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PULSE WAVE ANALYSIS IN THE FIRST TRIMESTER OF PREGNANCY: A
POSSIBLE PREDICTIVE TEST TO IDENTIFY WOMEN AT RISK OF
PLACENTAL OR MATERNAL PREECLAMPSIA AND IUGR
SSD MED/40

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Ai miei due Darietti e a Diego in arrivo...

Pulse Wave Analysis in the first trimester of pregnancy: a possible predictive test to identify women at risk of placental or maternal preeclampsia and IUGR

Background:

Preeclampsia and intrauterine growth restriction are major contributors to maternal and/or perinatal mortality and morbidity worldwide. At present preeclampsia is classified based on time domain. Just few Authors proposed classification based on different origin of the diseases: placental and maternal. The former involves inadequate placentation and consequently placental insufficiency and IUGR; the latter is thought to be caused by maternal "metabolic syndrome" characterized by low grade chronic inflammation and android obesity, but associated with normal placental function and appropriate fetal growth (AGA).

Independently on the classification of the disease, it is well known that women with a history of preeclampsia are at increased risk of cardiovascular events later on in life.

Recent developments in cardiological technology provided useful non-invasive tool capable to assess peripheral and central vascular resistance: applanation tonometry. By assessing the radial pulse wave it is possible to derive indices of arterial stiffness (Augmentation Index) and compliance (Pulse Wave Analysis and Pulse Wave Velocity). In the literature there are few studies that investigated arterial stiffness in preeclamptic women, but limited mostly by low study population. Just one report investigated applanation tonometry in the first trimester of pregnancy. None of Authors explored the role of pulse wave analysis considering the above proposed classification of preeclampsia.

Aim: to investigate maternal indices of central and peripheral vascular resistance (arterial stiffness) and indices of central pressure in aorta, in the first trimester of pregnancy, in preeclampsia of maternal and placental origin and fetal growth restriction.

Methods: applanation radial tonometry together with uterine artery Doppler have been performed between 11-13+6 wg in general population attending to our hospital for Down syndrome screening. Augmentation index corrected for heart rate (AIX75) and Aortic systolic peak have been calculated. PE was defined as placental when associated with IUGR and of maternal origin in cases with clinical manifestation of hypertension/PE but with appropriate fetal growth, independently of time of onset.

Results: 308 pregnancies were recruited: four (1%) developed PE/IUGR; four (1%) PE/AGA; seven (2,3%) GH; 16 (5,2%) IUGR, and eight (2,6%) SGA. None of the seven women with gestational hypertension had associated fetal growth restriction, so they were included in maternal preeclampsia group (PE+AGA).

Patients with maternal PE showed a statistically higher BMI and higher rate of IVF pregnancy when compared to controls ($p=0,011$), while placental PE showed a higher incidence of previous pregnancy affected by preeclampsia ($p=0,004$). There were no statistical differences for other demographic data.

Both maternal and placental PE group delivered at an earlier GA, but only placental PE had smaller babies and major incidence of admittance to NICU ($p < 0,001$). There were no significant differences in heart rate and Augmentation index at 75 bpm between the two groups of PE compared with controls. Mean arterial pressure was significantly higher in both placental and maternal preeclampsia when compared to the control

group, while central systolic pressure was significantly higher only in placental PE group ($p < 0,001$).

The mean uterine artery PI was significantly higher in placental PE group ($p < 0,001$) and maternal serum PAPP-A resulted significantly lower only in maternal PE group ($p = 0,024$).

Conclusions:

Although, the classification of preeclampsia based on time domain, at the moment the most used, brought to some improvements in terms of biochemical and biophysical tests prediction, at present is still not able to fulfill all diagnostic and preventive needs. Indeed, despite all scientific effort for the past three decades, at the present there does not exist universally recognized screening test of any kind capable to predict preeclampsia or IUGR and the severity of the disease.

With this pilot study, we wanted to investigate the characteristics of preeclampsia of maternal and placental origin and pregnancies with fetal growth restriction in terms of peripheral and central vascular resistance by applanation tonometry in the first trimester of pregnancy. Due to the smallness of the cohort, we did not try to assess the prediction of the test. Nevertheless, the newness of our work stand in the understanding of the underlying physiopathology of preeclampsia.

Our data confirmed the hypothesis regarding different origin of PE: indeed, in PE of maternal origin we found the highest BMI and the highest percentage of IVF-pregnancies. Both this factors are well known to correlate to metabolic syndrome, low grade chronic inflammation and insulin resistance.

Conversely, in PE of placental origin we found the highest number of women with reoccurrence of preeclampsia that supports the immunological/genetic hypothesis that causes inadequate placentation. This hypothesis is supported also by the observation that women with preeclampsia of placental origin present significantly higher mean uterine artery PI, sign of an impaired placentation as soon as in the first trimester of pregnancy.

As it concern the hemodynamic parameters, in accordance to the literature, we found the mean arterial pressure significantly higher in both preeclampsia of placental and maternal origin when compared to the control group. Interestingly, the central pressure, both systolic and diastolic, was significantly higher only in placental PE group suggesting lower central vascular compliance in women with inadequate placentation. This could suggest a different and more severe physiopatological pathway at the basis of preeclampsia of placental origin when compared to maternal one.

Several Authors found increased values of augmentation index in women with preeclampsia (more pronounced in early and less important in late PE) at the time of onset of the disease. Conversely, we found no significant differences in Augmentation index at 75 bpm between groups, suggesting that in the first trimester the biochemical and hormonal modifications still does not reflect on peripheral vascular resistance both in preeclampsia of maternal and placental origin.

In conclusion, we found that the classification of preeclampsia based on its origin, maternal and placental, is supported by the demographic data. Our data suggest that, as soon as in first trimester, for arterial mean pressure been equal in both women that will develop PE of maternal and placental origin, and higher in respect to controls, only PE of placental origin presents higher central pressure. Nevertheless, no differences were found for wave reflection, suggesting later development of the peripheral vascular alteration.

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INTRODUCTION

Definition, etiology, physiopathology, diagnosis and clinical manifestation of Preeclampsia and IUGR

Preeclampsia (PE) and intrauterine growth restriction (IUGR) are major contributors to perinatal mortality and morbidity [1]. Affecting more than half a million pregnancies delivered in the United States alone, these pregnancy complications not only alter the immediate outcomes of pregnancy at the time of delivery but also the long-term cardiovascular health of the affected women and children. For example, a history of preeclampsia increases a female's risk of myocardial infarction, stroke or diabetes mellitus by two to eight folds over the next two decades [2].

Moreover, newborns diagnosed with IUGR at birth have a two to eightfold increased risk for hypertension, cardiovascular disease, diabetes mellitus or renal disease as adults [3,4].

Preeclampsia

Preeclampsia is a newly onset hypertension in previously normotensive women coupled with elevated urine protein in women without previous kidney failure, developed after 20 weeks of gestation, as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [5-8]. The syndrome can be exacerbated to severe hypertension and proteinuria ("severe preeclampsia") that can lead to eclampsia, an obstetric emergency associated with brain convulsions, cerebral edema and stroke, a life threatening condition for the mother and her baby [9]. HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome may correlate to severe preeclampsia and is characterized by elevated liver enzyme activities and reduced numbers of platelets indicating injury to the liver, blood system and potentially other organs. The HELLP syndrome occurs primarily in white, multiparous women above the age of 25 years [10,11].

Preeclampsia affects 2–8% of all pregnant women and it is the second cause of maternal death during pregnancy, comprising 18% of pregnancy-associated maternal mortality worldwide [12,13]. According to the National Institute of Child Health and Human Development (NICHD) [14], confirmed by a large scale studies of the Maternal-Fetal Medicine Foundation [15] and other international surveys [16], 25–27% of

preeclamptic patients deliver prematurely (before 37 weeks of gestation and approximately 10% before 34 weeks), and the earliest the delivery occurs the most severe are the complications for both the mother and the baby. Approximately 90% of early preeclamptic patients (cases with severity requiring delivery before 34 weeks), and more than 50% of preterm preeclamptic patients require a cesarean section compared with approximately 30% in preeclampsia at term and 15–18% in the unaffected population [16-19]. Studies have revealed that although preterm preeclampsia affects only about 1/4 of all preeclampsia cases (1–2% of the entire pregnancy population in Canada, Netherlands, Denmark, Finland, USA and 0.7% in UK), the frequency of eclampsia, stroke, cerebral vascular accident and other severe complications in this sub-group of preeclampsia is higher compared to term preeclampsia. More than 75% of babies born from early preeclampsia (<34 weeks) and over 50% of those born preterm (34–37 weeks) are either small for gestational age (SGA) or show IUGR. Newborns of early preeclampsia account for the major fraction of intra-partum and post partum death, cerebral palsy, blindness and motor and cognitive disorders. These complications are less severe in term preeclampsia [20-26].

This definition of preeclampsia is based on clinical manifestations of the disease, but the knowledge about the pathogenesis and etiology is still unclear. Extensive research in the last 15 years has demonstrated that preeclampsia is characterized by abnormal vascular response to placentation that is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction, when there is a wrong recognition of immune system [27]. The opinion was that the clinical findings of preeclampsia could manifest as either a maternal syndrome (hypertension and proteinuria with or without other multisystem abnormalities) or fetal syndrome (fetal growth restriction, reduced amniotic fluid, and abnormal oxygenation) [27-29].

Over the past decade, the knowledge about preeclampsia has changed significantly by virtue of increased recognition of the heterogeneous nature of this syndrome. The physicians observed that the manifestations of preeclampsia can develop before than 34 weeks (early onset) or after 34 weeks (late onset), during labor, or postpartum. They suggested that early and late onset preeclampsia could have different etiologies and should be

regarded as different forms of the disease [29,30]. Early onset preeclampsia was commonly associated with abnormal uterine artery Doppler, fetal growth restriction, evidence of ischemic lesions on placental examination and adverse maternal and neonatal outcomes. Whereas late onset preeclampsia was mostly associated with normal or slight increased uterine resistance index, a low rate of fetal involvement and more favorable perinatal outcomes [16,31-33]. Furthermore, they observed that pregnancy is characterized by certain structural and functional changes in the cardiovascular systems that are necessary to accommodate the growing demands of the fetus and placenta. Adequate cardiovascular adaptation during early pregnancy leads to a state of high blood flow and low vascular resistance, which is a prerequisite to successful pregnancy outcome. In contrast, inadequate or excessive cardiovascular adaptation before 20 weeks gestation is associated with pregnancies complicated by gestational hypertension, preeclampsia, IUGR or a combination of these [33,34].

In 2008, Valensise [35] observed two different groups of women that subsequently develop early or late preeclampsia. Patients with early onset preeclampsia had significantly higher rates of advanced maternal age and bilateral uterine arteries notching and lower gestational age at delivery and lower neonatal weight centile compared to both control and late preeclampsia groups. In contrast, patients with late onset preeclampsia had higher body mass index compared to the other two groups.

Moreover he proposed that early and late onset preeclampsia develop from two distinct hemodynamic states: patients with early preeclampsia had significantly high total vascular resistance and lower cardiac output compared to those with late preeclampsia that present low vascular resistance and high cardiac output.

The author concludes that early preeclampsia appears to be more related to the evolution of an extremely altered cardiovascular response probably triggered by a placental disorder; instead, late preeclampsia seems to be more linked to maternal constitutional factors.

Two years before Redman [36] wrote an article about the different kind of inflammation in preeclampsia and he suggested that the disease constitutes a spectrum that includes so-called 'maternal' and 'placental' preeclampsia. Redman supports the theory that consider placental preeclampsia as an abnormal placenta in a normal woman, and the maternal preeclampsia as a normal placenta within a woman who suffers from a preexisting problem,

such as obesity, cardiovascular disease or diabetes. Consequently, the pregnancy become a systemic inflammatory stress for women, particularly during the second half of gestation, to which both endocrine and placental factors contribute. The placental stimulus may comprise debris released into the maternal circulation from the syncytiotrophoblast, signaling danger to the maternal innate immune system. Preeclampsia ensues when the threshold for sustaining homeostasis is reached and excessive involvement of maternal endothelial integrity occurs. Many, but not all, cases of preeclampsia are associated with poor placentation. This comprises the first stage, which appears to involve decidual immune responses. Second stage responses are secondary to the systemic inflammatory response, which could explain why women bearing pregnancies with unusually large placentas (an excessively large inflammatory stimulus) are susceptible to preeclampsia. In contrast in obese women, chronic inflammation contributes to preeclampsia superimposed on the added stimulus from a normal pregnancy.

Summarizing, placental preeclampsia is caused by an inadequate trophoblastic invasion of the maternal spiral arteries, that cause first a local inflammatory process and later a systemic inflammation which has been documented by altered Doppler ultrasound of uterine arteries and often associated with a higher incidence of fetal growth restriction. Its hemodynamic system is characterized by low cardiac output and high total vascular resistance.

Conversely, maternal preeclampsia is associated with normal placentation and fetal growth and is thought to be a manifestation of an underlying metabolic disorder with chronic inflammatory state and hemodynamic system characterized by high cardiac output and low total vascular resistance.

Therefore, actually there is an evidence that preeclampsia is an heterogeneous condition with early disease, thought to be a consequence of impaired placentation [37-39], whereas in late preeclampsia the main pathophysiological processes resemble those of the metabolic syndrome with increased insulin resistance [40-43].

IUGR

Occasionally, severe placental disease can result in IUGR without evidence of preeclamptic manifestations or maternal endothelial dysfunction.

In the group of fetuses with a decrease of growth we can classify IUGR and fetuses small for gestational age.

Intrauterine growth restriction refers to a condition in which a fetus is unable to achieve its genetically determined potential size. This functional definition seeks to identify a population of fetuses at risk for modifiable but otherwise poor outcomes.

IUGR is defined by the coexistence of abdominal circumference (AC) below the 5th percentile for local standards (or a decrease of AC percentile >40 percentile from mid trimester to third trimester) [44] and an abnormal uterine Doppler waveform according local standards [45]. Growth retardation is also confirmed at delivery against the standards of weight for gestational age population reference.

The etiology of IUGR is an impaired placentation as described above and this etiology explain the asymmetrical growth restriction and altered Doppler velocimetry of uterine artery and consequently of umbilical artery. Conversely, SGA fetuses are defined as constitutionally smaller for gestational age and presenting a weight at birth below the 10th percentile for the gestational age population reference. This group presents normal uterine and umbilical artery Doppler and usually a symmetrical growth restriction and better outcome.

The differentiation between SGA and IUGR fetuses during prenatal life is not always simple and clear.

In fact, there is some confusion in terminology for the lack of uniform diagnostic criteria. Furthermore almost of authors use the terms small for gestational age and intrauterine growth restriction as synonymous. Others authors think that the term SGA is more appropriate referring to infant while IUGR referring to fetus. By definition, 10% of people in any population have a weights, as well as heights, below the 10th percentile. This is the cut-off value mainly used for defining the IUGR. A minority of authors define the cut-off value at the 5th or at 3th percentile. There are many evidence demonstrating that the adverse perinatal outcome are mainly confined to infants below the 5th or 3th percentile [46].

It is very important specify that fetal growth depends by two broad and overlapping stages during the pregnancy.

During the first period the growth is characterized as a germinal and embryonic period while during the last period there is a differentiation's prevalence depending by genetical characteristics. This is the reason because there is less biologic variability in growth during the first period of pregnancy. On the contrary, there is an increasing variability during the pregnancy progress. Therefore, also the placenta effects are more evident in the third trimester of pregnancy when the fetus need more nutriment.

It has been suggested that these variable presentations of growth should be regarded distinct disease entities in etiology and in abnormal placentation [33,47].

For this reason in the last years the physicians had proposed the hypothesis of a different etiology of IUGR, according to its age of onset: early and late. The early onset cases are caused by an impaired placentation during the first trimester, while for late onset cases there are placental abnormalities that have arisen late in women with pre-existent diseases. Therefore, the fetuses with growth restriction are an heterogeneous group with etiology and pathophysiology still unclear. Maybe the early IUGR can derive from an abnormal placentation and late IUGR from a backward different placental alteration in women who had metabolic syndrome.

Prevention of Preeclampsia and IUGR

The primary prevention of any preeclampsia or IUGR remains a considerable challenge in obstetrics. Although the symptoms of preeclampsia and IUGR generally manifest in the second to third trimester of pregnancy, their underlying pathology takes place in the first trimester [45].

It is the assumption taken by many researchers and physicians that identifying a woman at risk for preeclampsia or IUGR may help managing her risk and potentially use several promising prophylactics to improve her outcomes [12].

Today it is a standard practice in perinatology to evaluate a woman's prior risk based on previous medical, obstetric and demographic questions characterized by relatively low sensitivity and specificity. Thus, for women considered at high risk for preeclampsia, due to previous preeclampsia or chronic hypertension or diabetes or multi-fetal pregnancy, the frequency of those who will develop preeclampsia is 19% (previous preeclampsia), 22% (diabetes) and 25% (chronic hypertension) [48].

About IUGR, maternal smoking, low educational level, advanced maternal age and black race are associated with increased risk of the pathology [49]. The same is the case for maternal medical conditions like gestational hypertensive disorders, pre and gestational diabetes, systemic lupus erythematosus, chronic renal disease, and thyroid disorders [50]. Finally, there is a strong association between IUGR and prior pregnancy with a growth restricted fetus.

Furthermore, nulliparity is one of the major clinical risk factor for the development of preeclampsia and IUGR [51]. Although the screening by maternal history alone will detect only 30% of women who will have preeclampsia [39], the clinical risk-based strategy is not effective for nulliparous women without other risk factors.

Estimating each woman's individual risk would allow appropriate antenatal surveillance, and would also enable to test preventive strategies such as low-dose aspirin in selected high-risk groups [52]. However, the use of prophylactic treatments is likely to be more beneficial when started earlier in pregnancy, ideally before 16 weeks [53]. It would be thus important to develop an effective method of early identification of high risk groups.

To improve the prediction of the disease, many authors have combined patient history with a series of biophysical and biochemical markers that change from as early as the first trimester of pregnancy in cases that subsequently develop preeclampsia or IUGR. Studied biophysical markers include mean arterial blood pressure [54], uterine artery Doppler [55,56] and more complex evaluations such as maternal cardiac output [57], brain hemodynamic measurements [58] and more recently pulse wave analysis [59]. Several biochemical markers have been tested for the prediction of preeclampsia and IUGR, including products of fetal and placental origin, markers of renal or endothelial damage, angiogenic and antiangiogenic factors, and markers of oxidative stress as reviewed by Giguère et al. in 2011 [60].

Currently, clinical history, maternal serum biochemistry and uterine artery Doppler sonography before 14 weeks have been investigated, even though with limited success[39,61-63]. In the second trimester, uterine artery Doppler can claim a detection rate of only 63.1% for a high (25%) false-positive rate [64] for preeclampsia and only 20% for IUGR [65] . First-trimester uterine artery Doppler studies have been shown to have high sensitivity but poor specificity, with a high FPR [66]. The combination of

first-trimester uterine artery Doppler indices and placental protein 13 (PP13) holds promise in this respect, but further evidence is needed [61]. Maternal serum markers, such as inhibin A, activin A, soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin, when used alone are proved poor predictors of preeclampsia [67-69].

A systematic review of screening tests for preeclampsia concluded that no single test is yet available to provide a good diagnostic accuracy [12]. A combined screening involving several relevant markers is more likely to provide the best prediction.

First-trimester screening would represent a major advantage over a second-trimester approach because it opens prospects for early and more efficient interventions.

Pulse wave analysis

In the latest years the physician's attention was posed on the hemodynamic changes in preeclamptic women.

In women affected by preeclampsia, the normal maternal cardiovascular adaptation, characterized by increased intravascular volume, cardiac output, heart rate (HR), aortic distensibility, compliance and by a marked decrease in vascular resistance [70-72], fails [73]. Several studies, using two-dimensional echocardiography, have confirmed that preeclampsia is characterized by a marked reduction of the maternal cardiac output and an increase of peripheral resistance [73-75].

Despite the extensive number of studies in the maternal hemodynamic adaptation during preeclampsia, the available information on maternal central hemodynamics, wave reflection, and arterial stiffness, in this condition, is however scarce.

In non-pregnant subjects, examination of the characteristics of the peripheral and central arteries provides valuable information about the circulatory changes associated with hypertension and/or vascular disease [76,77].

Outside pregnancy, arterial stiffness has been shown to be increased in hypertensive patients, using a variety of methods such as Doppler color echocardiography [78] and pulse wave velocity [77,79,80-83]. Another technique, pulse wave analysis, the noninvasive analysis of the aortic pressure waveform and aortic stiffness, is possible by the simple, validated, and reproducible technique of applanation tonometry [84-90]. Pulse wave

analysis has been widely studied in the general population [84-90] and can quantify alterations in vascular compliance associated with conditions that cause endothelial dysfunction, such as diabetes, renal disease, and arteriosclerosis. Central pressures may be more relevant than brachial artery blood pressure to cardiovascular pathophysiology; for example, central pulse pressure is a better predictor of cardiovascular events than is brachial blood pressure [91,92].

Studies in nonpregnant women have found differential effects of antihypertensive drugs on central hemodynamics, despite similar effects on peripheral blood pressure measurements [93-95]. These findings have contributed to a major change in the guidelines on the management of hypertension outside pregnancy.

Moreover, the arterial stiffness is an independent predictor of cardiovascular events and mortality even in healthy subjects [96]. Interestingly, women with a history of preeclampsia are also at increased risk of cardiovascular events later on in life [97], and this association may be mediated by an increased arterial stiffness.

In pregnancies with preeclampsia, there is some evidence that in addition to the vascular changes in the uteroplacental unit there is a generalized increase in maternal arterial stiffness [98-103].

Normal values for pulse wave analysis in uncomplicated pregnancies have recently been established [99]. Three studies using pulse wave analysis [101,103,104] showed that arterial stiffness is increased in women with hypertensive disorders of pregnancy compared with normotensive pregnant women.

Recent studies using PWA have confirmed a reduced arterial compliance (in other words, increased arterial stiffness) in women with clinically established preeclampsia [99,101,103].

Only one study is done in the first trimester of pregnancy and it supposed that PWA could predict preeclampsia and it could be used like a screening test [105].

Data respect to maternal vascular function regarding women with a history of a normotensive IUGR pregnancy, are currently limited and inconsistent. Only one article by Elvan-Taspinar [106] underlined as an increased in arterial stiffness, in normotensive pregnancy, is associated with a decrease in birth weight centile and catch up growth after birth, independently from mean arterial pressure.

Basis of PWA physiology

Each heartbeat generates a pulse wave that travels away from the heart and is reflected back at the areas of high resistance. The reflected wave travels back towards the heart and meets the advancing wave, augmenting its height. Generally, the reflected wave reaches the aorta during diastole, enhancing the cardiac perfusion. When arterial stiffness is increased, the arterial pulse wave travels faster, so the reflected wave reaches advancing wave in the systole, resulting in significant augmentation of the systolic peak. This can be measured as increased augmentation index. Interrogation of the radial artery waveform (pulse wave analysis of the radial artery) can provide information on augmentation index and the central, aortic haemodynamics [77,81,107].

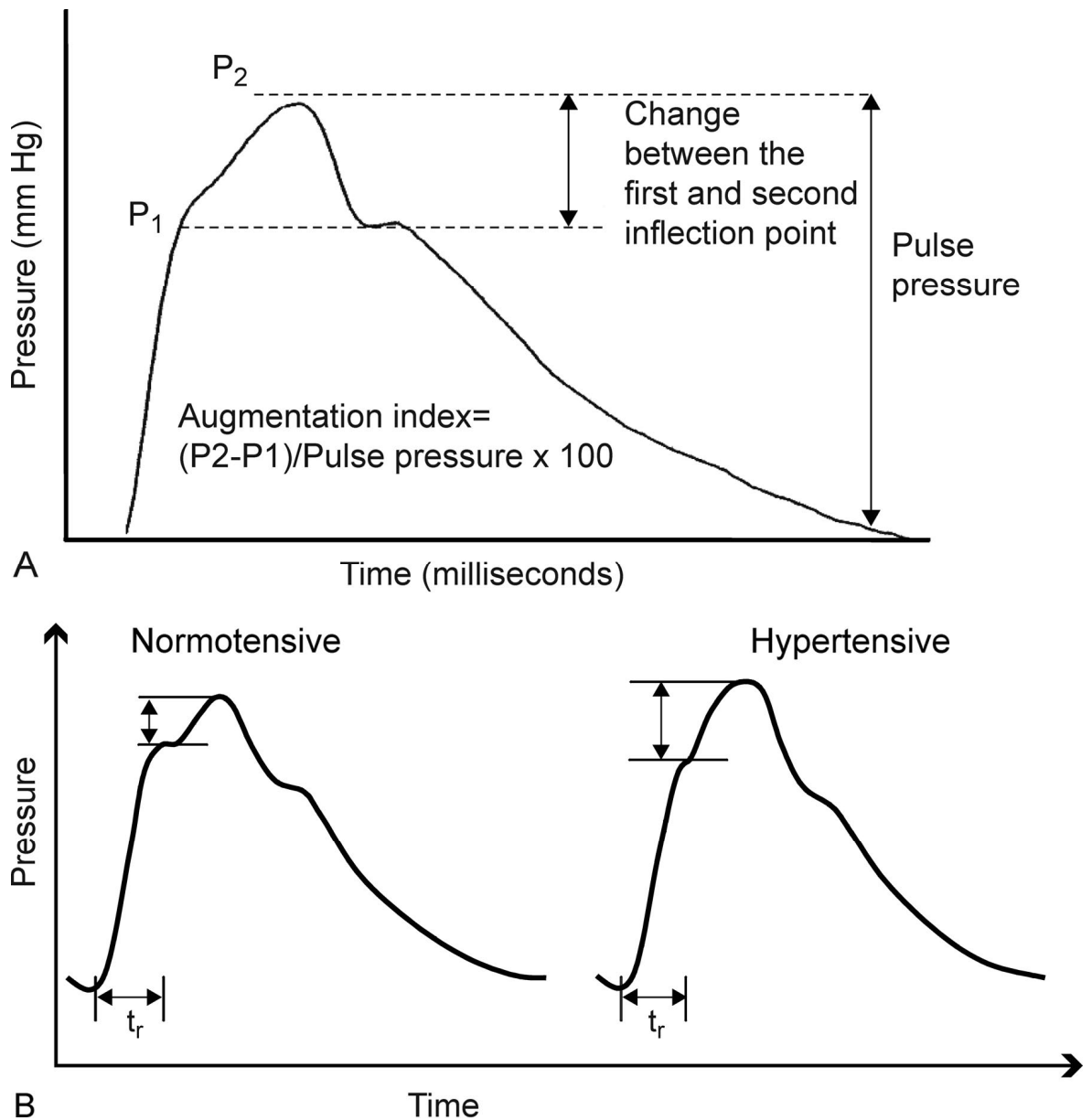


Fig. 1. A. Typical ascending aortic pulse waveform, showing two systolic peaks (P_1 and P_2). Augmentation index is calculated as the difference between P_2 and P_1 (ΔP), expressed as percentage of pulse pressure. The designation P_1 is the first inflection point; P_2 is the second inflection point. **B.** In hypertensive disorders, arterial wall stiffness is increased; the arterial pulse wave travels faster, so the reflected wave reaches the advancing wave in systole, resulting in greater augmentation of the systolic peak. Time t_r is the time to reach the reflected wave.

Khalil. Antihypertensives and Pulse Wave Analysis. Obstet Gynecol 2009.

STATE OF THE ART

Preeclampsia and intrauterine growth restriction are major contributors to maternal and/or perinatal mortality and morbidity worldwide. Despite improvement in the understanding of the pathophysiology of these conditions, ability to accurately predict pregnant woman who will develop PE and/or IUGR is limited. This greatly impairs the development and testing of preventive interventions.

While different measures of placental dysfunction have been associated with increased risk for adverse pregnancy outcomes, the ability of any single indicator to accurately predict these outcomes is poor. Developing predictive tests is further challenged by difficulty in the timing of the measurements, as both the structural and biochemical characteristics of the placenta change with gestational age. The ideal screening test would accurately predict the development of adverse pregnancy outcomes early enough to provide a window for preventive interventions.

Over the past decade, the knowledge about preeclampsia has changed significantly by virtue of increased recognition of the heterogeneous nature of this syndrome.

The definition of preeclampsia, based on clinical manifestations of the disease or based on the time domain onset of the disease, does not consider the etiology of this pathological syndrome.

Actually, there is an evidence that preeclampsia is an heterogeneous condition with two different clinical scenarios: the first one, typically, with early onset (< 34 weeks) associated with fetal growth restriction, alteration of placental and fetal Doppler velocimetry and important maternal involvement, thought to be a consequence of impaired placentation; the second one, mainly with late onset normal fetal growth, normal fetoplacental blood flow and rarely with important clinical involvement for the mother. The underlying pathophysiological process to this condition is thought to be the metabolic syndrome with chronic low-grade inflammation and increased insulin resistance characterizing typically women with android obesity.

This is the rationale to support the theory that stress mainly the etiology of the disease, and that considers preeclampsia of placental origin associated

with growth restricted fetus (IUGR), while preeclampsia of maternal origin associated with appropriately growth fetus (AGA).

It is well known that women with a history of preeclampsia are at increased risk of cardiovascular events later on in life.

Improvements in non-invasive technology, as applanation tonometry, provided useful novel tool to assess peripheral and central vascular resistance. The arterial stiffness is an independent predictor of cardiovascular events and mortality even in healthy subjects. Recent studies using Pulse Wave Analysis confirmed a reduced arterial compliance (in other words, increased arterial stiffness) in women with clinically established preeclampsia [99-103].

Only one study was performed in the first trimester of pregnancy stating that PWA was a good predictor of early preeclampsia and, therefore, potentially could be used as screening test [105].

Data regarding maternal vascular function in women with a history of a normotensive IUGR pregnancy, are currently limited. Only one article by Elvan-Taspinar found an increased arterial stiffness, in normotensive pregnancy, to be associated with a lower birth weight centile and decreased catch up growth after birth, independently from mean arterial pressure [106].

Most of the studies are limited by the small cohort, and none considered preeclampsia divided by the underlying etiology.

AIM OF THE STUDY

The aim of the study is to investigate maternal indices of central and peripheral vascular resistance (arterial stiffness) and indices of central pressure in aorta, in the first trimester of pregnancy, in preeclampsia of maternal and placental origin and fetal growth restriction.

MATERIAL AND METHODS

This is a prospective longitudinal cohort study offered to pregnant women at the time of screening for Down syndrome at 11 to 13+6 weeks, between January 2011 and December 2011, in the Maternal Fetal Medicine Unit,

Department of Obstetrics and Gynecology, Buzzi Children's Hospital, University of Milan.

The study was approved by Ethics Committee of Istituti Clinici di Perfezionamento (ICP)-Buzzi Children's Hospital (CE approval 277/2011). Written informed consent was obtained from all women before the enrollment. At the time of inclusion, 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 (Caucasian, African, Asian, East Asian and Mixed), smoking habit, family history of hypertension, medical pathologies, drug assumption, parity (parous or nulliparous if no delivery beyond 20 weeks), method of conception (spontaneous or IVF), obstetrical history.

The maternal weight and height were measured and the body mass index (BMI) was calculated.

The inclusion criteria were:

- single pregnancy;
- absence of fetal anomalies;
- age major to 18;
- obtained informed consent;

The exclusion criteria were:

- multiple pregnancy;
- presence of fetal anomalies;
- miscarriage before 20 weeks;
- age inferior to 18;
- informed consent not obtained.

Routine risk assessment for chromosomal aneuploidies included the measurement of the fetal crown-rump length (CRL), nuchal translucency, and ultrasound screening for major fetal abnormalities. Maternal serum PAPP-A and free β Human Chorionic Gonadotropin were determined to calculate the combined patient-specific risk for trisomy 18 and 21 [108,109].

During the ultrasound examination, Doppler velocimetry of uterine arteries (left and right) was performed. All indices were recorded: Pulsatility Index (PI), Resistant Index (RI), Peak Systolic Velocity (PSV). For the purposes of this study the mean value of the pulsatility index from the left and right

uterine artery was used (Mean UtA PI) [39]. Brachial blood pressure was measured by an aneroid sphygmomanometer, while central blood pressure and pulse wave reflection was assessed by applanation tonometer.

Uterine arteries Doppler velocimetry assessment

Both uterine arteries were examined as suggested by the Fetal Medicine Foundation, London, UK (www.fetalmedicine.com/fmf) by an operator certified by the Fetal Medicine Foundation (DD, GP, TS) for the first trimester screening with at least 3 years of experience in Doppler ultrasonography. A sagittal section of the uterus was obtained and the cervical canal and internal cervical os identified. The transducer was tilted from side to side and color flow mapping was used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler was used with the sampling gate set at 2mm to cover the whole vessel and with care taken to ensure that the angle of insonation was less than 30°. When three similar consecutive waveforms were obtained the uterine artery PI was measured and the mean UtA PI was determined. The treating physicians were blinded for the first trimester Doppler results, which were not shown in the ultrasound report. Mean PI has been registered and classified in normal or pathological, accordingly if lower or higher to 2,3 PI limit value (95° percentile) [110].

Laboratory technique

Once the ultrasound examination was performed and the gestational age confirmed, a blood sample (around 5 cc) was taken from each woman. Maternal serum PAPP-A was measured using a kit for B.R.A.H.M.S KRYPTOR automated immunofluorescent assays (Hennigsdorf, Germany; www.kryptor.net). Samples were measured within two hours.

Blood pressure (BP)

Peripheral blood pressure was measured from the right arm, after at least 5 minutes of rest, using an aneroid sphygmomanometer. During the measurement the patient did not move or speak. Auscultatory Riva-Rocci-Korotkoff measurements were performed. Brachial systolic BP was defined by the first Korotkoff sound and brachial diastolic BP was defined by the fifth Korotkoff sound.

Applanation tonometry and Pulse wave analysis (PWA)

The applanation tonometry (Sphygmocor® system Atcor Medical, West Ryde, Australia) was performed as follows: the radial artery was gently compressed with the tip of the tonometer at the site of maximal pulsation. The tonometer contains a micromanometer (Millar Instruments, Houston, TX, USA) that provides very accurate recording of the pressure within the radial artery [82]. A generalised transfer function was applied to the radial artery waveform to derive the aortic pressure waveform [107,111,112]. From the aortic pressure waveform, the augmentation pressure (AP) and augmentation index (AIx) were calculated. The AP is defined as the height of the late systolic peak above the inflection point on the waveform.

The AIx is defined as AP expressed as a percentage of the aortic pulse pressure (PP=systolic pressure minus diastolic pressure) [76,77].

AIx is affected by changes in the heart rate. An increase in heart rate shortens the duration of systole. As a result, the reflected wave reaches the advancing wave in diastole (rather than the usual systole), resulting in reduced augmentation of the advancing wave, that is reduced AIx. As there is a linear relationship between maternal heart rate and AIx, the AIx was standardized to a heart rate of 75 beats per minute (AIx-75) [113].

The Sphygmocor system [77] was used for the analysis of the radial pressure wave contour. All measurements were made by six observers (SZ, ER, GC, VS, CM, DC). Prior to commencing the study, there was an initial learning period of repeated measurements until satisfactory reproducibility was achieved. Moreover, the Sphygmocor software has incorporated a quality control feature that is displayed on the screen and only recordings with success rate equal or higher to 85% were used. Ten sequential pulse wave forms were recorded, and the average peripheral and derived aortic waveform were generated and analyzed. The following hemodynamic data were derived from the recorded radial and the reconstructed central pressure waveform:

- with an integrated software Augmentation index was determined, a composite measure of systemic arterial stiffness and wave reflection amplitude;
- aortic waveform with central systolic and diastolic pulse pressure.

All acquired data were hidden to the patients or their doctors and, therefore, did not influence in any way subsequent management of the pregnancy.

Outcome data collection

Pregnancy outcome data were collected as follows: fetal and maternal outcomes were obtained either directly from the clinical record if the delivery occurred in Buzzi Hospital or by a telephone interview.

Definition of outcomes

The diagnosis of GH and PE was made according to the criteria of the International Society for the Study of Hypertension in Pregnancy [8]. Under this classification, GH was defined as diastolic blood pressure above 90 mm Hg or more on at least two occasions, at 4 hours apart, developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria. PE was defined as diastolic BP of at least 110 mmHg on one occasion or diastolic BP of at least 90 mmHg on two consecutive occasions more than four hours apart, in combination with proteinuria (≥ 300 mg total protein in a 24-hour urine collection or, if this was not available, $\geq +2$ proteinuria by dipstick analysis on two consecutive occasions at least four hours apart) developing after 20 weeks of gestation in previously normotensive women.

The IUGR was defined as a birth weight below the 5th percentile according to standards references for weight based on gestational age [44]. Other causes of IUGR such as infection, anomalies and abnormal chromosomes were excluded in all cases.

SGA was defined as a birth weight below the 10th percentile but major of 5th percentile for the gestational age at birth. Also in this group we excluded cases with infections, anomalies or abnormal chromosomes.

For the purposes of the analysis we considered preeclampsia classification based on the different etiology: preeclampsia of placental or maternal origin. As previously stated, placental PE is associated to impaired fetal growth–IUGR, while in preeclampsia of maternal origin the fetal growth is appropriate for gestational age, independently of gestational age at diagnosis.

Statistical analysis

Patients were classified accordingly to pregnancy outcome:

- control group: uneventful pregnancy with normal fetal and maternal outcome;

- women that developed preeclampsia divided in two subgroups: of placental or maternal origin;
- Isolated fetal growth disorders: IUGR or SGA.

We compared demographic characteristics, hemodynamic parameters and placental parameters among preeclampsia group and controls and among growth restriction fetus group and controls. Therefore, we compared placental and maternal preeclampsia for hemodynamic and placental parameters. The same for SGA and IUGR group. Otherwise, we compared placental and maternal preeclampsia each other and also SGA and IUGR.

Data were expressed as mean \pm standard deviation or as median and interquartile range for normally and non-normally distributed data, respectively.

Comparisons between groups were performed using t-test or chi-square test for numerical and categorical data, respectively.

For comparison of all groups, one-way analysis of variance (ANOVA) with Dunnett's post-hoc test was used.

Data were analyzed using IBM SPSS Statistics 19.0.

Results were considered statistically significant for $p < 0.05$.

RESULTS

Between January 2011 and December 2011, 687 pregnant women were recruited in occasion of their Down screening ultrasound examination. At the moment of the analysis, 326 pregnancies were still on-going, 26 patients were lost to follow-up, while 27 patients were excluded because of incomplete data acquisition: failed tonometer analysis (12 women) and failed uterine Doppler Velocimetry evaluation (15 women). This resulted in the cohort of 311 women with complete outcome follow-up, of which two women had second trimester miscarriage, while one woman performed a termination of pregnancy for fetal abnormality; these three patients were excluded from analysis.

As showed in Table 1 from the cohort of 308 women that was analyzed, eight women developed (2,6%) preeclampsia: of which four were of placental origin (PE+IUGR), while remaining four of maternal origin (PE+AGA). Seven women developed gestational hypertension (GH) and in

all cases the fetus presented appropriate growth for gestational age. Therefore, they were included in maternal preeclampsia group (PE+AGA). Sixteen pregnancies (5,2%) were complicated by intrauterine growth restriction (IUGR), eight (2,6%) had small for gestational age newborns (SGA) and finally 269 (87%) women had normal outcome of pregnancy and were considered as controls.

Table 1 reports the maternal or fetal outcomes and complications occurred in the study groups.

OUTCOME IN THE STUDY GROUP	308
PLACENTAL PE (PE+IUGR)	4/308 (1,3%)
MATERNAL PE (GH/PE+AGA)	4+7=11/308 (3,6%)
IUGR (Birthweight < 5° pcle)	16/308 (5,2%)
SGA (Birthweight < 10° pcle and > 5° pcle)	8/308 (2,6%)
COMPLICATION OCCURRED IN THE STUDY GROUP	17/308 (5,5%)
INTRAUTERINE DEATH	1/308 (0,3%)
ABRUPTIO PLACENTA	2/308 (0,6%)
ADMITTANCE TO NICU	11/308 (3,6%)
PERINATAL DEATH	2/308 (0,6%)

Table 1: Main maternal and fetal/neonatal complications subsequently developed in the study group.

The intrauterine death occurred in a first pregnancy woman at 38 weeks of gestation with a fetus had a birth weight < 3° pcle. Two cases of placental abruptio occurred during labour; in one case associated with gestational hypertension.

One case of perinatal death occurred in a premature newborn at 24,5 weeks of delivery with sepsis. The other one in another premature infant at 28 weeks of delivery with a congenital cardiac anomaly. Finally of the 11 newborn admittance to NICU, five were premature, two presented a pulmonary distress, three were IUGR and the last one had hypoglycemia.

Demographic variables into groups

Table 2A and 2B show the main features of the control group and preeclampsia group of maternal and placental origin.

There were no statistically significant differences in age, ethnicity, parity, smoking habit, family history of hypertension, gestational age (GA) and CRL at recruitment and sex, between controls and subjects who developed maternal or placental preeclampsia.

Patients with maternal PE showed a statistically higher BMI compared to controls ($p=0,011$), while placental PE showed a higher incidence of previous pregnancy affected by preeclampsia ($p=0,004$). Both maternal and placental PE group delivered at an earlier GA, but only placental PE had smaller babies and major incidence of admittance to NICU ($p < 0,001$). 27% of women that developed maternal PE applied to IVF ($p < 0,001$).

When comparing placental to maternal PE, differences for gestational age at delivery, birth weight and admittance to NICU were noticed ($p < 0,001$).

VARIABLE	CONTROLS	MATERNAL PE	p value	PLACENTAL PE	p value
MATERNAL AGE (years)	32,2±11,2	32,2±3,2	0,98	32,7±4,9	0,92
MATERNAL BMI (Kg/m ²)	22,54±3,5	25,3±4,2	0,011	23,3±2,8	0,66
ETHNICITY	96%	100%	0,5	100%	0,68
NULLIPARITY	71%	73%	0,92	75%	0,87
SMOKING	7,8%	0%	0,34	0%	0,56
CONCEPTION (spontaneous)	95%	73%	< 0,001	100%	0,88
FAMILY HYPERTENSION	37%	36%	0,97	50%	0,59
PREVIOUS PE	2,2%	9,1%	0,15	25%	0,004
GA AT RECRUITMENT (w)	12,3±0,5	12,2±0,5	0,56	12,1±0,5	0,53
CRL AT RECRUITMENT	59,9±7,0	58,3±5,5	0,47	59±4,5	0,81

Table 2A: Demographic characteristics of the study population

VARIABLE		CONTROLS	MATERNAL PE	PLACENTAL PE
GA AT DELIVERY (w)		39,6±1,7	38,3±1,6	33,7±5,1
BIRTHWEIGHT (g)		3380±450	3118±490	1680±850
NICU		1,9%	9,1%	75%
SEX	M	47,8%	45,5%	50%
	F	52,2%	54,5%	50%

Table 2B: Neonatal characteristics of the study population

Table 3 shows the main features of the control, SGA and IUGR groups. There were no significant differences in baseline characteristics. Birth weight and gestation at delivery were statistically lower in women with IUGR or SGA compared with controls. Only IUGR group presented a higher prevalence to admittance to NICU ($p=0,048$).

The gestational age and CRL at recruitment were smaller than controls in IUGR and SGA group, but statistical significant only for IUGR ($p < 0,001$). The IUGR group differ from SGA only for the percentage of babies admittance to NICU ($p=0,05$).

VARIABLE	CONTROLS	SGA	p value	IUGR	p value	
MATERNAL AGE (years)	32,2±11,2	32,5±3,9	0,95	29,9±4,3	0,074	
MATERNAL BMI (kg/m ²)	22,54±3,5	20,2±2,9	0,07	22,9±6,0	0,78	
ETHNICITY : caucasian or asian or afro-caribbean	96% 4%	100% 0%	0,56	94% 6%	0,64	
NULLIPARITY	71%	87,5%	0,32	87%	0,16	
SMOKING	7,8%	12,5%	0,63	0%	0,25	
CONCEPTION (spontaneous)	95%	100%	0,78	100%	0,61	
FAMILY HYPERTENSION	37%	37,5%	0,97	56%	0,12	
PREVIOUS PE	2,2%	0%	0,67	6,3%	0,31	
GA AT RECRUITMENT (w)	12,3±0,5	12,2±0,5	0,67	11,9±0,3	< 0,001	
CRL AT RECRUITMENT	59,9±7,0	55,5±4,1	0,10	55,1±3,9	< 0,001	
GA AT DELIVERY (w)	39,6±1,7	38,4±0,7	0,048	38,2±1,9	0,002	
BIRTHWEIGHT (g)	3380±450	2633±65	< 0,001	2390±294	< 0,001	
NICU	1,9%	0%	0,58	12,5%	0,048	
SEX						
	M	47,8%	25%	0,18	38%	0,37
	F	52,2%	75%		62%	

Table 3: Demographic characteristics of growth restriction groups

Hemodynamic characteristics:

The hemodynamic parameters for preclamptic groups are given in Table 4 A.

There were no significant differences in heart rate and Augmentation index at 75 bpm between the two groups of PE compared with controls and also between each other (Figure 3).

Mean arterial pressure was significantly higher in both placental and maternal preeclampsia when compared to the control group (Figure 1), while central systolic pressure was significantly higher only in placental PE group ($p < 0,001$) (Figure 2).

Table 4 B shows the comparison between the hemodynamic parameters in IUGR, SGA and controls. There were no statistically significant differences between groups (Figure 4).

VARIABLE	CONTROLS	MATERNAL PE	p VALUE	PLACENTAL PE	p VALUE
MEAN ARTERIAL PRESSURE (mmHg)	77,7±8,4	85,8±12,4	0,002	87,5±12,6	0,02
HEART RATE (bpm)	79,2±11	83,4±9,4	0,25	77,5±8,0	0,72
CENTRAL SYSTOLIC BLOOD PRESSURE (mmHg)	92,3±9,4	101,4±16,6	0,076	107±21,3	< 0,001
AUGMENTATION INDEX (%) AT 75 bpm	16,14±11	19±11,2	0,36	21,75±14,6	0,29

Table 4 A: Maternal haemodynamic and vascular characteristics of the PE group

VARIABLE	CONTROLS	SGA	p VALUE	IUGR	p VALUE
MEAN ARTERIAL PRESSURE	77,7±8,4	76,7±8,4	0,73	78,7±11,2	0,62
HEART RATE	79,2±11	77,4±8,9	0,60	75,9±11,1	0,21
CENTRAL SYSTOLIC BP	92,3±9,4	88,5±11	0,41	93,7±12,9	0,44
AUGMENTATION INDEX (%) AT 75	16,14±10,8	17,5±7,6	0,68	18,7±13	0,33

Table 4 B: Maternal haemodynamic and vascular characteristics of the SGA and IUGR group

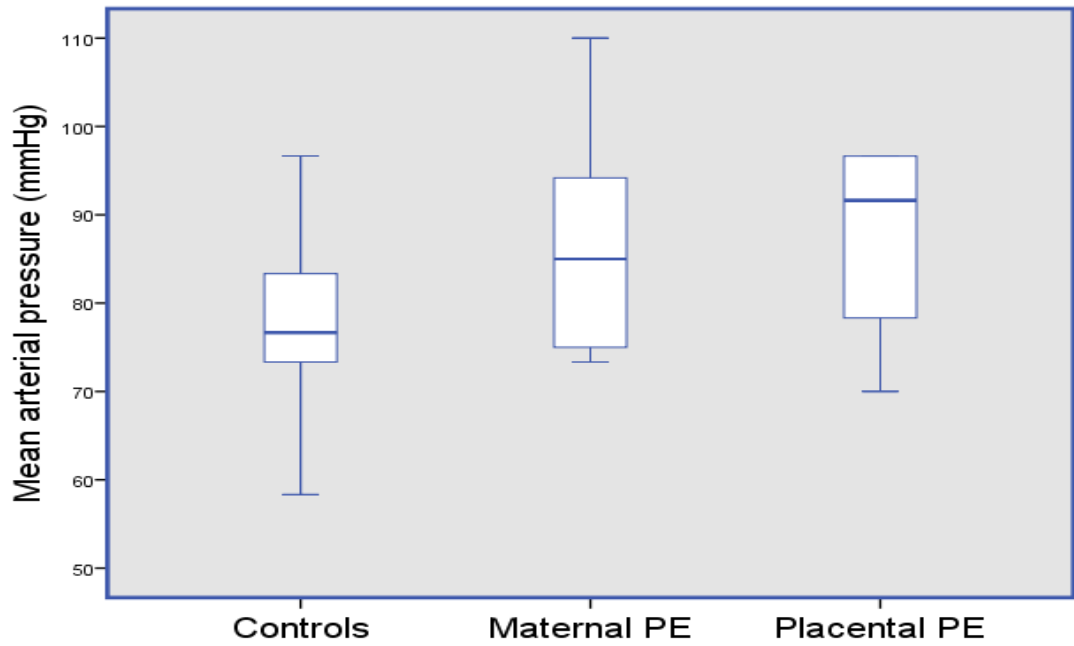


Fig. 1: Boxplots of Mean arterial pressure in preeclampsia of placental or maternal origin and controls.

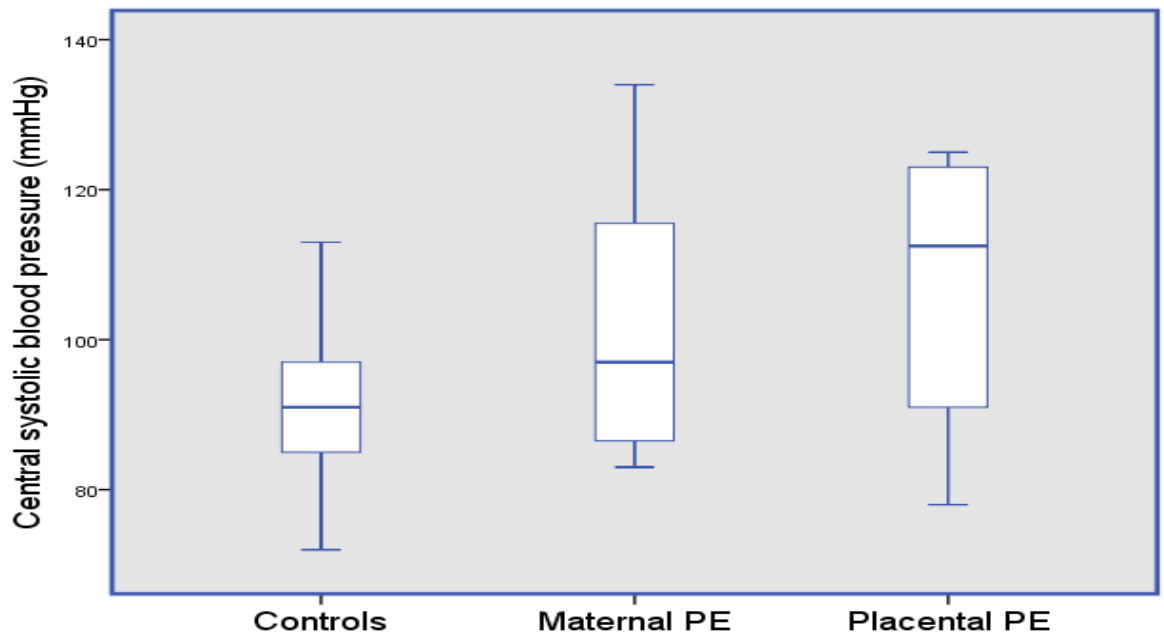


Fig. 2: Boxplots of Central systolic blood pressure in preeclampsia of placental or maternal origin and controls.

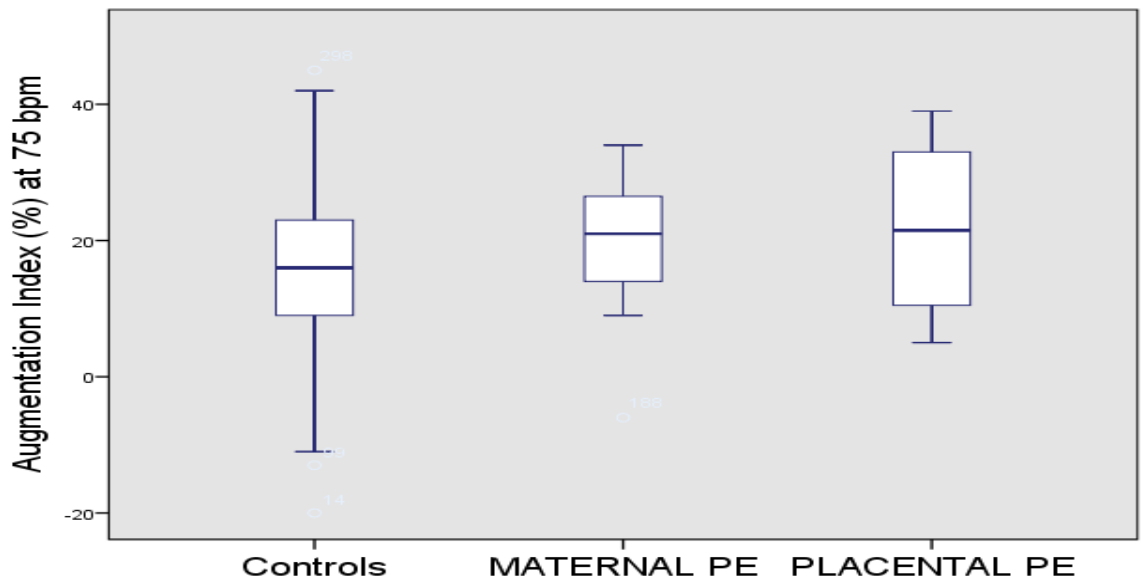


Fig. 3: Boxplots of Augmentation index at 75 bpm in preeclamptic groups and controls

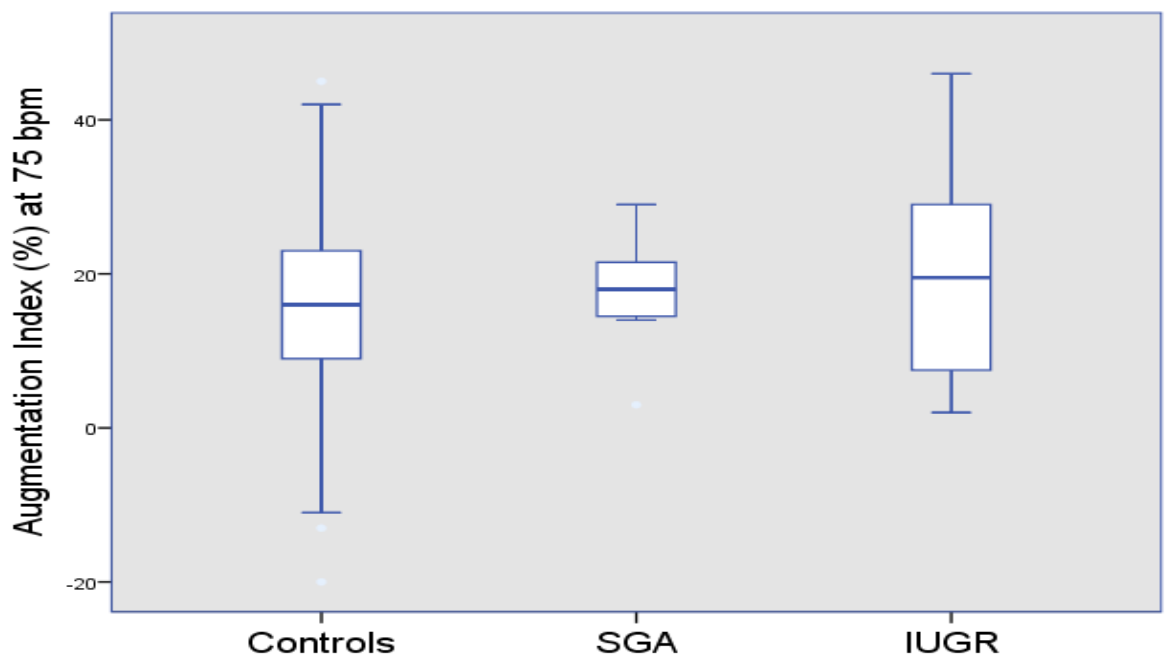


Fig. 4: Boxplots of Augmentation index at 75 bpm in growth restriction groups

Placental parameters:

The results of the Doppler examination of the uterine arteries are represented in Table 5 for preeclampsia groups.

The mean uterine artery PI was significantly higher in placental PE group ($p < 0,001$) when compared with the other groups (Figure 6). Furthermore, in preeclampsia of placental origin, 50% of women presented abnormal uterine artery PI ($> 95^{\circ}$ pcle) as soon as in first trimester in comparison with only 9% in preeclampsia of maternal origin ($p < 0,001$ vs $p=0,42$) (Table 5).

Maternal serum PAPP-A, which is known to be altered in pregnancies that subsequently develop PE, was significantly lower only in maternal PE group ($p=0,024$).

IUGR group presented, similarly to placental PE group, a mean uterine artery PI higher than controls and SGA group ($p < 0,001$) (Table 6).

VARIABLE	CONTROLS	MATERNAL PE	p value	PLACENTAL PE	p value
MEAN UTERINE ARTERY PI	1,5±0,5	1,4±0,7	0,30	2,5±0,5	< 0,001
ABNORMAL UtA	5%	9%	0,42	50%	< 0,001
MOMM PAPP-A	0,94±0,6	0,58±0,2	0,024	0,77±0,3	0,52

Table 5: Placental parameters of study population in preeclampsia groups.

VARIABLE	SGA	p value	IUGR	p value
MEAN UTERINE ARTERY PI	1,4±0,6	0,70	1,8±0,5	0,032
ABNORMAL UtA	12,5%	0,25	19%	0,008
MOMM PAPP-A	0,98±0,4	0,89	0,74±1	0,16

Table 6: Placental parameters in IUGR, SGA and controls.

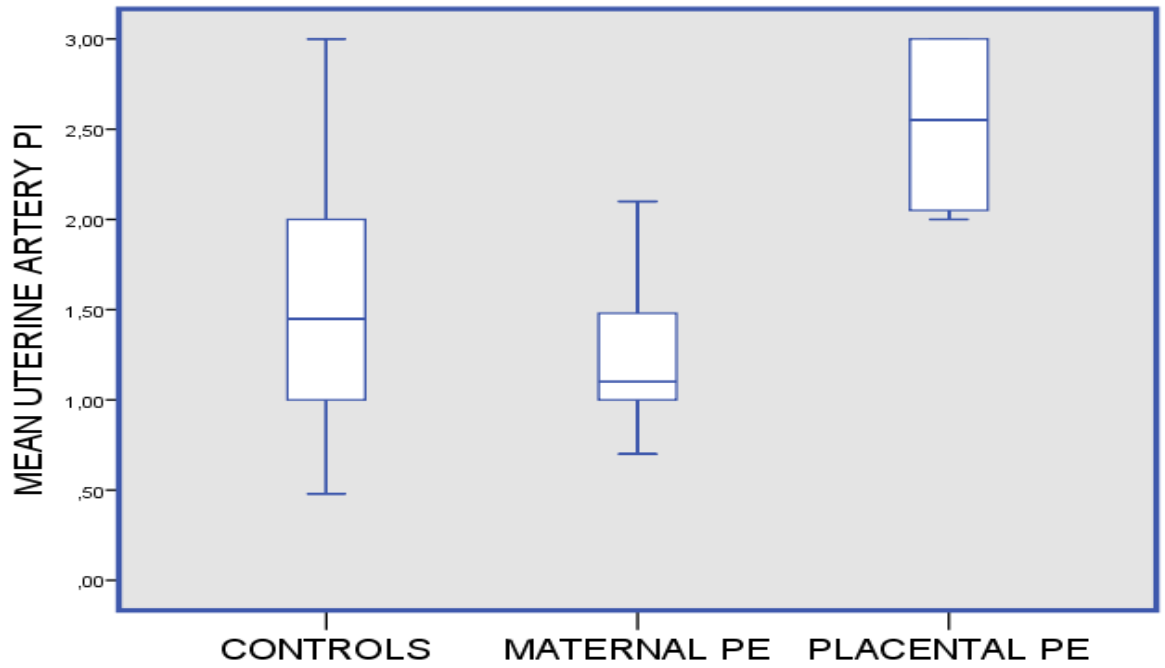


Fig. 5: Boxplots of Mean uterine artery PI in preeclampsia of placental or maternal origin versus controls.

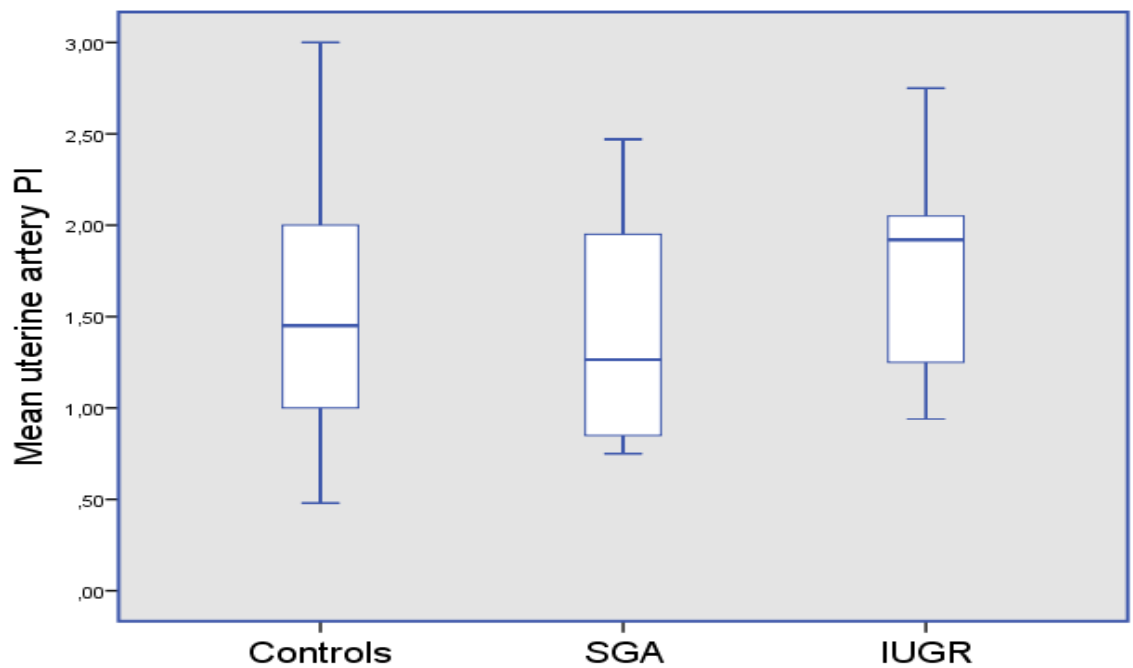


Fig. 6: Boxplots of Mean uterine artery PI in growth restriction fetuses

DISCUSSION

The aim of the current study was to investigate the maternal cardiovascular adaptation and in particular arterial stiffness in women destined to develop PE and IUGR. Furthermore, we adopted a new classification of PE based on the underlying etiology: PE of placental origin when associated to IUGR and maternal when the fetal growth appears within normal ranges, independently of gestational age at the diagnosis.

Placental and maternal preeclampsia recognize different etiologies and, therefore, develop through different models of maternal cardiovascular adaptation in the latent phase of the disease. In the same way, IUGR and SGA fetuses present different etiologies.

Accurate prediction of preeclampsia and intrauterine growth restriction is crucial to allow judicious allocation of resources for monitoring and the development of preventive treatment to improve maternal and perinatal outcomes.

Early identification of women at risk of pre-eclampsia facilitates targeted surveillance and intervention [114-115]. There are likely to be significant advantages in predicting preeclampsia in the first, as opposed to the second trimester; given that the disease process is already established by the mid second trimester, it seems likely that any successful preventative measure will need to be instituted as early in pregnancy as possible.

Because the incidence rates of preeclampsia and IUGR are relatively low (1.3–6.7% in developing and 0.4–2.8% in industrialized countries) [116], any screening tests will need to have high levels of both sensitivity and specificity. Currently, none of the measurements in the first trimester meets these criteria. While different measures of placental dysfunction have been associated with increased risk adverse pregnancy outcomes, the ability of any single one to accurately predict these outcomes is poor. Attempts to use predictive models combining analytes and measurements of placental structure and blood flow have so far produced mixed results. The use of first trimester biochemical markers in combination with uterine artery Doppler screening shows promise as potential screening tools. Improvement in ultrasound technology provides potentially useful novel tools for evaluating placental structure, but measurements need to be standardized in order to be useful. One potential area, in the first trimester,

that is yet few explored is the valuation of central hemodynamic and arterial stiffness by pulse wave analysis.

Maternal factors

Among the maternal factors that may contribute to the development of maternal PE, body mass index and conception by IVF seem to play an important role. In our study maternal PE showed the highest values of BMI and the highest percentage of IVF conceived pregnancies; both factors known to be well related to metabolic syndrome, low grade chronic inflammation and insulin resistance.

Conversely, placental PE showed the highest number of women with reoccurrence of preeclampsia that supports the presence of immune/genetic predisposition.

It is interesting to observe that the BMI of women with SGA babies is higher when compared to controls and IUGR group, suggesting a possible similar etiology to maternal PE.

Uterine artery

Doppler studies suggest that preterm preeclampsia/IUGR is associated with defective invasion of the spiral arteries, whereas the spiral artery defect plays a much smaller role in the cases nearer term [117]. Thus, term preeclampsia/IUGR seem to be associated with normal trophoblast transformation in the first trimester, and late atherosclerotic changes in spiral arterioles. Such late changes may be the consequence of increased placental mass, as occurs in diabetic and twin pregnancies, related to the senescence of the placenta in prolonged pregnancy or as a result of placental edema and necrosis in fetal hydrops [32,118].

Abnormal uterine artery Doppler studies in the first trimester have been shown to be associated with preeclampsia/IUGR. Gomez et al. reported that the sequence of changes in uterine artery Dopplers between the first (11 and 14 weeks) and second (20 and 24 weeks) trimesters correlates with the subsequent development of preeclampsia and IUGR [119].

The detection rate of uterine artery screening for preeclampsia or IUGR at any gestation is better for severe than for mild disease. Increased resistance indices in the first trimester are particularly effective in identifying preterm, rather than term, preeclampsia [120-122].

On the other hand, Martin et al. (2001) reported that uterine Doppler PI at 11–14 weeks had a disappointing sensitivity of 11.7% for all IUGR, but for IUGR requiring delivery by 32 weeks sensitivity increased to 27.8% [110]. This disparity may result from the distinction between the pathophysiology of preterm and term preeclampsia/IUGR discussed earlier or from the different methodologic approaches used in the different studies. In addition, uterine artery Doppler in the first and the second trimesters was shown to have a remarkably higher sensitivity in women with preeclampsia complicated by small-for-gestational-age (SGA) babies compared with uncomplicated preeclampsia or SGA alone [123].

Our study are in accordance with the literature data and showed that the mean uterine artery PI was significantly higher in women who subsequently developed placental PE or IUGR, but not in maternal PE and SGA, confirming indirectly our hypothesis that maternal PE is not associated with impaired placentation.

Moreover, after dividing the uterine artery in two groups: normal and pathological according to the PI value ($PI > 2,3$) [110], half of women in placental PE group presented pathological uterine artery PI in comparison to only nine percent in maternal PE group.

PAPP-A

PAPP-A is an insulin-like growth factor binding protein (IGFBP) protease with specificity for IGFBP 2 and 4. Reduced levels of PAPP-A may result in increased amounts of insulin-like growth factor (IGF) being bound to its carrier proteins and hence not available at the cell receptor level to stimulate fetal growth and trophoblast invasion of the decidua [124]. Many studies have reported reduced maternal serum PAPP-A concentration at 11–14 weeks and increased risk for subsequent development of preeclampsia, SGA and preterm delivery [125-127].

For IUGR, the sensitivity of PAPP-A below 5 th percentile in the first trimester were 8–33% [125-127].

Our data show that MOMM PAPP-A was significantly lower only in maternal PE group, thus indicating, probably, its association with metabolic syndrome.

Our assumption is supported by Sifakis et al [128] that in 2011 has demonstrated that at 11–13 weeks' gestation in pregnancies destined to develop PE compared with unaffected controls, the median maternal serum

IGFBP-3 and uterine artery PI were higher and serum PAPP-A was lower. Evidence from both in vitro and in vivo studies suggested that increased levels of IGFBP-3 are associated with hyperglycaemia, metabolic syndrome and increased insulin resistance [129-135].

In women destined to develop late PE, placental perfusion and fetal growth are often normal and the main pathophysiological processes resemble those of the metabolic syndrome with an increase in adipose tissue, impaired glucose tolerance and increased insulin resistance [40-43]. In non-pregnant women, insulin is the main regulator of IGFBP-1, and studies in pregnancy reported that IGFBP1 production by the decidualized stroma is inhibited by insulin [136,137]. Always in 2011, Sifakis et al [138] wrote that the low levels of IGFBP-1 in women destined to develop PE may be the consequence of the associated hyperinsulinemia and increased insulin resistance [139,140].

Haemodynamic parameters

Pregnancy is associated with major hemodynamic changes such as increased cardiac output and heart rate and the presence of placental fistulae.

There is a marked increase in vascular compliance in normal pregnancy so as to accommodate the major cardiovascular changes taking place within the mother as a whole and within the uterus in particular.

Previous studies have demonstrated that, in normal pregnancy, aortic compliance increases in response to increased levels of estrogen, mediated by increased circulating nitric oxide levels: resistance remains low until delivery [102].

We know that there is little or no difference in vascular compliance between women with established preeclampsia and nonpregnant women.

The pulse wave analysis (PWA) has been shown in nonpregnant individuals to accurately evaluate arterial stiffness in cardiovascular disorders. Preeclampsia is a disorder of vascular endothelium, and recent studies have shown that PWA can successfully assess the increased arterial stiffness that results [99,141].

In recent years, it has been shown that serum and placental levels of angiogenic factors such as sFlt1 and soluble endoglin are altered in women with preeclampsia not just at the time of the clinical manifestations of the disease but often many weeks prior its clinical onset [76,142,143]. This led

us to hypothesise that the increase in arterial stiffness might occur in advance of the clinical disease, that this might be measurable using arterial PWA and that, if so, these observations might allow us to identify early those women who subsequently developed preeclampsia and IUGR.

Each heartbeat generates a pulse wave that travels away from the heart. This waveform is reflected from bifurcations within the arterial tree and from the junctions of the preresistance and resistance vessels [87-89]. The reflected wave travels back toward the heart and meets the advancing wave, augmenting its height (Fig. 1A). Generally, the reflected wave reaches the aorta during diastole, boosting the height of the diastolic portion of the wave. This also helps to maintain coronary artery perfusion. When arterial wall stiffness is increased (as in hypertensive disorders of pregnancy) the arterial pulse wave travels faster, so the reflected wave reaches the advancing wave in systole, resulting in significant augmentation of the systolic peak (Fig. 1B). This can be measured as raise augmentation index.

Previous studies, in women with established PE have revealed inconsistent results, which could be due to the lack of number of women with severe PE, we establish that PE is characterized by increased arterial stiffness.

Some of them, assessing the arterial stiffness of other vascular pathways such as base of the aorta to popliteal artery [99] and abdominal aorta [83], have also confirmed increased arterial stiffness in women with established PE by pulse wave velocity (PVW).

The findings of this study demonstrate that in women destined to develop PE, during the second or third trimester of pregnancy, there is not an increase in maternal arterial stiffness as assessed by pulse way analysis.

The Augmentation index at 75 bpm values were similar to the normotensive group and in the women who developed preeclampsia, both placental or maternal type and also in women that developed IUGR or SGA fetuses.

This is compatible with the results of previous study of Kaihura et al [100].that showed, in women with established PE, there was an increase in pulse way velocity but not in Augmentation index. However, it is in contrast with a study by Khalil et al [127] that suggested that AIx could be used as a first trimester predictor of PE. In this study is important observed that about 14 cases of preeclampsia, 8 were early preeclampsia.

Aix refers to the difference between the second and first systolic peaks, expressed as a percentage of the aortic pulse pressure. When compared with normotensive women, women with established PE had higher first systolic peak, which provides an estimate for stroke volume, higher second systolic peak, and shorter aortic *Tr* (time to reach the reflected wave).

Furthermore, Aix depends on the intensity of the reflected wave, and, as such, it will depend on the diameter and elasticity of the small muscular arteries/arterioles at the major sites of pressure wave reflection. Therefore, alterations in muscular smooth muscle tone affecting mainly the small muscular arteries but not the elastic aorta might influence reflected wave intensity and hence Aix just in the first trimester of pregnancy.

In addition to increased arterial stiffness, women who subsequently developed PE demonstrated increased peripheral and central BP. Studies in non-pregnant hypertensive patients have shown that central and peripheral BP are not synonymous and antihypertensive agents can exert differential effects on the two types of BP [128]. In patients with end-stage renal disease, central aortic pulse pressure was of greater predictive value for cardiovascular outcomes than brachial pulse pressure [129,130].

Previous studies assessing peripheral BP have reported that in women destined to develop PE, the BP is higher than in the non PE group both during the second but also in the first-trimester of pregnancy [130]. It would be interesting to investigate the extent to which the prediction of PE can be improved by the measurement of central rather than peripheral BP [131-133].

Our data showed that the mean arterial pressure was significantly higher in both placental and maternal preeclampsia compared with the control group, but central systolic pressure was statistical significant only in placental PE group. In conclusion, we can hypothesize that PE is associated with increased maternal central pressures, but not altered wave reflection, suggesting that maternal large artery stiffness in this population is increased compared with women with uncomplicated pregnancies, also if is not possible register with PWA.

As expected, the hemodynamic characteristics between normotensive pregnancies affected by IUGR or SGA were no significant differences for all hemodynamic parameters between groups and controls.

Limits of the study

We acknowledge that the number of participants in the study is too small to draw firm conclusions, and confirmation from larger studies will be required.

The outcomes derived for about 60% from telephone interview and not always from clinical sheet.

Finally the diagnosis of IUGR is based on birth weight and not on fetal ultrasound evaluation and Doppler velocimetry.

CONCLUSION

Although, the classification of preeclampsia based on time domain, at the moment the most used, brought to some improvements in terms of biochemical and biophysical tests prediction, at present is still not able to fulfill all diagnostic and preventive needs. Indeed, despite all scientific effort for the past three decades, at the present there does not exist universally recognized screening test of any kind capable to predict preeclampsia or IUGR and the severity of the disease.

With this pilot study, we wanted to investigate the characteristics of preeclampsia of maternal and placental origin and pregnancies with fetal growth restriction in terms of peripheral and central vascular resistance by applanation tonometry in the first trimester of pregnancy. Due to the smallness of the cohort, we did not try to assess the prediction of the test. Nevertheless, the newness of our work stand in the understanding of the underlying physiopathology of preeclampsia.

Our data confirmed the hypothesis regarding different origin of PE: indeed, in PE of maternal origin we found the highest BMI and the highest percentage of IVF-pregnancies. Both this factors are well known to correlate to metabolic syndrome, low grade chronic inflammation and insulin resistance.

Conversely, in PE of placental origin we found the highest number of women with reoccurrence of preeclampsia that supports the immunological/genetic hypothesis that causes inadequate placentation. This hypothesis is supported also by the observation that women with preeclampsia of placental origin present significantly higher mean uterine artery PI, sign of an impaired placentation as soon as in the first trimester

of pregnancy. A further confirmation of a poor placentation derives from the presence of the highest percentage of babies admittance to NICU in preeclampsia of placental origin and IUGR group.

As it concern the hemodynamic parameters, in accordance to the literature, we found the mean arterial pressure significantly higher in both preeclampsia of placental and maternal origin when compared to the control group. Interestingly, the central pressure, both systolic and diastolic, was significantly higher only in placental PE group suggesting lower central vascular compliance in women with inadequate placentation. This could suggest a different and more severe physiopatological pathway at the basis of preeclampsia of placental origin when compared to maternal one.

Several Authors found increased values of augmentation index in women with preeclampsia (more pronounced in early and less important in late PE) at the time of onset of the disease. Conversely, we found no significant differences in Augmentation index at 75 bpm between groups, suggesting that in the first trimester the biochemical and hormonal modifications still does not reflect on peripheral vascular resistance both in preeclampsia of maternal and placental origin.

In conclusion, we found that the classification of preeclampsia based on its origin, maternal and placental, is supported by the demographic data. Our data suggest that, as soon as in first trimester, for arterial mean pressure been equal in both women that will develop PE of maternal and placental origin, and higher in respect to controls, only PE of placental origin presents higher central pressure. Nevertheless, no differences were found for wave reflection, suggesting later development of the peripheral vascular alteration.

Future studies should also aim at improving our knowledge of the biological mechanisms to understood the pathofisiology of placental pathology resulting in the changes seen in IUGR and placental preeclampsia and mechanisms on basis of maternal preeclampsia and SGA.

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