

November 2017, Girona

Pravastatin as a new treatment at High Risk Women for Preterm Preeclampsia

A controlled, randomized, double-blind, clinical trial

Final Degree Project

Author: Guillermo Chueca Cortés

Tutor/a: Dra. Borrell Molins
Dr. Marcos Gragera

Gynecology and Obstetrics Department

ACKNOWLEDGMENT

Gracias al Servicio de Ginecología y Obstetricia del Hospital Josep Trueta por dedicarme su tiempo y atención durante estos meses de forma desinteresada.

A la Dra. Anna Borrell, por su paciencia y disponibilidad para resolver mis dudas.

Finalmente, a mis padres y mi hermano, les debo todo lo que soy. Gracias por creer en mí.

“La ciencia se compone de errores, que a su vez, son los pasos hacia la verdad” Julio Verne. -

ABBREVIATIONS

ASA	Aspirin
CK	Creatine Kinase
Cmax	Maximum concentration
CRL	Crown-Rump Length
DBP	Diastolic Blood Pressure
eNOs	Endotelial Nitric Oxide Synthase
ET-1	Endothelin-1
FPR	False Positive Rate
GA	Gestational Age
HO-1/CO	Heme oxygenase-1/Cicloxygenase
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme-A
iv	Intravenous
IUGR	Intrauterine Growth Restriction
NST	NonStress Test
PAPP-A	Pregnancy-associated plasma protein-A
PE	Preeclampsia
PI	Pulsatility Index
PIGF	Placental growth factor
SBP	Sistolic Blood Pressure
sFlt-1	Soluble fms-like tyrosine kinase 1
US	Ultrasound
VEGF	Vascular endothelial growth factor

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1. ABSTRACT

Background

Preeclampsia complicates approximately 3% to 5% of pregnancies and remains a major cause of neonatal and maternal morbimortality. The pathophysiological similarities with adult cardiovascular disease, risk factors and its pleiotropic effects give an important role to Pravastatin, a hydrophilic 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor. This statin has shown in preclinical studies and pilot clinical trials compares to placebo, to restore several pathogenic pathways associated with preeclampsia, providing biological feasibility and security for its use for preeclampsia. Although many therapeutic interventions have been proposed, aspirin is the only prevent method with clinical evidence that seems to decrease the incidence of the disease. Nevertheless, mortality and morbidity rates still remain considerable.

Objective

The aim of this study is to determine the efficacy of Pravastatin compared to Aspirin treatment in pregnant women at high risk for preterm preeclampsia. We are interested in finding as well clinical severity differences depending on patient's treatment when episodes are happening by measuring analytical parameters (thrombocytopenia and seric creatinine level).

Study design

It will be a multicentre, controlled, randomized, double-blind clinical trial involving women at high-risk for preterm preeclampsia. It will be executed at Hospital Universitari Josep Trueta of Girona, Hospital Universitari de Vall'Hebron, Hospital Sant Pau, Hospital Sant Joan de Déu of Barcelona, Hospital Germans Trias i Pujol of Badalona, Hospital Arnau de Vilanova of Lleida and Hospital Universitari Joan XXIII of Tarragona.

Methods

An estimated sample size of 4.646 women with singleton and non-anomalous pregnancies older than 18 years of age that they are at a high risk of preterm preeclampsia at first trimester will be assigned to daily aspirin 150 mg (Group 1) or pravastatin 10 mg (Group 2) by oral administration before going to bed until 36 weeks of gestational age. The study will be approximately conducted in four years.

Keywords

Preeclampsia; endothelial dysfunction; placenta; angiogenic imbalance; pravastatin; aspirin

2. INTRODUCTION

2.1 Definition

Preeclampsia is characterized by the presence of elevated blood pressure and proteinuria after 20 weeks of GA due to an endothelial systemic dysfunction.

2.2 Epidemiology

Preeclampsia remains one of the most important and devastating complications of pregnancy, affecting 2–5% of pregnancies worldwide and causing an estimate of >60,000 maternal deaths per year (1–3).

Although symptomatic management has improved, in developing countries preeclampsia remains one of the top 5 causes of maternal death. There is currently no curative treatment (4) and although morbidity, in most of cases is temporal (5), there are some cases with permanent consequences (*Table 1*).

Maternal complications	Perinatal complications
Seizures (eclampsia)	Fetal Growth Restriction
Stroke	Preterm delivery
Renal failure	Neonatal death
Acute pulmonar edema	Long-term neurological disabilities
Maternal death	
Disseminated intravascular coagulation	
Liver hematoma	

Table 1. *Maternal and perinatal complications of preeclampsia (4)*

Perinatologists (obstetricians and neonatologists) have to deal with a tremendous rate of prematurity in PE since 24% of cases of PE involve very low birthweight (<1500 g) and 10% are below 1000 g (6).

Furthermore, it has been observed geographical differences between preterm-preeclampsia (before 37 weeks of GA) and term-preeclampsia, (after 37 weeks of GA), but there is a lack of data in order to support this affirmation (6). Another reason for these differences among countries can be explained by terminology disparity and classifications used by different authors. Also, there might be other factors such as nutrition or genetics (7,8).

Because of these facts, epidemiology cannot be universalized (7) and It could be a future research field, because of the high mortality in developing countries (6).

2.3 Risk factors

The exact cause of preeclampsia remains unknown, and it seems to be an agreement that its etiology is a multifactorial (Table 2), although there is a tendency to divide etiological factors into two large groups: placental and maternal ones (9).

One of the etiological factors responsible for the onset of preeclampsia would directly affect the relationship between mother and fetus. Thus, a possible cause for poor placentation would be the existence of an immunological alteration. The fact that the fetoplacental unit has, from the immunological point of view, the characteristics of an allograft, when the normal immunotolerance mechanisms between *trophoblast* (cells forming the outer layer of a blastocyst, which provide nutrients to the embryo and develop into a large part of the placenta since at the third month of gestation this will receive the name placenta) (10) and maternal tissue fail, an abnormal immune reaction is initiated when the paternal antigens are brought into contact with the maternal ones.

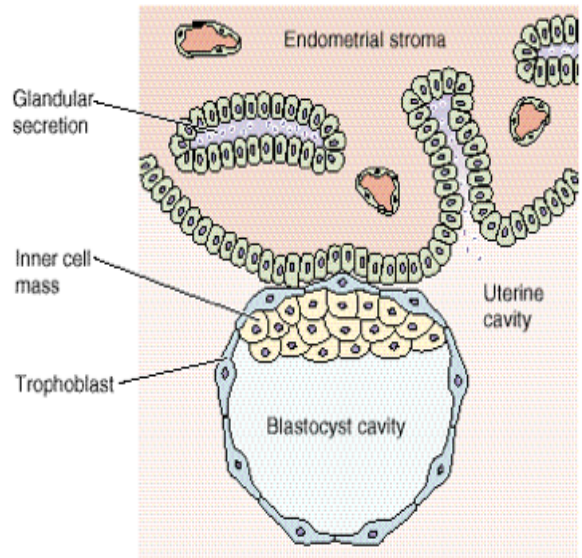


Figure 1. *Trophoblast* (11)

Furthermore, the risk of PE increases in the first pregnancy (nulliparity), with a new paternity in subsequent pregnancies, with the previous use of barrier contraceptives or in pregnancies with donation of oocytes. Instead, the risk decreases with duration of sexual activity before pregnancy with the same partner provided no barrier methods have been used (7,8).

Different immunological alterations have been demonstrated in PE:

- A decrease in circulating levels of IgG and IgM.
- Absolute or relative deficit of blocking antibodies.
- Fetal antigens can induce a cell-mediated immune reaction, which would most likely be located in the decidua which is the responsible for the immunological recognition of the trophoblast (12). Until recently, it was considered that only humoral immunity was involved in the development of preeclampsia.

Other possible placental and non-immune causes are the excessive size of this organ or alterations in the placental microvasculature (13) that would lead to a reduction of perfusion.

Within the maternal causes, the genetic cause is relevant. Some types of PE show a familiar predisposition. Preeclampsia might involve: 1) a recessive gene, 2) a dominant gene of incomplete penetrance that would depend on the fetal genotype, or 3) multifactorial inheritance. The genes that have been implicated in preeclampsia are related to genes in the mitochondrial respiratory chain, the TNF gene (14), the angiotensinogen gene and the gene encoding the enzyme nitric oxide synthase of endothelial origin. All these genes are

related to the endothelium, sometimes directly, or in other cases indirectly, such as the case of TNF that can act as a tissue factor activator and consequently activate coagulation cascade and generate an endothelial injury (7).

The risk of recurrence in the subsequent pregnancy depends on the severity and the gestational age (GA) at delivery in the index pregnancy: it can range from 10% to 15% for women who had term-preeclampsia to 50% to 60% for women who had severe preterm-preeclampsia that required delivery before 28 weeks (15).

INMUNITARY FACTORS	<ol style="list-style-type: none"> 1. Nulliparity 2. Partner-related factors (limited sperm exposure, donor insemination)
GENETICAL FACTORS	<ol style="list-style-type: none"> 1. Family history of preeclampsia or eclampsia 2. Fetal aneuploidy 3. Ethnicity (black and indian race twice)
MATERNAL FACTORS	<ol style="list-style-type: none"> 1. Obesity and insulin resistance (DM II) 2. Chronic or vascular disease (Pregestational diabetes, renal disease, rheumatic disease, connective tissue disease) 3. APS (Antiphospholipid syndrome) 4. Trombophilia 5. Maternal infections 6. Extreme maternal age (> 35 years old)
GESTATIONAL FACTORS	<ol style="list-style-type: none"> 1. Molar pregnancy 2. Fetal hydrops 3. Multifetal gestation 4. Known history of preeclampsia

Table 2. Risk factors of preeclampsia (13)

2.4 Pathogenesis

Over the last 10 years, a great progress has been made in the understanding of the mechanism of PE, in which placental insufficiency plays a central role (4). It is associated with an altered expression of angiogenic and antiangiogenic factors, also called “angiogenic imbalance”.

The integrity of endothelial cells is crucial for the maintenance of angiogenic balance. Any endothelial damage such as deficient spiral arteries remodeling (8,12), responsible for uterine vascularization, can lead to placental oxidative stress and imbalance in the production of vasoconstrictive and vasodilator factors (3,16,17).

The trophoblast differs in two layers: the cytotrophoblast and the syncytiotrophoblast (outermost layer). By day 13, the cytotrophoblast layer has differentiated into invasive and non-invasive components. The invasive cytotrophoblast forms cell columns that anchor the trophoblastic tissue to the uterine epithelium and establish blood flow to the placenta and fetus.

During this process, it performs the following actions:

- Migration through the syncytiotrophoblast and into the decidualized endometrium and myometrium,
- Invasion of the vessel walls of the maternal spiral arteries,
- Induction of spiral arteries' remodelling from high-resistance to low-resistance vessels.

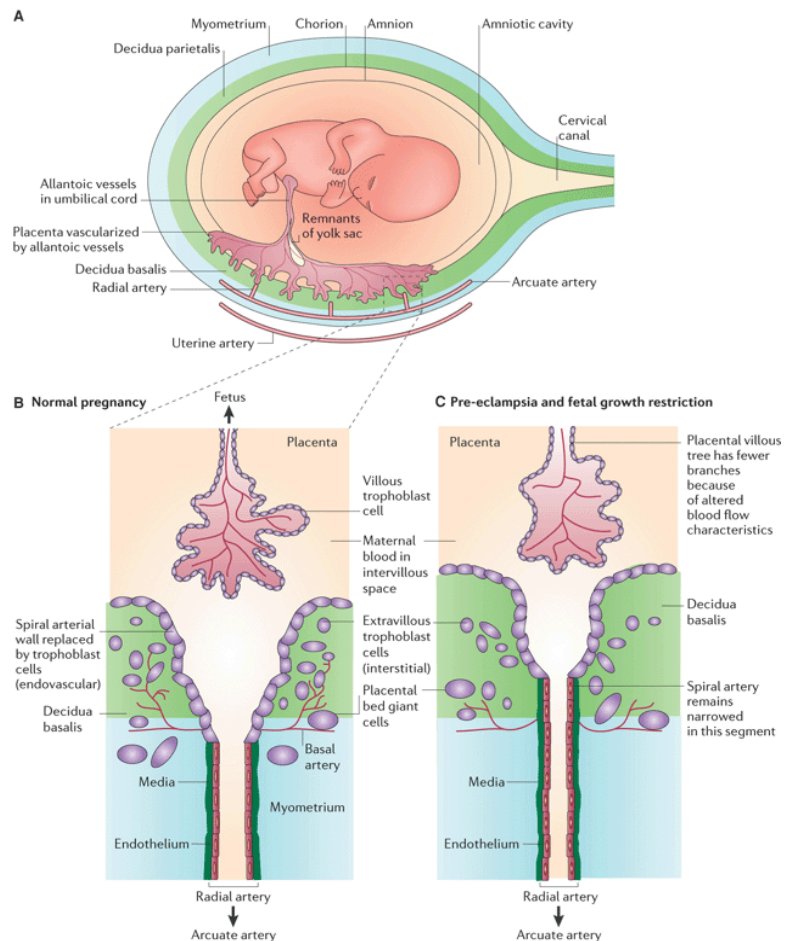


Figure 2. Remodeling of maternal vessels (18)

The decrease in resistance is aided on the fetal side by further villous vascular branching. Concerning about this, Doppler velocimetry reflects it in an increase of end-diastolic velocities of both uterine and umbilical arteries during the pregnancy development (12,19).

During this penetration, syncytiotrophoblast is filled with maternal blood, forming the vascular *lacunae* and causing the beginning of the exchange of products between mother and fetus, since syncytiotrophoblast is composed by epithelial cells specialized in the transport of gases and nutrients.

However, in PE, there is an incomplete trophoblastic invasion limited to the decidualized endometrium but not to myometrial vessels. This abnormality can be detected by Doppler flow velocimetry waveforms (FVW). This imaging test for uterine arteries at first trimester can be done by abdominal or transvaginal (much easier) Doppler US (13,19). It is important to consider that this procedure is operator dependent.

These abnormalities are identified by :

- **PI Doppler > 1,5**, which means a high-resistance pattern (low velocity of flow at end-diastole relative to that at systole)
- **Protodiastolic** (early diastolic) **Notch**

Worst prognosis is associated with bilateral notch and PI > 1,5 beyond 24 weeks of GA (19).

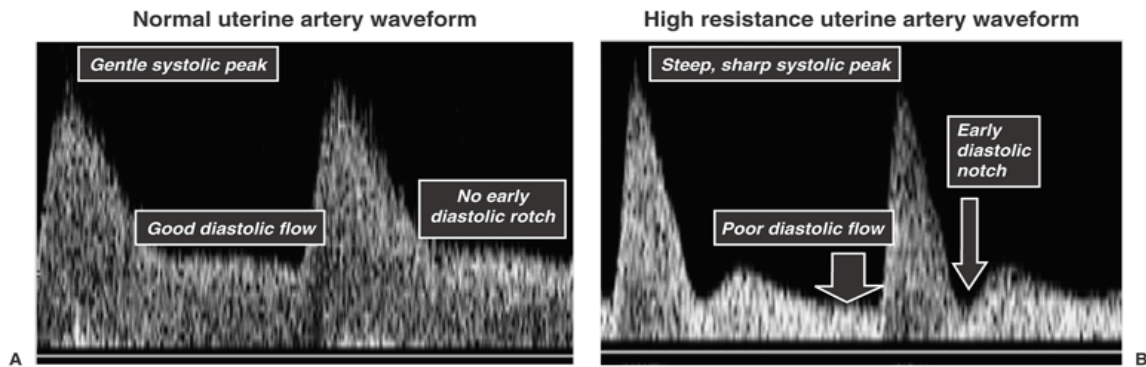


Figure 3. Comparing uterine artery FVWs from normal pregnancy versus preeclampsia case (19)

Vasospasm is the key mechanism for developing the disease. It means there is a resistance to blood flow leading to hypertension. The endothelium of the renal glomerulus is especially sensitive to this phenomenon, explaining the almost constant proteinuria in all these patients and a characteristic histopathological lesion, *glomerular endotheliosis*. However, glomerular filtration is not reduced as a result of this lesion, but due to reactive changes of the disease regarding plasma volume and blood pressure (8).

Soluble Fms-like tyrosine kinase 1 (sFlt-1), a circulating antiangiogenic protein, and vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), two proangiogenic growth factors that are secreted as dimeric glycoproteins detected by Roche Elecsys® immunoassays, have an important role on the physiopathology (20). VEGF promotes the proliferation and survival of endothelial cells and induces vascular permeability. PlGF is a VEGF homolog released by the placenta, which also has proangiogenic activity and has approximately 50% homology with VEGF (2,4,7).

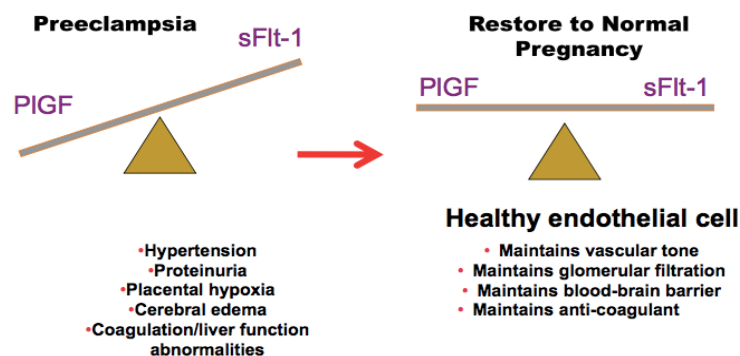


Figure 4. Increased levels of sFlt-1 and decreased levels of PlGF are detected. This is the main aim of recent treatments for restoring “angiogenic balance”(2)

During healthy pregnancies sFlt-1 levels in the maternal blood are low until the second trimester, and only start to rise after 33–36 weeks, when sFlt-1 might be associated with a tempered vascular growth and physiological “ripening” of the placenta. In contrast, in preeclamptic pregnancies, sFlt-1 is produced excessively by the placenta much earlier and secreted into the maternal bloodstream, where it is thought to bind and neutralize VEGF and PlGF (17,21). This causes a decrease of proangiogenic factors in the maternal blood, and VEGF-signalling in the endothelial cells is disrupted as less VEGF receptors are bound (2,16).

This results progressively in placental hypoperfusion, which induces trophoblast dysfunction and the release in maternal circulation of trophoblastic factors leading to an excessive inflammatory response, endothelial dysfunction and glomerular damage. This results in an inhibition of the effects of VEGF and PlGF on maternal endothelial cells and podocytes (4). Moreover, this increase of sFlt-1 correlates with the severity of clinical disease, and sFlt-1 levels rapidly normalize after the delivery of the placenta (17,22).

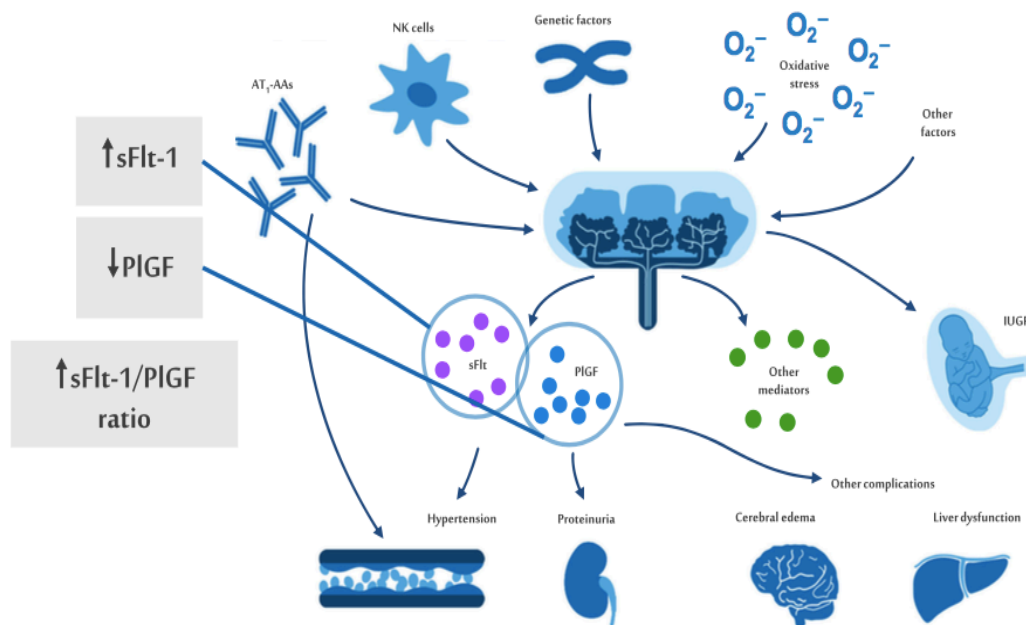


Figure 5. The role of angiogenic factors and its effects in fetus and different maternal organs(2)

Recently, sFlt-1/PlGF ratio has been introduced for prediction and diagnosis of preeclampsia in singleton pregnancy (20,23,24). An increase in the sFlt-1 / PlGF ratio can be detected between 24.0 to 33.6 weeks of gestation in women at risk of developing complications resulting from placental insufficiency like IUGR or fetal death. It is important to remark that this ratio during first trimester has contradictory results, but both factors (angiogenic and antiangiogenic) are used separately in a risk calculator at this period (23) (this concept will be developed in section 2.7 Prevention).

Angiogenic factors are correlated with uterine artery PI (Doppler) and the combination of both tests seems to improve the sensibility and specificity of the screening algorithm (24).

Due to the fact that it is detectable prior to the appearance of clinical disease, it allows its potential clinical use for discrimination of women with normal pregnancies and those at high risk of developing placental complications, especially preterm-PE (21,23).

Meaning of sFlt-1/PIGF	Cut-off point	
	Preterm-preeclampsia	Term-preeclampsia
Suspicion of PE	38	38
Diagnostic of PE	85	110
Uncertain (repeat in 2 weeks)	38-85	38-110

Table 3. Cut-off point of sFlt-1/PIGF ratio for prevention and diagnostic of PE in singleton pregnancies.

Finally, PAPP-A is considered to be involved in local proliferative processes such as wound healing and bone remodeling. Low plasma level has been suggested as a biochemical marker of aneuploid fetuses such as Down Syndrome. Furthermore, low levels may alternatively predict IUGR, placental abruption, PE, preterm delivery or fetal death (25).

2.5 Diagnosis and clinical spectrum

The classification system of Hypertension Disorders in Pregnancy was designed originally by American College of Obstetricians and Gynecologists (ACOG) in 1972. Further modifications were made in 2000 in order to achieve the classification scheme used currently (13). It describes five major categories (7) listed in *Table 4*.

DISORDER	DEFINITION
Gestational hypertension	Hypertension > 20 weeks of gestation or during first 24 hours postpartum WITHOUT proteinuria or signs of preeclampsia
Transient hypertension	Hypertension that resolves by 12 weeks postpartum
Chronic hypertension	Hypertension diagnosed prior to pregnancy, prior to 20 weeks of gestation, or not resolve by 12 weeks postpartum
Preeclampsia or eclampsia	Hypertension >20 weeks of gestation (except trophoblastic diseases or hydrops) WITH proteinuria; eclampsia is the occurrence of seizure activity without other identifiable causes
Preeclampsia superimposed	The development of preeclampsia or eclampsia in a woman with preexisting or chronic hypertension

Table 4. Classification and definitions of hypertensive disorders in Pregnancy (13).

To diagnose preeclampsia, the following criteria should be present (13,26):

1. SBP of more than 140 mmHg and/or DBP of more than 90 mmHg after 20 weeks' gestation in a previously normotensive patient. This measurement must be present at least twice, measured at least 6 hours apart but no more than 1 week apart.
2. New-onset proteinuria (> 300 mg of protein in a 24 h - urine collection, a random urine protein/ creatinine ratio of $> 0,3$ or 2 + protein or greater on dipstick urinalysis) present at least twice at least 6 hours apart but no more than 1 week apart.

It is always potentially dangerous for the mother and the fetus, but there are criteria for **severe preeclampsia** (7):

1. SBP > 160 mmHg and/or DBP > 110 mmHg on two occasions at least 6 hours apart
2. Seric creatinine $> 1,2$ mg/dL
3. Thrombocytopenia (< 100.000 platelet/mm³) or hemolytic anemia with microangiopathy
4. Elevated liver function test (GOT and GPT x 2)
5. Headache, visual disturbances or epigastric pain
6. Retinal haemorrhage, papilledema or exudate on eye fundus
7. Pulmonary edema
8. Oliguria (< 600 ml in 24 hours)

It is important to educate patients regarding the signs and symptoms to be aware of. They should return immediately to the hospital if any of them is happening (13):

1. Nausea and vomiting
2. Persistent severe headache
3. Right upper quadrant or epigastric pain
4. Scotoma
5. Blurred vision
6. Decreased fetal movement
7. Rupture of membranes
8. Vaginal bleeding
9. Regular contractions

An atypical form of severe preeclampsia is **HELLP syndrome**, diagnosed by the following criteria (20):

- Hemolysis: LDH>700 UI/L
- GOT or GPT twice the upper limit of normality
- Platelets < 100.000/mm³

2.6 Management and treatment

Normally, preeclampsia will end with the delivery of the placenta (13,26) but in some cases, preeclampsia can occur up to several days after delivery (2). Antihypertensive treatment does not prevent fetal events, it only reduces maternal complications and maintains stable BP until fetal lung maturity.

2.6.1 Mild preeclampsia

Hospitalization should be performed if ambulatory treatment does not stabilize BP <160/110. It is not necessary if the patient correctly follows the controls at home and the fetus presents correct tests of fetal well-being (20,26).

- Relative rest.
- Normocaloric, normoproteic and normosodic diet.
- Go to the emergency room if the patient is experiencing prodromal symptoms
- BP self-monitoring: 2-3 times / day.
- Analytical control (hemogram, renal and hepatic function) every 2 weeks or if there are clinical changes.
- Control of fetal well-being every 15 days or if there are clinical changes.
- *Oral labetalol* (alfa-beta blocker) is considered the first line antihypertensive treatment with SBP between 130-155 and DBP between 80-105 mmHg goal. Other drugs may be used depending on the existence of contraindications and the medical experience. (ANNEX 2)
- Delivery at 37-38 weeks of GA, according to BISHOP test and clinical situation of the patient. (ANNEX 3)

2.6.2 Severe preeclampsia

Hospitalization should be performed in all cases including general obstetric exploration (TNS, estimation of fetal growth and uterine-umbilical-fetal Doppler) (20,26).

- BP control every 5 minutes until stabilizing clinical situation. After that, control every hour.
- Normocaloric, normoproteic and normosodic diet.

- Analytical control (hemogram, renal and hepatic function) every 12/24 hours.
- Streptococcus group B (SGB) culture if >32 weeks of GA.
- *Glucocorticoids (iv betamethasone)* for fetal pulmonar maturation between 24-34.6 weeks
- *iv labetalol* with SBP between 140-155 and DBP between 90-105 mmHg goal.
- *Magnesium sulfate (SO₄Mg)* bolus for anticonvulsive treatment is indicated until clinical / analytical stabilization if:
 - Hypertension refractory to treatment with two oral drugs.
 - Criteria of severe preeclampsia or prodromes.

It is a sedative drug at neuromotor plaque level. It is contraindicated in patients with myasthenia gravis. It can produce deficit of visual accommodation, risk of cardiorespiratory arrest if the drug accumulates and interaction with other muscle relaxants. Controls must be followed during its administration (every 2-3h) and if there is a suspicion of intoxication (obnubilation, bradypnea or abolition of patellar reflexes), the antidote is *calcium gluconate* (bolus of 1 g iv in 3-4 min).

-Delivery will be performed depending on different parameters. (ANNEX 4)

2.6.3 HELLP syndrome

Hospitalization should be performed in all cases including general obstetric exploration (NST, estimation of fetal growth and uterine-umbilical-fetal Doppler) (20,26).

- Anticonvulsive treatment with *Magnesium sulfate*.
- Antihypertensive treatment with *iv labetalol*.
- Pulmonary maturation treatment with *iv glucocorticoid*.
- *Glucocorticoids (iv dexamethasone)* if there is thrombocytopenia.
- Criteria of immediate delivery.

Immediate delivery criteria (apart from GA) (20):

1. Pharmacologically uncontrollable PA (despite the combination of 2 hypotensive drugs at maximum doses)
2. Non clinical stabilization although treatment of seizures
3. Signs of fetal distress
4. HELLP syndrome
5. Severe maternal complications: cerebral hemorrhage, refractory pulmonary edema, hepatic rupture, placenta previa

2.7 Prevention

Nowadays, in Spain, during the first trimester counseling visit (11.0-13.6 weeks of GA), the preeclampsia risk calculation (*Gestational Calculator v2013.1*) (ANNEX 4) is performed and the individual risk of preeclampsia is assessed. Risk $> 1/70$ is considered high risk preterm-preeclampsia. It means: every 70 pregnancies, 1 will develop PE. It is important to remember to give the risk report to the patient (20).

Another risk calculator has been released recently (*Fetal Medicine Foundation Calculator*) (ANNEX 6) and it is expected to be implemented in the National Health System in the following months, due to its positive and significative results, overpassing *Gestational Calculator v2013.1* (24,27). It combines:

- Maternal factors
- Uterine artery PI (Doppler)
- Mean arterial pressure ($[2DBP+SBP]/3$)
- Serum PAPP-A
- Serum PIGF and sFlt-1

In this improved calculator, **risk $> 1/100$** is traduced as a high risk and It can predict 75% of preterm-PE cases (delivered at < 37 weeks' gestation) and 45% term-PE cases (delivered at > 37 weeks' gestation) although there is a false positive ratio of 10%. In addition, there is a screen-positive rate of 10-11% (24,28). In fact, in most of clinical trials its effectiveness has been proved in detection of preterm-PE.

Current treatment: Aspirin

If the screening is considered pathological ($> 1/100$), the patient should start the profilactic administration of ASA at or before 16 weeks' gestation at a dose of 100-150 mg per day until 36 weeks' gestation (29-31) taken at night, before going to bed (30) in order to reduce the PE and IUGR by 50%. Another meta-analysis from PARIS CollaborativeGroup determined a reduction of just 10% (32).

According to "low doses" of ASA, a nonsteroidal anti-inflammatory drug, 150 mg/day or less, generates a selective inhibition of platelet cyclooxygenase from arachidonic acid, which leads to a decrease in thromboxane A_2 (TX), without affecting the endothelium and a constant production of prostacyclin (PG), reversing the existing TX/PG ratio, in order to achieve a decrease of vasoconstrictor factor and dominant platelet aggregation without modifying prostacyclin production. In addition, ASA prevents angiotensin II-induced hypertension and cardiovascular hypertrophy, mainly through its antioxidative properties in preventing the generation of superoxide (5,7,33)

The potential mechanism of the time-of-day-dependent differences in the BP responsiveness to ASA are as yet unknown: Circadian rhythms in TX and PG production, circulating platelets, platelet aggregation, clotting and fibrinolytic inhibitors, angiotensin sensitivity in pregnancy, as well as in the inhibition of platelet aggregation produced by ASA. Another potentially

relevant factor to be taken into consideration is the pharmacokinetic observation that ASA exhibits a faster rate of clearance when administered in the morning as compared with the evening. It has been also reported that effects of ASA upon α - and β -adrenergic receptors depend on the circadian timing of ASA ingestion. α - Adrenoceptor blockade reduces peripheral resistance more effectively in the early morning hours than at other times of the day.

There are considerable disparities among the results of randomised trials involving ASA treatment due to subjects enrolled into trials (low risk vs high risk), GA at randomisation (First trimester vs Second trimester), and the dose of ASA (32).

Side effects of ASA at low doses are minimal (gastritis) or null. However, in the case of using ASA 500 mg dose, it increases the risk of bleeding, urticaria, rhinitis, asthma and nasal congestion(34).

New treatment option: Pravastatin

Related to sFlt-1/PlGF and the similarities in pathophysiology between PE and cardiovascular disease, recent research has raised statins as a new preventing drug that would restore angiogenic balance (3,9,15,16,35), particularly, Pravastatin, a HMG-CoA reductase inhibitor (ANNEX 1). Despite the few studies conducted, the administration schedule is introduced between 12.0-16.7 weeks of GA as following ASA protocol (15).

By oral administration, it has a rapid absorption (time to achieve Cmax is 1-1.5h) and short elimination half-life (1.77h) in non-pregnant patients. Transplacental transfer of pravastatin is minimal, and higher in the fetal-to-maternal direction than the maternal-to-fetal direction because of its low passive diffusion, hydrophilicity, and because it is subject to placental efflux transporters. It has a hepatoselectivity and it is considered one the lowest potent inhibitors of HMG-CoA enzyme. In addition, CYP3A-dependent metabolism is minimum (this route increase the activity during gestation so it is important not to saturate it) and there is dual elimination (relevant in cases of liver or renal impairment, making pravastatin relatively safe (36).

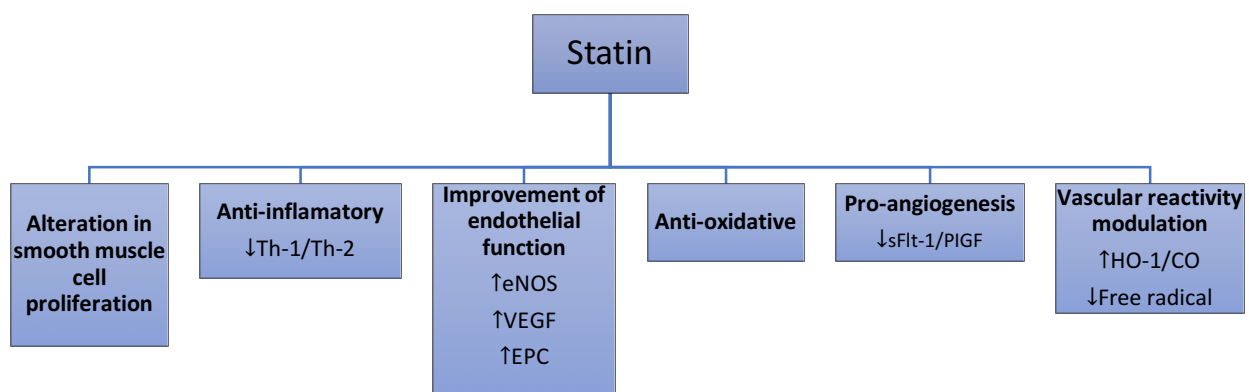


Figure 6. Statin’s biological plausibility and pleiotropic actions to prevent preeclampsia (15).

Apart from lowering cholesterol levels, statins have other pleiotropic actions such as antioxidant, anti-inflammatory and antithrombogenic effects (16,37). They have been shown to increase eNOs activity *in vitro* and *in vivo*, resulting into the overexpression of vasodilating factor NO. Moreover, statins induce the activity of HO-1/CO pathway and reduce platelet aggregation (38).

More recent epidemiologic data does not support teratogenicity concerns of statins in general and for pravastatin in particular (15,36). Despite this, they are designated by FDA administration pregnancy “category X”. By definition, category X is assigned to drugs for which “studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits.”(36)

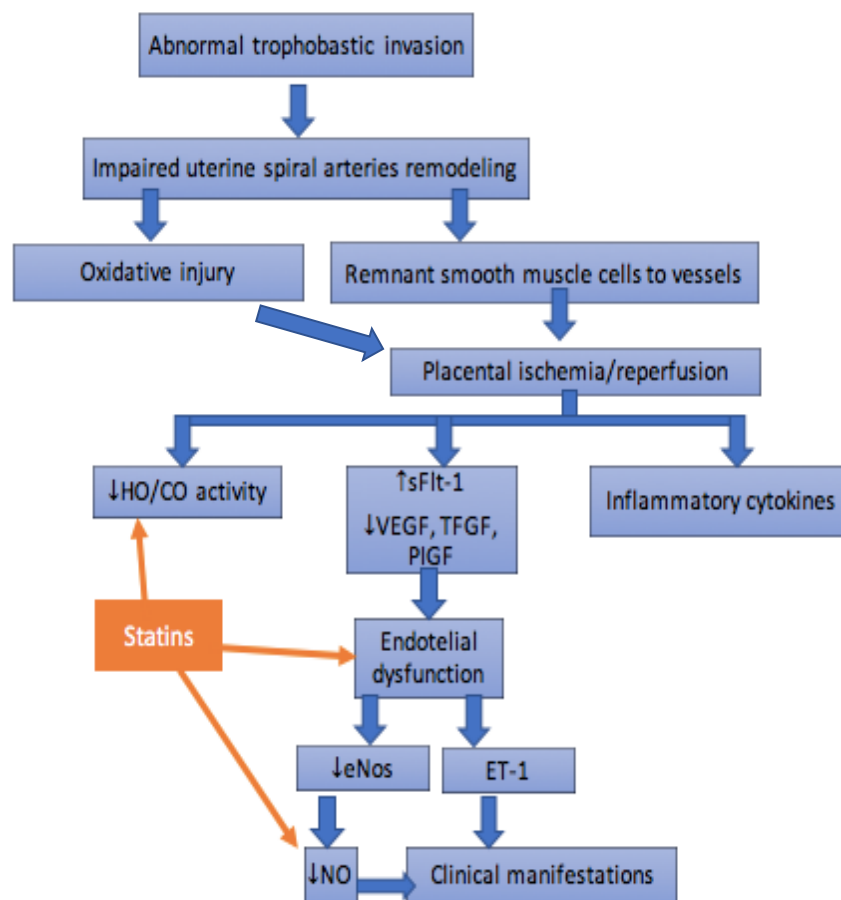


Figure 7. *The preeclampsia’s cascade and statins targets* (16)

Side effects of pravastatin at low doses are also minimal. The most noticed are musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevations of CK and serum transaminase. It is important to know these effects have been especially detected with 20 and 40 mg doses (39).

Other treatments:

Frequency of hypertension in pregnancy was lower in those communities that consumed calcium-rich diets. A possible action of calcium supplementation would be the arrest on the parathormone production, which generates a decrease in the intracellular calcium deposits, thus reducing vascular reactivity.

Although no adverse effects of calcium administration have been observed, there is not enough evidence to prescribe it. Another hypothesis that should be investigated is the verification of its possible effect in populations with low calcium intake (7).

Other methods has been proposed to prevent preeclampsia such as reduction of physical exercise, hyposodic diet, hypocaloric diet, hyperproteic diet, and supplements of zinc, magnesium, iron or folates, but there are insufficient evidence to recommend any of them (7,13).

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4. JUSTIFICATION

Throughout all introduction it has been describe these protective properties and the pathophysiological similarities between preeclampsia and adult atherosclerotic cardiovascular disease (40). For this reason, statins are considered as a potential preventive therapy for preeclampsia. Preeclampsia risk calculation and preventive treatment should be performed at first trimester due to the fact the pathogenesis still remains incomplete (23,31).

However, despite their widespread use among adults at risk for cardiovascular disease, and although, pravastatin has a favourable safety profile and known pharmacokinetic properties, the data on their maternal and fetal safety after exposure during pregnancy are limited, and nowadays for which entails the use of a pregnancy class X medication for an off-label indication in pregnancy (15,36).

All pilot studies performed until nowadays explain the effect of this drug on the reduction of the incidence of PE although there are not clinical trials comparing the efficacy of the currently accepted treatment (aspirin) respect to the new therapeutic proposal (pravastatin). It is known the economic cost care of the complications derived from PE is considerable (41). For this reason, it is important to determine the most effective treatment.

Although the indication of pravastatin seems to be beneficial in pilot studies, its benefits need to be investigated in a large and adequately powered, randomized and controlled clinical trial, taking into account that earlier attempts to prevent PE except from aspirin have had limited success (3,13,32,40,42).

5. HYPOTHESIS

Main hypothesis

Early pravastatin treatment in high-risk women for preterm preeclampsia will reduce the incidence of new episodes compared to aspirin.

Secondary hypothesis

1. Early pravastatin treatment in high-risk women for severe preterm preeclampsia has less severe thrombocytopenia compared to patients treated with aspirin.
2. Early pravastatin treatment in high-risk women for severe preterm preeclampsia has better renal function compared to patients treated with aspirin.

6. OBJECTIVES

Main objective

To assess pravastatin compared to aspirin in reduction of the incidence of new episodes in high-risk women for preterm preeclampsia.

Secondary objectives

1. To assess pravastatin compared to aspirin in reduction of severity of thrombocytopenia in high-risk women for severe preterm preeclampsia.
2. To assess pravastatin compared to aspirin in increase of renal function in high-risk women for severe preterm preeclampsia.

7. SUBJECTS AND METHODS

7.1 Study design

It will be performed in a multicentre, double-blind, randomized, parallel-group trial that compares ASA versus Pravastatin, in patients with high risk for preterm PE. It will be executed at Hospital Universitari Josep Trueta of Girona, Hospital Universitari de Vall'Hebron, Hospital Sant Pau, Hospital Sant Joan de Déu of Barcelona, Hospital Germans Trias i Pujol of Badalona, Hospital Arnau de Vilanova of Lleida and Hospital Universitari Joan XXIII of Tarragona.

7.2 Study population

The patients of the study would be pregnant women older than 18 years of age that they are at a high risk of preterm PE at first trimester. In order to determine this high risk (> 1/100) we will use a calculator that combines ([ANNEX 6](#)):

1. Maternal factors by a clinical interview
2. PI uterine arteries
3. Mean Pressure (SBP/DBP)
4. Analytical parameters (PAPP-A, sFlt-1, PlGF)

The estimated time of recruitment is two years and half during the first trimester counselling visit (11.0-13.6 weeks of GA). Patients that obtained an individual high risk will be asked to participate in our study. After completing all the following inclusion and exclusion criteria and signing the informed consent, patients will be randomly distributed to 1 of the 2 groups.

7.3 Inclusion criteria

1. Age of 18 years old or more
2. Singleton pregnancy
3. Alive fetus (present Fetal Heart Beat)
4. High risk for preterm PE according to the risk calculator ($>1/100$)

7.4 Exclusion criteria

1. Fetal genetic or major malformations
2. HIV infection
3. Chronic renal disease
4. Familial hypercholesterolemia
5. Hipersensitivity to pravastatin
6. Hipersensitivity to aspirin
7. Long-term use of nonsteroidal anti-inflammatory treatment
8. Coagulation disorders (haemophilia, hypothrombinaemia)
9. Mental disorders

7.5 Sample size

To calculate the estimated sample size, the online tool GRANDMO© has been used.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 2323 subjects are necessary in Group 1 (Aspirin) and 2.323 in Group 2 (Pravastatin) to find the statistically significant proportion difference, expected to be of 0,0788 in Group 1 and 0,058 in Group 2. It has been anticipated a drop-out rate of 1%. The ARCSINUS approximation has been used. So, the total number of participants needed for the study is 4.646.

Reduction percentage	Total sample size (N)
1%	21.654 patients
2%	4646 patients
4%	1016 patients

Table 5: *Estimated sample size respect from Pravastatin expected effectiveness.*

According to a meta-analysis about aspirin treatment, including data of 32.217 women from 31 randomized trials, it was shown that among high risk women, the incidence observed in patients treated with aspirin was 7.88%. (32).

To achieve a representative sample size according to Catalonia's population and the epidemiology of PE, we estimate a reduction of incidence PE about 2% (Table 5).

7.6 Time of recruitment

Incidence of pregnancies with a high risk of PE is considered to be 11% according to an article published in New England Journal of Medicine (28), and assessing the number of pregnancies registered in Hospital Universitari Josep Trueta per year, there are approximately 165 patients at high risk of PE per year.

A multicentre study should be performed taking into account the reference centers of all Catalonia in order to recruit 4.646 patients for two years and half. Thus, we decided to include seven hospitals mentioned in *Section 7.1 Study design*.

7.7 Sample collection

A non-probabilistic consecutive sampling method will be performed. This recruitment consists on selecting patient who fulfil diagnose criteria listed in *Section 2.5 Diagnosis and Clinical Spectrum* and do not meet exclusion criteria admitted at participating hospitals. An intention-to-treat analysis will be used in this study, so if a patient leaves during it or her follow-up is lost, data will not be excluded. Subjects withdrawn from the trial will not be replaced.

An information sheet of the study ([ANNEX 9](#)) for participants enrolled will be given. If the patient agrees with it, she will sign the informed consent ([ANNEX 10](#)).

7.8 Randomization and masking

The patients will be randomly divided in two groups (1:1 ratio) and it will be performed with a randomized electronic procedure.

-Group 1: 2.323 patients. Aspirin 150 mg by oral administration every night before going to bed until 36 weeks of GA.

-Group 2: 2.323 patients. Pravastatin 10 mg by oral administration every night before going to bed until 36 weeks of GA.

In order to maintain double-blind criteria, aspirin and pravastatin tablets will be identical in color, shape and size.

7.9 Variables

7.9.1 Independent

Aspirin: 150 mg by oral administration every night before going to bed.

Pravastatin: 10 mg by oral administration every night before going to bed.

7.9.2 Dependent

Incidence of Episode of Preeclampsia before 37 weeks of GA: Dichotomous nominal qualitative variable. It will be expressed by *yes or not*.

The diagnosis includes two criteria:

1. SBP of more than 140 mmHg and DBP of more than 90 mmHg after 20 weeks' gestation in a previously normotensive patient. This measurement must be present on at least two occasions at least 6 hours apart but no more than 1 week apart.

The assessment of BP should be done as follows sphygmomanometer (OMRON M2 Classic-vHEM-7121-E©):

a) The pregnant woman seated and the arm resting on a table at heart level having remained in this position at least 5 minutes before the measurement. It could also be done in a position of slight left lateral decubitus position, because the important thing is that it is always done in the same position and same arm.

b) The cuff that will have an air bag about 12-15 cm wide, which surrounds at least 80% of the circumference of the arm, should fit tightly in the arm at the level of the heart.



2. New-onset proteinuria (> 300 mg of protein in a 24-urine collection or a random urine protein/creatinine ratio of $> 0,3$ or 2 + protein or greater on dipstick urinalysis) present on at least two occasions at least 6 hours apart but no more than 1 week apart.

Thrombocytopenia: Continuous quantitative variable. It is considered less than 100.000 platelets/ mm^3 and measured in platelets/ mm^3 . The assessment of this parameter should be done with a blood test when the episode happens.

Renal function: Continuous quantitative variable. Determined with seric creatinine level and it will be measured by mg/dL . *Renal impairment* is considered when seric creatinine level superior than $1,2$ mg/dL . The assessment of this parameter should be done with a blood test when the episode happens.

7.9.3 Co-variables

Age: 18 or more years age. It is a discrete quantitative variable. It will be measured in *years*.

Body Mass Index (BMI): Continuous quantitative variable. It will be measured in kg/m^2 .

Height: Continuous quantitative variable. It will be measured in *centimetres (cm)*.

Weight: Continuous quantitative variable. It will be measured in *kilograms (kg)*.

Smoking: Dichotomous nominal qualitative variable. It will be expressed by *yes* or *not*.

Race: Categorical nominal qualitative variable. It will be expressed by five different groups: *Black, White, Mixed race, South Asian, East Asian*.

Method of conception: Categorical nominal qualitative variable. It will be expressed by three different groups: *Spontaneous, Assisted by use of ovulation drugs, In vitro fertilization*.

Period from last pregnancy: Discrete quantitative variable. It will be measured in *years*

Gestational Age: Discrete quantitative variable. It will be measured in *weeks.week's days*. (i.e. 16 weeks and 3 days =16.3 GA)

Medical history: Categorical nominal qualitative variable. It will be expressed by six different groups: *Diabetes Mellitus type 1, Diabetes Mellitus type 2, Chronic hypertension, Systemic Lupus Erythematosus, Antiphospholipid Syndrome, Thrombophilia*.

Family history of preeclampsia (First degree member): Dichotomous nominal qualitative variable. It will be expressed by *yes* or *not*.

Parity: Categorical nominal qualitative variable. It will be expressed by three different groups: *Nulliparous, Multiparous without preeclampsia, Multiparous with preeclampsia*.

Risk calculator: Continuous quantitative variable. It will be measured in *proportions* (i.e $1/97 = 0,010$).

7.10 Study procedures

Day 0: Considering standard prenatal counselling visits during pregnancy, the matron has previously requested a blood and urine analysis that includes:

- Hemogram, Blood group and Rh
- Screening for chromosomal abnormalities
- Glycaemia
- Pro and anti-angiogenic factors (sFlt-1, PlGF, PAPP-A)
- Serology's (Toxoplasma, Rubella, Syphilis, Hepatitis B, HIV)
- Culture urine, renal function, creatinine and proteinuria

Visit of the first trimester of pregnancy:

- Patient receives analytical results
- Maternal factors clinical history
- Weight and height
- US: Calculating PI Uterine Arteries, CRL and Present Fetal Heart Beat
- Blood pressure

With all these data the individual risk of PE is calculated and the patient is informed. If it is considered high risk ($>1/100$) it is proposed to participate in the patient. In case she accepts, she would sign informed consent. From this moment, she will start her treatment following the schedule that has been agreed (every night before going to bed until 36 weeks of GA).

Recommendations to participants:

- Measure BP by herself as mentioned in *Section 7.6 Variables* to perform at home once a day at home (optional). In the case of 140/90 must be notified immediately.
- Check if the urine volume corresponds approximately to the daily intake of fluids.
- Know guiding symptoms of PE listed in *Section 2.5 Diagnosis and Clinical Spectrum*. In this case, it must be notified immediately.
- Register any side-effects in a diary.
- If there is any doubt, event or lack of medication there is a telephone number.

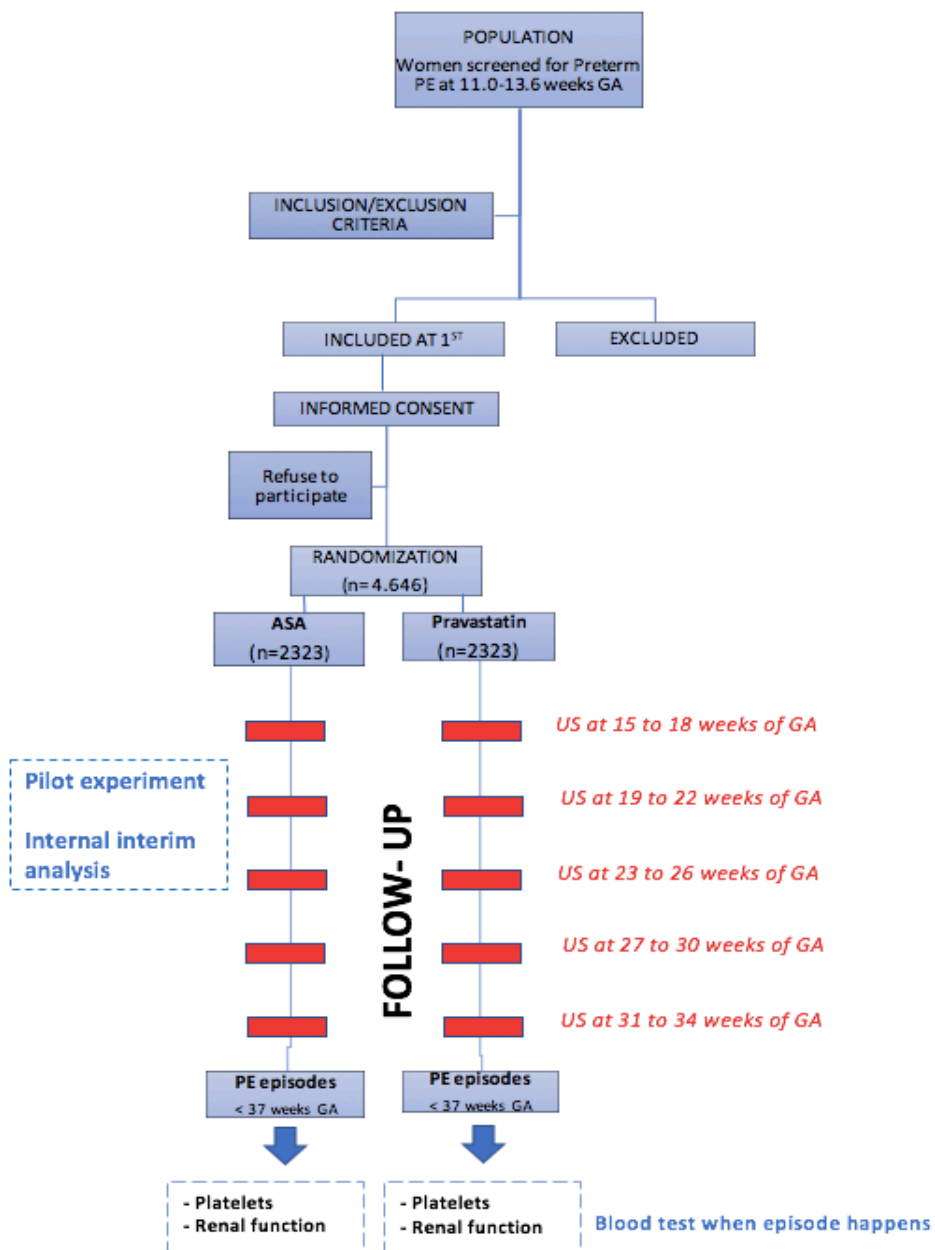
Follow-up by US controls: It will be performed a US every four weeks in order to assess:

- Biophysical profile (**ANNEX 7**)
- NST (**ANNEX 7**)
- Biometrics
- Amniotic Liquid
- Doppler US: Uterine arteries, umbilical vessels and fetus middle cerebral artery
- Register any side-effects, deliver and control tablets

Treatment Adherence: The study team should count the tablets that are returned by patients at each visit. The total number of tablets taken is calculated by subtracting the number of tablets prescribed expressed by *percentage (%)*. For our study, it is considered an acceptable adherence of 90%. Those with a lower percentage would not be included in the multivariate analysis but they will be take into account in the rest of the analysis.

Pilot experiment and Internal interim analysis: A pilot experiment will be conducted for the first seven months to evaluate the case report form, the possible difficulties for obtaining the data and analysing the correct coordination between hospitals. This task should be controlled by the data manager hired for the study.

In order to stop the study if there are clinically relevant differences between the two groups, the statistician will analyse data from the outcomes – Incidence of PE, thrombocytopenia, renal function and side effects – every 500 deliveries consecutively until 4500 are reached.



8. STATISTICAL ANALYSIS

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS©) and Microsoft Excel Windows to manage computed data. Analysis will be performed in intention to treat and the results should be stratified for the different hospitals. P value of $< 0,05$ will be considered statistically significant.

As it is mentioned before, the study includes patients with an adherence treatment of 90%.

UNIVARIATE ANALYSIS: Defining variables as:

- Categorical (qualitative): expressed by *percentages (%)*.
- Discrete or quantitative continuous: expressed by *mean \pm standard deviation (SD), median or interquartile range (IQR)* depending on whether or not the distribution is symmetrical or not (i.e. follow or not a normal distribution).

BIVARIATE ANALYSIS: Comparisons of the incidence of PE between the control and the intervention group, stratified by the covariables.

- Categorical (qualitative): χ^2 test
- Discrete or quantitative continuous: *T- Student* will be applied if the distribution is symmetrical (i.e. normal distributed) or *Mann-Whitney's U* should be applied otherwise.

MULTIVARIATE ANALYSIS: It will be performed with the aim of introducing covariates and cofounding factors in the relationship of interest.

Logistic regression model will be applied in order to estimate odds ratio with 95 % confidence interval. It will be evaluated the relationship between incidence of PE and the effect of pravastatin adjusted by confounders.

Once the model is estimated, we will compute the (*adjusted*) *mean \pm standard deviation* of 'renal function' and 'thrombocytopenia' for the intervention groups. Then, a *T-Student* will be applied.

9. ETHICAL CONSIDERATIONS

This protocol will be evaluated and approved by the Clinical Research Ethics Committee (CEIC) of Hospital Universitari Josep Trueta of Girona, considered as the coordinating study centre.

This committee will ensure the study respects Helsinki's Declaration according to the 64th General Assembly (Fortaleza, Brazil, October 2013) that defines the ethical principles for medical research involving humans' subjects. In case the CEIC considers modifications of the protocol will be considered and introduced.

It is compulsory the Management Department's approval of all the hospitals participating in the study. Then, the protocol must be approved by the Spanish Association of Medicines and Sanitary Products (AEMPS).

This clinical trial will be registered in *ClinicalTrials.gov*. as preventive action to avoid publication bias.

Related to clinical trials, following the "*Real Decreto 1090/2015, de aprobación de la Ley de garantías y uso racional de los medicamentos y productos sanitarios*" from 24th December, patients who receive any drug that may imply any physical or psychic risk, shall be insured. Thus, we will include in our study an insurance policy and all participants will be insured if any damage is caused. Furthermore, *RD 1090/2015* also specify that the study must be a non-commercial clinical research.

Every single patient will be properly informed and with this purpose, an information sheet about the study protocol (**ANNEX 9**) will be given. Then, patients will sign voluntarily the informed consent (**ANNEX 10**). Participants have the right to withdraw the consent without having a negative effect on the relationship with your assigned doctor or treatment received. The principle of autonomy will be respected in all the process.

According to Spanish legislation, "*Ley Orgánica 15/1999 sobre la Protección Personal de Datos*" from 13th December and "*Real Decreto 1720/2007 aprobándose el reglamento de desarrollo de la Ley Orgánica 15/1999*" from 21st December, we ensure the protection of confidentiality of all participants while collecting data and instead of patient's name will be use an identification number in the database of this study.

All the investigators will have to declare no conflict of interest.

10. LIMITATIONS

There are some potential limitations that should be considered because they can interfere in our research:

- Possible loss of participants during the follow-up due to the fact we defined a strict treatment adherence rate (90 %). Because my sample size is enough large (n = 4646), the study would not almost lose statistical power. This trial requires a lot of patient participation, such as several counselling visits, daily treatment with specific indications, etc.
- Candidates women to participate in the study, may refuse the invitation. This fact, as we have seen in the literature review, may imply an extension of the data collection period in order to reach the sufficient sample size. Taking into account this and the incidence of high risk of PE, we have designed a multicentre study in order to achieve conclusive results.
- Ultrasound scanner, a highly operator-dependent test, is used to calculate PE risk and it may generate an information bias. Thus, when the protocol is explained to the study team, we should emphasize on the standardization of the measurements with this device and will ensure that all participating hospitals use an ultrasound scanner with similar strength.
- Due to the fact we have designed a consecutive sampling method, we should try to avoid “selection bias” by selecting our sample based on specific inclusion and exclusion criteria. Only when patients fulfils the first ones and none of the exclusion ones, she will be invited to participate in the trial.
- The study accounts with multiples covariates that can be confounders of the relationship between treatment (intervention) and incidences of PE. For that reason, we have decided to perform a multivariate logistic regression method. Although, there may be other unrecorded covariates despite an exhaustive bibliography, being an open-door to further studies with these possible confounders.
- It may be an ethical limitation for Group 2 (Pravastatin). These patients will not receive the effective current treatment (ASA) . In this way, a possible masking of the effect of pravastatin is avoided and justify this intervention. Future studies may test a combination of ASA + Pravastatin in a hypothetic Group 3.

11. WORK PLAN AND CHRONOGRAM

STAGE 0: STUDY DESIGN (May 2017 - December 2017)

- **First meeting:** Dra. Borrell and I decided to start the study in May 2017.
- **Study protocol development:** The investigators will define the hypothesis and objectives of the study in order to delimit an accurate bibliographic research. The final protocol elaboration will be finished by November 2017.
- **Coordination meeting:** It is an all-member meeting in order to defines the roles of each participant and to clarify and arrange all formation activities to develop it.
- **Gynecology and Obstetrics Department meeting:** The professional in charge of the study (Dra. Borrell) and I will inform to the entire department in each participating hospital about the aim of the study and specify relevant information such as data needed to collect, the importance of having a signed informed consent of the patient with a clear information about the study, protocol of preeclampsia. To emphasize the importance of this meeting will help us to adequately conduct the study.
- **Presentation and approval of the CEIC and AEMPs** by December 2017.

STAGE I - STUDY CONDUCT (January 2018 - June 2020)

- **Database elaboration:** The statistician will create a common database and will encode each patient with a number, in order to avoid confidentiality problems.
- **Data collection:** For two years and half, patients will be recruited following all criteria that have been mentioned previously. Furthermore, their follow-up will be performed until delivery. Because of the multicentre aspect of the study, all devices (US scanner, sphygmomanometers and dipstick urinalysis) must be the mostly the same in order to avoid significant differences in measurement. Internal interim analysis will be performed every 500 patients by the statistician.
- **Control meetings:** Twice a year, study members of the seven teams will meet by video conference in order to inform all centres of the study any relevant situation to deal with and how the study is going. It is important to mention the reduction cost with this step.
There will be an e-mail and telephone number available for any incidence.

STAGE II - DATA ANALYSIS (July 2020 - December 2020)

- **Statistical analysis**: Finally, once all needed data is gathered and registered in IBM SPSS Statistics 24.0©, the statistician will analyse it. Firstable, it will be performed seven analysis (one for each centre) and then, an integrate and final analysis.

STAGE III - INTERPRETATION AND DISCUSSION RESULTS (January 2021 - May 2021)

- **Conclusion meeting**: The seven teams will meet in order to evaluate and discuss the findings.
- **Study writing**: The results will be interpreted by the main investigators and finally edit the conclusions of the study.

STAGE IV - PUBLICATION AND DISSEMINATION OF THE RESULTS (June 2021 - December 2021)

- **Publication of the results**: Final results and conclusion will be written and published in journal article.
- **Dissemination of the results**: Attendance to conference at national and international congresses.

ACTIVITY	RESPONSIBLE PERSONNEL	2017												2018			2019			2020			2021			
		M	J	J	A	S	O	N	D	J→D	J→D	J→D	J→D	J→D	J→D	J→D	J→D	J→D	J→D	J→D	J→D					
First meeting	Dra. Borrell and G. Chueca	[Bar]																								
Study protocol development	Dra. Borrell and G. Chueca	[Bar]																								
Coordination meeting	Whole team	[Bar]																								
G&O Department meeting	Whole team	[Bar]																								
CEIC and AEMPs approval	Dra. Borrell and G. Chueca	[Bar]																								
STAGE 0																										
Database elaboration	Statistician	[Bar]																								
Data collection	Whole team	[Bar]																								
Control meetings	Whole team	[Bar]																								
STAGE I																										
Statistical analysis	Statistician	[Bar]																								
STAGE II																										
Statistical analysis	Statistician	[Bar]																								
STAGE III																										
Conclusion meeting	Whole team	[Bar]																								
Study writing	Dra. Borrell and G. Chueca	[Bar]																								
STAGE IV																										
Publication of the results	Whole team	[Bar]																								
Dissemination of the results	Whole team	[Bar]																								

12. FEASIBILITY

This study will take place in seven centres from Girona, Barcelona, Badalona, Lleida and Tarragona which are full equipped with necessary material in order to follow this protocol. We have to consider if the study only includes Girona's population, it will last more than ten years. On the other hand, if the study reduces this period focusing in this concerned population, there is a risk to obtain results that would not be statistically significant.

Having in consideration the budget, we know that this proposed clinical trial is an important invest. However, the majority of budget is due to the treatment cost (106.858 €) because other material needed is included in routine hospital care practice. Additional clinician personnel are not needed. However, we will hire a data manager during data collection period (two years and half) and statistician in order to analyze our database.

We know that is difficult to enrol 4646 high risk of preterm PE patients for our clinical trial, but the relevance of the study and the possible impact of the results, justifies the efforts.

13. BUDGET

In order to calculate accurately the needed budget for this trial we have divided the costs in personnel, materials, meetings and publication results costs.

PERSONNEL

Most of the activities will be performed by professionals of the participating hospitals within their assistance labour timetable. The follow-up will be performed monthly in contrast to "normal" pregnancy but it won't be an extra-cost. In fact, for a pregnant woman at high risk of PE counselling visits are performed each month.

The study need a qualified statistician in order to design the database and the data analysis period.

There should be a contract of 20 hours per week of work coordination (data manager) during two years and half (STAGE I), due to the fact of being a multicenter study requires a constant review of the information is being collected correctly.

MATERIALS and SERVICES

Devices will be the same used in the routine hospital care practice. As detailed in previous sections, we will try to use the same or very similar brand devices to avoid bias in measurements among hospitals. The same will happen with laboratory tests, which not entailed an additional cost for the study because they are performed routinely.

It should be included treatment cost because modified tablets with the same appearance of aspirin and pravastatin will be used to maintain the double-blind of the study. The treatment cost per patient is 23 €.

The budget does not include material office supplies and software such as SPSS© and Microsoft Windows© software, because our participating centers hold the correspondent licenses.

Finally, we must hire an insurance policy in our study, which all participants will be covered by if any damage is caused, apart from hospital civil liability insurance.

MEETINGS

In order to minimize the cost of meetings, they will be made by videoconference (the participating centers have a meeting room with electronic devices to carry them out). In each meeting, a professional of Gynecology and Obstetrics Department of each hospital will be representing the entire unit.

There will be only a final conclusion meeting at Hospital Vall'Hebron of Barcelona in order to evaluate and discuss the findings.

PUBLICATION AND DISSEMINATION RESULTS

Established taxes to include are: AEMPS authorization, publication cost.

We will try to publish our study in *SEGO Journal* as well as other suitable journals. Furthermore, we attempt to assist to National and International congress, if it is possible.

	Price per unit	Amount	Total
PERSONNEL			
Statistician	25€	150 hours	3750€
Data manager	22.000€/year	2'5 years	55.000€
MATERIALS and SERVICES			
Treatment	23€	4646 Patients	106.858€
AEMPS authorization	1300€	1	1300€
Insurance	-	-	12.000€
MEETINGS			
Final conclusion meeting	-	-	1500€
PUBLICATIONS AND DISEMINATION			
Publication cost	1200€	1	1100€
Inscription National Obstetrics Congress	350€	2	700€
Inscription International Obstetric Congress	750€	2	1500€
Travel, accommodation and food	800€	2	1600€
TOTAL			185.308€

14. CONFLICT OF INTEREST

The authors declare no conflict of interest.

15. PROJECT IMPACT ON THE NATIONAL HEALTH SYSTEM

Preeclampsia remains one of the top 5 causes of maternal death in developing countries as we have mentioned above. It is a disease that increases morbidity in both, the fetus and the mother. In the case of the newborn, the association with preterm birth is frequent, and despite the neonatal intensive care unit that increases the survival rate, the economical cost of this health care is very high.

This study would be the first about comparing these two drugs nationally and also internationally. As it is mentioned above, race is an influential factor. Nowadays, in a global world with important migratory movements, the population is a mixture of races, being a health problem concerning our population.

It is also expected that if our hypothesis is not confirmed or we find new relationships between the outcomes, this could be an open door that encourage other research teams to perform new studies about this promising treatment.

16. ANNEXES

16.1 ANNEX 1.- Studies reporting about effects of pravastatin in animal models (16)

Preclinical model	Agent	Results	Reference
CBA/J × DBA/2 mice	Pravastatin (20 ug/kg)	↓ sFlt-1 ↓ Hypersensitivity to Ang II ↑ VEGF	Ahmed et al., 2010
CD-1 mouse injected with adenovirus carrying sFlt-1	Pravastatin (5 mg/kg/d)	↓ sFlt-1 Restoration of glucose response in females	McDonnold et al., 2014
CD-1 mouse injected with adenovirus carrying sFlt-1	Pravastatin (5 mg/kg/d)	Regularization of impaired vestibular function, balance and coordination linked with preeclampsia	Carver et al., 2014
CD-1 mouse injected with adenovirus carrying sFlt-1	Pravastatin (5 mg/kg/d)	↓ sFlt-1 ↓ sEng ↓ Overexpression of TGF-β in placenta ↓ HIF-1α	Saad et al., 2014
CD-1 mouse injected with adenovirus carrying sFlt-	Pravastatin (5 mg/kg/d)	↑ eNOS in the aorta	Fox et al., 2011
CD-1 mouse injected with adenovirus carrying sFlt-1	Pravastatin (5 mg/kg/d)	↓ sFlt-1 ↑ PIGF ↓ Hypertension ↓ Proteinuria	Kumasawa et al., 2011
CD-1 mouse injected with adenovirus carrying sFlt-1	Pravastatin (5 mg/kg/d)	↓ sFlt-1 ↓ Contractile response to phenylephrine ↑ Vasorelaxant response to ACh	Costantine et al., 2010
C1q deficient (C1q ^{-/-}) mouse	Pravastatin (5 mg/d)	↑ VEGF ↓ sFlt-1 ↓ Albumin creatinine ratio (ACR) ↓ STAT-8 ? Matrix metalloproteinase (MMP) activity Normal aortic ring response to AngII	Singh et al., 2011
Reduced utero-placental perfusion pressure (RUPP) rats	Pravastatin (1 mg/kg/d)	↓ MAP ↓ sFlt-1 ↑ VEGF ↓ sFlt-1/VEGF ratio ↓ Thiobarbituric acid reactive substances ↑ Total antioxidant capacity ↓ Endothelial tube formation No effect on HO-1 expression	Bauer et al., 2013

16.2 ANNEX 2.- Antihypertensive pharmacological treatment (7)

Labetalol (Trandate®): (1 amp=20ml=100mg). Fármaco alfabetabloqueante.

- Posología: iniciar la medicación con un bolus ev lento (1-2 minutos) de 20mg. Repetir al cabo de 20 minutos si no se controla la PA doblando la dosis (40, 80, 80 mg. No sobrepasar los 200 mg). Seguir con perfusión continua (dosis comprendida entre 50-400 mg/6h). Si la PA no se controla se puede doblar la perfusión cada 15 minutos hasta llegar a una dosis máxima de 600 mg/6h, aunque con dosis >300 mg/6h se aconseja asociar hidralazina antes de aumentar perfusión labetalol.
- Dosis máxima diaria: 2400 mg = 600mg/6h.
- Efectos secundarios: bradicardia fetal. En prematuros se ha de alejar el máximo posible del nacimiento.
- Contraindicaciones: insuficiencia cardíaca congestiva, bradicardia materna <60 latidos/minuto y asma.

Nifedipino (Adalat® 1 comp=10 mg, Adalat Retard® 1 comp= 20 mg y Adalat Oros® 1 comp= 30 o 60 mg). Fármaco antagonista del calcio.

- Posología: dosis inicial: 10 mg vo o masticada. Se puede repetir en 30 min. Dosis de mantenimiento: 10-20 mg/6-8h.
- Dosis máxima diaria: 60 mg.
- Contraindicada la vía sublingual por el riesgo de hipotensión severa.
- Efectos secundarios: cefalea, rubor, taquicardia y edemas.
- Contraindicación relativa en pacientes con estenosis intestinal (posibilidad de clínica obstructiva).

Hidralazina (Hidrapress®): (1 amp= 20ml = 20mg). Fármaco vasodilatador.

- Posología: iniciar la medicación con bolus ev lento (1-2 minutos) de 5 mg. Se pueden repetir un máximo de 4 bolus en intervalos de 20 minutos. Continuar perfusión de 3-7 mg/h ev.
- Dosis máxima diaria: 200 mg.
- Efectos secundarios: taquicardia materna y cefalea.
- Contraindicaciones: taquicardia, enfermedad coronaria y cardiopatía.

Nitroglicerina:

- Posología: 5 mcg/min y aumento gradual doblando la dosis cada 5 minutos si precisa (dosis máxima de 100 mcg/min)
- Contraindicada en encefalopatía hipertensiva ya que puede aumentar el flujo sanguíneo cerebral y la presión intracraneal.
- Es una buena opción de tratamiento para la HTA asociada a edema pulmonar.

Nitroprusiato sódico:

- Posología: 0.25 mcg/kg/min aumentando la dosis 0.25 mcg/kg/min cada 5 minutos si precisa (dosis máxima 10 mcg/kg/min)
- Sólo indicado si han fracasado los otros tratamiento ya que es fetotóxico por acumulo de cianida si se utiliza más de 4 horas. Por lo tanto, se trata de un agente de último recurso para el control urgente de la HTA severa y refractaria y un máximo de 4 horas.

16.3 ANNEX 3.- BISHOP test and interpretation (43)

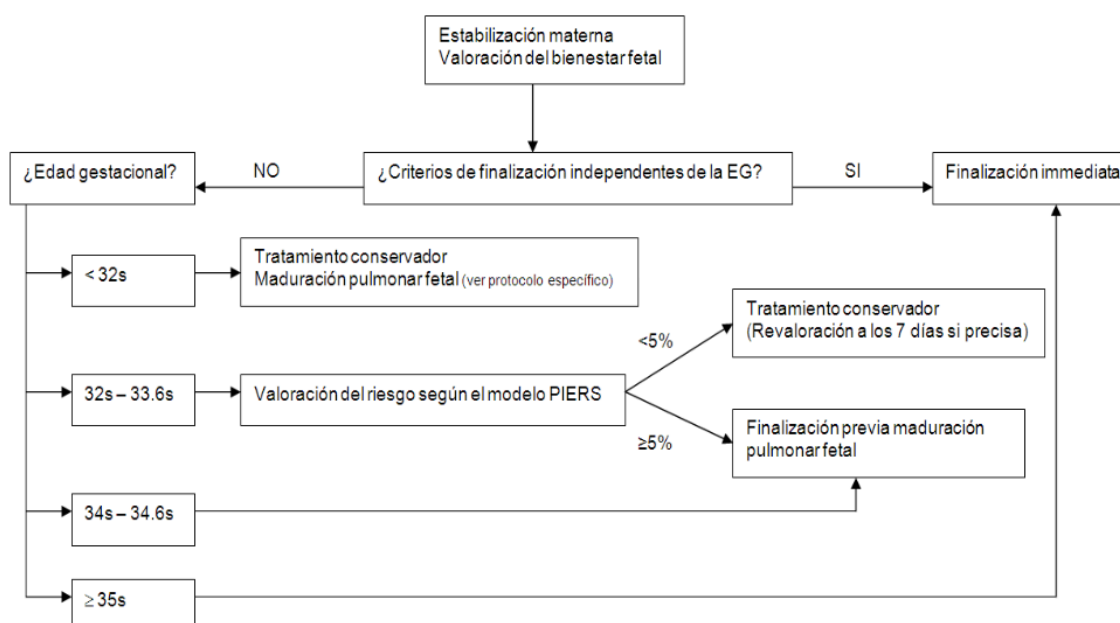
Puntuación	0	1	2	3
Posición cérvix	Posterior	Media	Centrado	---
Consistencia	Dura	Media	Blanda	---
Longitud Borrado	3 cm 0-30%	2 cm 40-50%	1 cm 60-70%	Borrado >70%
Dilatación	0 cm	1-2 cm	3-4 cm	>4 cm
Plano de Hodge	Libre	I-II	III	IV

- **Si Bishop \leq 6:** Maduración cervical previa con dispositivo liberación de prostaglandinas (Propess®). El misoprostol está contraindicado.

- **Si Bishop $>$ 6 o fracaso de maduración:** Inducción con oxitocina:

- o *Monitorización externa continua de la FCF y DU* (salvo en caso de no conseguir registrar correctamente la dinámica uterina, exista una progresión anormal del parto o un alto riesgo de rotura que se indicará monitorización interna).
- o Iniciar la administración de oxitocina, siempre con bomba de infusión y diluida en suero fisiológico (5 U en 500 ml ó 10 U en 1000 ml).
- Dosis de inicio: 1 mU/min. (6 ml/h).
- El *aumento de dosis*, si fuera necesario: 1-2 mU/min (6-12 ml/h) cada 20 min. Interrumpir la administración de oxitocina si se registra polisistolía o más de 200 UM.
- El tiempo de inducción del parto con oxitocina no debería exceder las 8 horas.

16.4 ANNEX 4.- Algorithm of delivery depending on GA (20)



16.5 ANNEX 5.- Gestational Calculator v2013.1 (44)

Preeclampsia 1T		Biometric data	
Epidemiologic data		Age (years):	
Parity:	<input type="text" value="Nulipara"/>	<input type="text"/>	
Previous PE:	<input type="text" value="No"/>	Height (cm):	
Hypertension:	<input type="text" value="No"/>	<input type="text"/>	
Renal disease:	<input type="text" value="No"/>	Weight (kg):	
Coagulopathy:	<input type="text" value="No"/>	<input type="text"/>	
Diabetes:	<input type="text" value="No"/>	First Trimester Data	
Ethnic group:	<input type="text" value="European"/>	CRL(mm):	
		<input type="text"/>	
		PAPP-A(MoMs):	
		<input type="text"/>	
		Systolic BP (mmHg):	
		<input type="text"/>	
		Diastolic BP (mmHg):	
		<input type="text"/>	
		IPmAUt:	
		<input type="text"/>	
		Calculate	
		Risk early PE:	
		<input type="text"/>	

16.6 ANNEX 6.- Fetal Medicine Foundation Calculator (27)

Maternal characteristics

Date of birth

Height cm ft in

Weight kg lbs

Racial origin

Conception method

Smoking during pregnancy Yes No

Mother of the patient had PE Yes No

Medical history

- Chronic hypertension
- Diabetes type I
- Diabetes type II
- Systemic lupus erythematosus
- Anti-phospholipid syndrome

Obstetric history

- Nulliparous (no previous pregnancies at ≥24 weeks)
- Parous (at least one pregnancy at ≥24 weeks)

Pregnancy dating (select one of the methods below)

Fetal crown-rump length (45-84 mm)

Fetal head circumference (158-226 mm)

Manual (any gestation)

Gestational age weeks

Date of measurement

Date of measurement	Weight ⁱ	MAP (mmHg) ⁱ	Mean UTPI ⁱ
<input type="text" value="dd-mm-yyyy"/>	<input type="text" value=""/> kg <input type="text" value=""/> lbs	<input type="text"/>	<input type="text"/>

Date of measurement	Weight ⁱ	PLGF (MoM) ⁱ	PAPP-A (MoM) ⁱ	sFLT-1 (MoM) ⁱ
<input type="text" value="dd-mm-yyyy"/>	<input type="text" value=""/> kg <input type="text" value=""/> lbs	<input type="text"/>	<input type="text"/>	<input type="text"/>

16.7 ANNEX 7.- Biophysical profile and NST (Non Stressed Test) (45)

Each of the five parameters represents a separate evaluation of fetal behaviour and function and they are scored as either 0 (absence) or 2 points (presence).

Score 8-10 (Normal); 6 (suspicious, to repeat the following day); less than 6 (hospitalization for further evaluation).

Parameter	Normal
1.Breathing	At least 1 episode of 30 seconds during an observation period of up to 20 minutes.
2.Movement	At least 3 gross body movements during a 20-minutes observation period.
3.Heart Rate Monitoring	At least 2 accelerations of 15 BPM above baseline that last for at least 15 seconds in total duration in a 20-minute tracing.
4.Muscular Tone	At least 1 episode of extension with a return flexion to flexion for 20 minutes period observation.
5.Amniotic Liquid	At least 2 cm vertical pocket.

Breathing, Movement, Muscular tone and Amniotic liquid are measured by US scanner. However, Heart rate monitoring is measured by NST.

NST is the combination of Fetal Heart Rate with fetal movements, obtaining different patterns. A normal or reactive NST usually is defined by 2 accelerations in a 20-minute period, each lasting at least 15 seconds and peaking at least 15 beats per minute above the baseline.

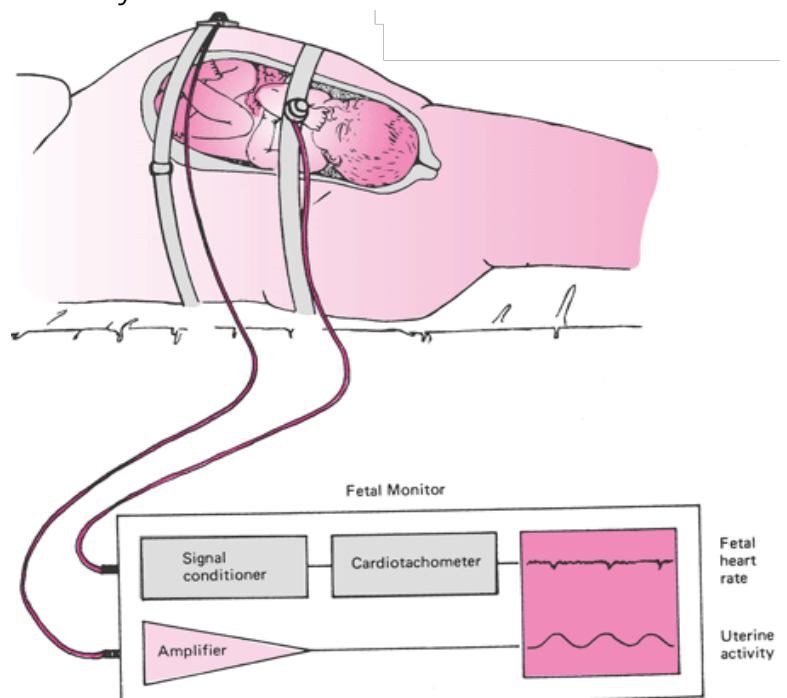


Figure 8. NST. US waves from the transducer penetrate the tissues and are reflected by tissue interface.

16.8 ANNEX 8.- Pulsatility Index by Doppler ultrasound (19)

In US terms, Doppler depends on the ability of an ultrasound beam to be changed in frequency when encountering red blood cells. This data is transformed into a waveform that represents a clear systolic (S) and diastolic (D) components.

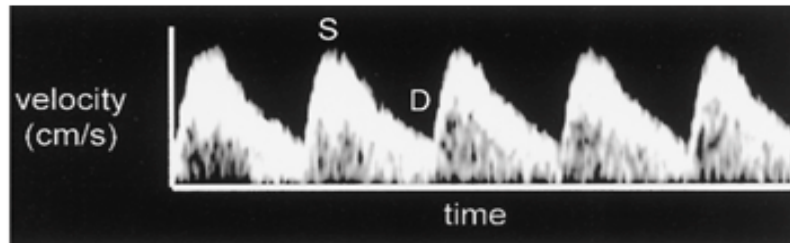


Figure 9. Doppler ultrasound demonstrating S and D velocities

From these data, it can be calculated a resistance index (RI) and a pulsatility index (PI) which have a clinical representation of fetal and maternal vessel such as umbilical and uterine arteries, middle cerebral artery, cardiac flow, umbilical vein, ductus venous or hepatic veins.

$$\text{systolic/diastolic (S/D) ratio} = \frac{S}{D}$$

$$\text{pulsatility Index (PI)} = \frac{S - D}{\text{mean velocity}}$$

16.9 ANNEX 9.- Information sheet

HOJA DE INFORMACIÓN AL PACIENTE

[Versión castellano]

Principales investigadores: Anna Borrell & Guillermo Chueca Cortés.

Título del ensayo clínico: Pravastatin as a new treatment at High Risk Women for Preterm Preeclampsia? A controlled, double-blind, randomized, clinical trial.

Introducción: Agradecemos su colaboración en el presente estudio que tendrá lugar en el Servicio de Ginecología y Obstetricia en el Hospital Universitari Josep Trueta, en Girona, Hospital Vall'Hebron y Hospital Sant Pau de Barcelona. La finalidad de este documento es que usted reciba la información pertinente y fidedigna para considerar si desea o no participar en el presente estudio.

Finalidad: Nuestro objetivo es conocer si la pravastatina resulta más eficaz respecto a la aspirina (el tratamiento vigente) en mujeres embarazadas de alto riesgo de padecer preeclampsia antes de las 37 semanas de gestación. Este fármaco actualmente no está indicado en esta patología, pero estudios *in vitro* y posteriormente en humanos comparado con placebo ha dado resultados positivos. De esta manera, compararemos cuál de estos dos fármacos previene más eficazmente los episodios de preeclampsia, con la hipótesis de que la pravastatina supondrá una disminución de la morbimortalidad considerable tanto para el feto como para la madre.

Participación voluntaria: La participación en este estudio es totalmente voluntaria. Además, tiene derecho a solicitar a los investigadores responsables, en cualquier momento, y sin necesidad de detallar los motivos, retirar el consentimiento. Esto no implicará un efecto negativo sobre la relación con su médico asignado ni sobre el tratamiento recibido.

Descripción del proceso: Durante su participación en el estudio le informaremos sobre los objetivos del protocolo y resolveremos las dudas que le puedan surgir durante el proceso.

Actualmente, todas las pacientes que tengan la primera visita para seguimiento del embarazo entre 11.0-13.6 semanas de gestación, se les ofrece un algoritmo de screening de riesgo de preeclampsia que constará de: 1) Cuestionario sobre factores maternos, 2) Medición de la Presión Arterial, 3) Medición mediante Ecografía Doppler del Índice de Pulsatilidad de arterias uterinas, 4) Utilización de parámetros extraídos de la analítica rutinaria de primer trimestre.

El resultado obtenido de esta calculadora será informado individualmente a cada paciente. Aquellas embarazadas que obtenga un riesgo alto ($> 1/100$) se les invitará a participar en el estudio voluntariamente, donde se les asignará de forma randomizada y aleatorizada en dos grupos: *Grupo 1* recibirá aspirina y *Grupo 2* recibirá aspirina. Es importante destacar el carácter de doble ciego del estudio, es decir, ni paciente ni facultativo sabrán cuál de los dos tratamientos está recibiendo cada participante

El tratamiento será autoadministrado oralmente con duración desde el día que se acepte participar en el estudio (semana 11.0-13.6) hasta la semana 36.0 de gestación. Las participantes del estudio recibirán un número determinado de comprimidos que en cada visita con el personal del estudio será contabilizado, con el objetivo de comprobar que ha cumplido la pauta del tratamiento acordado. Ambos grupos tomarán un comprimido cada noche antes de ir a dormir.

Controles del estudio: A lo largo del proceso serán citadas cada cuatro semanas en la consulta para realizar una ecografía doppler y entrevista clínica. Estas revisiones incluyen la visita de segundo y tercer trimestre de cualquier embarazada junto con las pruebas que se requieran en dichos controles de forma rutinaria. Además, existe un número de teléfono disponible para cualquier duda e incidencia que surja a lo largo del proceso.

Riesgos y beneficios: Con este estudio se pretende hallar un tratamiento preventivo de la preeclampsia más eficaz respecto al ya existente. Para ello, periódicamente se realizarán evaluaciones internas para descartar que no existen diferencias clínicamente relevantes entre los dos grupos del estudio.

Cualquier evento o efecto secundario derivado del tratamiento será registrado en las consecutivas visitas clínicas o bien por vía telefónica, recomendando a los participantes anotar en un diario cualquier incidencia que se produzca para comunicarlo al personal del estudio. Además, al comienzo del estudio, se le explicará a la paciente que en el caso de que aparezca alguno de los “signos guías” de la enfermedad (fotopsias, cefalea, vómitos, epigastralgia, edemas maleolares bruscos), debe notificarlo inmediatamente. Otras medidas domiciliarias recomendadas, son la automedición de la Presión Arterial una vez al día junto con el control aproximado de la cantidad de orina respecto de la ingesta de líquidos.

Aspirina 150 mg describe mínimos efectos adversos con respecto a dosis habituales: gastritis.

Pravastatina 10 mg describe como efectos adversos (con frecuencia mínima): dolores musculoesqueléticos, incluyendo artralgias, calambres musculares, mialgias, debilidad muscular y elevación sérica de creatin kinasas y función hepática.

Se le puede facilitar la ficha técnica de ambos medicamentos por si desea consultar cualquier duda.

Compensación por los daños: Se ha contratado una póliza de seguro, cubriendo a todos los pacientes del estudio de acuerdo con el *RD 223/2004 de 6 de Febrero*.

El seguro no cubre los daños o complicaciones derivadas de la progresión natural de la enfermedad.

La participación en el estudio no supondrá gasto económico alguno. El tratamiento será facilitado por el personal del estudio gratuitamente y no recibirá ninguna compensación económica.

Confidencialidad: Su información médica y aquella obtenida sobre usted derivada de este estudio será codificada y archivada confidencialmente de acuerdo con la *Ley Orgánica 15/1999 sobre la Protección Personal de Datos* y el correspondiente *RD 1720/2007* y no podrá ser hecha pública.

El acceso a su información personal quedará restringido al personal del estudio, autoridades sanitarias (AEMPS) y CEIC cuando lo consideren oportuno siempre y cuando sea respetada la legislación vigente.

[En caso necesario, hay disponibles versiones del formulario en otros idiomas]

FULL D'INFORMACIÓ AL PACIENT

[Versió català]

Principals investigadors: Anna Borrell & Guillermo Chueca Cortés.

Títol de l'assaig clínic: Pravastatin as a new treatment at High Risk Women for Preterm Preeclàmpsia? A controlled, double-blind, randomized, clinical trial.

Introducció: Agraïm la seva col·laboració en el present estudi que tindrà lloc al Servei de Ginecologia i Obstetrícia a l'Hospital Universitari Josep Trueta, a Girona, Hospital Vall'Hebron i Hospital Sant Pau de Barcelona. La finalitat d'aquest document és que vostè rebí la informació pertinent i fidedigna per considerar si desitja o no participar en el present estudi.

Finalitat: El nostre objectiu és conèixer si la pravastatina resulta més eficaç respecte a l'aspirina (el tractament vigent) en dones embarassades d'alt risc de patir preeclàmpsia abans de les 37 setmanes de gestació. Aquest fàrmac actualment no està indicat en aquesta patologia, però estudis in vitro i posteriorment en humans comparat amb placebo ha donat resultats positius. D'aquesta manera, compararem quin d'aquests dos fàrmacs prevé més eficaçment els episodis de preeclàmpsia, amb la hipòtesi de que la pravastatina suposarà una disminució de la morbimortalitat considerable tant per al fetus com per a la mare.

Participació voluntària: La participació en aquest estudi és totalment voluntària. A més, té dret a sol·licitar als investigadors responsables, en qualsevol moment, i sense necessitat de detallar els motius, retirar el consentiment. Això no implicarà un efecte negatiu sobre la relació amb el seu metge assignat ni sobre el tractament rebut.

Descripció del procés: Durant la seva participació a l'estudi l'informarem sobre els objectius del protocol i resoldrem els dubtes que li puguin sorgir durant el procés.

Actualment, totes les pacients que tinguin la primera visita per a seguiment de l'embaràs entre 11.0-13.6 setmanes de gestació, se'ls ofereix un algorisme de screening de risc de preeclàmpsia que constarà de: 1) Qüestionari sobre factors materns, 2) Mesura de la Pressió arterial, 3) Mesura mitjançant Ecografia Doppler de l'Índex de pulsatilitat d'artèries uterines, 4) Utilització de paràmetres extrets de l'anàlítica rutinària de primer trimestre

l resultat obtingut d'aquesta calculadora serà informat individualment a cada pacient. Aquelles embarassades que obtinguin un risc alt ($> 1/100$) se'ls convidarà a participar en l'estudi voluntàriament, on se'ls assignarà de forma randomitzada i aleatoritzada en dos grups: Grup 1 rebrà aspirina i Grup 2 rebrà aspirina. És important destacar el caràcter de doble cec de l'estudi, és a dir, ni pacient ni facultatiu sabran quin dels dos tractaments està rebent cada participant.

El tractament serà autoadministrat oralment. Durarà des del dia que s'accepti participar en l'estudi (setmana 11.0-13.6) fins a la setmana 36.0 de gestació. Les participants de l'estudi rebran un nombre determinat de comprimits que en cada visita amb el personal de l'estudi serà comptabilitzat, amb l'objectiu de comprovar que ha complert la pauta del tractament acordat. Els dos grups prendran un comprimit cada nit abans d'anar a dormir.

Controls de l'estudi: Al llarg del procés han de ser citades cada quatre setmanes a la consulta per fer una ecografia doppler i entrevista clínica. Aquestes revisions inclouen la visita de segon i tercer trimestre de qualsevol embarassada juntament amb les proves que es requereixin en aquests controls

de forma rutinària. A més, hi ha un número de telèfon disponible per a qualsevol dubte i incidència que sorgeixi al llarg del procés.

Riscos i beneficis: Amb aquest estudi es pretén trobar un tractament preventiu de la preeclàmpsia més eficaç respecte al ja existent. Per a això, periòdicament es realitzaran avaluacions internes per descartar que no hi ha diferències clínicament rellevants entre els dos grups de l'estudi.

Qualsevol esdeveniment o efecte secundari derivat del tractament serà registrat en les consecutives visites clíniques o bé per via telefònica, recomanant als participants anotar en un diari qualsevol incidència que es produeixi per comunicar-ho al personal de l'estudi. A més, al començament de l'estudi, se li explicarà a la pacient que en el cas que aparegui algun dels "signes guies" de la malaltia (fotòpsies, cefalea, vòmits, epigastràlgia, edemes mal·leolars bruscs), ha de notificar-ho immediatament. Altres mesures domiciliàries recomanades, són la automesurament de la Pressió Arterial un cop al dia juntament amb el control aproximat de la quantitat d'orina respecte de la ingesta de líquids.

Aspirina 150 mg descriu mínims efectes adversos pel que fa a dosi habituals: gastritis.

Pravastatina 10 mg descriu com efectes adversos (amb freqüència mínima): dolors musculoesquelètics, incloent artràlgies, rampes musculars, miàlgies, debilitat muscular i elevació sèrica de creatin kinases i funció hepàtica.

Se li pot facilitar la fitxa tècnica de tots dos fàrmacs per si voleu consultar qualsevol dubte.

Compensació pels danys: S'ha contractat una assegurança, cobrint a tots els pacients de l'estudi d'acord amb el RD 223/2004 de 6 de Febrer.

L'assegurança no cobreix els danys o complicacions derivades de la progressió natural de la malaltia.

La participació en l'estudi no suposarà cap despesa econòmica. El tractament serà facilitat pel personal de l'estudi gratuïtament i no rebrà cap compensació econòmica.

Confidencialitat: La seva informació mèdica i aquella obtinguda sobre vostè derivada aquest estudi serà codificada i arxivada confidencialment d'acord amb la Llei Orgànica 15/1999 sobre la Protecció Personal de Dades i el corresponent RD 1720/2007 i no podrà ser feta pública.

L'accés a la seva informació personal quedarà restringit al personal de l'estudi, autoritats sanitàries (AEMPS) i CEIC quan ho considerin oportú sempre que sigui respectada la legislació vigent.

[En cas necessari, hi ha disponibles versions del formulari en altres idiomes]

16.10 ANNEX 10.- Informed consent

HOJA DE CONSENTIMIENTO INFORMADO

[Versión castellano]

TÍTULO DEL ESTUDIO: Pravastatin as a new treatment at High Risk Women for Preterm Preeclampsia. A controlled, double-blind, randomized, clinical trial.

Yo, Sr/Sra _____, con DNI _____

Afirmo que:

- He leído y entendido la Hoja de Información para el paciente y la Hoja de Consentimiento Informado, pudiendo conservar una copia de ambos documentos.
- He sido informada de las implicaciones y finalidades del presente estudio, entendiendo que mi participación es totalmente voluntaria y podré abandonar el estudio en cualquier momento que lo requiera sin suponer ninguna implicación en mi futura atención sanitaria.
- Asumo los riesgos y beneficios derivados del estudio.
- Permitiré al personal del estudio consultar datos sobre mi Hª clínica personal durante el periodo especificado del estudio conforme con la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal.
- Se me ha dado el tiempo y la oportunidad de realizar las preguntas pertinentes obteniendo respuestas satisfactorias.

Conforme a lo anteriormente mencionado, acepto voluntariamente participar en este estudio.

Doy permiso para que la información resultante de este estudio sea utilizada en futuras investigaciones relacionadas con esta patología.

En Girona, a _____ de _____ de 20_____

Firma de la participante: _____ Firma del investigador/a: _____

[En caso necesario, hay disponibles versiones del formulario en otros idiomas]

FULL DE CONSENTIMENT INFORMAT

[Versió català]

TITLE DEL ESTUDI: Pravastatin as a new treatment at High Risk Women for Preterm Preeclampsia.
A controlled, double-blind, randomized, clinical trial.

Jo, Sr / Sra, _____, amb DNI

Afirmo que:

- He llegit i entès el *Full d'Informació per al pacient* i el *Full de consentiment informat*, podent conservar una còpia de tots dos documents.
- He estat informat de les implicacions i finalitats del present estudi, entenent que la meua participació és totalment voluntària i podré abandonar l'estudi en qualsevol moment que ho requereixi sense suposar cap implicació en la meua futura atenció sanitària.
- Assumeixo els riscos i beneficis derivats de l'estudi.
- Permetré al personal de l'estudi consultar dades sobre la meua H^a clínica personal durant el període especificat de l'estudi d'acord amb la Llei Orgànica 15/1999, de 13 de desembre, de protecció de dades de caràcter personal.
- Se m'ha donat el temps i l'oportunitat de realitzar les preguntes pertinents obtenint respostes satisfactòries.

D'acord amb l'anteriorment esmentat, accepto voluntàriament participar en aquest estudi.

Dono permís perquè la informació resultant d'aquest estudi sigui utilitzada en futures investigacions relacionades amb aquesta patologia.

A Girona, a _____ de _____ de 20

Signatura de la participant:

Signatura de l'investigador/a:

[En cas necessari, hi ha disponibles versions del formulari en altres idiomes]