placenta and premature placental separation.

Table VI. Multivariate regression of factors associated with ICU admission due to MOH

Factor	ICU admission	OR	95% CI	P value
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	No n (%)	Yes n (%)			
MOH cases, n (% of total n, 249)	139 (56%)	110 (44%)			
Starting INR value after MT commenced					
INR result not available	32 (23%)	31 (28%)	1 (ref)	-	-
≤1	35 (25%)	8 (7%)	0.3	0.1-0.7	0.006
>1 to ≤1.3	53 (38%)	41 (38%)	0.8	0.4-1.6	0.5
>1.3	19 (14%)	30 (27%)	1.2	0.5-2.8	0.6
Number of RBC units before first cryoprecipitate unit					
Cryoprecipitate not given	78 (56%)	36 (33%)	1 (ref)	-	-
≤5 RBCs before first cryoprecipitate	23 (17%)	21 (19%)	1.3	0.6-3.2	0.5
≥6 RBCs before first cryoprecipitate	38 (27%)	53 (48%)	2.5	1.3–5.0	0.007
Number of RBC units before first FFP unit					
FFP not given	35 (25%)	30 (27%)	1 (ref)	-	-
≤5 RBCs before first FFP	69 (50%)	57 (52%)	0.4	0.2–1.0	0.05
≥6 RBCs before first FFP	35 (25%)	23 (21%)	0.2	0.1-0.6	0.002
Number of RBC units before first platelet unit					
Platelets not given	67 (48%)	25 (23%)	1 (ref)	-	-
≤5 RBCs before first platelet	33 (24%)	36 (33%)	3.0	1.3–6.9	0.01
≥6 RBCs before first platelet	39 (28%)	49 (44%)	3.0	1.4-6.6	0.006

Figure Legends

Figure 1. Flow chart of massive obstetric haemorrhage (MOH) cases from the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR) dataset. MOH cases and specific cause of bleeding that resulted in massive transfusion (MT) were identified from hospital diagnostic and procedure coding data provided to the ANZ-MTR. MOH cases were from 19 hospitals – see inset box for details. *Other possible causes included uterine rupture and other placenta causes such as retained placenta and premature placental separation.

Figure 2. Box and whisker plots of haematological parameters at the closest time-point after the start of MT (white boxes) and the most abnormal values in the 24h period after massive transfusion commenced (grey boxes), by cause of massive obstetric haemorrhage. Boxes are inner quartile ranges, whiskers indicate 95% confidence intervals, horizontal lines within boxes are median values, 'x' are mean values, and points indicate outliers. *Other possible causes included uterine rupture and other placenta causes such as retained placenta and premature placental separation.

Abbreviations: APTT, activated partial thromboplastin time; INR, international normalised ratio.

Figure 1.

Figure 2.

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Author/s:

Lasica, M;Sparrow, RL;Tacey, M;Pollock, WE;Wood, EM;McQuilten, ZK

Title:

Haematological features, transfusion management and outcomes of massive obstetric haemorrhage: findings from the Australian and New Zealand Massive Transfusion Registry

Date:

2020-02-16

Citation:

Lasica, M., Sparrow, R. L., Tacey, M., Pollock, W. E., Wood, E. M. & McQuilten, Z. K. (2020). Haematological features, transfusion management and outcomes of massive obstetric haemorrhage: findings from the Australian and New Zealand Massive Transfusion Registry. BRITISH JOURNAL OF HAEMATOLOGY, 190 (4), pp.618-628. <https://doi.org/10.1111/bjh.16524>.

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