

Special article

# Fibrinogen concentrate as a treatment for postpartum haemorrhage-induced coagulopathy: A study protocol for a randomised multicentre controlled trial. The fibrinogen in haemorrhage of DELivery (FIDEL) trial

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## ARTICLE INFO

Article history:  
Available online xxx

Keywords:  
Postpartum haemorrhage  
Fibrinogen concentrate  
Blood transfusion

## ABSTRACT

**Background:** Postpartum haemorrhage (PPH) remains the leading cause for maternal mortality worldwide. Hypofibrinogenaemia has been identified as a major risk factor for progress towards severe PPH. The efficacy of fibrinogen concentrate supplementation in PPH has been shown in various clinical settings but the level of evidence is not sufficient to prove the benefit, evaluate the risks, and determine the value, timing and dose of fibrinogen supplementation in PPH. The FIDEL trial objective is to evaluate the impact of a therapeutic strategy based on the early administration of human fibrinogen concentrate compared to the current practice based on late administration in severe PPH patients requiring second line uterotonics.

**Methods/design:** This is a prospective multicentre, randomised, double-blind, placebo-controlled trial. A total of 412 patients will be randomised if they meet the following criteria: female patients  $\geq 18$  years old, vaginal delivery, PPH requiring IV administration of prostaglandins (sulprostone) after 20 to 30 minutes of oxytocin failure. The participants are assigned to receive either fibrinogen 3 g or placebo infusions. The primary endpoint is a composite endpoint defined as the percentage of patients losing at least 4 g/dL of Hb, and/or requiring a transfusion of at least 2 units of packed red blood cells, within the 48 hours following fibrinogen administration.

**Discussion:** The purpose of this study is to demonstrate the efficacy and safety of an early fibrinogen concentrate infusion in uncontrolled active PPH.

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## 1. Background

PPH remains the leading cause of maternal mortality worldwide, and the first cause of postpartum intensive care unit (ICU) admission [1]. Most of these maternal deaths occur in low-resource countries,

but the incidence of PPH is increasing in high-resource countries as well [2]. The most common causes of PPH related to vaginal delivery are uterine atony, retained placental products and genital-tract trauma. Acquired coagulopathy, especially decreases in fibrinogen that may predict and influence the severity of blood loss, is an important aggravating factor [3,4].

### 1.1. Hypofibrinogenaemia: a risk marker for severe PPH

Fibrinogen is a central substrate for clot formation. It is the main thrombin substrate leading, through fibrin monomers and their

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polymerisation, to fibrin clot formation. Fibrinogenolysis has been identified as a major component in PPH, trauma, and massive haemorrhage-induced coagulopathy [5–7]. Charbit et al. [3] demonstrated, in 128 women with PPH requiring prostaglandin administration, that plasma fibrinogen concentration at enrolment (h0) was the sole independent predictive factor for poor outcome. A plasma fibrinogen level under a 2 g/L threshold had a predictive value of 100% for progression towards severe bleeding [CI 95% 79–100]. This level was higher than the “historical” threshold of < 1 g/L, which indicated in the general population the need to initiate replacement therapy, or the 1.5 g/dL threshold identified by Grottko et al. [8] in an experimental animal setting. This higher threshold could be explained by a higher than normal plasma fibrinogen level during pregnancy and the postpartum period [9]. An analysis by Cortet et al. [10] involving 738 women with PPH clearly confirmed the importance of fibrinogen levels. The mean plasma fibrinogen concentration at diagnosis was 4.2 g/L (SD = 1.2 g/L) among patients without progression towards bleeding, and 3.4 g/L (SD = 0.9 g/L) ( $P < 0.001$ ) in the group developing severe PPH. The plasma fibrinogen level was again associated with PPH severity, independently of other factors, with an adjusted odds ratio of 1.90 (1.16–3.09) for fibrinogen levels between 2 and 3 g/L, and 11.99 (2.56–56.06) for fibrinogen levels less than 2 g/L. Several comparative trials have also shown an early fibrinogen decrease in PPH, detected by thromboelastometry [11–14].

### 1.2. Fibrinogen concentrate for supplementation in PPH

The place of fibrinogen supplementation in the management of massive haemorrhage has recently been highlighted in the literature [7–15]. The efficacy of fibrinogen concentrate supplementation in PPH has been suggested by case reports in various clinical settings [8–18]. Two recent observational studies from the UK and Japan give additional information [19,20]. The Japanese 5-year national survey collected 101 severe PPH cases who received 3 g of fibrinogen concentrate (repeated in 17 patients). The initial plasma fibrinogen level was 0.705 g/L. Final blood loss was  $4562 \pm 3198$  mL. The single dose infusion increased the plasma fibrinogen level to  $1.87 \pm 0.72$  g/L but did not reach the 1.5 g/L in two maternal deaths. The second survey by Mallaiah et al. [20] was an historical comparison of the use of a massive transfusion strategy during a first stage versus the use of an adapted dose of fibrinogen concentrate in coagulopathic PPH diagnosed by point of care devices during the second stage. They demonstrated a significant reduction in the number of patients requiring more than 6 RBC and in overall blood product requirements, in maternal morbidity but not on hysterectomy rate. They also observed a trend in reducing the costs due to PPH bleeding patient management.

To date, the only prospective, double-blind, placebo-controlled, randomised study available, the FIB-PPH trial [21], has shown that the pre-emptive administration of 2 g of fibrinogen concentrate in haemorrhagic parturients did not change transfusion rates (21% compared to 22% in the placebo group). However, the population studied was mostly surgical bleeding (caesarean section and genital-tract injury) with a median estimated blood loss at inclusion of 1500 mL, but that was inconsistent with a mean haemoglobin (Hb) level remaining above 10 g/dL and no need for invasive procedures in both groups. In fact, the patients enrolled were non-severe and normofibrinogenaemic. Moreover, the delays preceding study product administration were long in both groups (119 and 95 minutes after delivery, respectively), suggesting that the bleeding was already under control.

The main objective of the present trial is to assess the early administration of 3 g of fibrinogen concentrate versus placebo in more severe and on-going PPH cases resistant to first line uterotonics.

## 2. Methods and design

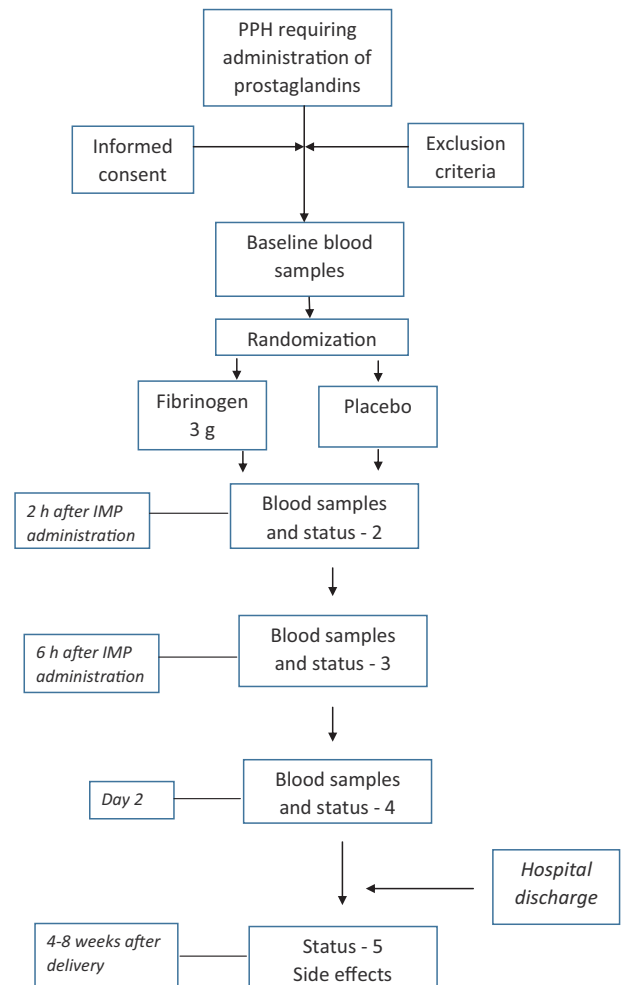
### 2.1. Overview

The FIDEL trial is a French, multicentre, randomised, double-blind, placebo-controlled trial sponsored by LFB (Laboratoires Fractionnement et Biotechnologies, Les Ulis, France). The flow chart for the trial is displayed in Fig. 1. The FIDEL protocol has been approved by the French Ethics Committee of Lille (CPP Nord-Ouest IV) and has been registered on clinicaltrials.gov (NCT02155725).

### 2.2. Inclusion criteria

The study population is composed of patients with severe PPH at risk of developing coagulopathy. The inclusion criteria are:

- signed and dated informed consent form;
- female patients 18 years of age and older;
- vaginal delivery;
- PPH requiring a second line uterotonic treatment (IV administration of sulprostone as recommended by the French guidelines);



**Fig. 1.** Flow chart. Parturients developing PPH after vaginal delivery requiring IV administration of sulprostone will be screened for inclusion and non-inclusion criteria and asked for informed consent. Baseline status and blood samples are taken before randomisation to IMP (fibrinogen concentrate 3 g) and placebo groups. Clinical status and blood samples are monitored after 2 hours and 6 hours after the intervention, as well as on day 2 and 4 to 8 weeks after delivery.

- at least one available result of Hb level during the third trimester of pregnancy.

### 2.3. Non-inclusion criteria

Participants fulfilling one or more of the following criteria will not be included:

- invasive haemostatic intervention already decided at the time of inclusion;
- known placenta praevia or accreta;
- third trimester Hb level < 10 g/dL;
- known inherited bleeding or thrombotic disorders;
- any anticoagulant or antiaggregant treatment;
- administration of:
  - fibrinogen concentrate within 48 hours prior to inclusion,
  - fresh frozen plasma (FFP), platelet units or prohaemostatic drugs, tranexamic acid and rFVIIa or prothrombin complex concentrates (PCC) within 48 hours prior to inclusion,
  - red blood cells (RBCs) within 3 months prior to inclusion.

### 2.4. Informed consent

Initial abbreviated information may be given to the patient during the last prenatal consultation if the centres prefer to anticipate this information procedure. Patients with significant blood loss may be unable to give properly informed consent. In this study, initial informed consent will be obtained from either the patient or a family member or the nominated trustworthy person, depending on the patient's level of consciousness and/or ability to consent. In all cases, when the patient regains competence after haemorrhage control, she will receive the full-required information about the study and her post-inclusion consent must be obtained to continue with study participation.

### 2.5. Treatment allocation, investigational medicinal product and associated treatments

Patients will be randomised in a 1:1 ratio to either a fibrinogen group or placebo group in a double-blind manner. The randomisation will be stratified by centre. Each treatment unit contains 2 vials of powder and 2 solvent vials of 100 mL. Treatment units are numbered and allocated in chronological order of inclusion by ascending number. The investigational medicinal product (IMP) is administered within the 30 minutes after the start of prostaglandin infusion. The dose and dose-rate of prostaglandin is chosen according to the 2004 recommendations provided by the French National Authority for Health (Haute Autorité de santé [HAS]) [22,23].

The participants are assigned to either fibrinogen (Clotfact<sup>®</sup> LFB Biomédicaments, Les Ulis, France): 3 g (2 vials of 1.5 g/100 mL) or placebo: 2 vials of 100 mL. The IMP is administered intravenously (IV) with a flow rate  $\leq$  20 mL/min during the 30 minutes following the start of prostaglandin infusion. In order to prevent unblinding, product preparation is systematically performed by a person that will not otherwise be involved in the patient's care and using a masking system and tinted tubing.

Following the administration of the IMP, therapeutic management is left to the discretion of the investigator, according to French guidelines [22]. Nonetheless, rescue fibrinogen (whatever the allocated group) can be administered only at least 60 minutes after the start of the IMP administration or if the primary outcome criterion is already attained. This procedure permits rescue fibrinogen administration even in the blinded placebo group, if

needed, without excessive delay and harm for the patient. For both groups, the administration of tranexamic acid is allowed after prostaglandin infusion depending on the centres' own routines. The recommended dose is 1 g IV to be renewed once after 30 min. Transfusion is managed according to the following objectives:

- haemoglobin  $\geq$  8 g/100 mL;
- prothrombin time (PT)  $\geq$  40%;
- platelet count  $\geq$  50,000 G/L, but it may be performed before availability of laboratory results, when indicated.

The maximum volume of hydroxyethyl starch (HES), if used, will be restricted to 1.5 L during the first 24 hours.

### 2.6. Outcomes and safety measures

The primary efficacy variable is a binary composite endpoint (failure versus success). Failure is defined when a patient loses at least 4 g/dL of Hb, and/or requires the transfusion of at least 2 units of packed RBCs within 48 hours following the administration of the IMP. The Hb reference level is defined as the last Hb value recorded within the third trimester of pregnancy.

The secondary objectives of this trial are to evaluate PPH evolution, anaemia, the need for transfusion and invasive procedures, and maternal morbi-mortality: Hb drop compared to the reference level, percentage of patients developing anaemia (Hb < 8 g/dL), the need for PRBC transfusion or any other blood products, the requirement for intrauterine balloon tamponade and/or invasive procedures (arterial ligation, or embolization, or hysterectomy), and calculated blood loss.

Maternal morbi-mortality will be evaluated at each follow-up assessment and up to  $6 \pm 2$  weeks after delivery by:

- the need for intensive care admission and length of stay in the intensive care unit;
- the need for a high dependency unit and/or post anaesthesia care units (PACU) as well as for obstetric units;
- the percentage of patients with organ failure (defined as single or multi-organ failure [SOFA score]);
- death during the study period.

Laboratory assessments will include plasma fibrinogen levels and the influence of fibrinogen concentrate supplementation on decreasing levels of plasma fibrinogen.

The tolerance of fibrinogen concentrate administration will be assessed by systematically recording serious adverse events (SAE), such as thromboembolic complications, and non-serious adverse events (AE). Thromboembolism is a known complication of severe PPH [24]. Indeed, although Chauleur et al. [25] found no evidence supporting the influence of haemostatic treatment on the occurrence of thromboembolic events in the only large epidemiologic survey published, some rare case reports underline the need for strict follow-up regarding this adverse event during interventional studies.

### 2.7. Monitoring

Demographic parameters, history of thromboembolic disease, pregnancy and delivery parameters will be registered. All the haemostatic interventions and clinical events until hospital discharge will be monitored. From the moment the informed consent is signed to the end-of-study visit ( $6 \pm 2$  weeks after delivery), SAEs and AEs will also be recorded, whether or not considered to be causally related to the IMP. Laboratory parameters will be evaluated at inclusion, h2, h6 and D2 and will include a blood count (haemoglobin, haematocrit and platelet count), plasma fibrinogen, a

haemostatic profile (prothrombin time, aPTT, D-dimers), plasma creatinine and urea at inclusion and D2.

### 2.8. Sample size determination

The sample size calculation is based on the primary endpoint. Based on unpublished data, the failure risk is expected to be 42% in the control group. Expecting a 15% absolute reduction in failure risk, that is, assuming a failure risk of 27% in the fibrinogen group, 206 patients per group are needed to achieve a 90% power considering a Z-test based on unpooled variance at the 0.05 two-sided significance level. To account for a 5% expected rate of drop-outs, 434 patients will be included in the trial.

### 2.9. Statistical methods

All statistical tests will be performed at the two-sided significance level of 0.05. Efficacy analyses will be performed in the intent-to-treat set (ITT) defined as the set of all patients “as randomised” (i.e. regardless of the received treatment). A sensitivity analysis will be performed in the per-protocol set (PP) defined as the set of patients without any major protocol deviation. Rules for excluding patients will be defined in the statistical analysis plan before breaking the code.

The primary efficacy analysis of the primary endpoint will be conducted in a logistic regression model including terms for treatment and baseline plasma fibrinogen level categorized into three classes ( $\leq 2 \text{ g}\cdot\text{L}^{-1}$ ,  $2 \text{ g}\cdot\text{L}^{-1}$ – $4 \text{ g}\cdot\text{L}^{-1}$ ,  $> 4 \text{ g}\cdot\text{L}^{-1}$ ). Missing data with regard to the primary endpoint will be estimated as failures.

Secondary efficacy analyses will be primarily performed in the ITT set and sensitivity analyses will be performed in the PP set as well. For these analyses, missing data will not be replaced. Continuous efficacy variables will be analysed in an Analysis of Covariance Model and binary variables in a logistic regression model.

Analyses of safety endpoints will be conducted in the safety set, i.e. patients considered “as treated” and receiving at least one dose of IMP. AEs and SAEs will be tabulated by treatment group, system organ class and preferred term.

## 3. Discussion

FIDEL is the second randomised double-blind clinical trial evaluating the efficacy of fibrinogen concentrate in patients with PPH. The previous FIB-PPH trial failed to show a difference between placebo and fibrinogen in terms of transfusion rate in non-coagulopathic patients [20]. In this trial, patients were recruited in case of blood loss due to manual removal of placenta ( $\geq 500 \text{ mL}$ ), manual exploration of the uterus after the birth of placenta ( $\geq 1000 \text{ mL}$ ), or C-section (perioperative blood loss  $\geq 1000 \text{ mL}$ ). Patients were randomised to receive a single fixed dose of 2 g fibrinogen or placebo systematically, i.e. independently of the laboratory or the point of care plasma fibrinogen level. The primary endpoint was the impact of this fixed dose of 2 g fibrinogen concentrate on the transfusion rate.

The authors rightly underlined certain limitations:

- obtaining informed consent in severe PPH emergency situations was difficult, hence the study population was mostly non-severe PPH patients with a plasma fibrinogen level assessed at inclusion. The study design did not anticipate this non-severe recruitment selection;
- the primary endpoint was the maternal transfusion rate, and the decision to transfuse was based on national ESA Guidelines; however, it has been reported that delay and reticence for PRBC transfusion can occur [26];

- finally, the transfusion rate in the FIB-PPH trial, in both treated and untreated groups, was lower than initially expected due to the low severity of the study population, erasing any differences between groups. Consequently, despite the pioneer character of the FIB-PPH trial, the scientific question about the efficacy, safety, timing and dose of fibrinogen concentrate in on-going severe PPH with hypofibrinogenaemia has not yet been answered. Further randomised trials with designs avoiding these FIB-PPH downsides are therefore needed and hopefully the FIDEL trial will fulfil this objective.

Regarding the population selection, evidence has shown that fibrinogen supplementation may be more efficacious in patients with hypofibrinogenaemia. The study population may therefore be better selected among patients with quite severe PPH at risk of developing coagulopathy. To target this population, the scientific committee of the FIDEL trial analysed various patient identification opportunities that might benefit from fibrinogen supplementation. The final decision was to recruit patients at the beginning of prostaglandin (sulprostone – Nalador<sup>®</sup>) administration (h0), which is a time-validated second step of uterotonic treatment in the algorithm of French PPH management guidelines that is followed by all recruiting centres. Prostaglandins are advocated after no more than 30 minutes of on-going PPH and oxytocin failure. This inclusion criterion has been used previously [4]. Randomisation stratification by centres should protect against the bias of variable team reactivity times in taking the decision for oxytocin-prostaglandins switch. Other criteria for patient enrolment could have been taken into consideration. The measurement of blood volume loss is often started too late, and information is sometimes lost or may be imprecise in the presence of amniotic fluid or antiseptics. The measurement of plasma fibrinogen levels should be the best way to select hypofibrinogenaemic patients. However, sampling and laboratory measurements require time during which coagulopathy may worsen. As demonstrated by Huissoud et al. [11] and Collins et al. [13], early point of care (POC) diagnosis was thought to be a valuable solution for the rapid evaluation of plasma fibrinogen levels, but not all the centres are equipped with POC devices. Moreover, even if these techniques were to become more popular in the future and seem helpful in an observational study [20], the reference and haemorrhagic values, as well as inter-centre variations are still in an evaluation phase and waiting verification with the on-going OBS2 trial [26]. Thus, the thromboelastometric method was not chosen in the FIDEL protocol in order to be closer to the real world practice in French maternities.

The primary criteria elaboration had been thoroughly discussed:

- to choose the transfusion rate alone raises the risk of over-evaluation due to an excessive transfusion policy or, a contrario, under-evaluation;
- the volume of bleeding requires strict measures of blood loss in delivery bags that is unrealistic in most centres. In addition, it has been shown that this method is often unreliable and underestimates the actual volume of blood loss [27];
- considering haemoglobin drop criteria alone raises the risk of over-evaluation in cases of haemodilution or haemolysis or under-evaluation in cases of haemoconcentration or transfusion. To avoid these misvaluation risks, the scientific committee used a composite criteria taking into account the transfusion rate of at least 2 RBP or a haemoglobin drop of more than 4 g/dL from the end of pregnancy to postpartum day 2 (D2) when normovolaemia is recovered.

Regarding the fibrinogen concentrate dosage to be administered according to the current Clottafact<sup>®</sup> Summary of Product

Characteristics (SPC) [28], the fibrinogen dose depends on the haemorrhage severity as well as on the patient's clinical condition: "an initial dose of 2 g is usually administered in trauma or cardiovascular settings and could possibly be repeated if needed [29]. In case of severe acute obstetrical haemorrhage, larger doses of fibrinogen concentrate (4 to 8 g) may be necessary". In a study by Kikuchi et al. [18], 1 g of fibrinogen concentrate increased the plasma fibrinogen level to approximately 400 mg/L only. Fenger-Eriksen [16] showed that 2 g of fibrinogen concentrate increased plasma fibrinogen by 1 g/L. Makino et al. [19] obtained a similar increase of 32 mg/dL/g fibrinogen concentrate administered, which was insufficient to correct properly severe hypofibrinogenaemia in deep coagulopathic atonic patients. This survey highlights the importance of our trial to determine the more efficient place of fibrinogen concentrate infusion, likely by administering it earlier in coagulopathic patients before PPH becomes life threatening. In the FIDEL trial, fibrinogen will be administered at a bolus dose of 3 g. This dose was selected based on the anticipated amount of blood loss and corresponding fibrinogen loss at the time of prostaglandin administration. As the main objective of the study is to assess the benefit associated with an early administration of fibrinogen as a therapeutic strategy, the 3 g dose required in the protocol is lower than the 4 to 8 g dose recommended in the SPC to treat the most severe forms of PPH at a later time point [28]. Additional open-label administrations of fibrinogen concentrate will be allowed in both groups, as a rescue therapy, if the severity of the clinical situation requires it and as per investigator discretion.

To avoid or minimize bias and/or a centre effect, the primary endpoint has been defined independently of therapeutic obstetrical interventions and/or clinical practices such as surgical ligation or embolization.

#### 4. Conclusion

Postpartum haemorrhage remains the main cause of maternal death worldwide [30]. An early correction of the PPH associated coagulopathy process (i.e. hypofibrinogenaemia) is expected to contribute to better management. Fibrinogen supplementation appears to be one of the most promising targets for this haemostatic intervention. However, the current level of scientific evidence that supports the indications, doses and timing for this supplementation is insufficient [31]. The FIDEL trial objectives are to demonstrate the efficacy and safety of the early administration of a 3 g fibrinogen concentrate given in patients experiencing PPH and resistant to oxytocin, using a randomised, double-blind multicentre design.

#### 5. Trial status

The FIDEL trial started in April 2014. Nineteen French centres are participating in the trial. As of September 2015, 166 patients have been included.

#### Disclosure of interest

Anne-Sophie Ducloy-Bouthors, member of the FIDEL trial scientific committee and coordinator of the study, was an invited speaker for Laboratoire Fractionnement Biomédicaments, which included honorarium.

Alexandre Mignon, member of the FIDEL trial scientific committee, was an invited speaker for Laboratoire Fractionnement Biomédicaments, which included honorarium.

Cyril Huissoud, member of the FIDEL trial scientific committee, was an invited speaker and medical writer for Laboratoire Fractionnement Biomédicaments, which included honorarium.

Jean-Marie Grouin has performed statistical advisor consultancy for Laboratoire Fractionnement Biomédicaments.

Frédéric J. Mercier, member of the FIDEL trial scientific committee, was an invited speaker and medical writer for Laboratoire Fractionnement Biomédicaments, which included honorarium.

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