

**TITLE**

**THE EFFICACY OF FIBRINOGEN CONCENTRATE COMPARED TO CRYOPRECIPITATE IN  
MAJOR OBSTETRIC HAEMORRHAGE – AN OBSERVATIONAL STUDY.**

**AUTHORS**

S. Ahmed<sup>1</sup>, C. Harrity<sup>1</sup>, S. Johnson<sup>1</sup>, S. Varadkar<sup>2</sup>, S. McMorrow<sup>2</sup>, R. Fanning<sup>3</sup>, C. M. Flynn<sup>2</sup>, J.M. O’Riordan<sup>4</sup>, B.M. Byrne<sup>1</sup>.

Department of Obstetrics and Gynaecology<sup>1</sup>,

Haematology and Transfusion Medicine<sup>2</sup>

and Perioperative Medicine<sup>3</sup>,

Coombe Women and Infants University Hospital, Dublin, Ireland.

Irish Blood Transfusion Service, National Blood Centre, Dublin 8, Ireland<sup>4</sup>.

CORRESPONDING AUTHOR

Dr. Bridgette Byrne MD FRCPI FRCOG,

Consultant Senior Lecturer,

Department of Obstetrics and Gynaecology,

Coombe Women and Infants University Hospital,

Dublin 8,

Ireland.

Telephone: 00353-1-4085200

E-mail: [bbyrne@coombe.ie](mailto:bbyrne@coombe.ie)

RUNNING TITLE: Fibrinogen concentrate in major obstetric haemorrhage.

## ABSTRACT

### Background

Fibrinogen replacement is critical in major obstetric haemorrhage (MOH). Purified, pasteurized fibrinogen concentrate appears to have benefit over cryoprecipitate in ease of administration and safety but is unlicensed in pregnancy. In July 2009 the Irish Blood Transfusion Service replaced cryoprecipitate with fibrinogen.

### Objectives

To examine the impact of this externally imposed change on blood product use and clinical outcomes in MOH.

### Methods

Women with MOH requiring fibrinogen between January 1<sup>st</sup> 2009 and June 30<sup>th</sup> 2011 were identified from an MOH database. Aetiology of MOH, medical treatments, blood product use and clinical outcomes were compared between the cryoprecipitate and fibrinogen groups.

### Results

77 cases of MOH were identified out of 21,614 deliveries. 34/77 (44%) received cryoprecipitate (n=14) or fibrinogen concentrate (n=20). The mean ( $\pm$ SEM) dose utilised was  $2.21 \pm 0.35$  pools of cryoprecipitate and  $4 \pm 0.8$  grams of fibrinogen. There was a stronger correlation between the increase in fibrinogen level and dose of fibrinogen (Pearson co-efficient 0.5; p=0.03) than dose of cryoprecipitate (Pearson co-efficient 0.32; p=0.3). Mean ( $\pm$ SEM) **estimated blood loss (EBL), red cell concentrate (RCC)** and

Octaplast transfused was greater (but not significantly) in the cryoprecipitate group; **EBL = 5.2 ± 1.1 > 3.3 ± 0.5 L (p=0.1)**; **RCC = 7.2 ± 1.2 > 5.9 ± 1.0 Units (p=0.4)**; **Octaplas = 4.1 ± 0.7 > 3.2 ± 0.7 Units (p=0.36) respectively**. Haemostasis was secured and there were no adverse reactions or thrombotic complications.

#### Conclusion

Purified virally inactivated fibrinogen concentrate is as efficacious as cryoprecipitate in correcting hypofibrinogenemia in MOH.

KEY WORDS: Fibrinogen; obstetric; haemorrhage.

#### INTRODUCTION

Obstetric Haemorrhage is a leading cause of maternal mortality worldwide predominantly affecting resource poor countries (Hogan *et al.*, 2010) but remains a major cause of severe maternal morbidity in resource rich countries with preventable deaths still occurring (Lynch *et al.*, 2008; Knight *et al.*, 2009; CEMACE 2011). Management is multidisciplinary, requiring early diagnosis, early identification of the underlying aetiology and rapid intervention in terms of resuscitation and medical and surgical treatment (Johnson *et al.*, 2010). Early replacement of blood volume and blood components is critical to successful resuscitation when major obstetric haemorrhage (MOH) occurs. Traditionally, crystalloid or colloid is administered to replace circulating volume followed by red cell concentrate (RCC), fresh frozen plasma (FFP) and cryoprecipitate. Fibrinogen is a 340kDa plasma glycoprotein

synthesized in the liver. It is a critical factor involved in both primary and secondary haemostasis, playing an important role in platelet aggregation and the establishment of a fibrin network. When bleeding occurs, a platelet plug is formed, thrombin is generated on the platelet surface and cleaves fibrinogen which polymerizes to form fibrin strands which provide the structural network required for effective clot formation. When MOH occurs, hypofibrinogenaemia can be dilutional or consumptive and its onset can be rapid and profound when compared to surgical or trauma related coagulopathy. It is particularly severe in placental abruption, amniotic fluid embolism, retained fetus following intrauterine death and acute fatty liver of pregnancy (McClintock and James 2011).

Fibrinogen has traditionally been replaced using FFP/ Octaplas (Octapharma limited, 6 Elm Court, Coventry UK) or cryoprecipitate. A purified, pasteurized fibrinogen concentrate derived from pooled human plasma has become available. Cryoprecipitate, in comparison, is a diverse product, prepared by the controlled thawing of frozen plasma from a pool of donors to precipitate high molecular weight proteins. It contains Factor VIII, Von Willebrand Factor, Fibronectin, Factor XIII, immunoglobulins (IgM and IgG), albumin and platelet micro-particles in addition to fibrinogen (Callumet *al.*, 2009). Fibrinogen concentrate appears to have some advantage over cryoprecipitate in terms of ease of administration and safety. It offers standardized fibrinogen content in smaller volumes, faster reconstitution and, unlike cryoprecipitate, does not require thawing or ABO compatibility. The pasteurisation and purification process employed in the preparation reduces the risk of pathogen transmission and immune-mediated complications, and the cost of both products is comparable (Fenger-Eriksen *et al.*, 2008; Sorenson and Bevan 2010)

Human fibrinogen concentrate is well established for decades for substitution therapy in hypofibrinogenemic, dysfibrinogenemic and afibrinogenemic states (Fenger-Eriksen *et al.*, 2008). Although there are recent data addressing the efficacy of fibrinogen concentrate in the treatment of low plasma fibrinogen in major haemorrhage (Fenger-Eriksen *et al.*, 2008; Sorensen and Bevan 2010) it is not licensed for use in pregnancy and the data supporting its efficacy in the treatment of obstetric haemorrhage is limited to small case series (Fenger-Eriksen *et al.*, 2008; Weinkove and Ranjarajan 2008; Bell *et al.*, 2010). This area warrants further study since rapid consumption of fibrinogen is recognised in MOH, target fibrinogen levels for control of haemostasis are higher in pregnant than non-pregnant patients (Charbitet *et al.*, 2007) and early and rapid replacement of fibrinogen (using a concentrated product) may have benefits over cryoprecipitate in the bleeding parturient.

In July 2009, the Irish Blood Transfusion Service (IBTS) withdrew cryoprecipitate made from recovered plasma from Irish donors and replaced it with a purified pasteurized fibrinogen concentrate (Haemocomplettan P<sup>TM</sup>. Aventis Hering GmbH, Marburg, Germany) derived from pooled human plasma of US origin. CSL Behring changed the proprietary name of their fibrinogen concentrate from Haemocomplettan P to Riastap with the licence acquisition in 2010 in Ireland (as well as the UK and the USA) for the treatment of patients with congenital hypo, or afibrinogenaemia with a bleeding tendency. The IBTS's rationale was to lower the potential risk of pathogen transmission, especially variant Creutzfeldt Jacob Disease (vCJD), and was supported, in the limited amount of published evidence, by the absence of any documented benefit of cryoprecipitate over fibrinogen concentrate in the management of acquired hypofibrinogenaemia and haemorrhage. In our study we aimed to assess the

impact that this externally imposed change in the product used to replace fibrinogen would have on blood product utilisation and clinical outcome of MOH in our unit.

## MATERIALS AND METHODS

Detailed prospective audit of MOH began at our institution in January 2009. A multi-disciplinary team of obstetricians (SA, SJ, BB), an anaesthetist (RF), Haematologist (CF), Haemovigilance officer (SV) and a midwife (JF) agreed the proforma and method of data collection. The team reviews the case details and chart usually within a week of the event and the proforma is completed and data entered into the database. MOH was defined as either an **estimated blood loss** (EBL) of 2.5 litres or more, transfusion of five or more units of RCC, or treatment of a coagulopathy in the acute event (Brace *et al.*, 2007). Patients who required treatment with either cryoprecipitate or fibrinogen concentrate between January 1<sup>st</sup> 2009 and June 30th 2011 were identified from the database retrospectively. All of these patients had a fibrinogen level less than 2gm/L, the cut-off below which fibrinogen replacement is recommended (Charbitet *al.*, 2007; Bell *et al.*, 2010). **Cryoprecipitate had been supplied by the IBTS in pools of 5 donor units with a minimum fibrinogen content of >700mg/pool and a mean fibrinogen content of 1470 ( $\pm$  263, range 727 to 2182) mg/ pool (IBTS quality control data for manufacture of cryoprecipitate 2008/2009, personal communication J.O'Riordan).** It was withdrawn by the IBTS in July 2009 but patients continued to receive it until stocks were depleted. Fibrinogen concentrate was first used in November 2009. One patient received both products and was excluded from the study. Patient demographics, cause of haemorrhage, medical and surgical management, EBL, transfusion of RCC, Octaplas and platelets, clinical outcomes and adverse reactions were

recorded. Plasma fibrinogen levels were quantified using the Clauss method. **The minimum fibrinogen level before treatment was subtracted from the fibrinogen level post treatment to calculate the change in fibrinogen level.**Data was compared between those that received cryoprecipitate and those that received fibrinogen concentrate. Data from MOH proformas is stored electronically in a Microsoft Excel spreadsheet on a secure university server. The MOH audit is approved by the hospital Research and Ethics Committee. Statistical analysis was performed using SPSS Inc. Chicago, IL, USA version 18.0. Normality testing was employed, and normally distributed data was analysed using independent samples t-tests to compare mean values, with a Mann-Whitney U being applied to non-parametric data. Categorical variables were compared using Chi Square, or Fisher's exact test if  $df < 2$  and any expected counts  $< 5$ . Correlations were assessed using Pearson's coefficient. Statistical significance was considered at a level of  $p < 0.05$ .

Uterine atony was defined as failure of the uterus to contract following delivery of the placenta. Placenta accreta was defined as a placenta that has pathologically invaded the myometrium such that separation requires surgical intervention. Retained placental tissue was defined as a portion of, or the entire placenta, remaining in the uterus after delivery necessitating either manual removal of placenta (MROP) or evacuation of the uterus (ERPC) under anaesthesia. MOH is managed using the hospital MOH guideline (CWIUH 2010).

## RESULTS

21,614 women delivered a baby weighing 500 grams or more during the two and a half year period of the study. 77 cases of MOH were identified yielding an incidence of 3.6/1000.

**Approximately, half of these women (34/77) received treatment for hypofibrinogenaemia. 14 had cryoprecipitate and 20 had fibrinogen concentrate.** There was no significant difference between the two groups in age, parity, ethnicity, BMI, gestation at delivery and fetal birth weight (Table 1). Women in the cryoprecipitate group **(6/14)** were more likely to have a previous caesarean section compared to women in the fibrinogen group **(2/20); p= 0.04. (Table 1).** One patient in the fibrinogen group delivered triplets. The main causative factor for MOH in the two groups is shown in Table 2. However, some patients had multiple causative factors and these are shown in Table 3. The predominant cause of haemorrhage was uterine atony. One woman with three previous caesarean sections had failed medical management of a missed first trimester miscarriage and had MOH at the time of surgical evacuation of the uterus. There were four intrauterine deaths (three placental abruptions and one uterine rupture) and three stillbirths (two following placental abruption and one as a result of severe intrauterine growth restriction as a complication of pre-eclampsia).

**The mean EBL was greater in the cryoprecipitate group compared to the fibrinogen group  $5.2 \pm 1.1$  SEM L versus  $3.3 \pm 0.5$  SEM L but this was not statistically significant ( $p= 0.10$ ). The number of units of RCC and Octaplas used was greater in the cryoprecipitate group  $7.2 \pm 1.2$  SEM Units versus  $5.9 \pm 1.0$  SEM Units, and  $4.1 \pm 0.7$  SEM Units and  $3.2 \pm 0.7$  SEM Units, but this difference was not statistically significant ( $p=0.40$  and  $p=0.36$  respectively). The use of platelets was similar in both groups (Table 4).**

Hypofibrinogenaemia was corrected with the use of both products. The mean dose of cryoprecipitate and fibrinogen used was  **$2.2 \pm 0.35$  SEM pools and  $4 \pm 0.8$  SEM grams respectively.** **The mean minimum fibrinogen recorded was  $1.04 \pm 0.13$  g L<sup>-1</sup> SEM in the cryoprecipitate group compared to  $1.23 \pm 0.18$  g L<sup>-1</sup> SEM in the fibrinogen group ( $p = 0.42$ )**

and the mean levels following treatment were  $3.05 \pm 0.19 \text{ g L}^{-1} \text{ SEM}$  and  $3.34 \pm 0.22 \text{ g L}^{-1} \text{ SEM}$  respectively ( $p=0.35$ ) [Table 4]. Although the increase in fibrinogen level achieved with treatment was identical in both groups ( $2.01 \pm 0.19 \text{ g L}^{-1} \text{ SEM}$  versus  $2.11 \pm 0.26 \text{ g L}^{-1} \text{ SEM}$ ;  $p=0.8$ ), the correlation between the increase in fibrinogen level and dose administered was stronger for fibrinogen (Pearson co-efficient 0.5;  $p=0.03$ ) than for cryoprecipitate (Pearson co-efficient 0.32;  $p=0.3$ ) [Figure 1]. Medical and surgical treatments are shown in Figure 2 and are similar in both groups. **Seven intra-uterine hydrostatic balloons were employed in each group and there were three hysterectomies in the cryoprecipitate group and two in the fibrinogen group.** Internal iliac artery ligation was used to arrest bleeding in two of the women in the cryoprecipitate group and recombinant Factor VII was used in one other woman in the cryoprecipitate group.

Bleeding was arrested in all cases and there was no maternal death. One patient in the fibrinogen group was transferred to intensive care as she continued to require ventilation following transfusion of 12 units of RCC and hysterectomy for placenta accreta. All other patients were nursed in the obstetric high dependency unit following the event for a mean duration of  $34.1 \pm 4.3 \text{ SEM hours}$  in the cryoprecipitate group and  $33.6 \pm 5.4 \text{ SEM hours}$  in the fibrinogen group. **The haemoglobin one to three days post the event was  $8.55 \pm 0.49 \text{ SEM g dL}^{-1}$  in the cryoprecipitate group and  $8.79 \pm 0.20 \text{ SEM g dL}^{-1}$  in the fibrinogen group;  $p = 0.46$ .** There was no adverse reaction to RCC, cryoprecipitate or fibrinogen and there were no thrombotic complications recorded up to hospital discharge. **The mean duration of hospital stay was  $5.2 \pm 0.3 \text{ SEM days}$  in the cryoprecipitate group and  $6.5 \pm 0.8 \text{ SEM days}$  in the fibrinogen group;  $p=0.2$  (Table 4).**

Figure 1: The correlation between dose of cryoprecipitate (pools) and fibrinogen (grams) and plasma fibrinogen level change (Post – pre fibrinogen level  $gL^{-1}$ ).

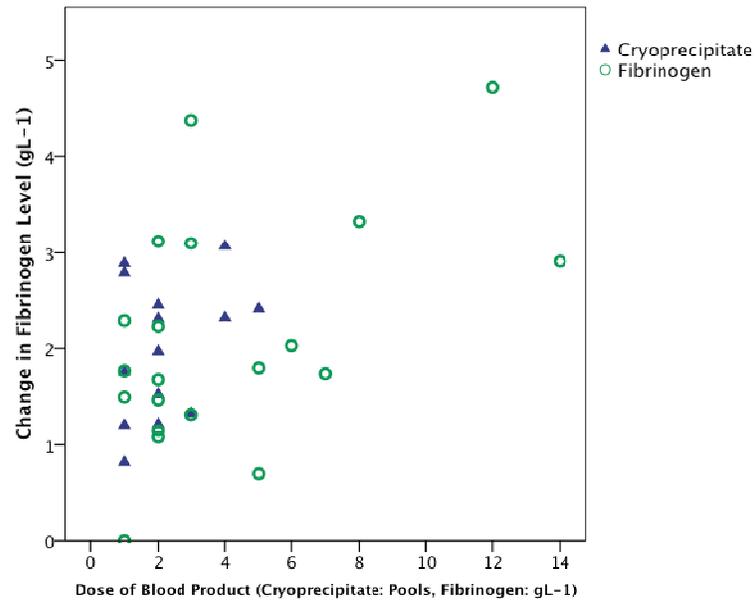
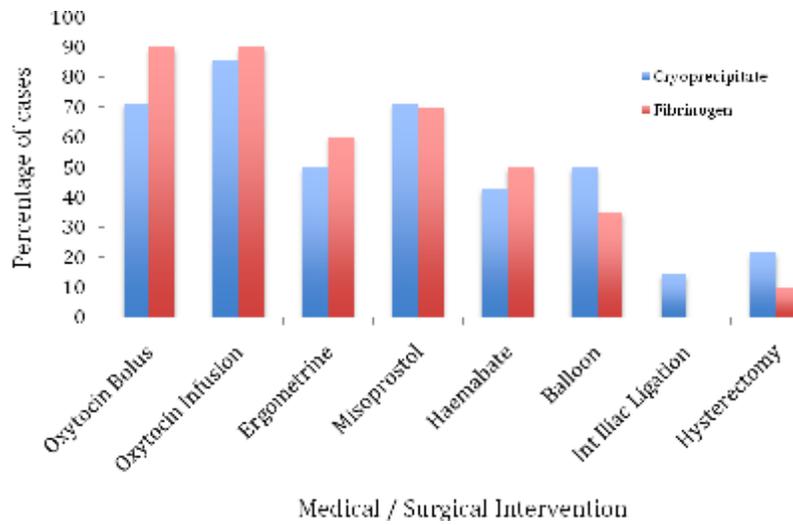


Figure 2: Medical and surgical interventions



## DISCUSSION

The pregnant woman is physiologically adapted to cope with potential haemorrhage through a combination of blood volume expansion, increased circulating clotting factors and suppressed fibrinolysis (McClintock and James 2011). MOH can be sudden and catastrophic and requires a co-ordinated multidisciplinary response with appropriate resuscitative measures in association with medical and surgical therapy. Clotting factors and particularly fibrinogen can be consumed rapidly and particularly in the setting of placental abruption or amniotic fluid embolism. The associated DIC activates coagulation and triggers fibrinolysis. D-dimers and fibrin degradation products are increased and may further aggravate obstetric haemorrhage by impairing myometrial contractility (Sher 1977). Traditionally, fibrinogen replacement is recommended when fibrinogen levels fall below  $1\text{gL}^{-1}$  in the context of bleeding or disseminated intravascular coagulation (O'Shaughnessy *et al.*, 2004) but recent evidence suggests that the threshold for fibrinogen replacement should be **higher** in some groups. A recent European multidisciplinary task force for advanced bleeding care in trauma recommended replacement if the fibrinogen level was  $< 1.5 - 2\text{ gL}^{-1}$  (Rossaint *et al.*, 2010). Fibrinogen levels increase in pregnancy such that they are 2 to 4-fold higher than in the non-pregnant woman at term (Kratz and Lewandrowski 1998) and recent work suggests that the threshold for fibrinogen replacement in the bleeding parturient should be  $2\text{ gL}^{-1}$  as fibrinogen concentrations below this level are highly correlated with a risk of severe postpartum haemorrhage (Charbitet *et al.*, 2007). Traditionally FFP and cryoprecipitate have been used to replenish fibrinogen but both are administered in significant volumes with a litre of FFP or 260mls of cryoprecipitate required to increase plasma fibrinogen

concentration by  $1 \text{ gL}^{-1}$  (Stainsby *et al.*, 2006). Fibrinogen concentrate provides rapid replacement in low volumes with limited evidence suggesting that 3 grams of fibrinogen concentrate increases the plasma fibrinogen by  $1 \text{ gL}^{-1}$ . It has been used successfully in pregnancy in women with acquired hypofibrinogenaemia in case reports and retrospective series and data in approximately 28 cases of obstetric haemorrhage are encouraging (Fenger-Eriksen *et al.*, 2008; Weinkove and Ranjarajan 2008; Bell *et al.*, 2010).

Over the 30 months of this study, the incidence of MOH was 3.6 per 1000 deliveries, a figure that is equivalent to the rate reported in Scotland using the same definition (Brace *et al.*, 2007). Secondary hypofibrinogenaemia necessitating fibrinogen replacement complicated approximately half of these cases. External factors, namely, a change in the policy of the IBTS, and not clinical grounds, determined the use of either cryoprecipitate or fibrinogen concentrate. The decision to supply fibrinogen to the hospitals in the form of fibrinogen concentrate was made on the basis of safety, particularly the potential for transfusion acquired vCJD from cryoprecipitate made from Irish donor plasma. The source plasma for fibrinogen concentrate used from a country with a low exposure to BSE such as the United States must substantially reduce any risk. In addition the manufacturing process for fibrinogen concentrate has the ability to remove or reduce abnormal prion protein (Foster 1999; Foster *et al.*, 2000). A further safety advantage over cryoprecipitate is the viral inactivation of the fibrinogen concentrate by pasteurization. Less immune mediated complications have also been reported (Fenger-Eriksen *et al.*, 2008; Sorensen and Bevan 2010). When compared to cryoprecipitate and FFP, freeze-dried fibrinogen concentrate offers rapid restoration of fibrinogen levels with a smaller volume of infusion and minimal preparation time. In fact when all costs associated with administration are taken into

consideration, the cost of fibrinogen concentrate is not substantially different to that of cryoprecipitate (Sorensen and Bevan 2010).

In this study both products as evidenced by the fibrinogen levels documented following treatment corrected hypofibrinogenemia efficiently. Guidelines for use of these products is based on expert opinion and advise that 1 unit of cryoprecipitate per 7-10 kgs body weight increases the plasma fibrinogen by  $0.5 \text{ gL}^{-1}$  (Rossaint *et al.*, 2006) and 3 grams of fibrinogen concentrate will increase the plasma level by  $1 \text{ gL}^{-1}$  (Levi 2009). The correlation between the dose of fibrinogen concentrate administered and the increase achieved in plasma fibrinogen level was stronger than for cryoprecipitate in our study. EBL, and transfusion with RCC and Octaplas was less in the group treated with fibrinogen concentrate but this difference did not reach statistical significance and the study numbers are small. This would be consistent with recent data emphasising the importance of fibrinogen alone in haemostasis and there is some evidence in trauma medicine that higher fibrinogen to RCC ratio can improve survival (Stinger *et al.*, 2008). Fibrinogen constitutes an important component of the haemostatic process and in addition to its roles in the formation of platelet aggregates and generation of a stable fibrin network, it is also required for the optimal effect of other haemostatic interventions such as the infusion of antifibrinolytic drugs, activated factor VII, prothrombin complex concentrate and platelet transfusion (Fenger-Eriksen *et al.*, 2008). It appears to be the coagulation factor first reaching a critically low threshold in major haemorrhage, particularly when intravenous fluids and plasma poor red cells are used (Hiippala *et al.*, 1995). Hence, it seems reasonable to expect an overall beneficial haemostatic effect with less use of other blood products when it is replaced in sufficient and adequately monitored amounts as is the case with fibrinogen concentrate. Fibrinogen

replacement, however, is only part of the management of these complex cases that require early diagnosis, resuscitation, medical and surgical intervention (Johnson *et al.*, 2010).

The two groups in this study were comparable in age, parity and gestation at delivery. The predominant cause of MOH was uterine atony and the medical treatments employed were similar in both groups. There were, coincidentally, an equal number of hydrostatic balloons used and **a similar incidence of hysterectomy** performed in both women who received cryoprecipitate and fibrinogen. It is therefore, unlikely that differences in aetiology, medical or surgical treatment contributed significantly to the results.

We have shown that a purified virally inactivated fibrinogen concentrate is as efficacious as cryoprecipitate in correcting hypofibrinogenemia in MOH. There was no adverse outcome associated with its use. Haemostasis was secured in all cases and there were no thrombotic complications. Evidence from an animal model and a review of clinical studies indicates that the thrombogenic potential of fibrinogen concentrate is low (Dickneiteet *al.*, 2009). The study numbers are small but the trend of less blood loss and less blood product utilisation in the fibrinogen group merits further evaluation. This paper contributes to the evidence that fibrinogen concentrate has a valuable role in the clinical management of major obstetric haemorrhage.

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and performed the research. C. Harrity performed the statistical analysis on the data. C. M. Flynn (Consultant haematologist) and R. Fanning (Consultant anaesthetist) reviewed the data and assisted in writing the paper. J.M. O' Riordan is a Consultant haematologist in the Irish National Blood Transfusion Service who critically reviewed the paper and advised on the content and conclusions. B. M. Byrne (Consultant Obstetrician and Senior Lecturer) was the lead author who designed the project, analysed and reviewed the primary data and had major contribution to the writing of the paper.

**CONFLICT OF INTEREST:** The authors have no competing interests.

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