**The effect of Upfront Administration of Fibrinogen concentrate in Obstetric Haemorrhage – A Pilot study.**

**FibUpFront PPH (Pilot Study)**

**Double blind randomised pilot study trial of efficacy of upfront fibrinogen in management of postpartum haemorrhage.**

**Clinical Trial Protocol**

**The Universal Trial Number (UTN) is U1111-1157-9979**

Version 1.14 jw/CMcL 16/04/2014

**1. Signature Page**

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**List of abbreviations**

**EBL Estimated blood loss**

**FBC Full blood count**

**FFP Fresh frozen plasma**

**FIBTEM Fibrinogen thromboelastometry**

**MOH Massive obstetric haemorrhage**

**NWH National Women’s Hospital**

**PRC Packed red cells**

**PPH Postpartum haemorrhage**

**ROTEM Rotational thromboelastometry**

**MTP Massive transfusion Protocol**

**DIC Disseminated intravascular coagulation**

1. **Background**
	1. **Introduction**

Postpartum haemorrhage (PPH) is a major global cause of maternal mortality and morbidity. Attempts to reduce PPH rates must be multifaceted and include measures to increase the awareness of women at risk from PPH, ensuring access to effective uterotonic agents, enabling rapid transfer of women with uncontrolled bleeding to facilities equipped to manage their care and facilitating access to blood and blood products for transfusion. The aim of our study is to assess whether early replacement of fibrinogen in women with major PPH reduces morbidity. We propose a randomised, double blind, placebo /standard of care (placebo from here referred to as standard of care) controlled study of fibrinogen concentrate given “up front” in the management in women with PPH of >1000ml and evidence of ongoing bleeding. This will be a Pilot study, possible including other local centres to broaden capture of all women in our population who present during pregnancy. A Pilot study will enable us to establish recruitment rates, bleed rates and review our current protocol.

* 1. **Literature Review**

Postpartum haemorrhage is one of the most important global causes of maternal morbidity and mortality. Each year 14 million women will have a postpartum haemorrhage (PPH) and of these as many as 280 000 will die. While 99% of maternal deaths due to PPH occur in resource-poor countries, [[1](#ENREF_1)] haemorrhage is also an important cause of maternal mortality in resource-rich countries. Obstetric haemorrhage accounted for 8.4% of direct maternal deaths in the UK [[2](#ENREF_2)] and 14.3% of direct maternal deaths in New Zealand [[3](#ENREF_3)]. Major obstetric haemorrhage also results in morbidity and increased length of hospital stay. The most recent Scottish Confidential Audit of Severe Maternal Morbidity (SCAMM) reported that massive obstetric haemorrhage (MOH) continues to be the leading cause of severe maternal morbidity accounting for 73% of reported cases. Rates of postpartum haemorrhage are increasing in resource–rich countries but the reasons for this are unclear and the increase is not solely explained by factors such as caesarean section, increased maternal body mass index and induction of labour [[4](#ENREF_4)]. A number of risk factors for PPH can be identified in the antenatal and intra-partum period however the majority of women who develop PPH do not have any recognisable risk factors [[5](#ENREF_5)] and every pregnant woman must be considered to be at risk.

A critical feature of obstetric haemorrhage is development of coagulopathy, particularly early-onset coagulopathy that develops even before massive transfusion causes haemodilution. Early consumption of fibrinogen followed by hyperfibrinolysis is a feature of obstetric complications such as placental abruption, amniotic fluid embolism and retained foetus after intrauterine demise but even in PPH not due to these conditions early consumption of fibrinogen is described. Two studies [[6](#ENREF_6), [7](#ENREF_7)] have shown that when PPH is diagnosed, women with lower mean levels of fibrinogen go onto develop more severe haemorrhage. These hypothesis-generating observational studies support the association of a low fibrinogen concentration with development of more severe haemorrhage. They do not answer the important question as to whether early replacement of fibrinogen will modify the risk of severe haemorrhage developing subsequently.

The approach to management of obstetric haemorrhage involves immediate resuscitation with fluid to maintain circulating blood volume, with rapid recourse to transfusion of red blood cells to maintain tissue oxygenation. At the same time an obstetric survey is required to identify and treat the cause of bleeding, which in the majority of cases will be due to uterine atony, with retained placenta and genital tract trauma remaining important causes. Coagulopathy frequently occurs early in the setting of PPH and urgent bloods should be taken for standard coagulation studies, which are increasingly being supplemented by point-of-care testing using thromboelastography TEG or ROTEM.

***Role of fibrinogen in transfusion – general considerations.***

A reduction in coagulation factors has been recognised as a contributory factor to development of coagulopathy with massive transfusion. However, depletion of fibrinogen appears to occur more rapidly than that of other clotting factors or platelets in patients undergoing massive transfusion with red cells and volume expanders. Whereas critical levels of prothrombin, FV, FVII and platelets are reached after a loss of > 200% calculated blood volume, critical levels of fibrinogen are reached after a loss of only 140% of the calculated blood volume [[8](#ENREF_8)]. Standard teaching recommends that in the setting of major hemorrhage fibrinogen replacement should be considered once the fibrinogen level is <1g/L as levels above this are thought to be sufficient to allow normal coagulation [[9](#ENREF_9)]. This teaching is being challenged and transfusing at higher levels of fibrinogen may be especially relevant in the setting of obstetric haemorrhage where pregnancy-related increases in fibrinogen mean that the starting level of fibrinogen is as high at 4-6 g/L (compared to non-pregnancy normal range of 2-3g/L) so by the time levels of <1g/L are reached there has already been significant consumption of fibrinogen. Moreover, studies that helped derive this “transfusion trigger” for fibrinogen did not include patients with PPH [[10](#ENREF_10)]., A recent *in vitro* study showed that a fibrinogen level of 2.0 g/L was required to improve clot formation and that optimal clot formation occurred with fibrinogen levels of >2.5 g/L. However, even at optimal fibrinogen levels the clot wassensitive to lysis [[11](#ENREF_11)].

A number of retrospective observational studies have raised the profile of transfusion of plasma products including fibrinogen in massive trauma, in particular in casualties in military settings where increased ratios of FFP and fibrinogen to red cell units have been associated with reductions in mortality overall and mortality due to haemorrhage [[12](#ENREF_12), [13](#ENREF_13)]. Despite the fact that in these retrospective studies many other factors are likely to have contributed to differences in mortality, these studies have nonetheless prompted recommendations for wholesale change in massive transfusion protocols in the trauma setting. Some authors have recommended caution until prospective studies using up-front transfusion with plasma products such as FFP and fibrinogen have been completed to examine if these practices are associated with improved overall outcomes. Such caution seems even more warranted given data from studies that show increased rates of multi-organ failure (MOF) and acute-respiratory distress syndrome in survivors of trauma in civilian settings who have received higher volumes of FFP in massive transfusion protocols. In contrast, fibrinogen replacement in the form of cryoprecipitate, was not associated with an increase in MOF [[14](#ENREF_14)].

In a prospective pilot study of perioperative fibrinogen concentrate administration during cardiothoracic surgery, Rahe-Meyer et al demonstrated significantly lower total transfusion requirements (0.7 units ± 1.5 vs 8.2 units ±2.3) in the fibrinogen group verses the control group [[15](#ENREF_15)]. They repeated these results in a follow-up trail, which demonstrated reduced transfusion of allogeneic blood products. However they comment that larger multicentre studies are necessary to confirm the role of fibrinogen concentrate in the management of perioperative bleeding in patients with life-threatening coagulopathy [16]. Another randomized controlled trial (RCT) has been published investigating the use of fibrinogen concentrate to reduce perioperative bleeding. In this study fibrinogen concentrate was administered to patients undergoing radical cystectomy, which demonstrated a reduction in RBC transfusion requirements (2 out of 10 vs 8 out of 10) in the treatment group versus placebo [17].

Point-of-care devices such as the ROTEM or TEG have been incorporated into clinical practice since the 1980s and are widely used in hepatic, cardiothoracic and trauma surgeries [18] to guide transfusion of plasma products. Modifications of thromboelastography have been developed that are specific for individual components of coagulation such as FIBTEM, which has a reagent that inactivates platelets and is used to assess fibrin polymerisation. More recently these are being used in obstetric settings but are limited by the availability of appropriate reference ranges for pregnancy. Huissoud et al demonstrated the significant increase in maximum clot firmness (MCF), clot amplitude at 5 minutes (CA5) and clot amplitude at 15 minutes (CA15) in healthy pregnant subjects that correlates to the hypercoagulable state in pregnancy. Similar findings by Hill et al, in their observational study comparing and validating reference values for non-activated, kaolin-activated and kaolin and tissue factor-activated TEG [19]. A recent prospective observational study that assessed the use of TEG during PPH demonstrated that fibrinogen concentration of 2g/L corresponded to a CA5-FIBTEM and CA15 of 6mm and 8mm respectively [18].

**Options for transfusion of fibrinogen**

Standard preparations of FFP contains average of 2.0 g/L fibrinogen (range 0.9-3.2 g/L) so that a 300ml unit FFP is equivalent to 0.6 grams. In NZ, one unit of cryoprecipitate contains an average fibrinogen dose of 1.4g/L (range 0.75-2.0g/L) in a volume of 80-120ml. An estimated 1000mL FFP or 233 mL of cryoprecipitate is required to raise plasma fibrinogen concentration by 1g/L in a 70kg adult [20]. In addition FFP preparations are associated with potential risk of pathogen transmission, allergic reactions and transfusion-related acute lung injury [[21].](#ENREF_20) Cryoprecipitate is a human plasma concentrate that is manufactured from plasma. It contains a higher concentration of fibrinogen per unit than FFP, but each unit exposes the recipient to approximately four to six donors. Both products require thawing prior to infusion.

Fibrinogen concentrate is derived from human plasma, is pasteurized and lyophilized and stored at room temperature in powder form. It is typically reconstituted in 50ml of sterile water and each vial of cryoprecipitate contains 1.0 grams (range 0.9-1.3 grams) of fibrinogen. The final concentration of fibrinogen concentrate is 10 times higher than FFP, is more rapidly available and can be administered without the need for thawing. Although derived from a large pool of donors, the risk of viral transmission is significantly reduced because of viral inactivation and removal processes [23].

**4.2 Justification**

**Investigating the role of fibrinogen administration in obstetric haemorrhage**

Given the known association of low fibrinogen and development of severe PPH it seems a logical next step to examine whether up-front administration of fibrinogen early in the course of PPH may modify the severity of the haemorrhage and reduce morbidity and mortality. This could be of particular relevance in smaller, geographically isolated and rural obstetric units with limited access to blood and plasma products for transfusion. Amelioration of the haemorrhage may obviate the need to transfer women to a larger centre or allow clinical stabilization prior to transfer.

MOH occurred in one in 280 women (77 of 21,614 deliveries) from an Irish database. Fourteen of these women received fibrinogen concentrate and 20 received cryoprecipitate and although both agents lead to increases in the fibrinogen level, the correlation between the increase in fibrinogen level and dose administered was stronger for fibrinogen than for cryoprecipitate [24].

To our knowledge there are no published RCTs to assess efficacy in the obstetric setting. High-level evidence demonstrating the efficacy of early fibrinogen supplementation in severe obstetric haemorrhage is critical prior to recommendation of more widespread use. A small double blind Danish study [25], was recently completed but results not yet published, that is randomising women with PPH to receive either 2 g fibrinogen concentrate or placebo. The study plans to enrol women after loss of either >500ml and intended manual removal of placenta or estimated blood loss exceeding 1000 ml and intended manual exploration of the uterus due to continuous bleeding after the birth of placenta following vaginal delivery or blood loss exceeding 1000 ml following delivery by caesarean section. However, as the authors state this dose of fibrinogen will increase the fibrinogen level by an estimated 0.6 g/L. (N=107 each group – total 245 allowing for drop outs).

Our clinical trial outlined below differs from the Danish study in that it will enrol women with more severe bleeding and administer a higher dose of fibrinogen concentrate (4g), TEG or FIBTEM will be done as baseline test at enrolment but there will be intention to treat regardless of results in cases of evidence of persistent PPH or ongoing bleeding. Risk of treatment in the group with normal TEG/ FIBTEM – fibrinogen > 4 g at baseline will be reviewed by follow up of safety outcomes. The aim is to increase the fibrinogen concentration by 1-2g/L and to evaluate which concentration is most efficacious. We propose that it be run as parallel pilot studies in multiple international sites, New Zealand and United Kingdom. (Though set up as individual studies with similar protocols). The study may itself provide a reliable scientific basis for recommendations as to whether fibrinogen concentrate should be used early in the treatment of severe postpartum haemorrhage or may demonstrate an effect that requires assessment in a larger study. This study will be powered to assess reductions in important clinical morbidity - total estimated blood loss, rather than mortality as death as a result of severe obstetric haemorrhage is a rare event in countries such as the UK, New Zealand and Australia.

If upfront fibrinogen concentrate administration proves effective in reducing morbidity and overall blood loss in high-income countries, further research could be conducted to evaluate its use in resource-poor countries. Because maternal haemorrhage accounts for over a quarter of maternal deaths this study could have a significant impact worldwide.

**Hypothesis:**

Fibrinogen replacement (4g dose) early in the course of severe, persistent PPH will reduce the total blood volume lost by 25%.

The reduction in total blood volume loss is a surrogate measure of improved clinical outcomes including a reduction the need for transfusion of red blood cells and other blood products (FFP, cryoprecipitate and platelets), a reduction other measures of maternal morbidity and the requirement for haemostatic interventions such as balloon tamponade, uterine artery embolisation and peripartum hysterectomy.

The early upfront use of fibrinogen has the potential to improve maternal complications related to PPH that will outweigh the risk of increased maternal thromboembolic complications.

1. **Aims**
2. To assess the impact of early administration of fibrinogen in additional to standard management of women with persistent severe PPH (ongoing blood loss >1000ml in the postpartum period that is unresponsive to first line uterontonic therapy and manual uterine compression).
3. To observe correlation of fibrinogen levels with whole blood clotting point of care testing during persistent, severe PPH
4. **Study population**

**Inclusion criteria**

Insure both criteria 1) and 2) are satisfied;

1. Women with estimated blood loss greater than 1000mL in the immediate postpartum period (<4 hours postpartum).
2. Women with persistent PPH not responding to first line uterotonic therapy (i.e. syntocinon infusion), and manual uterine compression in whom further haemostatic intervention is being considered.

**Exclusion criteria**

* Women with coagulopathic disorder secondary to pre-existing liver disease
* Women with confirmed venous thromboembolism occurring in the last 4 weeks of pregnancy
* Women with confirmed allergy to fibrinogen concentrate
* Woman who refuse blood products
1. **Outcome Measures**

**Primary Outcome Measures**

Efficacy

25% reduction in total measured blood volume loss.

**Safety**

Adverse events from randomization until discharge

Serious adverse events until day 90 post randomization.

Rate of thromboembolic events at 3 months (including deep vein thrombosis, pulmonary embolism, cerebral sinus vein thrombosis, pelvic vein thrombosis, myocardial infarction and arterial thrombosis)

**Secondary outcome measures**

* Incidence of moderate PPH (blood loss between 1000 and 2000ml)
* Incidence of severe PPH (blood loss >2000 ml)
* Total blood product usage
* Total whole blood and / or packed red cells
* Total units of FFP
* Total units of platelets
* Total units of cryoprecipitate
* Activation of MTP
* Need for haemostatic intervention (balloon tamponade, uterine artery embolization, surgical arterial ligation, hysterectomy)
* Anaemia with Hb <80 g/L at 24 hours post delivery
* Anaemia at 6 weeks postpartum (Hb <100 g/L)
* Admission to ICU/ DCCM
* Maternal mortality
* Infection rates (wound infection, endometritis, pneumonia)
* Duration of postpartum hospital stay
* Breast feeding rates at hospital discharge and at 6 weeks
* Quality of life indicators as per WHODAS 2.0/ post-traumatic stress disorder score at 6 weeks

**Safety Outcome Measures**

**Other reactions or minor reactions related to drug administration.**

**Unexpected adverse reaction (anaphylaxis or allergic reaction, fever, headache, nausea or vomiting)**

1. **Methods**
	* + - 1. **Consent**

Postpartum haemorrhage is an unanticipated sudden complication of delivery and approaching women for informed consent for the first time when they develop PPH is unlikely to offer sufficient time to fully discuss the implications of the proposed intervention. We plan to provide written information sheets to women in the third trimester of pregnancy who are planning to deliver in the study sites when they attend routine antenatal visits. Woman booked with hospital LMC and private obstetricians and independent midwives will receive study information and will be eligible for enrolment.

Written consent will be obtained from all women who would be willing to participate either during the third trimester or when the woman presents to the labour ward.

 We anticipated that the majority of women will indicate consent in advance of labour but will be able. The consent form will be filed in an easily accessibly place, in the front of the participants’ hospital antenatal notes. This method ensures that women will be given the necessary information and can therefore provide informed consent with full mental capacity prior to the **Intervention** development of a PPH.

* 1. **Randomisation**

As per research department: Allocation by randomized envelope method.

* 1. **Intervention**

After eligibility is confirmed, women will be allocated to either standard of care or treatment arms (standard of care vs. 4mg of fibrinogen).

Fibrinogen concentrate (Haemocomplettan) is a purified concentrate of fibrinogen derived from human plasma that has been pasteurised and lyophilized and is stored at room temperature in powder form. Viral inactivation methods used are effective against enveloped viruses such as HIV, and hepatitis B and C viruses.

Potential thromboembolic risk. A 22-year pharmacosurveillance programme reported a prevalence of venous thromboembolism following fibrinogen concentrate administration of 3.4 per 100,000 [26].

Flow diagram of patient recruitment from initial consultation to discuss enrolment to study:

Total Births per year:

**n = 7695**

(Total number of women to be approached for possible inclusion in study - all pregnant woman presenting to National Woman’s Hospital for ante-natal care )

PPH > 1000mls

 n = **662**

(total of potential enrollments per year – minus those meeting exclusion criteria, numbers as per previous years : woman who had PPH over 1000mls )

Enrollment criteria met and patient enrolled into study. Blinded allocation to either standard of care arm or fibrinogen concentrated arm of study.

Total: n = **196**

Standard of care

Group:

**98**

Fibrinogen concentrate 4G group:

 **98**

* 1. **Obtaining blood samples**

**Baseline blood tests (Time 0)**  (total 15mL) will be obtained at the point of enrolment with 2 tubes of 5 mL each in 5mL vacutainer tubes containing 0.5mL sodium citrate (0.109mol/L) for routine coagulation and ROTEM analysis. 5mL will be obtained in a 5mL vacutainer tube containing EDTA for platelet and haemoglobin.

Blood samples will be analysed for APTT, PT, INR, Fibrinogen assay, FBC (platelet and haemoglobin), D-dimer assay.

The **ROTEM/TEG** will be performed as point-care- testing at 37°C to obtain the following parameters;

1. Clotting time (CT)
2. Clot formation time (CFT)
3. Maximum clot firmness (MCF)
4. Amplitude of clot at 15, 30, and 60 minutes (CA15, CA30, CA60)

Blood tests and ROTEM/TEG analysis will be taken at point 0/ Time 0 (at enrolment), then aim to repeat at **hourly intervals** when the bleeding is ongoing (during postpartum haemorrhage). Blood tests and ROTEM/TEG will be repeated **4 hours** (Time 4) and **24 hours (Time 24)**  after cessation of bleeding. **Measure of blood loss / volume:**

The volume of blood loss as measured in the setting of vaginal delivery using bags specifically designed for correct measurement, including establishing volume of liquor, swabs will be weighed and included in calculating total blood loss and in the caesarean section setting measure by collection of suction volumes, establishing volume of liquor and weighing swabs. The measure will be as accurate as possible in the setting of PPH, and meticulous care taken to achieve this. [27]

Secondary confirmation of blood volume loss by calculating blood volume, total RBC and products including intra-venous fluids with post stabilisation Hb check.

(refer to trauma study)

Total blood volume loss will be measured and recorded at point when control of bleeding as assessed by all parties involved in management of patient is achieved.

**NB** DEF of control: Evidence of control such as deemed by surgical and anaesthetic teams, Surgical observation and normalisation of blood tests as per TEG / FIBTEM/ coagulation screen. When there is no further need for administration of blood or blood products.

**6. Data Collection**

Estimated blood loss will be collected using gravidometric method of weighing swabs and using standardised under-buttock drape for all vaginal deliveries. All health care providers on labour ward will receive training on this aspect prior to the study commencing.

Outcome measures, blood and ROTEM results will be collected 6 weeks following randomisation. Medical complications including rate of VTE will be collected at 3 months.

**6.1 Data Handling and record keeping**

In the study, the participants’ demographic data (name, contact details, date of birth) and specific details related to pregnancy, ROTEM and blood results, and outcomes will be collected from patients in accordance with the patient consent form, patient information sheet and sections 7 this protocol.

The research department at Auckland City Hospital will store and dispose of the demographic data, ROTEM and blood results, and outcomes in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto.

The demographic data, ROTEM and blood results, and outcomes will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients’ consent.

**Statistical considerations**

Currently the only similar study investigating the use of Fibrinogen Concentrate is the Danish Study : Wikkelsoe et al [25], they looked at the reduction in need for allogeneic blood transfusion( to investigate a risk reduction of 33%) –these calculations were based on studies outside of obstetrics. Another trail currently underway is the WOMAN trial [26], they looked at a baseline worldwide event rate, and calculated a reduction of 25% from 4 to 3% in the primary endpoint of mortality or hysterectomy. This is a large multi-center randomized controlled trial.

We discussed the various markers for PPH, and the varied management of this group, including a range of transfusion triggers among clinicians. We felt using total blood loss as indicator of severity would be a robust endpoint.

We reviewed our own institution’s data over the last 5 years – an annual document is produced yearly. [28].

Based on this data we calculate the statistics for our institution:**Investigative sample size calculations for proposed Fib study**

1/ Assumptions (based on 2012 actual numbers)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ProportionOf Births | Proportion of PPH | Annual approx. | Goal of Fib therapy | Mean blood loss | SD | Reduction of Mean if goal achieved |
| Total Births | 100.0% |  | 7695 | - |  |  |  |
| PPH >1000ml | 8.6% | 100.0% | 662 | - | 1486 ml | 675 |  |
| PPH >1300ml | 4.2% | 49.4% | 327 | ~25% reduction in average blood loss | 1909 ml | 750 | -500 ml |

2/Sample size

Total Sample Size (unpaired t-test, 90% power, alpha = 0.05, 1 case per control).

|  |  |  |  |
| --- | --- | --- | --- |
|  | Required PPH (>1300ml)Sample size(per group = n/2) | Therefore Total Births | Therefore Months of Births |
| 500 ml reduction in >1300ml group with SD = 750 (ie difference = 0.667 of the SD) | 98 | 2282 | 3.6 |

**Data Analyses**

Total blood loss will be compared between the treatment group and controls using either the unpaired t-test or, if the distribution of the data is highly skewed, Wilcoxon’s rank sum test. Other secondary measures of interest will be compared using the t-test or Wilcoxon’s rank sum test, as appropriate, for continuous measures and Fisher’s exact test for categorical measures.

**Compliance**

Participants may withdraw from the study at any point. Ideally, a discussion with the clinical research team to determine the reasons for withdrawal should be made prior to formal withdrawal. Practical issues can be dealt with and any concerns will be addressed. The blood tests and data from interview and bleeding score collected up to the point of withdrawal will still be included in the study but no further data or blood tests can be obtained.

**Ethical considerations**

Ethical approval for the study will be applied for through the appropriate ethics committee

Obtaining valid consent for research purposes from patients in the acute emergency setting is not possible due to potential for participants’ impaired mental capacity. Therefore the researchers propose to obtain written informed consent from all women planning a delivery at the study centers in advance of labour. Participant information sheets will be given at booking antenatal visit which will allow adequate time for women to consider whether they wish to participate prior to 32 weeks gestation. The study doctors will be available to discuss any questions or concerns with potential participants during their pregnancy.

**Finance and Insurance**

Funding for Auckland site from various applications to A+ Trusts funds, Auckland Medical Research Foundation, through the Anaesthesia College: ANZCA for young investigators or Pilot projects.

**Reporting and Dissemination**

The results of this study will be widely disseminated and will be put forward for presentation at international and national conferences e.g. Women’s Health Issues in Thrombosis and Haemostasis, International Society of Thrombosis and Haemostasis, American Society of Hematology; meetings for the Royal College of Obstetricians and Gynaecologists UK and Royal Australian and NZ College of Obstetricians and Gynaecologists etc. The study results will also be submitted for publication in a high-impact, peer-reviewed journal such as British Journal Obstetrics and Gynaecology, The Lancet.

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