PROTOCOLO DE ESTUDIO

CARDIOVASCULAR RISK ASSESSMENT IN YOUNG WOMEN AFTER INDEX PREGNANCY WITH AND WITHOUT PLACENTAL COMPLICATIONS (CARDIOMOM STUDY)

Versión del protocolo y fecha	Versión: 1.0. Fecha: 12/1/23
Código del Protocolo	IIBSP-MOM-2022-87
Título abreviado	CARDIOMOM
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1. RESUMEN:

Identificación del promotor	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau – IIB Sant Pau c/Sant Quintí, 77-79 08041 Barcelona Tel : 93 553 78 69
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Comité ético de referencia	Comité Ético de Investigación Clínica del Hospital de la Santa Creu i Sant Pau
Objetivo principal	To identify individual predictors and develop integrated models for the prediction of cardiovascular risk later in life, based on placental dysfunction markers (angiogenic factors, placental Dopplers), clinical parameters (preeclampsia and pregnancy complications) during pregnancy, and postpartum variables (maternal socio-economic status, mental health, lifestyle, urbanome and cardiovascular evaluation up to 6 years after delivery).
Diseño	Prospective, multicenter, transverse study.
Enfermedad en estudio	Cardiovascular disease, preeclampsia
Metodología	We will take advantage of the BiSC, EuroPE and AngioCor cohorts. We will evaluate CV biophysical, imaging and biochemical variables 3-6 years after index pregnancy (approximate n=1260). Analyses will include urbanome, placental function and perinatal variables

	during index pregnancy and postnatal variables such as maternal socio-economic status, lifestyle, urban exposome, mental health, blood pressure, cardiac function, coronary artery disease by Coronary Computed Tomography (CCT) and CCT angiography, RM Quantitative Myocardial Perfusion, ophthalmic artery index, carotid intima- media thickness up to 6 years after delivery to predict higher risk for CVD later in life. Patients' needs and expectations according to CV health would be evaluated. A further aim is to develop and validate an eHealth solution for preventive interventions. ~~A proof-of-concept experimental study with high-dose endovenous atorvastartin in severe-PE rats would be tested in relation to CV variables later in life.~~
Población en estudio y número total de sujetos	Young women who presented an index pregnancy with and without placental complications, who have previously participated in cohort studies performed by our group identifying biophysical, biochemical, psychosocial and environmental cardiovascular risk factors during pregnancy. The approximate number or participants from which we expect participation is n = 1260
Calendario. Duración prevista del estudio.	The project will last 3 years and will start in January 2023. The follow-up will take 24 months. During the second year we will develop and validated the App. We will dedicate the last year of the project to conduct the statistical analysis of the data obtained and to write the scientific papers and final reports
Consideraciones éticas	El estudio se llevará a cabo siguiendo rigurosamente las recomendaciones éticas internacionales para investigación y ensayos clínicos en humanos. Así mismo, se garantizarán las normas recogidas en la Declaración de Helsinki y se desarrollará de acuerdo con el protocolo y con los procedimientos normalizados de trabajo (PNTs) que aseguren el cumplimiento de las normas de Buena Práctica Clínica (BPC). El investigador deberá explicar a las posibles participantes, la naturaleza del estudio, sus propósitos, procedimientos, duración estimada, los potenciales riesgos y beneficios relacionados con la participación en el estudio, así como cualquier inconveniente que éste le pueda suponer. Cada una de las participantes será advertida de que su participación en el estudio es voluntaria y de que puede abandonar el estudio en cualquier momento, sin que esto afecte a su tratamiento posterior, ni a su relación con los profesionales que le tratan. Para ello se ha diseñado una hoja de información y de consentimiento para las participantes que se adjunta. Cabe destacar que la realización de este estudio no lleva

	implícito ningún cambio en la atención y estudio en las pacientes. Los datos obtenidos de dichas pruebas se recogerán en una base de datos anonimizada y de acceso restringido a los investigadores, para su posterior estudio.
Fuente de Financiación	PI22/00462 (Instituto de Salud Carlos III)

2. MARCO TEÓRICO. PLANTEAMIENTO DEL PROBLEMA

2.1 Antecedentes y justificación

Cardiovascular disease in women

It's a sobering statistic to learn that heart disease and stroke cause 1 in 3 deaths among women each year - more than all cancers combined (1). In 2019, there were an estimated 275,2 million cases of cardiovascular disease (CVD) in women worldwide. By age 65, women's risk for heart disease is similar to men's. Women are less likely to receive lifesaving treatment for cardiogenic shock than men, according to research presented in March, 22 at ESC Acute CardioVascular Care 2022, a scientific congress of the European Society of Cardiology (ESC) (2).

Although classic type 1 myocardial infarction (MI) occurs three times more commonly in men than in women, the number of women under 65 years with MI is gradually increasing (3). Especially, the number of type II MI with no obstructive coronary arteries (MINOCAs) and spontaneous coronary artery dissections (SCADs) are more prevalent in younger women (4). In high-income regions, the decline in cardiovascular disease mortality has slowed, and in 2017 it increased in women from some countries (eg, the USA and Canada) (5). Additional alarming trends, such as the rise in acute myocardial infarction in younger women, have been documented in the past decade (6). It is a recognized that CVD in women remains understudied, under-recognised, underdiagnosed, and undertreated globally.

Fortunately, up to 80% of CVD may be prevented. There's an incredible window there --20 years --where women can do something if they realize their increased risk. Uncontrollable risk factors for heart disease include age, family history, prior cardiac events, or autoimmune disease. Additionally, pregnancy complications like preeclampsia, gestational diabetes, or postpartum depression have independent and important contributing factors. Among controllable risk factors there are LDL/HDL and triglyceride levels, blood pressure, body mass index, smoking, or sedentary lifestyle, which have the option to be modified (7).

Preeclampsia and cardiovascular disease

Preeclampsia (PE) remains one of the most prevalent complications of pregnancy. Recent statistics show that it may affect ~5 -7% of pregnancies in the UK (8), and approximately 4% in Spain (9). Although improved obstetrical care has significantly diminished PE- associated maternal mortality, it remains a leading cause of peripartum morbidity and a major cause of prematurity and neonatal complications. In severe cases of PE, serious complications can occur during pregnancy and puerperium, such as pulmonary edema, cerebral hemorrhage, hepatic insufficiency, renal failure and even death (10). Some of these can generate sequelae that entail a significant impact on life expectancy and quality of life of these young patients and their families. Severe PE is directly related to cardiac injury, characterized by cardiac remodeling, decreased myocardial relaxation and global left ventricular diastolic dysfunction (11).

In addition, it is known that CV lesions are not limited to the gestational period but evolve after delivery. Cardiac dysfunction evidenced by echocardiography have been found even in normotensive patients with history of PE (12). PE is associated with a 4-fold increase in heart failure and hypertension and a 2-fold increased risk in ischemic heart disease, stroke, and cardiovascular death (13). Thirty percent of previously preeclamptic women have signs of coronary artery calcium deposition around the age of 50, compared to 18% in a reference group (14). Previously preeclamptic women have more modifiable cardiovascular risk factors and develop coronary artery calcium deposition ≈5 years earlier, from the age of 45 onwards, compared to women with normotensive pregnancies (15). These findings are now endorsed by the 2018 American College of Cardiology (ACC)/American Heart Association (AHA), using a history of PE to justify statin prescription in asymptomatic middle-aged women with an intermediate 10-year risk (16). Severity, parity, and recurrence of this pregnancy-induced hypertension increase the risk of subsequent cardiovascular events. The ACC/AHA guidelines introduced the concept of women-specific factors to consider for risk, diagnosis, and treatment of cardiovascular disease; and these factors include PE (16).

¿What is the evidence of a common pathogenic pathway between Preeclampsia and CV disease?

PE is characterized by endothelial dysfunction resulting from an imbalance between maternal circulating angiogenic factors like pro- angiogenic placental growth factor (PlGF), and anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) (17). Placental expression and maternal circulating concentrations of sFlt-1 are increased in PE whereas PlGF is decreased by a combination of decreased expression, because of poor placentation, and reduced free PlGF due to sFlt-1 binding. This leads to an increase in the sFlt-1/PlGF ratio, which has been described as a better predictor for PE severity than either marker alone (18). Recently, our group reported an association between angiogenic factors during pregnancy and CV disease ≈12 years post-partum,

suggesting that angiogenic factors are critical players in PE-associated CV risk later in life (19).

¿What is the evidence linking exposome with Preeclampsia and CV disease?

Environmental urban factors (urbanome) is defined as the environmental factors that could affect health such as air pollution, noise and green spaces. Air pollution is the main environmental contributor to the global burden of disease, being responsible for an estimated 4.2 million deaths annually worldwide. Based on a recent report (2018) by the World Health Organization (WHO), 97% of cities in low- and middle-income countries and 49% of cities in high-income countries do not meet their standards for air quality (20). The CV consequences of air pollution have been strongly established over the past few years, and these consequences even exceed the harmful effects of air pollution on the pulmonary system. Consistent with the Air Quality in Europe-2019 report, the adverse health impact attributable to exposures to PM2.5, NO2 and O3 in Europe for 2016, were 412,000, 71,000 and 15,100 premature deaths, respectively (21). Cesaroni et al., within the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, demonstrated a significant association between PM10 and PM2.5 long-term exposures and an increased risk of first coronary events (22), which is in line with the substantial evidence informing the 2021 WHO Air Quality guidelines on the association between air pollution and cardiovascular mortality (23). In turn, the WHO noise guidelines and its associated systematic review have established that there is high-quality evidence for an association between road traffic noise and incidence of ischeamic heart disease in adults (24). Despite there is evidence in adults and suggestions of effects in pregnancy and PE, the latter is not yet fully established and there is limited evidence for the effects of these environmental factors on PE and also on future maternal CV health.

Aligning research and innovation with gender and women's values, needs and expectations.

Many factors contribute to inequity between men and women in the detection and management of cardiovascular disease. Women have been underrepresented in, or excluded from, cardiovascular clinical trials, which has reduced the ability to measure the safety and efficacy of therapies for women, the potential for identifying sex-specific differences in important outcomes, and the development of sex-specific strategies that could lead to improved guideline recommendations for the prevention and management of cardiovascular disease. Although overall awareness about cardiovascular disease in women has increased during the past decade, most health-care providers and patients still tend to underestimate the cardiovascular risk in women. The physicians who take direct care of women are underused in addressing cardiovascular risk and educating women about their individual risk (25). Although improvements have been made, current evidence suggests that women are still less likely than men to receive cardiovascular therapies recommended by guidelines, with the biggest shortfalls

occurring in young women (26,27). Women have the right to participate in their own healthcare and make their voice heard (28) and it is known that their implication in research process improve the success of the translation into real changes in health.

Why e-health technologies?

Electronic health (eHealth) provides solutions for patient empowerment and value-based health care. Women in the reproductive age are particularly frequent users of internet, social media, and smartphone apps. Most studies in gestational diabetes and mental health show that eHealth applications are good alternatives to standard practice. Apps and exercise programs show a direction toward less gestational weight gain, increase in step count, and increase in smoking abstinence (29, 30). Patients and clinicians report good overall satisfaction with new strategies that enable the shift from hospital-centered to patient-centered care (31).

Missing evidence justifying this study

Evidence currently available in studies conducted in patients with ischemic heart disease and in PE determines a possible common pathophysiological pathway that advises to continue studying causes and possibilities of prediction and prevention, especially in young women, a group that has not been specifically researched. Our main hypothesis is that pregnancy metabolic, angiogenic and cardiac changes and adaptations, determine a certain degree of cardiac injury and remodeling that can have an impact in CV risk later in life.

Since 2016, the Women and Perinatal Health Research Group within Sant Pau Biomedical Research Institute leading this proposal have been collecting clinical variables, biophysical and biochemical parameters, and cardiac parameters from women at risk for preeclampsia (AngioCOR study, NCT04162236) (39) and with diagnosed preeclampsia (EuroPE study; NCT03231657), and since 2018 a new project, the Barcelona Life Study Cohort (BiSC, http://projectebisc.org/en/home/), was started with the aim to evaluate the impact of exposure to air pollution and other urban-related exposures (including noise, green and blue spaces, altogether known as "urbanome") during pregnancy, on maternal and children's development.

Now, 3 to 6 years after delivery, the CARDIOMOM study has as primary objective from a multidisciplinary perspective to evaluate the potential of pregnancy exposome and placental disfunction markers (angiogenic factors, placental Dopplers), PE and its complications, and further postpartum variables such as maternal socio-economic status, lifestyle, urban exposome, mental health, blood pressure, pre-and-post pregnancy BMI, cardiac function, coronary artery disease by Coronary Computed Tomography (CCT) and CCT angiography, RM Quantitative Myocardial Perfusion, ophthalmic artery index, carotid intima-media thickness, up to 6 years after delivery in a large group of women, included in previous cohort studies of our research group, during pregnancy, to predict

higher risk for CV disease later in life. As secondary objective, endothelial and cardiac dysfunction parameters in women after PE would be related with antiangiogenic factors in maternal serum during pregnancy. A third objective will be to evaluate current cardiac risk scores and determine their performance in prediction of risk and use of machine learning tools to add, if necessary, data provided by this study to further tailored risk-assessment for women after index pregnancy. Moreover, women's needs and experience regarding their health would be evaluated, to be able to be transferred into real changes that impact in global women's health benefits. In addition to that, the CARDIOMOM study plans to include experimental data on possible therapeutic targets during and after PE to improve cardiovascular health, to this end, we will treat rats in a PE-model with parenteral high doses of atorvastatin and after index-pregnancy, we will test different prophylactic strategies such as lifestyle changes to improve cardiac risk markers. Finally, we plan to establish and validate a new digital application to introduce lifestyle behaviors that could potentially improve women's health, and this app will be then aplied in future studies within the group of primary and hospital care RICORs network, devoted to maternal and children's health, that involves more than 50 facilities around Spain, and covers half of Spain's nationwide deliveries.

In short, the CARDIOMOM study will provide evidence to evaluate and characterize the association between pregnancy and post- partum factors, and cardiac dysfunction and remodeling in women. We expect to provide evidence supporting systematic follow-up aimed at timely detection and control of all major risk factors for CV disease, and to identify a new therapeutic target for future studies, aiming at prevention of CV morbidity later in life. The final goal is to improve the cardiovascular heath of women and to reduce the burden of the disease.

2.2 Preguntas de investigación

¿Which effect do pregnancy and postnatal biophysical, biochemical, psychosocial and environmental urban factors have in the occurrence and evolution of cardiovascular risk in women?

3.3 Hipótesis

Evidence currently available in studies conducted in patients with ischemic heart disease and in preeclampsia shows a possible common pathophysiological pathway that advises to continue studying its causes and possibilities for prediction and prevention, especially in women, a group that has not been specifically researched. The **main hypothesis** is that pregnancy metabolic, angiogenic and cardiac changes and adaptations determine a certain degree of cardiac injury and remodeling that can make an impact in CV risk later in life. Moreover, we also hypothesize that lifestyle and

exposure to the urban environment during pregnancy and after childbirth can modulate and have an impact in evolving factors that underpin CV risk.

3. OBJETIVOS

3. 1. PRIMARY OBJECTIVE

To identify individual predictors and develop integrated models for the prediction of cardiovascular risk later in life, based on placental dysfunction markers (angiogenic factors, placental Dopplers), clinical parameters (preeclampsia and pregnancy complications) during pregnancy, and postpartum variables (maternal socio-economic status, mental health, lifestyle, urbanome and cardiovascular evaluation up to 6 years after delivery).

3.2. SECONDARY OBJECTIVES

1) To follow-up three existing maternal cohorts to assess endothelial and cardiac dysfunction parameters 3-6 years after delivery in relation to pregnancy complications, especially preeclampsia, compared to normal pregnancies.

2) To assess sociodemographic factors, life-style determinants, mental health, and maternal exposure to the urban environment ("urbanome") during and after pregnancy in relation to cardiovascular risk assessment.

3) To calculate current cardiac risk scores and determine their performance in prediction of risk, and use machine learning tools to add, if necessary, data provided by this study to further tailor risk-assessment for women after index pregnancy.

4) To evaluate women's needs and experience around their health to be transferred into a new eHealth solution to introduce lifestyle behaviors that could potentially improve women's CV health.

5) To test possible therapeutic targets during and after PE to improve cardiovascular health; for this end, we will treat PE-model rats with endovenous high-dose atorvastatin and test life-style changes after delivery.

4. METODOLOGÍA

4.1. Diseño del estudio

Prospective, multicenter, transverse study.

4.2. Población de estudio. Criterios de inclusión, exclusión

Young women who presented an index pregnancy with and without placental complications, who have previously participated in cohort studies performed by our group identifying biophysical, biochemical, psychosocial and environmental cardiovascular risk factors during pregnancy.

Inclusion criteria: patients who participated in the BiSC (Barcelona Life Study Cohort), EuroPE (Randomized open-label control trial to evaluate if the incorporation of sFlt1/PlGF ratio in the diagnosis and classification of PE improves maternal and perinatal outcomes in women with suspicion of the disease; PI16/00375) and AngioCor (Cardiac dysfunction and remodeling in patients with preeclampsia regulated by antiangiogenic environment: clinical and experimental approach, PI19/00702) cohort studies, who have delivered within the previous 3-6 years, and give written consent when invited to participate in this study protocol. The approximate number or participants in these studies is 1800 women, from which we expect participation of around 70% (n = 1260).

Exclusion criteria: unwillingness to participate in this study, probability of loss to follow-up.

4.3 Definición de variables

Predictive variables

Main predictive variable: index pregnancy with preeclampsia.

Outcome variables

Main outcome variable: Increased cardiovascular risk at 3-6 years after delivery, defined by one of more of the following conditions:

1. Presence of hypertension, defined as stage 1 hypertension (SBP of 130–139 or DBP of 80–89 mmHg) (PMID: 29146535).

2. High-risk CVD according to IBERLIFERISK score (https://www.iberliferisk.com) (score >50%)

3. Abnormal cardiac function in the echocardiographic ultrasound assessment. Abnormal values of the different parameters will be considered according to reference limits published in 2020 by the British Society of Echocardiography (PMID: 32196145)

4. Abnormal biochemical cardiac markers: NTproBNP >300 ng/L (PMID: 16293638) or high-sensitivity troponin>30 ng/L (PMID: 21219893)

5. Signs of coronary artery disease by computer tomography (CCT) myocardial perfusion imaging (mild (CACS≥10 AU and <100 AU); moderate (CACS≥100 AU and <400 AU) and severe (CACS ≥400 AU) (PMID: 28956774) and/or

6. Cardiovascular major events (ictus, coronary artery disease, cardiac insufficiency or myocardiopathy)

Other variables of interest

Patient basal characteristics: age, ethnicity, smoking status, menstrual type and presence of menopause, hypertension, diabetes, obesity, maternal diseases associated with cardiovascular risk, interval from index pregnancy. Pregnancy history: preeclampsia, pregnancy complications, gestational age at delivery, mode of delivery, labor induction, presence of fetal distress, perinatal mortality, gender, birth weight, birth weight centile, 5-minute Apgar score, neonatal morbidity, and neonatal mortality. BP and weight during pregnancy.

At 3-6 years after delivery:

a) Anthropometric measurements: height, weight, body mass index, percentages of body fat, basal metabolism, muscle mass, visceral fat, waist perimeter, hip perimeter, waist/hip ratio.
b) Cardiovascular evaluation: arterial blood pressure, heart rate, echocardiographic assessment, myocardial deformation (strain), carotid intima-media thickness, ophthalmic artery evaluation.

c) Computer tomography (CCT) myocardial perfusion imaging and RM Quantitative Myocardial Perfusion.

d) Cardiovascular markers in maternal blood: Venous blood samples will be collected without anticoagulant to obtain serum. Placental growth factor (PlGF), Troponin T and NTproBNP, GDF-15 will be measured using automated electrochemiluminescence immunoassays on the Roche Cobas platform (Roche Diagnostics GmbH, Mannheim, Germany).Intra-and interassay coefficients of variation were found to be <5%.

e) Other laboratory data: Basic blood count (hemoglobin, hematocrit, leukocytes, platelets), chemistry profile (glucose, sodium, potassium, uric acid, creatinine, glycated hemoglobin), liver profile (AST, ALT, bilirubin, LDH), lipid profile (VLDL, LDL, HDL, total cholesterol, triglycerides), renal profile (total proteins, albumin, albumin / creatinine ratio), hormonal profile (thyroid, gynecological).

f) Cardiovascular assessment according to IBERLIFERISK score (https://www.iberliferisk.com) (PMID: 30097396). A score >50% is considered as a high-risk for CVD.

g) Hair sampling for cortisol determination. Hair samples will be cut with scissors from the region of the posterior vertex, as close to the scalp as possible. Considering that hair grows approximately 1 cm per month, 3 cm will be obtained in order to evaluate hair cortisol levels representative of the last 3 months. Samples will be stored (in a dark container at room temperature) until analysis by liquid chromatography mass spectrometry.

h) Diet and nutrition: evaluated by means of the Short Diet Quality Screener by REGICOR (https://regicor.cat/en/ applications/diet/) and by means of the validated 14-item questionnaire of adherence to the Mediterranean diet.

i) Physical activity: evaluated by means of the Physical Activity Questionnaire by REGICOR, a validated questionnaire for quantifying physical activity in our population (https://regicor.cat/en/applications/physical-activity/).

j) Stress: evaluated by the Perceived Stress Scale (PSS) Questionnaire, validated for quantifying perceived stress in our population.

k) Mental health: evaluated by the Psychiatric Diagnostic Screening Questionnaire (PDSQ), a brief, psychometrically strong, self-report scale designed to screen for the most common disorders encountered in outpatient mental health settings and validated in our population.

l) Smoking habit: evaluated by the Fagerström Questionnaire, validated questionnaire for quantifying dependence on smoking in our population.

m) Assessment of pregnancy and postnatal exposure to "urbanome". Participants' residential addresses will be collected and geocoded. At these geocodes, we will estimate i) annual average levels of main air pollutants (nitrogen dioxide, particulate matter of <2.5 µm of aerodynamic diameter), ii) annual average noise levels at the most exposed façade and bedroom façade, i.e. equivalent noise levels for the 24h (EU indicator Lden), and night-time (Lnight), iii) green space (size in 50, 100, 300m buffer, proximity and urban canopy around home), iv) blue spaces (size in 50, 100, 300m buffer and proximity), v) gray spaces, i.e. urbanization level and building density

around home, vi) temperature in days 0 to 30 prior to cardiovascular assessments. Data will be based on remote sensing satellite data, GIS data sources, and modeling techniques and obtained with the support of the ISGlobal's GIS department staff. Air pollution levels will be based on land use regression models derived and validated in BiSC during 2020-2022 and noise levels will be obtained at the height of the floor of each residence from the European Noise Directive Barcelona's Noise Map of facades (2020), which represents long-term noise exposure.
Women experiences and eHealth (secondary objective 4)

For this aim, a team of anthropologists with a long experience in the fields of health and reproduction will use qualitative methods to understand the needs of women with and without CV risk after pregnancy. To this end, semi- structured interviews will be undertaken with patients with low and high risk of CV disease. These interviews will be useful to have a deep understanding of the difficulties, desires, and needs in relation to interactions with practitioners and available services in healthcare settings.
For proactive monitoring and follow-up of patients, a technological platform or App (CardioPlan), currently used for cardiac rehabilitation, will be restructured, which has a highly secure data repository located on the provider's server and then validated in a subgroup of patients (n=100).

4.4 Tamaño de la muestra previsto

The approximate number or participants in these studies is 1800 women, from which we expect participation of around 70% (n = 1260). Based on previous literature, the approximate incidence of hypertension is 4-fold in women with history of PE, with 30% showing coronary artery calcium deposition at 50 years of age, compared to 18% in non-PE patients. With a type I (alpha) error of 0.05, type II (beta) error at 0.20 aiming for a power of 80%, we would require around 246 patients with previous PE and 246 without to detect a minimum 2-fold relative risk; this would be covered by inclusion of patients from the previously mentioned studies. However, we plan to include 1260 women to obtain the maximum numbers of variables to perform a deep-analysis and correlations among different pathogenic mechanisms that could influence CVD in young women and to further follow-up studies. Due to the costs or/and invasive nature of the procedure's, we will select at least 50 women with history of severe and early (<34 weeks of gestation) placental disease (PE or IUGR), and 50 women with high risk of CVD according to IBERLIFERISK score, stage 1 hypertension, abnormal biochemical markers, or cardiac dysfunction by ultrasound for CCT, CCTA and cardioRM. Measurement of GDF-15 would be also done in this subset of women.

4.5 Metodología.

We will take advantage of the BiSC, EuroPE and AngioCor cohorts. We will evaluate CV biophysical, imaging and biochemical variables 3-6 years after index pregnancy (approximate n=1260). Analyses will include urbanome, placental function and perinatal variables during index pregnancy and postnatal variables such as maternal socio-economic status, lifestyle, urban exposome, mental health, blood pressure, cardiac function, coronary artery disease by Coronary Computed Tomography (CCT) and CCT angiography, RM Quantitative Myocardial Perfusion, ophthalmic artery index, carotid intima- media thickness up to 6 years after delivery to predict higher risk for CVD later in life. Patients' needs and expectations according to CV health would be evaluated. A further aim is to develop and validate an eHealth solution for preventive interventions.

5. Análisis Estadístico

5.1 Manejo y Análisis de los datos

A specific Clinapsis database will be designed for the study to protect patient confidentiality and register adequately all data for analysis; this database will be designed by the Bioinformatics Unit of the Epidemiology and Preventive Medicine Department of Sant Pau Hospital

5.2 Control de calidad

The investigator will guarantee the accuracy and integrity of the data, along with all the reports that are requested. The data included in the Case Report Form (CRF), derived from source documents, will be consistent with those documents or the discrepancies will be justified.

The researcher will keep the documents of the study at least 5 years after the finalization of the study.

The investigator will have all the documents related to the study available upon request.

5.3 Limitaciones del diseño, de la fuente de información y de los métodos de análisis

First, it is impossible to adjust for each different type of pregnancy or cardiovascular risk factors that may be present in the study population. Second, patient compliance to follow-up and subsequent participation may be limited, although this population is usually motivated and we expect to recruit around 70% of the women (around 1260 patients) with subsequent minimal losses. Third: The non-response bias is certainly a limitation of birth cohort studies, particularly families with lower educational attainment. Description of social and medical characteristics of the non-responders based on BISC, EuroPE and ANGIOCOR data, and apply corrections in the statistical models by using propensity models. On the other hand, one of the advantages of

CARDIOMOM is that the BiSC, EuroPE and ANGIOCOR birth cohorts, have already finished recruiting patients and thus the biggest efforts associated with a birth cohort – recruiting women during their pregnancy and babies after birth - are successfully done. The second advantage is that a lot of information on psychosocial, environmental exposures and genetic risk scores is already available for BISC mothers. Also, we have unique data on fetal growth, placental function, preeclampsia, diabetes or preterm birth and, these three cohorts are a highly valuable births cohort.

Finally, we also acknowledge that only subclinical differences may be observed between groups and long-term association with cardiovascular function and disease would have to be further studied. Thus, given the relatively short period of time since gestation and the young age of the patients, some of the proposed tests may not be sensitive enough to detect incipient cardiovascular disease. But, nevertheless, different and complementary tests proposed in this study would counteract this limitation and, in any case, being a prospective cohort, this study represents only the first stage of what is a prospective follow-up of a perfectly characterized and unique population.

6. PLAN DE TRABAJO (tareas, hitos y cronología del estudio):

The project will last 3 years and will start in January 2023. The follow-up will take 24 months. During the second year we will develop and validat the App. We will dedicate the last year of the project to conduct the statistical analysis of the data obtained and to write the scientific papers and final reports. The protocol and the consent form will be obtained from the Comitè Ètic d'Investigació Clíica (CEIC) - Hospital Sant Pau (HSP) and H Sant Joan de Déu (HSJD), as we have done in previous follow-up. The protocol and the ethical approval will be ready before the start of the project in April 2023.

Inclusion of patients would be carried out from HSP and HSJD, EAP Sardenya, ASSIR Guinardó and ASSIR Dreta were consent form will be obtained as well as lyfe-style, mental health and blood sampling. The cardiac assessment will be carried out in the Cardiology Ultrasound Unit of the Cardiology Department of HSP.

*Biochemical measurements will be carried out in the Clinical Biochemistry Department of HSP.

*Development and validation of the App will be carried out in the Pharmacology Department of HSP.

* Urbanome analysis would be carried out in IsGlobal (Parc Salut Mar).

The group will develop the following tasks:

- Elisa Llurba, (ELL, principal investigator): General coordination of the project, data collection supervision, follow-up, and analysis, interpretation and dissemination of results.

- Harmonization of interdisciplinary research activity-Steering Committee (ELl, A. Sionis-AS, Marta Campreciòs-MC, Olga Sánchez-OS, Maria Foraster-MF, Diana Fernández- DF, Mar Gomis-MG)

- Preparation documents for Ethical Committee approval (ELl, AS, OS, MG, MF, DF)

- Patient invitation into the study, epidemiological data and history risk factors are obtained prospectively via a patient-completed questionnaire on maternal age, race, smoking status, obstetric history (previous PE, IUGR, abruptio placentae or stillbirth), mental health, life-style, nutrition, physical activity, stress questionaires:

- Sant Pau Hospital: ELl, Johana Ullmo-JU, Carla Domínguez-CD, C Garrido-CG, C. Trilla-CT, Pablo Garcia Manau-PGM

- BCNatal-Sant Joan de Déu Hospital: Laura Almeida-LA and Silvia Ferrero-SF.

- Primary Care: Eva Vela-EV (ASSIR Eixample Dreta), Anna Ramos (ASSIR Guinardó) and Diana Fernández (DF) (EAP Sardenya)

- Anthropometric measures: height, weight, and blood pressure will be obtained and recorded (JU, CD, CG, CT, LA, SF).

- Maternal CV evaluation: ophthalmic artery, carotid intima media, echocardiographic and strain assessment, Computer tomography (CCT and CCTA) and RM myocardial perfusion imaging. All cardiovascular studies will be analysed by the cardiologist team accredited by the European Association of Cardiovascular Imaging or Society of Cardiovascular Magnetic Resonance (level 3). (Lidia Bos (LB), MC and AS).

- Maria Foraster (MF) as a member of ISGlobal will supervise, evaluate and analysis environmental risk factors for women .

- Biochemical markers in maternal blood: PlGF and cardiac function biomarkers (NT-proBNP, hsTnT and GDF-15) (J Mora- JM; A. García-AG, OS).

- Anna Molas (AM) will carry out social determinants and women experience study.

- Mar Gomis (MG) will assess and carry out the design and validation of App for women

follow-up.
- Experimental study in rats (OS, Animal Experimentation Service (SEA) Stuff).

- Statistical analysis (ELl, AS, OS, MF, MG, DF) supported by data scientists (IsGlobal and IIB-Sant Pau-Cochrane

Iberoamericana and Epidemiology Departement of Sant Pau Hospital, to identify complex relationships. - Guidelines and protocols for prevention of cardiovascular disease (ELl, AS, OS, MF, MG, DF)

- Preparation for biomarkers patens and future industry interests and spin off (ELl, AS, OS, MG, MF).

- Preparation for any future interventional studies (ELl, AS, OS, MF, MG, DF).

7. ASPECTOS ÉTICOS:

7.1 Evaluación beneficio-riesgo de la investigación

Debido a que se trata de un estudio observacional, no se esperan riesgos asociados a la participación, siendo el mismo tanto si las pacientes participan o no. Tampoco se esperan beneficios directos para las participantes, pero los resultados podrán ser de utilidad para determinar la relación entre el riesgo cardiovascular en mujeres jóvenes después de embarazo con o sin complicaciones placentarias.

7.2 Consideraciones éticas, sobre información a los sujetos y consentimiento informado

El estudio se llevará a cabo siguiendo rigurosamente las recomendaciones éticas internacionales para investigación médica en humanos. El investigador será responsable de garantizar que el estudio se realice de acuerdo con las normas recogidas en la Declaración de Helsinki.
Antes de iniciar el estudio, el Comité Ético del Hospital de la Santa Creu i Sant Pau debe de aprobar el protocolo del estudio, la información que se dará al sujeto y el modelo de consentimiento informado que se utilizará.

Se informará al comité ético de cualquier enmienda posterior al protocolo y se deberá solicitar su opinión en el caso de que fuera necesaria una nueva evaluación de los aspectos éticos del estudio.
Es responsabilidad del investigador obtener el consentimiento informado del paciente. El paciente no podrá participar en ningún procedimiento específico del estudio antes de obtener su consentimiento, o el de su tutor legal/familiar cuando el paciente no sea capaz de dar su consentimiento por su situación clínica.
Antes de incluir algún sujeto en el estudio y antes de la obtención del consentimiento informado, el investigador o la persona designada por el mismo, explicará al posible sujeto participante o a su tutor legal/familiar, los objetivos, métodos y riesgos potenciales del estudio y cualquier molestia que éste pueda ocasionar. La explicación acerca de la naturaleza, alcance y posibles consecuencias del estudio se realizarán en un lenguaje entendible.

El posible sujeto participante o su tutor legal/familiar deben tener tiempo para meditar su decisión de participar en el estudio, y tener la oportunidad de formular preguntas. Después de esta explicación, y antes de entrar en el estudio, el consentimiento deberá quedar adecuadamente registrado mediante la firma del sujeto o su tutor legal/familiar.

Como Anexo se presenta el Modelo de Hoja de Información al Paciente y de Formulario de Consentimiento.

Teniendo en consideración que el acceso a la historia clínica con fines diferentes a los asistenciales requiere el consentimiento específico del paciente, en el caso de los pacientes que estén siendo seguidos en la actualidad en el hospital, se plantea que el paciente otorgue su consentimiento para el acceso a los datos de la historia clínica necesarios para llevar a cabo el estudio. Por tanto, para estos casos se presenta la Hoja de Información / Formulario de Consentimiento Informado para su evaluación por el comité ético.

En aquellos casos en los que no sea posible obtener el consentimiento informado expreso (porque los pacientes no realicen seguimiento en el hospital, hayan fallecido o su obtención requiera esfuerzos desproporcionados) se solicita el visto bueno del comité ético para obtener los datos necesarios a partir de la historia clínica para la realización del estudio sin la obtención del consentimiento informado. En estos casos, el equipo investigador se compromete a verificar que no haya constancia en la historia clínica de oposición expresa de los sujetos y a cumplir con la normativa de confidencialidad.

Además, puesto que el uso de datos personales seudonimizados con fines de investigación biomédica requiere la separación técnica y funcional entre el equipo investigador, y quienes realicen la seudonimización y conserven la información que posibilite la reidentificación, la persona que realice la seudonimización para este estudio no formará parte del equipo investigador. Para el acceso a los datos seudonimizados se remite un compromiso expreso de confidencialidad y de no realizar ninguna actividad

de reidentificación, y que se adoptarán medidas de seguridad específicas para evitar la reidentificación y el acceso de terceros no autorizados.

7.3 Consideraciones sobre el tratamiento de las muestras biológicas

En lo referente a la obtención, manejo, identificación y almacenamiento de muestras biológicas, será de aplicación lo dispuesto en la Ley de Investigación Biomédica 14/2007, de 3 de julio, específicamente en los capítulos III y IV del título V, así como lo dispuesto en el Real Decreto 1716/2011, de 18 de noviembre, específicamente en el capítulo I del título II, por el que se establece el tratamiento de muestras biológicas de origen humano con fines de investigación biomédica.
De acuerdo con dichas normativas, la obtención de muestras biológicas con fines de investigación biomédica podrá realizarse únicamente cuando se haya obtenido previamente el consentimiento escrito del sujeto fuente y previa información de las consecuencias y los riesgos que pueda suponer tal obtención para su salud. Dicho consentimiento será revocable.
Una vez finalizado el estudio las muestras biológicas serán guardadas en la colección C.0007636 en el Biobanco del IIB Sant Pau, tras el consentimiento específico del participante para ello.

7.4 Confidencialidad de los datos

En lo referente a la confidencialidad de los datos del estudio se seguirá lo establecido en la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales y el Reglamento (EU) General de Protección de Datos 2016/679.

7.5 Interferencia con los hábitos de prescripción del médico

El manejo clínico de los pacientes se adecuará a los estándares de tratamiento del Servicio de Ginecología y Obstetricia del Hospital de la Santa Creu i Sant Pau, sin que la realización de este estudio influya en tal proceso.

7.6 Planes para la difusión de los resultados:

Todos los resultados se van a traducir en sesiones informativas para profesionales de salud, propuestas de nuevas herramientas y prácticas para la mejora de la satisfacción de las pacientes, material audiovisual para la mejor información de las madres, así como sociedades científicas (SEGO; SEC, SEAP, SEM, etc), artículos científicos en acceso abierto y divulgación en los medios de comunicación, conferencias en centros hospitalarios y civicos, a través de las redes sociales (@Dona SantPau), web (http://www. santpau.cat/web/public/go-inici), etc. La importante participación de las usuarias en este estudio permitirá también crear grupos de opinión entre las participantes para su divulgación a través de redes sociales y otros medios de

comunicación (https://inatal.org), premsa, radio, televisión, así como asociaciones de pacientes (el parto es nuestro, etc.)

El estudio se llevará a cabo mediante una Beca Fis (PI22_00462), solicitada para financiar los gastos generados por el mismo (ver documento adjunto: Memoria económica)

9. MODIFICACIONES DEL PROTOCOLO:

Cualquier modificación del protocolo del estudio adoptará siempre la forma de enmienda o *addendum* por escrito. Para su formalización, se requerirá la aprobación de todas las personas responsables del estudio. En caso de tratarse de modificaciones relevantes, se solicitará la aprobación expresa del Comité Ético de Investigación Clínica.

10. CONSIDERACIONES PRÁCTICAS:

Informes de inicio, seguimiento y final

Se notificará el inicio del estudio al comité ético. Posteriormente se enviarán informes de seguimiento anuales.
Tras obtener las conclusiones del estudio, se elaborará un informe final que será presentado al comité ético.

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12. ANEXOS:

Anexo 1: Evaluaciones del estudio
Anexo 2: Hoja de información a los sujetos (se presenta en documento aparte)
Anexo 3: Formulario de consentimiento informado (se presenta en documento aparte)

Anexo 1

ESQUEMA DE EVALUACIONES DEL ESTUDIO

PROJECT SCHEDULE