Maladaptation of the maternal cardiovascular system as a cause of fetal growth restriction: Study rationale and design

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INTRODUCTION

The mortality rate among pregnant women is low, nevertheless, cardiovascular diseases (CVD) are the leading cause of death (approximately 30%) in this particular population [1]. The clinical presentation of CVD might be miscellaneous as symptoms are commonly atypical and attributed to pregnancy itself [2, 3]. Pregnancy acts as a physiological stress test, thus the development of certain obstetric complications might be evidence of abnormal adaptation of the cardiovascular system to this condition. According to the latest research, particularly preeclampsia and impaired fetal growth may result from such a maladaptive process [3]. The importance of these associations has been raised by the current guidelines, which now recommend considering a pregnancy history as part of the routine evaluation of cardiovascular risk in women [2].

A condition called fetal growth failure includes both small gestational age (SGA) and fetal growth restriction (FGR) [4]. SGA refers to pregnancies with a constitutionally determined fetal weight between the third and tenth percentile accompanied by a normal vascular blood flow on ultrasound assessment and a good overall prognosis. In contrast to that, FGR is one of the most common adverse outcomes during pregnancy reported in up to 10% of cases, and a leading cause of infant morbidity and mortality [4, 5]. By definition, in FGR the fetus does not achieve its genetic potential with the programmed birth weight due to pathological reasons [4, 5]. FGR is classified based on gestational age at prenatal ultrasound diagnosis as early-onset — diagnosed before 32 weeks of gestation and late-onset — diagnosed at or after 32 weeks of gestation. The etiology of FGR remains unclear and can be caused by maternal factors (hypertension, diabetes, cardiopulmonary disease, anemia, malnutrition, smoking, and drug use), fetal causes (genetic factors, congenital malformations, fetal infection, and multiple pregnancies), and placental abnormalities (placental insufficiency, placental infarction, and placental mosaicism) [3, 5].

Having said that, it is important to thoroughly determine the cardiovascular profile of pregnant women with impaired fetal growth. Comprehensive profiling could be useful in identifying patients at high risk of both FGR development during pregnancy as well as subsequent cardiovascular complications in the mother.

METHODS

This interdisciplinary project is a single-center prospective study conducted in the 1st Department of Cardiology and the Department of Perinatology and Gynecology at the Poznań University of Medical Sciences, Poznań, Poland.

The research objectives are to establish the frequency of abnormalities in the maternal cardiovascular system and their correlation with fetal growth impairment.

Patients will be enrolled in the study in two stages. In the first stage, 150 patients between 24 and 38 weeks of pregnancy complicated

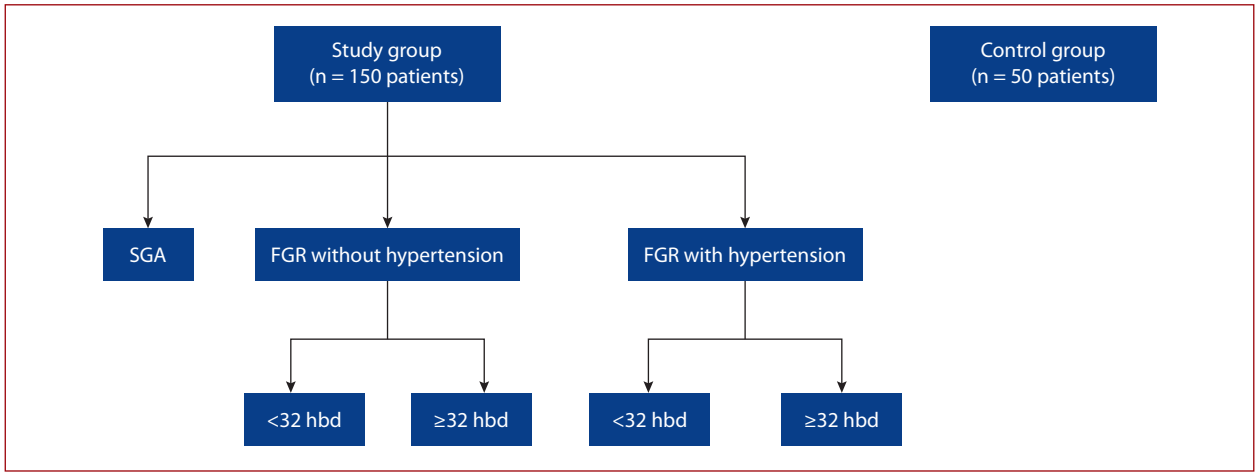

Figure 1. The study flow chart showing allocation of the enrolled pregnant women with regard to the type of the diagnosed fetal growth impairment

Abbreviations: hbd, week of gestation; FGR, fetal growth restriction; SGA, small gestational age

by impaired fetal growth will be enrolled. The diagnosis of FGR will be made based on the current Delphi criteria [6]. The control group will include 50 patients between weeks 24 and 41 of pregnancy with a physiologically normal pregnancy, who will give birth to appropriate for gestational age (AGA) children.

In the second stage, patients from the study group will be divided into 3 subgroups depending on the final diagnosis: Group 1: SGA; Group 2: FGR without pregnancy-induced hypertension; Group 3: FGR with pregnancy-induced hypertension (synonymous with the diagnosis of pre-eclampsia) (Figure 1).

The exclusion criteria are 1) multiple pregnancy, 2) fetal defects, 3) infections from the TORCH group, 4) a known significant cardiovascular disease in the mother, 5) pregnancy diabetes, 6) antiphospholipid syndrome, thrombophilia, and other recognized disorders of the coagulation system, 7) significant kidney disease with GFR <60/min before pregnancy, 8) significant autoimmune diseases of connective tissues (systemic lupus, antiphospholipid syndrome, etc.) 9) placental defects, 10) nicotine addiction, alcohol addiction, or other psychoactive substance addiction (regular substance intake at least twice a week three months before and/or during pregnancy).

The study protocol includes:

1. Detailed physical examination and collection of relevant clinical data.
2. Ultrasound assessment of the fetus, including fetal biometric assessment and doppler measurements.
3. Basic laboratory tests including the most commonly used cardiovascular parameters (complete blood count, creatinine, sodium, potassium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, C-reactive protein, total cholesterol, HDL-cholesterol, LDL cholesterol, triglycerides, Prothrombin Time, PT/INR, Activated Partial Thromboplastin Time (aPTT), D-dimer, N-terminal pro-brain natriuretic peptide (NT-proBNP), and cardiac troponin I.
4. Biochemical tests of advanced markers of cardiovascular dysfunction: lipocalin-2, retinol-binding protein 4, adiponectin, fibroblast growth factor 19 and 21, tissue plasminogen activator, angiotensin A and vasoconstriction inhibiting factor.
5. Echocardiographic examination of the mother (basic assessment of anatomy, systolic and diastolic function with advanced evaluation based on the tissue Doppler technique).
6. Routine electrocardiographic parameters at rest.
7. Functional assessment of the arterial bed, including examination of central pressure (central systolic and diastolic pressure in the aorta), and the parameters of arterial stiffness (pulse wave velocity [PWV]) by applanation tonometry.
8. Assessment of the daily profile of peripheral arterial pressure (ambulatory 24-hour monitoring of blood pressure ABPM).
9. The course and mode of delivery, the condition of the neonate and the mother.
10. Re-assessments of maternal echocardiographic parameters after puerperium (6–12 months after delivery).

The study design was approved by the local ethics committee (EC approval number 100/22 dated February 17, 2022). All patients gave informed written consent to participate in the study.

Statistical analysis

For continuous variables and ordinal variables, median values with minimal and maximal ranges were reported. Categorical data were reported as the number and percentage of patients. The statistics were calculated with STATISTICA 13 software (TIBCO Software, Palo Alto, CA, US)

PRELIMINARY RESULTS AND DISCUSSION

During the first six months of the study duration, 25 pregnant women (median age, 34 years; range 26–41 years) were recruited to the study. The majority of them (15 [60%]) were diagnosed with impaired fetal growth before the 32nd week of gestation. After labor, the final diagnosis of FGR was confirmed in 20 (80%) participants, whereas 5 (20%) were eventually classified as SGA. In eight patients (32%), preeclampsia complicated the course of pregnancy.

In terms of echocardiography, the dimensions of the heart chambers were within the normal range in all included patients, and so was left ventricular (LV) ejection fraction (median, 60.5%; range, 53–70%). The wider spread among calculated values was observed in LV global longitudinal strain which ranged from an abnormally low value of –10.4% to normal –22.6% (median, –17.6%). The systolic function of the right ventricle (RV) was assessed by the tricuspid annular systolic myocardial velocity S' measurement (median, 14 cm/s; range 7–22 cm/s). The assessment of RV global longitudinal strain turned out not to be technically feasible in the majority of our patients (16 [64%]) due to the poor-quality images.

Our preliminary results are consistent with the previous reports about the cardiovascular system in healthy pregnant women, particularly in the context of the left ventricular global strain [7, 8]. The other echocardiographic data are within the normal range. We are still expecting a biochemical profiling and vascular functional assessment to be analyzed along with the prospective data as the follow-up is scheduled 6–12 months after delivery.

CONCLUSIONS

Our study may provide important data on the detection, diagnosis, and management of pregnant women with a high cardiovascular risk.

Article information

Conflict of interest: None declared.

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