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Multicentre randomised trial of screening with sFlt1/PlGF and planned delivery to prevent pre-eclampsia at term: protocol of the PE37 study

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ABSTRACT

Introduction Pre-eclampsia affects ~5%–7% of pregnancies. Although improved obstetric care has significantly diminished its associated maternal mortality, it remains a leading cause of maternal morbidity and mortality in the world. Term pre-eclampsia accounts for 70% of all cases and a large proportion of maternal–fetal morbidity related to this condition. Unlike in preterm pre-eclampsia, the prediction and prevention of term pre-eclampsia remain unsolved. Previously proposed approaches are based on combined third-trimester screening and/or prophylactic drugs, but these policies are unlikely to be widely implementable in many world settings. Recent evidence shows that the soluble fms-like tyrosine kinase-1 (s-Flt-1) to placental growth factor (PlGF) ratio measured at 35–37 weeks' gestation predicts term pre-eclampsia with an 80% detection rate. Likewise, recent studies demonstrate that induction of labour beyond 37 weeks is safe and well accepted by women. We hypothesise that a single-step universal screening for term pre-eclampsia based on sFlt1/PlGF ratio at 35–37 weeks followed by planned delivery beyond 37 weeks reduces the prevalence of term pre-eclampsia without increasing the caesarean section rates or worsening the neonatal outcomes.

Methods and analysis We propose an open-label randomised clinical trial to evaluate the impact of a screening of term pre-eclampsia with the sFlt-1/PlGF ratio followed by planned delivery in asymptomatic nulliparous women at 35–37 weeks. Women will be assigned 1:1 to revealed (sFlt-1/PlGF known to clinicians) versus concealed (unknown) arms. A cut-off of >90th centile is used to define the high risk of subsequent pre-eclampsia and offer planned delivery from 37 weeks. The efficacy variables will be analysed and compared between groups primarily following an intention-to-treat approach, by ORs and their 95% CI. This value will be computed using a Generalised Linear Mixed Model for binary response (study group as fixed effect and the centre as intercept random effect).

Ethics and dissemination The study is conducted under the principles of Good Clinical Practice. This study was accepted by the Clinical Research Ethics Committee of Hospital Clinic Barcelona on 20 November 2020. Subsequent approval by individual ethical committees and competent authorities was granted. The study results will be published in peer-reviewed journals and disseminated at international conferences.

Trial registration number NCT04766866.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre open-label randomised clinical trial aimed at evaluating the impact of a screening of term pre-eclampsia at 35–37 weeks with the soluble fms-like tyrosine kinase-1/placental growth factor to placental growth factor (sFlt-1/PlGF) ratio followed by planned delivery in asymptomatic nulliparous women.
⇒ A total of 9132 women will be assigned 1:1 to revealed (sFlt-1/PlGF known to clinicians) versus concealed (unknown) arms.
⇒ A cut-off of >90th centile is used to offer planned delivery from 37 weeks in the revealed group.
⇒ As a primary outcome, the effect of the intervention on the occurrence of term pre-eclampsia will be evaluated.

INTRODUCTION

Background and rationale

Pre-eclampsia (PE) affects ~5%–7% of pregnancies worldwide[1] and remains a leading cause of maternal mortality and morbidity.[2] In addition, PE is also linked to neonatal complications mainly due to the associated placental insufficiency being responsible for

10% of stillbirths[3] and ranking first as a cause of iatrogenic prematurity.[4] In the long term, PE is associated with an increased risk of neurological, renal and cardiovascular disease[5] and also with delayed cardiovascular consequences in the offspring.[6]

PE can be grouped into two clinical forms in terms of disease onset and pathophysiology. Preterm PE (<37 weeks) is strongly associated with placental insufficiency that can be traced back to a defective trophoblastic invasion early in pregnancy.[7–9] On the other hand, in term PE (≥37 weeks), the degree of primary placental involvement is lower, suggesting a maternal cardiovascular maladaptation to the increased demands of advancing gestation,[10] together with a different pattern of endothelial dysfunction markers.[11]

Although adverse consequences are more severe in preterm than in term PE, the overall contribution is similar because term PE is five times more common than preterm PE.[12] Preterm PE is amenable to prevention by first-trimester combined screening followed by low-dose aspirin (LDA) in high-risk women.[13] However, strategies aimed to prevent term PE by LDA or statin administration to high-risk women have failed to demonstrate efficacy.[13 14]

Clinical diagnosis of term PE followed by planned delivery has been shown to reduce the rates of severe maternal complications[15] and is now the standard of care. However, such a strategy can only achieve the prevention of further complications of cases with established PE, while missing a large proportion of cases in the preclinical phase of the disease. Unlike preterm PE, most women developing term PE have no baseline risk factors that could rise clinical awareness, especially those without previous pregnancies. A strategy of planned delivery at term of women at high risk for developing PE has the potential to prevent most instances occurring at term and reduce its associated complications. Labour induction at term is well accepted by women[16] and seems a safe strategy for the neonate.[17] However, we and others have failed in developing a first or second-trimester predictive model with acceptable performance for term PE,[18 19] leaving a strategy of screening closer to the disease onset as an alternative option.

PE is characterised by a endothelial and placental dysfunction that results in high maternal levels of antiangiogenic factors (like soluble fms-like tyrosine kinase-1 (s-Flt-1)) and low maternal levels of proangiogenic factors (like placental growth factor (PlGF)).[20 21] Thus, these angiogenic factors have been proposed as markers of adverse perinatal outcomes in women with suspected PE.[22–24] Recent studies show that a model combining maternal risk factors, blood pressure and angiogenic factors at 35–37 weeks of pregnancy predicts PE within the next 2 and 4 weeks with detection rates of 92% and 72% respectively, for a 10% false positive rate.[25] Interestingly, in the same study, the performance of sFlt1/PlGF alone was remarkably high, with a DR of 82% and 62% for term PE within 2 and 4 weeks. A multicentre study carried out in 10 maternity hospitals centres has confirmed the good performance of the sFlt1/PlGF ratio measured at 35–37 in predicting the subsequence onset of PE.[26]

Justification of the study

A potential challenge in the prediction and prevention of term PE is achieving an effective, widely applicable and predictive strategy. Despite its high predictive efficacy, combined algorithms can be difficult to implement in real-setting large populations. Alternatively, a single laboratory test could be a pragmatic strategy with enhanced generalisability to those settings where the health burden of PE is greater. Given the reported performance of sFlt1/PlGF as a standalone screening,[25] angiogenic factors appear as a potentially suitable candidate for these purposes.

Once term PE is predicted, given the lack of evidence on effective pharmacological strategies, the prevention of term PE relies on timely delivery. However, the efficacy and safety of a policy of planned delivery based on the angiogenic profile at term have not been assessed in randomised trials.

We propose a clinical trial to evaluate the use of sFlt-1/PlGF ratio in asymptomatic nulliparous women at 35–37 weeks of gestation to select women at risk for PE for term planned delivery. The study has a pragmatic approach aiming to reflect real clinical practice rather than the very tightly controlled circumstances.

If successful, the results of this trial will provide evidence to support a simple universal screening strategy reducing the prevalence of term PE, which could be applicable in most healthcare settings and have enormous implications on perinatal outcomes and public health policies worldwide.

HYPOTHESIS

The main hypothesis is that a single-step universal screening for term PE based on sFlt1/PlGF ratio at 35–37 weeks of gestation, followed by planned delivery from 37.0 weeks in those women found to be at high risk, would reduce the prevalence of term PE without increasing caesarean section rates or adverse neonatal outcomes.

OBJECTIVES

Primary

This study primarily aims at demonstrating a reduction in the incidence of term PE by planned delivery based on sFlt1/PlGF ratio at 35–37 weeks of gestation.

Secondary outcomes

The effect of the intervention on perinatal morbidity, caesarean section rate, maternal pregnancy-related morbidity, maternal childbirth experience, maternal postpregnancy endothelial function and a cost-effectiveness analysis will be secondarily addressed.

METHODS

Study design

The study is a multicentre randomised clinical trial, open-label, study following a 1:1 ratio with parallel group allocation.

The study design adheres to standard criteria for randomised trials.

Participants

The study population is non-selected nulliparous pregnant women routinely attended at 35^{+0}–36^{+6} weeks' gestation.

Inclusion criteria are as follows: (1) nulliparous women; (2) singleton pregnancies; (3) 18 years old; (4) 35^{+0}–36^{+6} weeks of gestation; (5) non-previously suspected fetal growth restriction and (6) maternal written informed consent. Exclusion criteria are (1) major malformations or genetic anomalies that could modify the timing of delivery or have an impact on obstetric outcome; and (2) participation in another interventional study that could influence the timing of delivery.

Randomisation

An online service (http://www.clinapsis.com) was used to generate a randomised sequence for a block of 80 participants per centre. The allocation is sequestered internally by a Clinical Trials Unit. After enrolment, recruiting physicians obtain the allocation group from the Unit. Due to the nature of the intervention, it is not possible to blind participants or physicians from the Obstetric Department; however, obstetric management follows similar protocols in each of the participating centres. On agreement to participate in this study and obtention of informed consent by a research team member, participants are randomised to one of the following study groups:

1. *Revealed group*: known results of blood sampling to determine the sFlt-1/PlGF ratio.
2. *Concealed group*: unknown results of blood sampling to determine the sFlt-1/PlGF ratio.

Sample size

A sample size of 8302 is needed to guarantee a 90% statistical power for demonstrating a 50% reduction (assuming a detection rate of 70% and a 70% risk-reduction by timely induction) in the development of PE (from 1.5%).[27] Assuming a 10% loss, the investigators estimated a sample size of 9132 women.

Under a non-inferiority hypothesis testing design, assuming a composite adverse neonatal outcome incidence of 1% in the revealed group, 0.5% in the concealed risk and a prespecified non-inferiority margin of 0.25%; this sample size (4151 per arm) would result in a power of 99% to reject the null hypothesis that the reveal strategy increases the neonatal complications.[27]

Study intervention

In all women included in the trial, at 35^{+0}–36^{+6} weeks of gestation, 20 mL of maternal blood is taken for the measurement of PlGF and sFlt-1 serum concentrations, using automated platforms (Elecsys tests in Cobas platforms, Roche Diagnostics International, Switzerland).

According to their randomisation arm, the intervention is as follows:

- Revealed group: the result is known by managing clinicians and participants and, if >90th centile, planned delivery from 37.0 weeks is offered.
- Concealed group: the result ise unknown to both managing clinicians and participants. A standard of care is followed.

Irrespective of the study group, women with new onset hypertension or PE are attended according to the same standard of care protocols.

The 90th centile of sFlt1/PlGF ratio

The 90th centile cut-off was set at 25 between 35^{+0} and 35^{+6}; and 35 between 36^{+0} and 36^{+6}.

These thresholds were determined in a retrospective cohort of 600 nulliparas with uneventful pregnancy outcomes, consecutively attended at BCNatal (Barcelona), sampled between 35.0 and 38.0 weeks of gestation and measured by the same methods as in the trial. The 90th centile was calculated by quantile regression analysis.

Outcomes and measures

Primary

Rate of term PE, defined as hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure >90 mm Hg) at least 4 hour apart from 37 weeks to 24 hours postpartum, plus any of the following: (1) proteinuria (>300 mg/24 hours or a urine protein/creatinine ratio >0.3 mg/mmol); (2) end-organ dysfunction not attributable to other medical conditions: systolic blood pressure >160 mm Hg, diastolic blood pressure >110 mm Hg, platelet count<100×10^9/L, blood concentrations of alanine and aspartate transaminase >70 IU/L, serum creatinine concentration >1.1 mg/dL, lactate dehydrogenase >700 IU/L, presence of right upper quadrant or epigastric pain, dyspnoea and/or cerebral/visual disturbances (headache, blurry vision, diplopia, amaurosis, photopsia and scotomata) or (3) uteroplacental dysfunction (estimated fetal weight<3rd centile,[28] or <10th centile with abnormal uterine (above the 95th centile[29]) or umbilical Doppler (above the 95th centile[30]). In women with chronic hypertension, the blood pressure criterion to diagnose PE is a 20% increase of mean blood pressure compared with the highest baseline (before 20 weeks) record. In women with pre-existing proteinuria, the cut-off to define end-organ disease is a two-time increase compared with the highest value before 20 weeks of pregnancy.

Secondary

- Maternal pregnancy-related morbidity will be defined by a composite including any of the following: (1) HELLP syndrome (lactate dehydrogenase>700 IU/L, AST to twice normal values and platelet count<100×109/L);

(2) central nervous system dysfunction (eclampsia, Glasgow Coma Score<13, stroke, reversible ischaemic neurological deficit or cortical blindness); (3) hepatic dysfunction (INR>1.2 in the absence of disseminated intravascular coagulation, model for end-stage liver disease score>10[31] or hepatic haematoma or rupture); (4) renal dysfunction (dialysis, serum creatinine concentration greater than 150 µmol/L or urine output<0.5 mL/kg/hour during 12 hours, according to renal insufficiency by RIFLE criteria;[32] or need for treatment with furosemide to maintain urine output>0.5 mL/kg/h for 3 hours); (5) respiratory dysfunction (pulmonary oedema, requirement of invasive or non-invasive mechanical ventilation, oxygen requirement greater than 50% concentration for longer than 1 hour or severe breathing difficulty (no criteria of pulmonary oedema but presence of dyspnoea, crackles in pulmonary auscultation and SaO_2<90%); (6) cardiovascular dysfunction (need for inotropic support, left ventricle failure or myocardial infarction); (7) placental abruption or (8) a requirement for transfusion of blood products red cells, platelets, fresh frozen plasma and cryoprecipitate.

- Caesarean section rate.
- Perinatal morbidity will be defined by a composite including any of the following: (1) placental abruption (clinical suspicion plus confirmed retroplacental clot covering>15% of placental surface or clear evidence on histopatholgy); (2) severe fetal growth restriction (defined as birth weight<3rd centile); (3) perinatal mortality; (4) an Apgar score at 5 min below 7.0; (5) an umbilical artery pH below 7.10; (6) hypoxic–ischaemic encephalopathy (well-defined episode of fetal distress or an Apgar score of 5 or less at one or 5 min after delivery plus presence of seizures and/or altered consciousness within 72 hours of birth);[33] (7) need for respiratory support within 72 hours after birth (Continuous Positive Airway Pressure, Nasal Intermittent Positive Pressure Ventilation, High Flow Nasal Canula or Mechanical Ventilation); (8) neonatal intraventricular haemorrhage Papile grade III/IV; (9) necrotising enterocolitis (requiring surgery) and (10) sepsis.[34]

Exploratory outcomes

- Days of maternal admission after delivery
- Days of admission to the neonatal unit
- The impact of participating in the study on maternal well-being and anxiety (State-trait Anxiety Inventory-STAI[35] and WHO Five Well Being Index[36]) will be evaluated in a subsample of randomly selected 1000 women, within 2 weeks after the blood analysis. Childbirth experience will be evaluated in the same subsample using Labour Agentry Scale-LAS within 4 weeks after delivery.[37]
- Cost–benefit and cost-utility analyses will be performed to evaluate the economic impact of the intervention, with a time horizon of 5 years and a broad perspective of the health system. This analysis will be subcontracted to a dedicated research/university unit specialised in health economics. In brief, costs (capital and recurrent) will be imputed according to standard tariffs in each participating site. For the cost-utility analysis, the cost for QALY (quality-adjusted live years) gain will be calculated. QALY of averted PE will be calculated from previous estimations which combine maternal and neonatal health measures. A threshold of 25 m € per QALY gained will be used for cost-effectiveness.
- In a randomly selected subsample of 100 women with sFlt/PlGF ratio above the 90th centile and 100 women with sFlt/PlGF ratio <90th centile matched by age at delivery (1±years), the maternal endothelial function will be assessed at delivery and at 6 months postpartum. The endothelial function will be assessed by measuring circulating endothelial damage markers: (1) Vascular Cell Adhesion Molecule-1 (VCAM-1), using R&D systems, MN, USA; thrombomodulin; heparan sulfate (AttendBio Research, Spain); soluble receptor type I of tumour necrosis factor (sTNFRI), by Biomatik Corporation, DE, USA; von Willebrand factor antigen and activity, by immunoturbidimetry using Atellica 360 COAG, Siemens, Germany and ADAMTS-13 activity, by fluorescence resonance energy transfer. Additionally, endothelial cells (HMEC-1) will be exposed to the patient's serum to assess the expression of adhesion receptor and extracellular matrix proteins (VCAM-1, ICAM-1, TLR, NALP3, vWF and TF), c5b9 deposits and Neutrophil Extracellular Traps (by Quant-iTTM PicoGreenTM dsDNA Assay Kit, by Invitrogen, Thermo Fisher, MA, USA) will be analysed by fluorescence microscopy. Finally, carotid intima media thickness will be measured as previously described in studies from our group.[38]

Study timeline

Online supplemental table 1 shows the study timeline. The first patient recruitment was done on 2 March 2021. The planned end of the study is on 31 December 2024.

Statistical analyses

The efficacy variables will be analysed and compared between groups by OR and 95% CI. This value will be computed using a Generalised Linear Mixed Model for binary response (logit link function). In these mixed logistic effects models, we will define the study group as fixed effect and the centre as intercept random effect. For the main analysis, the Wald test will be used.

For the rest of the inferential analysis, due to the exploratory purpose, the statistical tests will be applied with 0.05 two-sided significance without alpha correction.

The following subgroups were prespecified as of special interest: age: ≤35/>35; ethnicity: white/non-white; BMI at booking: <30/≥30; chronic hypertension (yes/no); diabetes (no, gestational and pregestational); assisted reproductive technique (yes/no); high risk of PE requiring aspirin (yes/no) and academic level

(primary or secondary/superior). The same logistic mixed regression model used for the main analysis was applied to test the study group and subgroup interaction. The subgroup interaction will be statistically significant considering a significant level of 5%, nevertheless, the primary analysis will be performed separately by each category of subgroups as exploratory. These analyses will be shown by forest plot and no other subgroup analyses are planned.

Handling of missing data followed the principles specified in the ICHE9[39] and the CPMP/EWP/1776/99 Rev1 Guideline on Missing Data in confirmatory trials.[40] Missingness will be assumed to follow a non-random pattern. Formal imputations will be performed only for the main outcome (term PE) by multiple imputation (the worst-case will be imputed for all causes of missing data). A sensitivity analysis of complete cases was secondarily performed.

The primary analysis will be intention-to-treat (based on the groups to which they were initially randomly assigned). Secondary analyses that will be performed are as follows: (1) 'protocol' (restricted to those adhering to the proposed management); and (2) 'as treated' (according to the intervention received, regardless of the adherence to their randomisation assignment).

Data collection and access

Data of participants included in the study are codified and entered into an electronic case report form (https://www.clinapsis.com/). A specific database was designed for the study to protect patient confidentiality and register adequately all data for analysis; this database was designed by the Bioinformatics Unit of the Epidemiology and Preventive Medicine Department of Sant Pau Hospital.

All Principal Investigators were given access to the cleaned data sets. Project data sets are housed on a web site (http://www.clinapsis.com) and/or the file transfer protocol site created for the study, and all data sets are password protected. Project Principal Investigators have direct access to their own site's data sets, and have access to other sites data by request. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information. The members of the Data and Safety Monitoring Committee will have access to have access to unblinded data.

Protocol modification

Any modification to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed on by all the Principal Investigators prior to implementation and notified to the health authorities in accordance with local regulations.

Patient and public involvement statement

A pilot qualitative research study was conducted, where a focus group was created with three patients who had a previous term PE and three obstetricians not involved in the study. Before the focus group session, all participants were asked to complete a brief questionnaire to collect information on demographics and a personal history (age, work experience, parity and personal and general experience with PE). The focus group session was conducted using a semi-structured interview protocol which comprised the following topics: participants' knowledge of the target condition (ie, PE); participants experience and perception towards PE; preferences and need regarding utilisation of prediction and prevention for term PE; advantages and disadvantages of prediction and prevention for PE. Finally, they were asked to agree on a minimal clinically important effect that would justify the intervention (labour induction at 37–38 weeks based on abnormal angiogenic factors to prevent term PE).

A press release will be done after the publication of the study findings for dissemination. Dissemination will be also promoted among the participant institution through social media.

Safety issues

A Data and Safety Monitoring Committee is constituted of four members (two neonatologist and two fetal–maternal specialists), independent of the sponsors and without competing interests in the study.

Detailed information concerning adverse events are collected and evaluated throughout the conduct of the protocol. The Data and Safety Monitoring Committee is notified by email/phone of any maternal death; perinatal death; events resulting in inpatient hospitalisation or prolongation of hospitalisation; events potentially associated with persistent or significant disability/incapacity or life-threatening maternal events. These and other adverse events, deemed serious, unexpected and possibly or probably related, are immediately (within 24 hours of notification) forwarded to the Data and Safety Monitoring Committee. If maternal or perinatal death is reported, a copy of the patient's medical record will be made. Adverse events which do not qualify under the above definition are reported within 7 days. Definitions and severity grading criteria of adverse perinatal events are provided in the online supplemental table 2.

The study does not plan interim analyses. The DSMC have access to unblinded data and were asked to analyse accumulated neonatal outcomes every 3 months and propose stopping the trial if by consensus a deviation from the expected rate of morbidity is inferred.

Any protocol modifications will be communicated to the relevant parties in each participating site (investigators, ethics committee and regulator bodies) and trial registry will be amended.

Scientific dissemination plan

The study results will be submitted for publication in international, peer-reviewed and open-access journals. The investigators will run a dissemination event at the end of the project at the World Association of Perinatal Medicine (WAMP) congress, which draws obstetricians, fetal medicine specialists, perinatologists and neonatologists.

Data sharing plan

Individual participant data, study protocol, statistical analysis plan and informed consent form will be available with publication by email addresses after approval of a proposal with a signed data access agreement.

Ethical approval

The study protocol was approved on 16 December 2020 by the Ethics Committee of the coordinating centre (HCB/2020/1067), and ancillary approval was obtained from each participating site.

A model of the informed consent is provided as supplementary material.

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Contributors EL, FCri, FCro, FF, EG: conceived and designed the analysis; wrote the protocol. LY, IP, JM, KM, AR, MP and MFL-T: reviewed the protocol. JLD, LK, AM-V, AT, AP, FCha, CC and AK: conceived and designed the analysis; reviewed the protocol.

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Competing interests Roche Diagnostics International (Switzerland) will provide at no cost the assays for the sFlt-1 and PlGF measurements (Elecsys). EL has received financial support for her presentations from Cook and Roche Diagnostics. JLD has received fees for advisory services from Roche Diagnostics.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Supplementary table 1 Intended timeline of the study

	2020		2021				2022				2023				2024				2025			
Trimester	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Harmonization of the interdisciplinary research activity	X	X																				
Ethical Committee approval	X	X																				
Patient inclusion			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Laboratory analyses				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Outcome assessment					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Kick-off and follow-up meetings	X		X		X		X		X		X		X		X		X		X			
Data analysis																				X	X	
Dissemination																					X	X

Supplementary table 2. Maternal and fetal adverse event definitions and severity grading criteria

Maternal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Hemorrhage in pregnancy: maternal			Blood loss of 250-1000ml with no signs of clinical shock	Blood loss >1000ml; signs of clinical shock
Definition: Bleeding from or in the genital tract during pregnancy, before the birth of the baby				
Postpartum hemorrhage			Estimated blood loss >2000ml; transfusion <5 units packed red cells; balloon tamponade; surgical intervention (excluding hypogastric or uterine artery ligation or hysterectomy); interventional radiology	Hysterectomy; hypogastric or uterine artery ligation; shock; transfusion of 5 units or more of packed red cells; coagulopathy
Definition: The loss of 500ml or more of blood from the genital tract within 24 hours of the birth of a baby				
Amniotic fluid embolism	-	-	Clinical diagnosis of amniotic fluid embolism in the absence of	Clinical diagnosis of amniotic fluid embolism with cardiac arrest;

			life-threatening features	coma; seizures; disseminated intravascular coagulation; requirement for admission to the intensive care unit

Definition: Embolization of amniotic fluid into the maternal circulation

Maternal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Chorioamnionitis: maternal	Histological, biochemical, or microbiological evidence of chorioamnionitis from placental or amniotic fluid examination in the absence of clinical signs in the fetus or mother	Maternal fever of 38-40 °C (100.4-104.0 °F) and: maternal leukocytosis (>15,000 cells/mm3); fetal tachycardia (>160bpm); maternal tachycardia (>100bpm); foul odour of amniotic fluid; uterine tenderness between contractions	Clinically or pathologically diagnosed chorioamnionitis and fever >40 °C (104.0 °F) for <24 hours	Clinically or pathologically diagnosed chorioamnionitis and: fever >40 °C (104.0 °F) for >24 hours; septic shock; coagulopathy; adult respiratory distress syndrome;

Definition: Inflammation of the chorion, amnion, and/or placenta				
Fetal adverse event	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)
Hemorrhage in pregnancy: fetal	-	-	-	Evidence of fetal compromise including pathological cardiotocography, signs of fetal anemia or need for delivery
Definition: Bleeding from or in the maternal genital tract during pregnancy, before the birth of the baby				

If an adverse event fulfills the criteria for more than one grade of severity, the highest applicable grade should be used.

Maternal or perinatal death resulting from any of the adverse events is classified as grade 5.

A semicolon indicates 'or' within the description of a grade

Supplementary material

Model consent form and patient information sheet

INFORMATION SHEET FOR PATIENTS

STUDY TITLE: **PE37 study: A Multicenter Randomized Trial of Screening with sFlt1/PlGF and planned delivery to prevent Preeclampsia at term.**

PRINCIPAL INVESTIGATORS*: FRANCESC FIGUERAS RETUERTA, EDUARD GRATACOS*
CENTER: BCNatal | Maternal Fetal and Neonatal Medicine Center of Barcelona: Hospital Clínic and Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain.
PROJECT APPROVED BY THE Ethics Committee of the H.ospital Clinic (Barcelona).

We invite you to participate in a study at the Hospital Clínic of Barcelona to identify high-risk pregnancies and prevent complications by planned delivery at the end of pregnancy.

It is important that you read this informed consent and understand that participation in this study is voluntary.

In the paragraphs that follow, we will describe our study. Before you decide to participate, take the time to ask any questions about the study. You can also share the information with your family, friends, doctor or any other health professional.

THE PURPOSE OF THE STUDY:

Preeclampsia affects around 5% of pregnancies and is characterized by high blood pressure and transient damage to some organs. Preeclampsia that appears at the end of pregnancy represents 70% of all cases. It is known that most women (80%) who will develop preeclampsia have abnormal values of substances in their blood named angiogenic factors. Having altered values of these markers increases by 5 the possibility of having preeclampsia in the following 2-3 weeks (from 2% to 10%). We also know that planned delivery at the end of pregnancy (when the baby is mature) does not lead to worse perinatal outcomes and has the potential benefit of preventing complications that, such as preeclampsia, usually occur in those last weeks.

The objective of this study is to evaluate whether a strategy of measuring these markers at the end of pregnancy with planned delivery when they are abnormal brings a benefit in terms of reducing cases of preeclampsia.

STUDY PROCEDURES

If you have decided to participate in this study, we will perform a blood test around 37 weeks (5 ml of blood is drawn) to measure angiogenic factors.

You will be randomly assigned to be in one of the following groups:

- Group with standard care (periodic visits until labor onset if everything remains normal and a recommendation of labor induction at 41 weeks). In this group, the levels of angiogenic factors are not used in decision making and the health professionals will not have access to this information.
- Intervention group, in which when these factors are abnormal (occurs in 10% of cases) planned delivery will be proposed beyond 38 weeks, ultimately being your decision. In this group and when the results of these factors are normal (90% of cases), a standard of care will be carried out, as described above.

Induction is usually started with the painless insertion of a balloon into the cervix. This balloon is left for 12 hours and achieves delivery in less than 24 hours in 60% of women. When the balloon is not effective in initiating labor, the usual pharmacological methods in clinical practice are offered depending on the degree of modification of your cervix (prostaglandins or oxytocin).

POTENTIAL RISKS OF PARTICIPATING

Induction of labor will be done exclusively in full-term fetuses, thus minimizing the potential risks associated with preterm or early term delivery.

POSSIBLE BENEFITS OF PARTICIPATING

This research may benefit you if you are in the group in which we know this information and through it we detect an increased risk. In this case, when the measure is abnormal, the delivery will be planned, which may reduce the risk of maternal and fetal complications.

RIGHT TO WITHDRAW FROM THE STUDY

Your participation in this study is voluntary. For this reason, you can decide whether or not to participate or withdraw study, without any adverse consequence for you.

CONFIDENTIALITY

The treatment, communication and transfer of personal data of all participating subjects will comply with the provisions of Organic Law 03/2008, December 5 , on the protection of personal data. The data will be collected in a center research file and will be processed solely and exclusively within the framework of your participation in this study. In accordance with what is established by data protection legislation, you can exercise your rights of access, modification, opposition and cancellation of data, for which you must contact your study doctor.

The data collected for the study will be identified by a code and only your study doctor/collaborators will be able to relate this data to you and your medical history. Therefore, your identity will not be revealed to anyone, *only* in case of medical emergency or legal requirement.

Access to your personal information will be restricted to the study doctor/collaborators, health authorities, the Clinical Research Ethics Committee and

personnel authorized by the promoter, when they need it to verify the data and procedures of the study, but always maintaining the confidentiality of the data. themselves in accordance with current legislation

Only the data collected for the study will be transmitted to third parties and other countries, which in no case will contain information that can directly identify you, such as name and surname, initials, address, social security number, etc. In the event that this transfer occurs, it will be for the same purposes of the study described and guaranteeing confidentiality.

Study data may be processed, entered into databases, analyzed, verified and reported as necessary for scientific purposes, including medical use.

QUESTIONS

If you have any questions regarding this study, please contact our medical team.

Contact: ffiguera@clinic.cat

INFORMED CONSENT

Study title: **PE37 study: A Multicenter Randomized Trial of Screening with sFlt1/PlGF and planned delivery to prevent Preeclampsia at term.**

I, *(name and surname of participant)* .....

- I have read the information sheet that has been given to me about the study.

- I have been able to ask questions about the study.

- I have received enough information about the study.

- I have spoken with about the study: *(name of researcher)* .....

- I understand that my participation is voluntary.

- I understand that I can withdraw from the study:

  - Whenever I want.

  - Without having to give further explanations.

  - Without this affecting my medical care.

- In accordance with the provisions of Organic Law 03/2008, of December 5, Protection of Personal Data (article 3, point 6 of Royal Decree 223/2004), I declare that I have been informed of the existence of a file or processing of personal data, the purpose of its collection and the recipients of the information.
- I freely give my consent to participate in the study.

Signature of participant Signature of researcher

Date: ____/____/____ Date: ____/____/___

I want you to communicate to me the information derived from the research that may be relevant to my health:

☐YES ☐NO

Signature of participant Signature of researcher

Date: ____/____/____ Date: ____/____/____

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Signature of Patient/Authorized Legal Representative Date