PREECLAMPSIA AND FETAL HEART MALFORMATIONS:

LOOKING TO MATERNAL HEART

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STUDY PROTOCOL

PREECLAMPSIA AND FETAL HEART MALFORMATIONS: LOOKING TO MATERNAL HEART

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Background and rationale

Preeclampsia (PE) is the major cause of maternal morbidity and mortality, and it occurs in 2% to 5-8% of pregnancies worldwide (1). This condition is one of the "great obstetrical syndromes" in which multiple and sometimes overlapping pathologic processes activate a common pathway that leads to their clinical recognition. The opinion on the mechanisms underlying the pathogenesis of PE still divides scientists and clinicians. Traditionally, PE is thought to be due to an abnormal placental angiogenesis resulting from a defective remodeling of maternal spiral arteries (*first asymptomatic stage*) that leads to placental dysfunction with impaired fetal growth and diffuse maternal endothelial dysfunction and multiorgan damage, responsible for maternal sign and symptoms (*second clinically evident stage*) (2). Different angiogenic biomarkers have been demonstrated to be involved in the pathogenesis of PE: in particular, a marked increase of circulatory soluble fms- like tyrosine kinase-1 (sFLT-1) is detectable few weeks before the clinical manifestation of PE whereas placental growth factor (PlGF) concentrations are reduced in PE, as a consequence of its binding to the increased levels of circulating sFLT-1. PlGF levels are significantly lower in women who subsequently develop PE. This dysregulated expression of PlGF and sFlt-1 has been proposed to be a direct consequence of the placental syncytiotrophoblast stress (3; 4; 5).

Interestingly, an intrinsically angiogenic impairment is also described in pregnancies complicated by congenital heart disease (CHD). (6) In particular, PlGF levels are found to be significantly lower and sFlt-1 levels significantly higher in the maternal plasma from pregnancies with fetuses with CHD in comparison to controls; so, women with pregnancies complicated by CHD show a similar circulation profile of women developing PE (6). This has been the scientific rationale for investigating the relationship between CHD and maternal increased risk of PE.–A Norwegian register-based study recently found associations between PE and CHD: in particular, early-PE is strongly associated with infant risk of CHD (7). Simultaneously, a Canadian population-based study found that overall PE was significantly associated with noncritical heart defects in offspring, whereas early-PE was associated with critical heart defects (8). Boyd H et al. in their study including 18,000 fetuses with CHD and 55,000 pregnancies with preeclampsia, have demonstrated that women carrying a fetus

with CHD, regardless of the type of defect, had a 7-fold increase in the risk of early-PE and 3-fold increase in the risk of late-preterm PE, whereas the association with term PE was weakly (9). Interestingly, women who had a previous child with CHD had a 2-folder greater risk of early PE and a 25% greater risk of term PE. Conversely early PE in a previously pregnancy was associated with a 6-fold increased risk of offspring CHD in the current pregnancy (10; 9). Moreover, placental histopathology examinations from pregnancies who underwent termination of pregnancy because of severe CHD showed that placental vascular malperfusion lesions were more common as compared with other fetal malformations (11).

However, new interesting theories regarding the pathogenesis of PE have been recently highlighted: in particular, there is now emerging evidence that a suboptimal maternal cardiovascular performance resulting in uteroplacental hypoperfusion is more likely to be the first cause of placental dysfunction in preeclampsia. (12; 13) There are now several data from maternal echocardiography and angiogenic marker studies showing that cardiovascular dysfunction precedes the development of preeclampsia by several weeks or months (10). It is now well known that the cardiovascular system is markedly compromised in PE and plays a major role in the development of PE complications. Recent studies have elucidated the maternal hemodynamic profile associated with early-PE showing how this is typically associated to high maternal systemic vascular resistance (SVR) and low cardiac output (CO) (13). The recognition of the role of the cardiovascular etiology in PE has deep implications not only for the definition the pathophysiology of the disease but also for PE screening and diagnosis, clinical management, and therapy as recently the maternal hemodynamic assessment has entered in the clinical practice.

Although the similar pathogenic profile associated with PE and CHD and the well demonstrated data about the risk of PE in pregnancies complicated with CHD, to our knowledge, no investigations about maternal hemodynamic profile in these pregnancies has been previously proposed.

The aim of this study is to explore the maternal hemodynamic parameters detected by UltraSonic Cardiac Output Monitor (USCOM®) in women carrying a fetus with CHD and to eventually describe an association between those parameters and the presence of a fetal cardiac anomaly.

OBJECTIVES

Primary Objective: The aim of this study is to describe the maternal hemodynamic parameters detected by UltraSonic Cardiac Output Monitor (USCOM®) in women carrying a fetus with CHD and to possibly describe an association between those parameters and the presence of a fetal cardiac anomaly.

Secondary Objectives:

- To assess the number of cases of PE in our population of women carrying fetuses with CHD
- To assess the relationship between maternal hemodynamic profile and maternal and perinatal outcome
- To investigate associations between maternal hemodynamic parameters and the specific heart defect subtype
- To explore the relationship between maternal hemodynamic parameters and fetal cardiac function and morphology in our population

METHODS

Study design This is a prospective monocentric interventional study with the use of the medical device UltraSonic Cardiac Output Monitor (USCOM®).

Study Population: Singleton pregnancy with a diagnosis of CHD performed at the Fetal Medicine Unit of Fondazione Policlinico A. Gemelli IRCCS during the study period and delivered at Fondazione Policlinico A. Gemelli IRCCS.

Study duration

The study has an expected duration of 36 months (three years). The study will begin when the ethics committee has issued a favorable opinion.

Inclusion criteria

The inclusion criteria are:

- Informed consent accepted
- Maternal Age >18 years
- Singleton pregnancy with a viable fetus at >20 weeks of gestation, with a diagnosis of CHD detected on antenatal ultrasound assessment and postnatally confirmed.

Exclusion criteria

The exclusion criteria are:

- Multiple pregnancy
- Pregnancy complicated by aneuploidy, genetic syndrome, or major structural fetal abnormality.
- Maternal congenital heart disease (GUCH)
- Maternal known cardiac disease

Variables and procedures

The following maternal hemodynamic indices will be evaluated: heart rate (HR) (beats per min; bpm), mean arterial pressure (mmHg), stroke volume (mL), cardiac output (CO) (L/min), systemic vascular resistance (dynes/s/cm5). Data on the demographic and pregnancy characteristics of participants, hemodynamic and ultrasound investigations, perinatal and delivery features will be also collected. In particular, the following variables will be included in the study: type of congenital heart defect, gestational age at diagnosis, fetal weight (EFW) and fetal weight centile at diagnosis of CHD and at the last scan before delivery, mean uterine arteries pulsatility index (UtA-PI), fetal umbilical artery (UA-PI) and middle cerebral artery pulsatility index (MCA-PI) at diagnosis and at the last scan before delivery, maternal age, height, pre-pregnancy weight and gestational weight gain, systolic and diastolic blood pressure values (maximum and minimum values), presence of proteinuria, biochemical maternal assessment (maximun and miminum values of creatinine and uric acid level, platelet count, liver enzyme level), incidence of hypertensive disorders of pregnancy, antihypertensive drug administration (type and dosage) including magnesium sulfate, antenatal steroid administration, mode of delivery and indications, gestational age at delivery, birthweight and birthweight centile, need of respiratory or cardiac support, neonatal intensive care unit admission and number of days, major neonatal complications, maternal morbidities (HELLP, eclampsia, intravascular disseminate coagulation, post-partum hemorrhage), and mortality. The following definitions of hypertensive disorders will be used, according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2018 criteria (14): chronic hypertension (CH) will be defined as hypertension (≥140/90mmHg) that predates pregnancy or is present prior to 20 weeks' gestation; gestational hypertension was defined as de-novo hypertension (≥ 140/90 mmHg) after 20 weeks' gestation; and preeclampsia (PE) will be defined as de-novo hypertension (≥ 140/90 mmHg) after 20 weeks' gestation with coexisting proteinuria, other maternal organ dysfunction or fetal growth restriction; preeclampsia superimposed to chronic hypertension (PE-CH).

Maternal hemodynamics assessment: Hemodynamic indices will be obtained using the USCOM® system. Women will undergo a hemodynamic investigation at the time of first diagnosis of CHD

during pregnancy or at the first assessment in Fondazione Policlinico A. Gemelli during pregnancy and then every two weeks until delivery. An additional hemodynamics evaluation will be performed in the post-partum period (in the 72 hours immediately after delivery). All hemodynamic assessment will be performed under standardized conditions. Maternal height, weight and brachial blood pressure will be obtained prior to hemodynamic assessment. USCOM® system utilizes continuous-wave Doppler, with a non-imaging probe in the suprasternal notch, to obtain velocity-time integrals of transaortic blood flow at the left ventricular outflow tract. Using an internal anthropometric algorithm, which correlates the outflow tract diameter with the patient's height, USCOM-1A multiplies the velocity-time integral by the aortic root diameter to calculate stroke volume. By measuring the time interval between each Doppler profile, heart rate (HR) can be calculated. CO (stroke volume × HR) and SVR (MAP/CO) are calculated after inclusion of maternal mean arterial pressure. Participants remain in a semi recumbent position and a small amount of conducting gel is applied to their skin at the level of the suprasternal notch. The Doppler probe is applied and moved through three dimensions to ensure that the velocity of blood was being measured at the left ventricular outflow tract and not in the more distal aorta. Each Doppler acquisition used for analysis must register a minimum of two consecutive Doppler profiles (cardiac cycles). All hemodynamic measurements were performed by trained operators. USCOM-1A has been in clinical use since 2015. Its repeatability and reproducibility have been assessed in adult, pediatric and pregnant populations, demonstrating excellent agreement between operators with sufficient training (15; 16).

ENDPOINTS

Primary endpoint: To identify the maternal hemodynamic parametrics changes in pregnancies complicated by congenital heart diseases and immediately after delivery.

Secondary endpoints:

- prevalence of cases of preeclampsia in our population of pregnancies complicated by congenital heart disease
- To investigate association between maternal hemodynamic profile and perinatal outcome
- To calculate correlation coefficients between the maternal hemodynamic parameters to the specific heart defect type
- To calculate correlation coefficients between the maternal hemodynamic parameters and fetal cardiac function and morphology parameters

STATISTICAL ANALYSIS PLAN

Sample size calculation

108 patients will be recruited

Statistical analysis

The sample will be described in its clinical and demographic characteristics by descriptive statistics techniques. In depth, qualitative data will be expressed as absolute and relative percentage frequency, whilst quantitative variables either by mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate.

To verify the Gaussian distribution of quantitative variables, the Shapiro-Wilk test will be applied.

The discrete variables will be compared by Chi Square or Fisher Exact test.

Correlation analysis between hemodynamic parameters and variables related to the type of congenital heart defect of the fetus will be carried out by calculating and testing Pearson's and/or Spearman's correlation coefficient, when necessary Kendal's correlation coefficient will be used. Likewise, correlation analysis between hemodynamic parameters and fetal cardiac function parameters will be carried out.

To identify any differences in mean between baseline and immediate postpartum, continuous variables will be compared with the T test for paired data and/or the Wilcoxn test when appropriate.

Regression analysis will be performed to explore the relationship between maternal hemodynamic parameters and maternal and perinatal outcome and fetal cardiac parameters.

Mixed-effects models for longitudinal data will be fit to identify potential changes over time in maternal hemodynamic parameters also in relation to fetal cardiac parameters, controlling for any confounding variables.

All results will be considered statistically significant when $p<0.05$.

All analyses will be conducted with R statistical software (R, cran, 2023).

Safety/Adverse Event Management

All adverse events observed during the study will be collected and recorded.

Adverse events involving medical devices can be classified as incidents and deficiency, the aforementioned, as identified by the following definitions, will be reported to the National Competent Authority and to the Manufacturer according to the provisions of current legislation for medical devices (EU Regulation 745/ 2017 and Legislative Decree 5 August 2022, n.137 and subsequent communications from the Ministry of Health).

In the case of a medical device, it means for

• any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.;

• any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer;

• any incident, malfunction or alteration of the characteristics or performance of a device made available on the market, including the error of use caused by the ergonomic characteristics, as well as any inadequacy in the information provided by the manufacturer and any unwanted side effects.

A serious incident is defined as any incident which, directly or indirectly, has caused, may have caused or may cause one of the following consequences:

a) death of the patient, user or other person

b) serious deterioration, temporary or permanent impairment of the state of health of the patient, the user or another person;

c) a serious threat to public health

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