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Bedside cardiovascular maternal interrogation in the first trimester to predict different phenotypes of hypertensive disorders in pregnancy

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ABSTRACT

Objective: The aim is to evaluate if maternal cardiovascular indices, in the first trimester of pregnancy, might be useful to differentiate women who develop different hypertensive disorders of pregnancy (HDP).
Study design: Method: 1399 pregnant women attending screening for chromosomal aneuploidies were recruited. The following parameters were measured: Doppler Velocimetry of uterine arteries; Peripheral blood pressure; Aortic Pressure derived from applanation tonometry. Primary outcome were: women who developed HDP associated with newborns with an appropriate weight for local gestational age standards *(AGA) and women that developed HDP associated with a newborn weight below the 10th centile (SGA).*
Results: Mean UtA PI was significantly higher in the HDP-SGA compared with controls. HDP-AGA showed a higher rate of family history of hypertension and a higher BMI. In HDP-AGA Brachial and Aortic mean pressure were higher than controls. The most significant contributors for all forms of HDP were mean UtA PI for HDP-SGA and mean arterial blood pressure for HDP-AGA. The multivariate logistic regression for HDP-SGA shows an AUC 0.88, whereas the AUC for the prediction of HDP-AGA group was 0.71.
Conclusion: HDP-SGA were characterized by significantly higher values of UtA-PI, whereas HDP-AGA by mean aortic and brachial pressure and risk factors for endothelial dysfunction.
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1. Introduction

Clinical and epidemiological data suggest that preeclampsia (PE), as defined by high blood pressure and proteinuria, should be considered a common tertiary downstream feature of heterogeneous disorders [1–4]. Temporal classification of hypertensive disorders of pregnancy (HDP) and of PE, into early and late onset disorder, partially solved the partition of clinical features of hypertension, maternal organ functional damage and fetal and placental lesions [5,6]. Early onset disease is more frequently associated with abnormal uterine artery Doppler velocimetry, due to poor early placentation, and intrauterine fetal growth restriction (IUGR) [7–9]. Maternal cardiovascular or metabolic risk factors for endothelial dysfunction "might dominate in the origins of late onset pre-eclampsia" [4,9]. However "more frequently" does not mean always and these different prevalences varies across the populations, probably according to the prevalence of other risk factors, such as obesity, parity, ethnicity, etc.

Independently of the criteria used to classificate HDP, pregnancy is characterized by functional and structural changes in the maternal cardiovascular system that accommodates the growing demands of the fetus and placenta [10–12]. In women with poor placental development associated with IUGR these physiological changes do not occur and endothelial damage leads to vasoconstriction, hypertension and low cardiac output [3,13,14]. Opposite to this, low total vascular resistance and high or normal cardiac output characterize near-term and term HDP not associated with IUGR fetus [12,15].

It is likely that different patho-physiological pathways underlay different clinical phenotypes of HDP. These different phenotypes characterize also PE [14] associated with IUGR caused by early shallow trophoblastic invasion on one hand and PE associated with appropriate for gestational age fetal growth (AGA) with late histological abnormalities of the villous tree associated with maternal cardiovascular or metabolic risk factors. In this view, the prediction

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of HDP should be based on risk factor evaluation coherent with the pathophysiology of each disorder [16].

We hypothesize that non-invasive, bedside assessment of maternal cardiovascular indices (brachial, peripheral, and aortic, central, derived blood pressure, augmentation index [17], and uterine arteries Doppler velocimetry) might be helpful in identifying different maternal poor adaptation to pregnancy as early as the first trimester.

The aim of our study was to evaluate if maternal cardiovascular indices, interrogated by bedside diagnostic tools in the first trimester of pregnancy, might be useful to predict women who subsequently developed different phenotypes of HDP later in pregnancy.

2. Materials and methods

This prospective longitudinal study was conducted between July 2012 and July 2014 at Buzzi Children's Hospital, University of Milan, Italy. We recruited pregnant women attending the first trimester screening for aneuploidies between 11 + 0 and 13 + 6 weeks of gestation. The study was approved by the Ethics Committee MILANO Area C, Milan, Italy (CE approval 277/2011). Written informed consent was obtained from all women. At the time of recruitment, eligible women had an interview with a researcher and answered a standardized questionnaire on maternal characteristics and medical history. Demographic and clinical data included age, racial origin, smoking habit, family history of hypertension, chronic hypertension, chronic drug assumption, parity, method of conceivement (spontaneous or in vitro fertilization (IVF)) and obstetrical history. Maternal weight and height were measured and the body mass index (BMI) was calculated. The inclusion criteria were: singleton pregnancy, absence of fetal anomalies, maternal age >18 years old, able to understand and sign the informed consent. The exclusion criteria were: any maternal co-morbidity such as chronic hypertension, pregestational diabetes and other pre-existing medical conditions, multiple pregnancy, miscarriage before 20 weeks.

Routine sonographic examination for risk assessment for chromosomal aneuploidies was performed. Maternal serum Pregnancy-Associated Plasma Protein A (PAPP-A) and free β Human Chorionic Gonadotropin concentrations were determined in the maternal blood in order to calculate the combined patient-specific risk for trisomy 18 and 21 [18].

2.1. Uterine arteries Doppler velocimetry assessment

On the same occasion, Doppler velocimetry of left and right uterine artery (UtA) was performed. The uterine arteries Doppler waveforms were obtained as per *trans*-abdominal standard procedure [19] and by an experienced maternal fetal medicine sonologist. The mean UtA pulsatility index (PI) of the two uterine arteries was determined on more than three similar consecutive waveforms and was defined as abnormal if the mean UtA-PI was above the 95th percentile for gestational age [20].

2.2. Blood pressure (BP)

The peripheral blood pressure was measured from the right brachial arm using an aneroid sphygmomanometer and the mean brachial arterial pressure (Brachial MAP) was calculated [21]. During the measurement, the woman was requested to sit quietly for a 5 min rest.

2.3. Applanation tonometry and pulse wave analysis (PWA)

The applanation tonometry (Sphygmocor® system Atcor Medical, West Ryde, Australia) was performed by a gentle compression of the radial artery with the tip of the tonometer at the site of maximal pulsation. A generalized transfer function applied to the radial artery waveform derived the aortic pressure waveform [22,23]. The mean arterial aortic pressure (Aortic MAP) was calculated by the appropriate formula [21].

The augmentation index (AIx) was calculated from the aortic pressure waveform. The AIx is defined as augmentation pressure (AP) expressed as a percentage of the aortic pulse pressure (PP = systolic pressure minus diastolic pressure) [24]. The AIx was standardized to a heart rate of 75 beats per minute (AIx-75) [25]. Six physicians performed all measurements. Prior to commencing the study, there was an initial learning period of repeated measurements until satisfactory reproducibility was achieved according to the inbuilt quality control of the tonometric equipment.

2.4. Outcome data collection

Fetal and maternal outcomes were obtained either directly from the clinical records, if the delivery occurred in Buzzi Hospital, or by a detailed telephone interview to patients who delivered outside our hospital.

2.5. Primary outcome

The diagnosis of gestational hypertension (GH) and PE was made according to the criteria of the Canadian Hypertensive disorders of pregnancy working group [26]. Under this classification, GH was defined as blood pressure $\geqslant$140/90 mmHg or more on at least two occasions, 4 h apart, developing after 20 weeks of gestation in previously normotensive women. PE was defined as GH associated with IUGR or other maternal organ damage [26].

For the purposes of this study, HDP patients, that included women affected by GH and PE, were classified according to pregnancy outcome in three different groups: 1) women with HDP with an appropriate newborn's weight for local standards (HDP-AGA) [27]; 2) women with HDP associated with a newborn's weight below the 10th centile for local standards (HDP-SGA) [27]; and 3) women with uneventful pregnancy with normal fetal and maternal outcome (control group).

2.6. Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and were compared by means of the Mann-Whitney *U* test. Qualitative data are expressed as numbers and percentages and were compared using the Pearson test. For the first step of our analysis, we excluded from the study population those women who developed other pregnancy complications except for HDP (Fig. 1). Hence, we compared the demographic characteristics, pregnancy outcomes and first trimester biophysical parameters (brachial MAP, mean UtA-PI, and aortic MAP) between the HDP group taken as a whole (ALL-HDP) and healthy controls. Further, we separately compared HDP-AGA and HDP-SGA group for the same parameters. As second step, we performed a logistic regression analysis on the whole cohort, including the patients that were previously excluded for maternal or fetal complications during pregnancy (Fig. 1) and we calculated in each patient the risk to develop ALL-HDP and HDP-SGA or HDP-AGA. This was performed in order to determine which of the variables identified by the univariate analysis remained to be significantly associated with the main outcomes at the multivariate analysis. The values of brachial