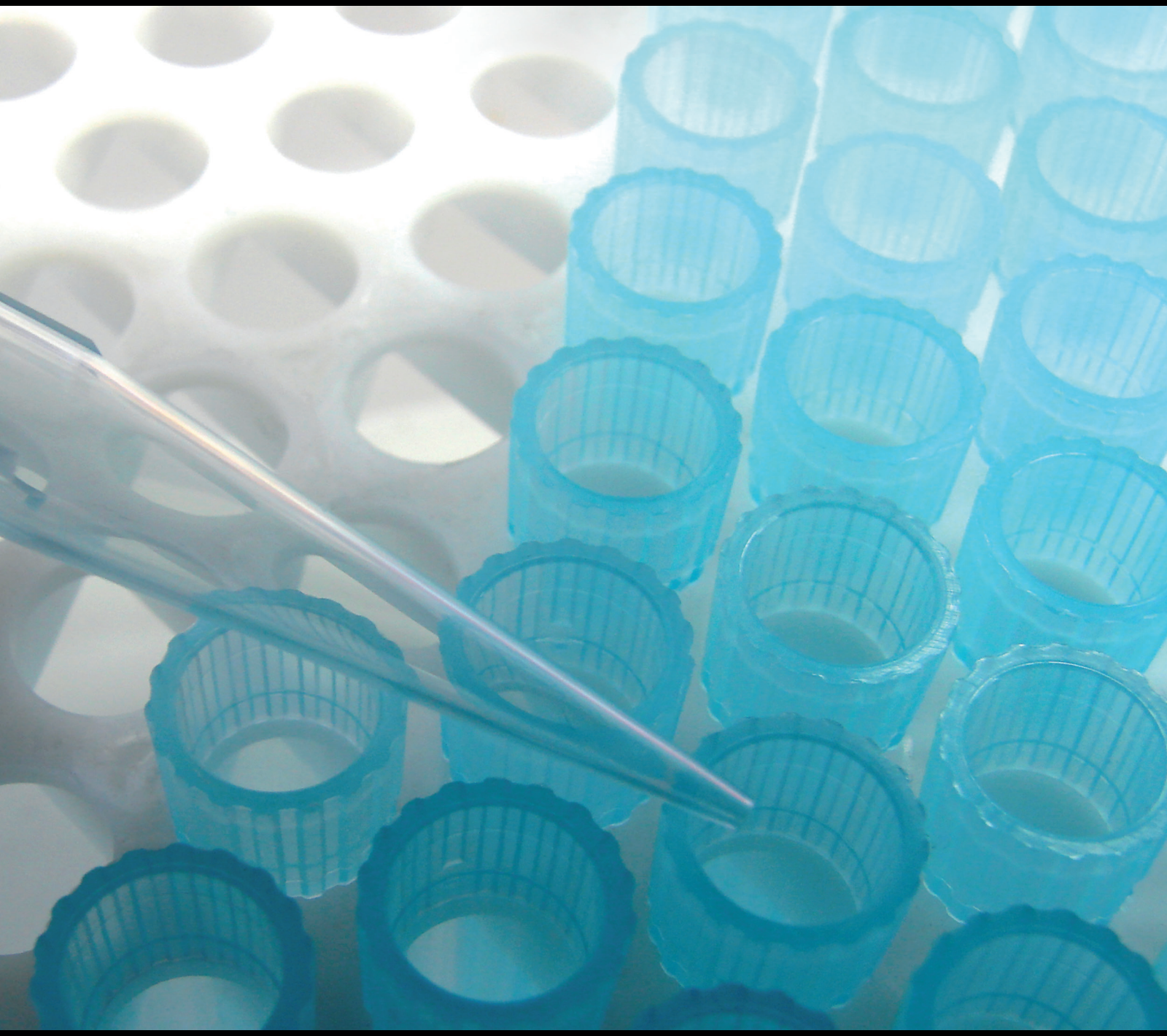
Obstetrics and Gynecology International

Preeclampsia Prediction and Management

Guest Editors: Irene Rebelo and João Bernardes



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Editorial

Preeclampsia Prediction and Management

Irene Rebelo[1,2] and João Bernardes[3,4,5,6]

[1] *Department of Biochemistry, Faculty of Pharmacy, University of Porto, Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal*
[2] *Institute for Molecular and Cell Biology (IBMC), University of Porto, 4150-180 Porto, Portugal*
[3] *Faculty of Medicine, University of Porto, 4200-319 Porto, Portugal*
[4] *Center for Research in Health Technologies and Information Systems (CINTESIS), Faculty of Medicine, University of Porto, 4200-450 Porto, Portugal*
[5] *Department of Obstetrics and Gynecology, Pedro Hispano Hospital, 4454-509 Matosinhos, Portugal*
[6] *Department of Obstetrics and Gynecology, S. João Hospital, 4200-450 Porto, Portugal*

Correspondence should be addressed to Irene Rebelo; irebelo@ff.up.pt

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International guidelines still simply define preeclampsia (PE) as an acute pregnancy related hypertensive condition characterized by hypertension and proteinuria that typically appears after the 20 weeks of gestation and resumes after delivery [1]. With these relatively simple guidelines centered on blood pressure and proteinuria assessment, along with eclampsia prevention with magnesium sulphate and fetal delivery in the most severe cases, the developed countries have managed to control the high maternal and fetal mortality rates related with PE that still affect the developing countries without adequate basic clinical ante- and intrapartum facilities [1].

However, we know today that PE is a more complex condition that develops during the first weeks of pregnancy and that may have consequences in the future health of the mother and child.

PE remains a leading cause not only of maternal and fetal mortality in the developing countries, but also of morbidity in the developed countries accounting for a high number of maternal admissions to intensive care units, fetal growth restriction, and premature iatrogenic deliveries, without effective early prediction and/or prevention. Moreover, with the increased life expectancy of the developed countries it is also known today that women with history of PE and their offspring present an increased risk of future hypertension and cardiovascular diseases, among others [1].

In this special issue, several authors address the above-mentioned issues, namely, on early PE prediction, management, and risk of future cardiovascular diseases [2].

L. C. Poon and K. H. Nicolaides remind us that PE screening by a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum pregnancy associated plasma protein-A, and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%. This excellent news can be already put in practice using specially commercialized kits. It opens new perspectives on early prediction and diagnosis, allowing better application of preventive and curative measures, namely, using, respectively, aspirin and timely antihypertensive treatment and/or pregnancy termination [1]. This hope for better perspectives on early prediction of PE has also been exposed by C. Teixeira et al., who managed to show that even a common program for first trimester screening of aneuploidies may already improve our current capabilities based only on the relatively soft above-mentioned clinical assessment of blood pressure and proteinuria [1], although in a much more modest way than when using the model presented by L. C. Poon and K. H. Nicolaides.

On the other hand, S. C. Kane et al. elaborate on contemporary management principles pertaining to maternal and fetal neurological sequelae of PE. As they outline, the neurological complications of preeclampsia and eclampsia

are major contributors of PE related maternal and fetal morbidity and mortality that need to be seriously taken into account and adequately addressed.

Finally, A. Matos et al. and P. V. Pinto et al. tackle the issue of PE and the risk of future cardiovascular disease. A. Matos et al. concluded that previously PE women, either subsequently hypertensive or normotensive, present significant differences in myeloperoxidase, nitrites, liver enzymes, and other cardiovascular risk biomarkers, whose variation may be modulated by haptoglobin 1/2 functional genetic polymorphism. They provide more evidence not only on the association between PE and future cardiovascular diseases, but also on the putative pathogenic paths underlying this situation. However, in contrast with all these developments on the recognition and understanding of the association between PE and the development of future cardiovascular disease, P. V. Pinto et al. showed that the majority of 141 cases of preeclampsia and chronic hypertension with superimposed preeclampsia diagnosed at their institution between January 2010 and December 2013, as well as general practitioners, did not take into consideration a previous pregnancy affected by preeclampsia as a risk factor for future cardiovascular disease, namely, in the implementation of healthy behaviours and/or adequate medical treatment. This shows that educational and prevention programs urge in this area, in both patients and the general practitioners levels.

We hope this special issue provides not only new data for daily clinical practice, but also inspiration to pursue the hard way of PE research, in all its multiple and complex areas.

Irene Rebelo
João Bernardes

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Review Article

Early Prediction of Preeclampsia

Leona C. Poon and Kypros H. Nicolaides

Harris Birthright Research Centre of Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK

Correspondence should be addressed to Leona C. Poon; chiu_yee_leona.poon@kcl.ac.uk

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Effective screening for the development of early onset preeclampsia (PE) can be provided in the first-trimester of pregnancy. Screening by a combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum pregnancy-associated plasma protein-A, and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%.

1. Introduction

Preeclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality [1–3] and is thought to be predominantly as the consequence of impaired placentation. Evidence suggests that PE can be subdivided into early onset PE, requiring delivery before 34 weeks' gestation and late onset PE, with delivery at or after 34 weeks, because the former is associated with a higher incidence of adverse outcome [4–7]. A major challenge in modern obstetrics is early identification of pregnancies at high-risk of early onset PE and undertaking the necessary measures to improve placentation and reduce the prevalence of the disease.

The prophylactic use of low-dose aspirin for prevention of PE has been an important research question in obstetrics for the last three decades. In 1979, Crandon and Isherwood observed that nulliparous women who had taken aspirin regularly during pregnancy were less likely to have PE than women who did not. Subsequently, more than 50 trials have been carried out throughout the world and a meta-analysis of these studies reported that the administration of low-dose aspirin in high-risk pregnancies is associated with a decrease in the rate of PE by approximately 10% [8]. In most studies that evaluated aspirin for the prevention of PE the onset of treatment was after 16 weeks' gestation. However, recent meta-analyses reported that the prevalence of PE can potentially be halved by the administration of low-dose aspirin started at 16 weeks or earlier [9–11].

Extensive research in the last 20 years, mainly as a consequence of the shift in screening for aneuploidies from the second- to the first-trimester of pregnancy, has identified a series of early biophysical and biochemical markers of impaired placentation [12, 13]. Using a novel Bayes-based method that combines prior information from maternal characteristics and medical history, uterine artery pulsatility index (PI), mean arterial pressure (MAP), and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11–13 weeks' gestation can identify a high proportion of pregnancies at high-risk for early onset PE [12, 13]. The performance of the different methods of screening for PE is summarized in Table 1.

2. Screening by Maternal History

Several professional bodies have issued guidelines on routine antenatal care recommending that, at the booking visit, a woman's level of risk for PE, based on factors in her history, should be determined and women at high-risk are advised to take low-dose aspirin daily from early pregnancy until the birth of the baby (Table 2) [14–17]. However, the performance of screening by the recommended method and the effectiveness of intervention have not been formally evaluated.

The majority of the studies that have reported on the maternal risk factors for the development of PE do not quantify the risk, although some studies do provide relative

risks. Most of the available literature is based on retrospective, epidemiological, cohort, or case-control studies though few prospective cohort studies are also reported. Only a few studies have reported on maternal risk factors according to the severity of the disease, that is, early onset PE versus late onset PE.

It has been demonstrated that maternal demographic characteristics, including medical and obstetric history (Table 2), are potentially useful in screening for PE only when the various factors are incorporated into a combined algorithm derived by multivariate analysis [18]. With this approach to screening the effects of variables are expressed as odds ratios for early onset, late onset, or total PE. In general, the maternal risk factor profiles vary between early onset PE and late onset PE. This has led to the view that early and late PE may be different diseases. An alternative view is that PE is a spectrum disorder the degree of which is reflected in gestational age at the time of delivery. Multivariate screening for PE with maternal risk factors has since evolved into a new approach in which the gestation at the time of delivery for PE is treated as a continuous rather than a categorical variable. This approach, which is based on a survival time model, assumes that if the pregnancy was to continue indefinitely, all women would develop PE and whether they do so or not before a specified gestational age depends on a competition between delivery before or after development of PE [12]. In this new approach the effect of various risk factors is to modify the mean of the distribution of gestational age at delivery with PE. In pregnancies at low-risk for PE the gestational age distribution is shifted to the right with the implication that in most pregnancies delivery will actually occur before the development of PE. In high-risk pregnancies the distribution is shifted to the left and the smaller the mean gestational age, the higher the risk for PE (Figure 1).

In this competing risk model the mean gestational age for delivery with PE is 54 weeks with estimated standard deviation of 6.9 weeks. Certain variables, including advancing maternal age over 35 years, increasing weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with PE, conception by in vitro fertilization (IVF) and a medical history of chronic hypertension, preexisting diabetes mellitus, and systemic lupus erythematosus or antiphospholipid syndrome, increase the risk for development of PE. The consequence of this increased risk is a shift to the left of the Gaussian distribution of the gestational age at delivery with PE (Figure 2). Estimated detection rates of PE requiring delivery before 34, 37, and 42 weeks' gestation in screening by maternal factors are about 36%, 33%, and 29%, respectively, at false-positive rate of 5%, and 51%, 43%, and 40%, respectively, at false-positive rate of 10% (Table 1) [12].

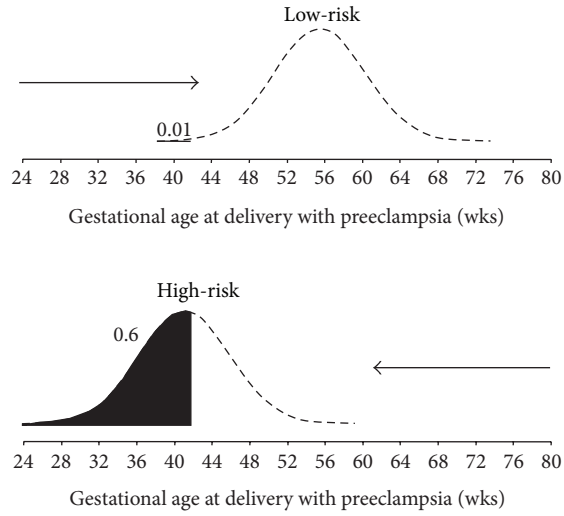

Figure 1: Distribution of gestational age at delivery for preeclampsia (PE). In pregnancies at low-risk for PE the gestational age distribution is shifted to the right and in most pregnancies delivery will occur before the development of PE. In pregnancies at high-risk for PE the distribution is shifted to the left. The risk of PE occurring at or before a specified gestational age is given by the area under the distribution curve (black). In the low-risk group the risk of PE at or before 34 weeks' gestation is 0.01 or 1% and in the high-risk group the risk is 0.6 or 60%.

3. Screening by Maternal Biophysical Markers

3.1. Uterine Artery Doppler. The most promising screening test for PE is uterine artery Doppler velocimetry. The spiral arteries undergo a series of morphological changes during normal pregnancy [19, 20]. The vessels are firstly invaded by trophoblast, which then becomes incorporated into the vessel wall and replaces the endothelium and muscular layer. This results in the conversion of the small spiral arteries into vessels of greater diameter with low resistance and high compliance, in absence of maternal vasomotor control. This vascular transformation in the uterus is necessary to ensure a dramatic increase in blood supply to the intervillous space. The underlying mechanism for the development of PE is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide nonmuscular channels [21–25]. Doppler ultrasound provides a noninvasive method for the assessment of the uteroplacental circulation. The finding that impaired placental perfusion, reflected in increased uterine artery PI, is associated with the development of PE is compatible with the hypothesis that PE is the consequence of impaired placentation and the results of previous first- and second-trimester Doppler studies as well as histological studies of the maternal spiral arteries [26–29]. Pathological studies have demonstrated that the prevalence of placental lesions in women with PE is inversely related to the gestation at delivery [30, 31].

The ability to achieve a reliable measurement of uterine artery PI is dependent on appropriate training of sonographers, adherence to a standard ultrasound technique in order to achieve uniformity of results among different operators. Using transabdominal ultrasonography, a sagittal section of the uterus should be obtained and the cervical canal and internal cervical os are identified. Subsequently, the transducer is gently tilted from side to side and color flow mapping is used to identify each uterine artery along the

Table 1: Estimated detection rates of preeclampsia (PE) requiring delivery before 34, 37, and 42 weeks' gestation, at false positive rates (FPR) of 5% and 10%.

Screening test	FPR (%)	Detection rate (%)		
		PE < 34 weeks	PE < 37 weeks	PE < 42 weeks
Maternal characteristics	5.0	36	33	29
	10.0	51	43	40
Uterine artery pulsatility index (Ut-PI)	5.0	59	40	31
	10.0	75	55	42
Mean arterial pressure (MAP)	5.0	58	44	37
	10.0	73	59	54
Pregnancy associated plasma protein-A (PAPP-A)	5.0	44	37	32
	10.0	55	48	42
Placental growth factor (PlGF)	5.0	59	41	29
	10.0	72	54	40
MAP and Ut-PI	5.0	80	55	35
	10.0	90	72	57
PAPP-A and PlGF	5.0	60	43	30
	10.0	74	56	41
Ut-PI, MAP, and PAPP-A	5.0	82	53	36
	10.0	93	75	60
Ut-PI, MAP, and PlGF	5.0	87	61	38
	10.0	96	77	53
Ut-PI, MAP, PAPP-A, and PlGF	5.0	93	61	38
	10.0	96	77	54

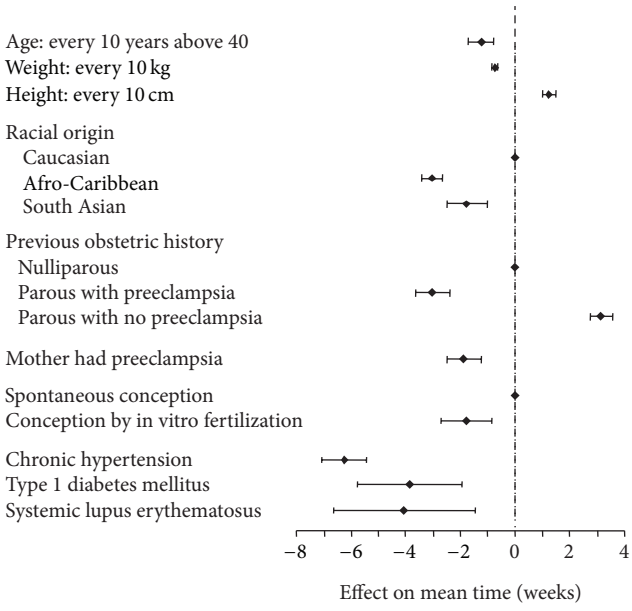

Figure 2: Effects of maternal characteristics (with 95% confidence intervals) on the gestational age at delivery for preeclampsia. This effect is expressed as gestational weeks by which the expected gestational age at delivery for preeclampsia is altered.

side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler is then used with the sampling gate set at 2 mm to cover the whole vessel and care should be taken to ensure that the angle of insonation is less than 30°. When three similar consecutive waveforms are obtained the PI is measured and the mean PI of the left and right arteries is calculated. It is important to ensure that the peak systolic velocity is greater than 60 cm/s to ensure that the arcuate artery is not being sampled instead of the uterine artery [29].

First-trimester uterine artery PI has been shown to be affected by gestational age at screening, maternal weight, racial origin, and history of preexisting diabetes mellitus, and consequently it should be expressed as multiple of median (MoM) after adjustment for these factors. The MoM value of uterine artery PI is significantly increased at 11–13 weeks' gestation in women who subsequently develop PE and there is a significant negative linear correlation between the uterine artery PI MoM with gestational age at delivery [12]. Estimated detection rates of PE, at false-positive rate of 5% and 10% in screening by maternal factors with uterine artery PI, are given in Table 1. The addition of uterine artery PI to maternal factors improves the detection rates from 36% to 59% and from 33% to 40%, at false-positive rate of 5%, and from 51% to 75% and from 43% to 55%, at false-positive rate of 10%, for PE requiring delivery before 34 and 37 weeks' gestation, respectively, but not for PE delivering before 42 weeks.

3.2. Blood Pressure. In PE, hypertension develops as a result of vasoconstriction and reduced peripheral vascular compliance [32]. Although hypertension is only a secondary sign of PE, it is an important sign as it is an early indication of the disease. This highlights the importance of accurate

Table 2: Recognized maternal risk factors for preeclampsia [14–17].

(i) Previous preeclampsia (PE)
(ii) Previous early onset PE and preterm delivery at <34 weeks' gestation
(iii) PE in more than one prior pregnancy
(iv) Chronic kidney disease
(v) Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
(vi) Heritable thrombophilias
(vii) Type 1 or type 2 diabetes
(viii) Chronic hypertension
(ix) First pregnancy
(x) Pregnancy interval of more than 10 years
(xi) New partner
(xii) Reproductive technologies
(xiii) Family history of PE (mother or sister)
(xiv) Excessive weight gain in pregnancy
(xv) Infection during pregnancy
(xvi) Gestational trophoblastic disease
(xvii) Multiple pregnancies
(xviii) Age 40 years or older
(xix) Ethnicity: Nordic, Black, South Asian, or Pacific Island
(xx) Body mass index of 35 kg/m^2 or more at first visit
(xxi) Booking systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg
(xxii) Increased prepregnancy triglycerides
(xxiii) Family history of early onset cardiovascular disease
(xxiv) Lower socioeconomic status
(xxv) Cocaine and methamphetamine use
(xxvi) Nonsmoking

monitoring of blood pressure during antenatal care. Accurate assessment of blood pressure has been hindered by the considerable variability that blood pressure exhibits within each individual. During blood pressure measurement at rest the first recording is often the highest recording, which decreases as the patients become more familiar with the procedure [33]. It is therefore recommended by professional bodies that a series of blood pressure measurements should be made until a prespecified level of stability is achieved [34, 35]. In current clinical practice, the use of mercury sphygmomanometers remains the gold standard for noninvasive blood pressure monitoring, but there are concerns for both the clinical performance and safety of these instruments [36–38]. Observer error is a major limitation of the auscultatory method [39] and terminal digit preference is perhaps the most common manifestation of suboptimal blood pressure determination. Other considerations include the rate of cuff deflation, the use of correct size cuff, the interarm difference in blood pressure, and the arm position and posture that are recognized to have significant effects on blood pressure determination.

The introduction of automated blood pressure monitoring allows simple, standardized, and repeated measurements to be taken. It also addresses many of the errors associated with the conventional sphygmomanometer but their use still requires the selection of the correct cuff size and proper patient positioning if accurate blood pressure is to be obtained. It has therefore been proposed that MAP should be measured by validated automated devices [40], with women in sitting position with back supported and legs uncrossed, that two measurements should be taken from each arm simultaneously with each arm supported at the level of the heart, and that the average of the four measurements should be used [33].

There is substantial evidence demonstrating that an increase in blood pressure in women destined to develop PE can be observed in the first- and second-trimesters of pregnancy [41–75]. Previous studies, including a mixture of prospective and retrospective and cohort and case-control studies and randomized controlled trials, reported widely contradictory results in the performance of screening (detection rate, median 43%, range 5–100%; false-positive rate, median 16%, range 0–66%) as a consequence of major methodological differences. The data from these studies, including more than 60,000 women with 3,300 cases of PE, were compiled into a systematic review, which concluded that the MAP is significantly better than systolic blood pressure or diastolic blood pressure in predicting PE [76].

First-trimester MAP has been shown to be affected by maternal weight, height, age, racial origin, cigarette smoking, family and prior history of PE, and history of chronic hypertension, and consequently it should be expressed as MoM after adjustment for these factors. Similar to the findings with uterine artery PI, the MoM value of MAP is significantly increased at 11–13 weeks' gestation in women who subsequently develop PE and there is a significant negative linear correlation between the MAP MoM with gestational age at delivery [12]. Estimated detection rates of PE, at false-positive rate of 5% and 10% in screening by maternal factors with MAP, are given in Table 1. The addition of MAP to maternal factors improves the detection rates from 36% to 58%, from 33% to 44%, and from 29% to 37%, at false-positive rate of 5%, and from 51% to 73%, from 43% to 59%, and from 40% to 54%, at false-positive rate of 10%, for PE requiring delivery before 34, 37, and 42 weeks' gestation, respectively.

There is a significant association between uterine artery PI and MAP in PE and unaffected pregnancies and therefore when combining the two biophysical markers in calculating the patient specific risk for PE the correlation factors must be taken into consideration to avoid overestimating the contributions from each marker in order to provide accurate risk assessment for PE. Estimated detection rates of PE requiring delivery before 34, 37, and 42 weeks' gestation in screening by maternal factors are 80%, 55%, and 35%, respectively, at false-positive rate of 5% and 90%, 72%, and 57%, respectively, at false-positive rate of 10% (Table 1).

Table 3: Proposed maternal biochemical markers for the prediction of preeclampsia.

A disintegrin and metalloprotease 12 (ADAM12)	L-Arginine
Activin-A	L-Homoarginine
Adiponectin	Leptin
Adrenomedullin	Magnesium
Alpha fetoprotein	Matrix metalloproteinase-9
Alpha-1-microglobulin	Microalbuminuria
Ang-2 angiopoietin-2	Microtransferrinuria
Antiphospholipid antibodies	N-Acetyl-β-glucosaminidase
Antithrombin III	Neurokinin B
Atrial natriuretic peptide	Neuropeptide Y
Beta2-microglobulin	Neutrophil gelatinase-associated lipocalin
C-reactive protein	P-Selectin
Calcium	Pentraxin 3
Cellular adhesion molecules	**Placenta growth factor**
Circulating trophoblast	Placental protein 13
Corticotropin release hormone	Plasminogen activator inhibitor-2
Cytokines	Platelet activation
Dimethylarginine (ADMA)	Platelet count
Endothelin	**Pregnancy associated plasma protein-A**
Estriol	Prostacyclin
Ferritin	Relaxin
Fetal DNA	Resistin
Fetal RNA	Serum lipids
Free fetal hemoglobin	Soluble endoglin
Fibronectin	Soluble fms-like tyrosine kinase
Genetic markers	Thromboxane
Haptoglobin	Thyroid function
Hematocrit	Total proteins
Homocysteine	Transferrin
Human chorionic gonadotropin	Tumor necrosis factor receptor-1
Human placental growth hormone	Uric acid
Inhibin A	Urinary calcium to creatinine ratio
Insulin-like growth factor	Urinary kallikrein
Insulin-like growth factor binding protein	Vascular endothelial growth factor
Insulin resistance	Visfatin
Isoprostanes	Vitamin D

4. Screening by Maternal Biochemical Markers

A large number of biochemical markers have been investigated for the prediction of PE (Table 3). Many such markers represent measurable manifestations of impaired placentation due to inadequate trophoblastic invasion of the maternal spiral arteries and reduced placental perfusion leading to placental ischemia related damage with the release of inflammatory factors, platelet activation, endothelial dysfunction, maternal renal dysfunction, or abnormal oxidative stress [19, 21–25]. Maternal serum PAPP-A and PlGF are two biochemical markers that have been investigated extensively and have shown promising results in the early prediction of PE. They have both been shown to be useful in screening for aneuploidies in combination with maternal age, fetal nuchal translucency thickness, and maternal serum free β-human chorionic gonadotropin at 11–13 weeks' gestation [77] and they are now part of the platform of automated machines that provide reproducible results within 30–40 minutes of sampling.

PAPP-A is a syncytiotrophoblast-derived metalloproteinase, which enhances the mitogenic function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins [78, 79]. The insulin-like growth factor system is believed to play an important role in placental growth and development; it is therefore not surprising that low serum PAPP-A is associated with a higher incidence of PE. Increased level of maternal

serum PAPP-A has been observed in established PE [80–82]. In chromosomally normal pregnancies there is evidence that low maternal serum PAPP-A in the first- and second-trimesters is associated with increased risk for subsequent development of PE. However, measurement of PAPP-A alone is not an effective method of screening for PE because only 8–23% of affected cases have serum levels below the 5th percentile, which is about 0.4 MoM. At the 5th percentile of normal for PAPP-A the reported odds ratios for PE varied between 1.5 and 4.6 [83–89].

PlGF, a glycosylated dimeric glycoprotein, is a member of the vascular endothelial growth factor subfamily. It binds to vascular endothelial growth factor receptor-1 which has been shown to rise in pregnancy. PlGF is synthesized in villous and extravillous cytotrophoblast and has both vasculogenetic and angiogenetic functions. It is believed to contribute a change in angiogenesis from a branching to a nonbranching phenotype controlling the expansion of the capillary network. Its angiogenetic abilities have been speculated to play a role in normal pregnancy and changes in the levels of PlGF or its inhibitory receptor have been implicated in the development of PE [90–93]. PE is associated with reduced placental production of PlGF and several studies reported that during the clinical phase of PE the maternal serum PlGF concentration is reduced. These reduced levels of serum PlGF precede the clinical onset of the disease and are evident from both the first- and second-trimesters of pregnancy [94–102].

In biochemical testing it is necessary to make adjustments in the measured maternal serum metabolite concentration to correct for certain maternal and pregnancy characteristics as well as the machine and reagents used for the assays and is then expressed in MoM of the normal [103]. First-trimester maternal serum concentrations of PAPP-A and PlGF have been shown to be affected by gestational age at screening, maternal weight, racial origin, cigarette smoking, conception by IVF, nulliparity, and preexisting diabetes mellitus [103, 104]. In addition, serum PlGF is also affected by maternal age [104]. Consequently, the measured concentrations of PAPP-A and PlGF must be adjusted for these variables before comparing results with pathological pregnancies. Contrary to the findings with biophysical markers, the MoM values of PAPP-A and PlGF are significantly reduced at 11–13 weeks' gestation in women who subsequently develop PE. There is a significant positive linear correlation between the MoM values of these biochemical markers with gestational age at delivery [13]. This observation further confirms that PE is a single pathophysiological entity with a wide spectrum of severity manifested in gestational age at which delivery becomes necessary for maternal and/or fetal indications.

Estimated detection rates of PE, at false-positive rate of 5% and 10% in screening by maternal factors with biochemical markers, are given in Table 1. The addition of maternal serum PAPP-A and PlGF to maternal factors improves the detection rates from 36% to 60% and from 33% to 43%, at false-positive rate of 5%, and from 51% to 74% and from 43% to 56%, at false-positive rate of 10%, for PE requiring delivery before 34 and 37 weeks' gestation, respectively, but not for PE delivering before 42 weeks.

5. Screening by Maternal Biochemical and Biophysical Markers

Analogous to the effective first-trimester combined screening for aneuploidies, effective screening for PE can also be achieved by a combination of maternal factors and biochemical and biophysical markers. Using the competing risk model, the gestational age at the time of delivery for PE is treated as a continuous variable. Bayes theorem is then used to combine prior information from maternal characteristics and medical history with the MoM values of uterine artery PI, MAP, serum PAPP-A, and PlGF. The major advantage of this model, compared to the other published models [105–107], is that it offers the option to clinicians and researchers to select their own gestational age cut-off to define the high-risk group that could potentially benefit from therapeutic interventions starting from the first-trimester of pregnancy [9–11].

It is important to recognize that there are significant associations between all biophysical and biochemical markers in PE and unaffected pregnancies and therefore when combining the four markers in calculating the patient specific risk for PE the correlation factors are taken into account to provide accurate risk assessment for PE. Estimated detection rates of PE requiring delivery before 34, 37, and 42 weeks' gestation in screening by maternal factors are 93%, 61%, and 38%, respectively, at false-positive rate of 5% and 96%, 77%, and 54%, respectively, at false-positive rate of 10% (Table 1).

6. First-Trimester Screening Followed by Third-Trimester Risk Assessment

Effective screening for early onset PE can be achieved in the first-trimester of pregnancy but late onset PE requiring delivery after 34 weeks' gestation accounting for two-thirds of all PE remains a significant challenge for effective early screening. We have therefore proposed a two-stage strategy for identification of pregnancies at risk of PE. The first stage, at 11–13 weeks, should be primarily aimed at effective prediction of early onset PE, because the prevalence of this condition can be potentially reduced substantially by the prophylactic use of low-dose aspirin started before 16 weeks' gestation [9–11]. The second stage, at 30–33 weeks, should be aimed at effective prediction of PE requiring delivery at or after 34 weeks because close monitoring of such pregnancies for earlier diagnosis of the clinical signs of the disease could potentially improve perinatal outcome through such interventions as the administration of antihypertensive medication and early delivery [108].

A competing risk model, using Bayes theorem, has been developed that combines maternal characteristics and history with biophysical and biochemical markers at 30–33 weeks' gestation to estimate the risk of developing PE requiring delivery within selected intervals from the time of screening. Preliminary results to date confirm that the *a priori* risk for PE depends on maternal characteristics and is increased with increasing maternal age and weight and in women of Afro-Caribbean and South Asian racial origin, in those with

personal or family history of PE, and in women with preexisting chronic hypertension, diabetes mellitus, and systemic lupus erythematosus or antiphospholipid syndrome [109]. The third-trimester uterine artery PI and MAP are affected by maternal characteristics and history and the corrected measurements as expressed in MoM values are inversely related to the severity of the disease reflected in the gestational age at delivery. At risk cut-off of 1 : 100, the estimated false-positive and detection rates for PE requiring delivery within the subsequent four weeks were 6% and 91% in screening by a combination of maternal factors, uterine artery PI, and MAP [109].

PE is thought to be the consequence of an imbalance in angiogenic and antiangiogenic proteins [110]. Recent studies have focused on the investigation of pregnancies presenting to specialist clinics with signs of hypertensive disorders with the aim of identifying the subgroup that will develop severe PE requiring delivery within the subsequent 1–4 weeks. In such high-risk pregnancies, measurement of serum PlGF or soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio is highly accurate in identifying the target group [111–116]. We have demonstrated that serum PlGF decreases with gestational age and maternal weight and is higher in women of Afro-Caribbean and South Asian racial origin than in Caucasians, in parous than nulliparous women, and in smokers than in nonsmokers. Serum sFlt-1 increases with gestational age and maternal age, decreases with maternal weight, is increased in women of Afro-Caribbean racial origin and in pregnancies conceived by IVF, and is lower in parous than nulliparous women [117]. In pregnancies complicated by PE, compared to normal pregnancies, serum PlGF MoM is decreased and sFlt-1 MoM is increased. At risk cut-off of 1 : 100, the estimated false-positive and detection rates for PE requiring delivery within the subsequent four weeks were 4% and 93% in screening by maternal factors, serum PlGF, and sFlt-1 [83] and the false-positive and detection rates improved to 2% and 95% in screening by maternal factors with all biomarkers [118].

7. Conclusion

Effective screening for early onset PE can be achieved in the first-trimester of pregnancy with a detection rate of about 95% and a false-positive rate of 10%. In a proposed new approach to prenatal care the potential value of an integrated clinic at 11–13 weeks' gestation in which maternal characteristics and history are combined with the results of a series of biophysical and biochemical markers to assess the risk for a wide range of pregnancy complications has been extensively documented [119]. In the context of PE the primary aim of such clinic is to identify those cases that would potentially benefit from prophylactic pharmacological interventions to improve placentation; the value of early screening and treatment of the high-risk group with low-dose aspirin is the subject of an ongoing randomized multicentre European study.

It is likely that a similar integrated clinic at 30–33 weeks will emerge for effective prediction of pregnancy complications that develop during the third-trimester. The potential value of such a clinic is to improve perinatal outcome by rationalizing and individualizing the timing and content of subsequent visits for selection of the best time for delivery.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

In Women with Previous Pregnancy Hypertension, Levels of Cardiovascular Risk Biomarkers May Be Modulated by Haptoglobin Polymorphism

Andreia Matos,[1] Alda Pereira da Silva,[1] Maria Clara Bicho,[1] Conceição Afonso,[1] Maria José Areias,[2] Irene Rebelo,[3] and Manuel Bicho[1,4]

[1] *Genetics Laboratory, Lisbon Medical School, University of Lisbon, 1649-028 Lisbon, Portugal*
[2] *Júlio Diniz Maternity, Maria Pia Hospital, 4050-371 Porto, Portugal*
[3] *Department of Biochemistry, Faculty of Pharmacy and Institute for Molecular and Cell Biology, University of Porto, 4050-313 Porto, Portugal*
[4] *Rocha Cabral Institute, 1250-047 Lisbon, Portugal*

Correspondence should be addressed to Andreia Matos; andreiamatos@fm.ul.pt

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Preeclampsia (PE) may affect the risk for future cardiovascular disease. Haptoglobin (Hp), an acute phase protein with functional genetic polymorphism, synthesized in the hepatocyte and in many peripheral tissues secondary of oxidative stress of PE, may modulate that risk through the antioxidant, angiogenic, and anti-inflammatory differential effects of their genotypes. We performed a prospective study in 352 women aged 35 ± 5.48 years, which 165 had previous PE, 2 to 16 years ago. We studied demographic, anthropometric, and haemodynamic biomarkers such as C-reactive protein (CRP), myeloperoxidase (MPO), and nitric oxide metabolites (total and nitrites), and others associated with liver function (AST and ALT) and lipid profile (total LDL and cholesterol HDL, non-HDL, and apolipoproteins A and B). Finally, we study the influence of Hp genetic polymorphism on all these biomarkers and as a predisposing factor for PE and its remote cardiovascular disease prognosis. Previously preeclamptic women either hypertensive or normotensive presented significant differences in those risk biomarkers (MPO, nitrites, and ALT), whose variation may be modulated by Hp 1/2 functional genetic polymorphism. The history of PE may be relevant, in association with these biomarkers to the cardiovascular risk in premenopausal women.

1. Introduction

Maternal hypertensive disorders are the most common complications of pregnancy. Pregnancy may be complicated by four distinct forms of hypertension: preeclampsia/eclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and gestational hypertension [1]. Arterial hypertension may be associated with inflammatory and oxidative stress. Preeclampsia as other forms of hypertensive conditions during pregnancy may affect the risk for future cardiovascular disease [2, 3].

Several authors described association between maternal pregnancy complications as preeclampsia—with greater future risk of mother to develop hypertension and atherosclerosis [2, 3]. Indeed, there are biomarkers associated with inflammatory process and blood pressure, which may lead to the future evolution of hypertensive disease of pregnancy and cardiovascular risk in women who previously developed hypertension during pregnancy [4, 5].

Haptoglobin (Hp) is an acute phase $\alpha 2$ plasma glycoprotein, synthesized in the hepatocyte and other peripheral tissues, which scavenge free haemoglobin and may modulate differentially cardiovascular risk through its antioxidant and anti-inflammatory different capacities associated with their genotypes [6, 7]. The Hp gene is expressed primarily in hepatocytes but also locally in other tissues or in cells related

with inflammatory processes, such as neutrophils [8]. This protein has a pronounced anti-inflammatory action and has high affinity to a specific receptor (CD163) located in circulating monocytes, resident macrophages (M2 type), and liver Kupffer cells [9–11]. The cellular expression of this pathway of Hp, CD163 and hemoxygenase (HO-1), is strongly activated directly or indirectly by cytokines, such as interleukins (IL-6, IL-1), tumor necrosis factor alfa (TNF-α), growth factors (M-CSF) [12], or hormones such as catecholamines and glucocorticoids [13].

Hp may have a role in the pregnant women with hypertension playing a protection role from further cardiovascular risk, once it prevents the formation of free radicals and its accumulation in endothelial cells, catalysed by heme, therefore preventing vessel injury [9, 11, 13].

Hp has a genetic polymorphism (Hp 1.1, 2.1 e 2.2) contributing to the great variability in anti-inflammatory responses; namely, Hp 2.2 phenotype is associated with a lower antioxidant capacity than the other two Hp phenotypes because of its higher molecular mass that restricts its extra vascular diffusion [6, 7, 14]. Also the Hp 2.2/Hb complex scavenges more nitric oxide (NO) than Hp 1.1/Hb due to its longer half-life in circulation [7, 15, 16].

The inhibitory effects on prostaglandin synthesis of Hp 2.2 and Hp 2.1 are less pronounced than those of Hp 1.1 contributing differently for its lower anti-inflammatory action [6, 17, 18]. However, Hp 2.2 is the most angiogenic form in the course of chronic inflammatory processes leading to greater ischemic tissue reparation and promoting of collateral vessel formation than the other two forms [19, 20].

The α-chain of haptoglobin and haptoglobin-related protein (Hpr), belonging to the cluster of Hp in chromosome 16, contains a hydrophobic signal peptide that may explain its association with lipoprotein particles (HDL) or membranes [21].

The objectives of the present work were to evaluate in women with history of hypertension in pregnancy/preeclampsia the susceptibility to develop hypertension in the future and the possible relationship with Hp phenotypes; the second objective was to evaluate the influence of the Hp genetic polymorphism on circulating cardiovascular risk biomarkers and the level of blood pressure in a prospective cohort.

2. Materials and Methods

2.1. Sample Population. We studied 352 women aged 35 ± 5.48 years, and from these, 165 had preeclampsia 2 to 16 (± 6.6) years ago, which was identified from medical records at the Department of Obstetrics and Gynecology from the Júlio Diniz Maternity, Maria Pia Hospital, OPorto. The diagnosis of preeclampsia was based on criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) [22]. Women of the control group of the same Hospital were matched for age within group on the study and similarly to the study group. They were firstly interviewed by phone. Then, they were invited to come to the research center during the same phase of their menstrual cycles for sample collection.

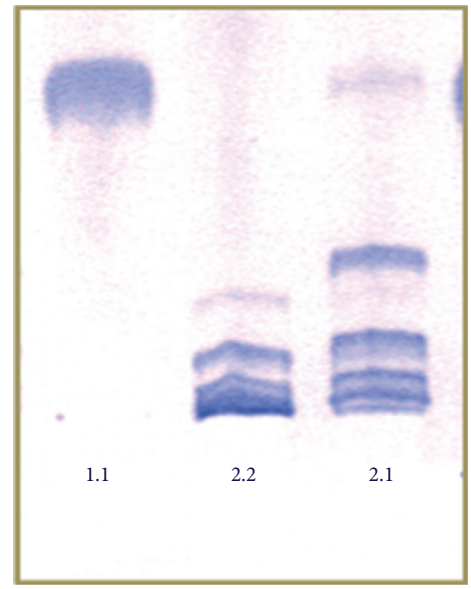

Figure 1: Polyacrylamide gel electrophoresis (PAGE) of Hp showing the typical pattern of bands of 1.1, 2.1, and 2.2 phenotypes.

We also evaluated some unhealthy behaviors as smoke and alcoholic habits through a questionnaire that determined women who smoked or drank after pregnancy, respectively.

Women were stratified accordingly to the criteria of the ISSHP [22] in preeclamptic (PE) and normal blood pressure in pregnancy (NBPP); in hypertensive after pregnancy (HTA), and normotensive after pregnancy (NBP), based on the criteria of European Society of Hypertension (ESH) and European Society of Cardiology (ESC) [23].

2.2. Haptoglobin Polymorphism Detection. The three phenotypes of Hp (1.1, 2.1 and 2.2) were separated from plasma using polyacrylamide gel electrophoresis (PAGE) and its presence was detected by the peroxidase activity of the complex haptoglobin—haemoglobin over the colour using substrate of o-dianisidine (Figure 1) [24, 25].

2.3. Circulating Cardiovascular Risk Biomarkers Determination. The different circulating biomarkers were determined by enzyme-linked immunosorbent assay (ELISA—R&D Systems Inc.) such as myeloperoxidase (MPO, ng/mL). Nitric oxide metabolites (NOx, mmol/L) and nitrites (μmol/L), transaminases—AST (Aspartate transaminase, UI/L), and ALT (alanine transaminase, UI/L) were determined by conventional standardized methods. Classical biomarkers as serum lipids and lipoproteins: total cholesterol (t-cholesterol, mg/dl) and HDL and LDL cholesterol, were measured by using automated enzymatic assays (ABX Diagnostic) and apolipoprotein A and B (Apo A and B, mg/dL) by using automated immunoturbidimetric assays (ABX Diagnostic). Serum C-reactive protein (CRP, mg/L) was assessed by an immunoenzymatic method (adaptation of the method of Highton and Hessian, 1984 [26].

Table 1: Distribution of Hp phenotypes in women with normal blood pressure in pregnancy (NBPP) and preeclamptic women (PE).

Phenotype	NBPP $n = 128$ n (%)	PE $n = 137$ n (%)	P value
Hp 1.1	28 (21.9)	22 (16.1)	
Hp 2.1	66 (51.6)	72 (52.5)	0.421
Hp 2.2	34 (26.5)	43 (31.4)	

Chi-square test.

2.4. Blood Pressure and Anthropometric Parameters Evaluation. Blood pressure in mmHg (BP) was measured by an oscillometric method. Anthropometric parameters such as BMI (body mass index, Kg/m^2) and hip (cm) and waist circumference (WC, cm) were evaluated using classic measurement instruments.

2.5. Statistics Analysis. In statistical analyses, we included departure from normality according to Kolmogorov Smirnov test and then adequate parametric or nonparametric tests to compare means. We also performed the Chi-square, and for pairwise comparisons between groups we used Student's t test or Mann-Whitney U test, with a probability value of <0.05 considered statistically significant. For this analysis, we used 21 version SPSS programme.

3. Results

The results are shown in two parts. The first one considers the risk of preeclampsia in accordance with Hp phenotype distribution in women during pregnancy (Study 1). The second one observes the susceptibility of cardiovascular risk in women with previous preeclampsia, considering also the influence of circulating cardiovascular risk biomarkers, and Hp phenotype, in a follow-up subsample of 2 to 16 years (Study 2) (Figure 1).

Study 1: Haptoglobin polymorphism and susceptibility for the development of preeclampsia.

Table 1 shows distribution of Hp phenotypes in a population of normotensive (normal blood pressure in pregnancy—NBPP) and hypertensive (Preeclampsia—PE) pregnant women ($N = 265$). The NT women were significantly younger (27.93 ± 4.91, mean ± S.D.) than women with preeclampsia (29.71 ± 5.97, mean ± S.D.) ($P = 0.011$). Most women have over 34 weeks of gestation, independently of hypertension degree, but before or 34 weeks of gestation there were more significantly preeclamptic women (30.3%) ($P < 0.001$) (data not shown).

In our population of 265 Caucasian pregnant women and concerning the Hp phenotype distribution, we found no statistical differences of Hp phenotype distribution (1.1, 2.1, and 2.2) between 128 normotensive women (NT) and 137 PE ($P = 0.421$) (Table 1).

We also evaluated the distribution of Hp phenotype in all preeclamptic women at age of diagnosis between ≤34 weeks of gestation and >34 weeks of gestation and we observed no significant differences (Table 2).

Study 2: The susceptibility of cardiovascular risk in women with previous preeclampsia and the influence of risk biomarkers and its modulation by the Hp phenotype at long term (2–16 years).

In the follow-up group we evaluated anthropometric and hemodynamic parameters and some biomarkers of cardiovascular risk in a sample of previously preeclamptic women and compared them with normotensive ones adjusted for age at pregnancy. We also study the influence of the Hp phenotype on the levels of biomarkers in circulation.

3.1. Anthropometric and Hemodynamic Parameters. This sample consisted of 150 women aged 20 to 35 years old (min.: 20–max: 47; 35.24 ± 5.48 (mean ± S.D.) and minimum BMI of 17.1 (underweight) to 42.7 (obesity) (26.39 ± 4.57 Kg/m^2, mean ± S.D.), who were recruited for this prospective study, 2–16 years after delivery. During pregnancy, 60 women were NT and 90 were preeclamptic. In this group, 16.2% have smoke habits and 4.7% consume alcoholic beverages, after pregnancy.

In this sample, when evaluating the values of blood pressure and anthropometric data we observed significantly mean higher values in previously preeclamptic women (PE) for BMI (27.05 ± 4.79, $P = 0.033$), WC (89.54 ± 15.64, $P = 0.004$), systolic blood pressure (134.99 ± 16.50, $P < 0.001$), and diastolic blood pressure (85.93 ± 18.28, $P < 0.001$), when compared with NBPP (Table 3).

3.2. Cardiovascular Risk Circulating Biomarkers. In order to evaluate biochemical biomarkers potentially implicated in cardiovascular risk, we found statistically significant differences with higher concentrations for previously PE comparing with NBPP, for MPO (85.67 ± 39.39, $P = 0.020$), nitrites (19.12 ± 7.01, $P < 0.001$), ALT (19.00 ± 1.36, $P = 0.003$), and Apo B (0.64 ± 0.14, $P = 0.023$) (Table 4) and slightly higher values for NOx (99.44 ± 39.52, $P = 0.061$).

According to classification during pregnancy [22] and considering the Hp phenotype, we found a variation in anthropometric characteristics and blood pressure and also in the cardiovascular risk biomarkers, classical or not between normotensive and preeclamptic women (Table 5). In women with Hp 1.1 and 2.1 phenotypes, we found significantly higher values in preeclamptic women (PE) in WC (90.78 ± 17.58), systolic and diastolic blood pressures (134.65 ± 18.31 and 86.19 ± 19.42, $P < 0.001$), MPO (94.17 ± 42.14, $P = 0.008$), nitrites (19.98 ± 8.53, $P < 0.001$), ALT (19.98 ± 8.53, $P = 0.005$), and Apo A (0.98 ± 0.16, $P = 0.011$) and also a trend in BMI (26.95 ± 5.46, $P = 0.061$) compared with normotensive ones (Table 5).

On the other hand, for Hp 2.2 phenotype we found also significant differences with higher levels in preeclamptic women, for systolic and diastolic blood pressures (135.61 ± 12.79 and 85.45 ± 16.26, $P < 0.001$) and nitrites (18.01 ± 4.44, $P = 0.007$) compared with normotensive ones (Table 5).

When comparing Hp phenotypes subgroups (1.1 plus 2.1 versus 2.2), within either NBPP or PE groups, we found

Table 2: Distribution of Hp phenotypes in the sample of preeclamptic women (PE) stratified by age of gestation at diagnosis.

	Hp 1.1 $n = 19$	Hp 2.1 $n = 66$	Hp 2.2 $n = 42$	P value
≤34 weeks of gestation, n (%)	6 (14.6)	23 (56.1)	12 (29.3)	0.791
>34 weeks of gestation, n (%)	13 (15.1)	43 (50.0)	30 (34.9)	

Chi-square test.
Preeclamptic women (PE) with diagnosis before 34 weeks of gestation (≤34 weeks of gestation) and after 34 weeks of gestation (>34 weeks of gestation).

Table 3: Comparison of anthropometric and blood pressure data in women with normal blood pressure in pregnancy (NBPP) and preeclamptic women (PE).

	NBPP n (mean ± SD)	PE n (mean ± SD)	OR	CI (95%)	P value[†]
Age (years)	60 (35.62 ± 5.62)	89 (34.99 ± 5.40)	0.979	(0.922–1.040)	0.492
BMI (Kg/m^2)	59 (25.40 ± 4.05)	88 (27.05 ± 4.79)	1.090	(1.007–1.180)	**0.033**
WC (cm)	56 (82.77 ± 9.85)	88 (89.54 ± 15.64)	1.048	(1.015–1.082)	**0.004**
Systolic BP (mmHg)	58 (118.88 ± 13.38)	88 (134.99 ± 16.50)	1.095	(1.059–1.133)	<**0.001**
Diastolic BP (mmHg)	58 (72.21 ± 10.08)	88 (85.93 ± 18.28)	1.076	(1.043–1.110)	<**0.001**
Pulse pressure	58 (46.67 ± 9.30)	88 (49.06 ± 11.91)	1.021	(0.990–1.053)	0.196

[†]Values adjusted for age (regression binary logistic).
Body mass index (BMI), waist circumference (WC), systolic blood pressure (Systolic BP), diastolic blood (Diastolic BP), and pulse pressure.

Table 4: Comparison of cardiovascular risk biomarkers in women with normal blood pressure in pregnancy (NBPP) and women with preeclampsia (PE).

	NBPP n (mean ± SD)	PE n (mean ± SD)	P value
CRP (mg/L)[††]	56 (0.40 ± 0.11)	83 (0.60 ± 0.07)	0.179
MPO (ng/mL)[†]	24 (62.27 ± 30.88)	32 (85.67 ± 39.39)	**0.020**
Nitrites (μmol/L)[†]	25 (10.12 ± 3.80)	32 (19.12 ± 7.01)	<**0.001**
NO_x (μmol/L)[†]	25 (79.18 ± 38.06)	29 (99.44 ± 39.52)	0.061
AST (UI/L)[††]	60 (18.00 ± 0.65)	90 (19.00 ± 0.72)	0.083
ALT (UI/L)[††]	60 (15.50 ± 1.03)	90 (19.00 ± 1.36)	**0.003**
t-Cholesterol (mg/dL)[†]	60 (206.57 ± 34.29)	90 (207.18 ± 39.33)	0.922
Non HDL cholesterol[†]	59 (157.00 ± 35.60)	90 (158.17 ± 37.96)	0.851
LDL (mg/dL)[†]	59 (138.75 ± 32.30)	90 (158.17 ± 37.96)	0.855
HDL (mg/dL)[††]	59 (50.00 ± 1.11)	90 (49.00 ± 0.89)	0.479
Apo A (mg/dL)[†]	58 (0.95 ± 0.20)	87 (0.99 ± 0.17)	0.129
Apo B (mg/dL)[†]	58 (0.59 ± 0.13)	87 (0.64 ± 0.14)	**0.023**

[†]Independent sample t-test; and values are means ± standard deviation (SD).
[††]Mann-Whitney U test; and values are median ± standard error (SE).
C-reactive protein (CRP), Myeloperoxidase (MPO), nitrites, nitric oxide metabolites (NO_x), aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (t-cholesterol), non HDL cholesterol, apolipoprotein A and B (Apo B and Apo A), low density lipoprotein (LDL), and high density lipoprotein (HDL).

significant differences as follows: higher values of Apo A (0.90 ± 0.17 versus 1.07 ± 0.22, $P = 0.002$) and CRP (0.50 ± 0.10 versus 0.70 ± 0.09, $P = 0.026$) associated with Hp 2.2, in NBPP and PE groups, respectively (data not shown).

Women after pregnancy were then stratified accordingly to previously preeclamptic (PE) or normotensive (NBP) women corresponding to reclassifying by the criteria of the ESH/ESC [23]. We found that 47.7% of preeclamptic women developed hypertension (Group 1) and that only 10.3% of normotensive women during pregnancy developed hypertension afterwards, Group 3 as in shown in Figure 2 ($P < 0.001$). Two other groups of women, such as Group 2 of previously preeclamptic women that became normotensive and Group 4 of previously normotensive women that maintain normotensive, were analysed (Figure 2).

When we evaluated circulating cardiovascular risk biomarkers, we found that preeclamptic women that subsequently became normotensive (Group 2, PE > NBP)

Table 5: Comparison of blood pressure, anthropometric characteristics, and classic or not biomarkers between women with normal blood pressure in pregnancy (NBPP) and preeclamptic women (PE) according to Haptoglobin phenotype.

	Hp 1.1 plus 2.1			Hp 2.2		
	NBPP *n* (mean ± SD)	PE *n* (mean ± SD)	*P* value	NBPP *n* (mean ± SD)	PE *n* (mean ± SD)	*P* value
BMI (Kg/m^2)†	41 (25.18 ± 3.80)	57 (26.95 ± 5.46)	0.061	18 (25.90 ± 4.65)	31 (27.23 ± 3.32)	0.249
WC (cm)†	38 (82.43 ± 10.0)	57 (90.78 ± 17.58)	**0.004**	18 (83.47 ± 9.84)	31 (87.26 ± 11.15)	0.238
Systolic BP (mmHg)†	40 (119.18 ± 13.67)	57 (134.65 ± 18.31)	**<0.001**	18 (118.22 ± 13.01)	31 (135.61 ± 12.79)	**<0.001**
Diastolic BP (mmHg)†	40 (72.80 ± 11.18)	57 (86.19 ± 19.42)	**<0.001**	18 (70.89 ± 7.15)	31 (85.45 ± 16.26)	**<0.001**
Pulse pressure†	40 (46.38 ± 8.12)	57 (48.46 ± 11.89)	0.308	18 (47.33 ± 11.76)	31 (50.16 ± 12.07)	0.429
CRP (mg/L)††	38 (0.40 ± 0.15)	55 (0.50 ± 0.10)	0.697	18 (0.40 ± 0.12)	28 (0.70 ± 0.09)	0.106
MPO (ng/mL)†	17 (57.89 ± 32.47)	18 (94.17 ± 42.14)	**0.008**	7 (72.89 ± 25.64)	14 (74.75 ± 33.89)	0.900
Nitrites (μmol/L)†	18 (9.57 ± 3.19)	18 (19.98 ± 8.53)	**<0.001**	7 (11.54 ± 5.06)	14 (18.01 ± 4.44)	**0.007**
NO_x (μmol/L)†	18 (79.04 ± 37.15)	17 (101.32 ± 48.79)	0.141	7 (79.53 ± 43.39)	12 (96.79 ± 22.34)	0.356
AST (UI/L)††	41 (18.00 ± 0.70)	59 (19.00 ± 0.66)	0.084	19 (8.00 ± 1.40)	31 (19.00 ± 1.67)	0.582
ALT (UI/L)††	41 (15.00 ± 1.13)	59 (18.00 ± 1.04)	**0.005**	19 (19.00 ± 2.11)	31 (20.00 ± 3.34)	0.234
t-Cholesterol (mg/dL)†	41 (203.73 ± 33.24)	59 (202.66 ± 38.65)	0.886	19 (212.68 ± 36.63)	31 (215.77 ± 39.81)	0.785
Non HDL cholesterol†	40 (155.58 ± 35.59)	59 (153.97 ± 37.03)	0.830	19 (160.00 ± 36.41)	31 (166.16 ± 39.03)	0.581
LDL (mg/dL)†	40 (137.90 ± 33.04)	59 (133.90 ± 33.04)	0.523	19 (140.53 ± 31.49)	31 (146.29 ± 37.61)	0.579
HDL (mg/dL)†	40 (49.00 ± 1.31)	59 (49.00 ± 1.08)	0.954	19 (56.00 ± 1.95)	31 (49.00 ± 1.59)	0.203
Apo A (mg/dL)†	41 (0.90 ± 0.17)	58 (0.98 ± 0.16)	**0.011**	17 (1.07 ± 0.22)	29 (1.02 ± 0.19)	0.405
Apo B (mg/dL)†	41 (0.58 ± 0.12)	58 (0.62 ± 0.14)	0.122	17 (0.61 ± 0.15)	29 (0.68 ± 0.13)	0.105

†Independent sample *t*-test; and values are means ± standard deviation (SD).

††Mann-Whitney *U* test; and values are median ± standard error (SE).

Body mass index (BMI), waist circumference (WC), systolic blood pressure (Systolic BP), diastolic blood (Diastolic BP), pulse pressure, c-reactive protein (CRP), myeloperoxidase (MPO), nitrites, total nitric oxide metabolites (NO_x), aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (t-cholesterol), non HDL cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), Apolipoprotein A and B (Apo B and Apo A).

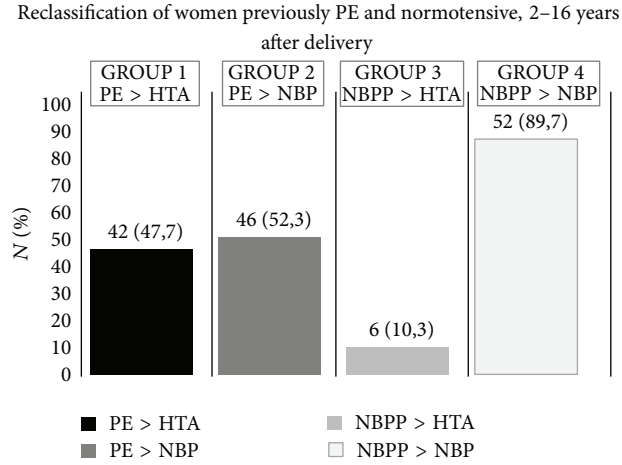

Figure 2: Reclassification of women previously PE and normotensive, 2–16 years after delivery. This reclassification took into account the definitions of hypertension according to diastolic and/or systolic pressures during pregnancy and 2–16 years after pregnancy and childbirth. Preeclamptic (PE), normal blood pressure in pregnancy (NBPP), hypertensive after pregnancy (HTA), and normotensive after pregnancy (NBP).

have some clear characteristics of the hypertensive subjects (Group 1, PE > HTA), namely, BMI, WC, pulse pressure, CRP, MPO, nitrites, nitric oxide total metabolites (NOx), transaminases, and lipid profile (Table 6). Moreover the preeclamptic women that developed hypertension were significantly older than the preeclamptic women that did not develop hypertension (Group 1, PE > HTA versus Group 2, PE > NBP) (36.64 ± 5.16 versus 33.50 ± 5.29, $P = 0.008$). The Groups 2 and 3 only differ significantly in systolic and diastolic blood pressures with higher levels for Group 3 (140.00 ± 6.23 and 86.00 ± 5.87, $P < 0.001$ and $P = 0.008$, resp.), and for nitrites with higher levels in Group 2 (18.02 ± 3.89, $P < 0.001$) (Table 6).

The pure normotensive group or Group 4 (NBPP > NBP) differs significantly in BMI (28.71 ± 5.11, $P = 0.033$), systolic (140.00 ± 6.23, $P < 0.001$), diastolic blood pressures (86.00 ± 5.87, $P < 0.001$), and pulse pressure (54.00 ± 9.53, $P = 0.040$) and slightly in CRP (0.70 ± 0.24, $P = 0.055$), when comparing with Group 3, with higher values for the this one (Table 6). When comparing this group (Group 4, NBPP > NBP) with women that became normotensive after a preeclamptic episode (Group 2, PE > NBPP) we found significant differences in BMI (26.85 ± 4.69, $P = 0.033$), WC (88.38 ± 12.01, $P = 0.005$), systolic blood pressure (125.04 ± 8.85, $P < 0.001$), pulse pressure (50.96 ± 8.38, $P = 0.004$), MPO (86.49 ± 44.39, $P = 0.032$), nitrites, (18.02 ± 3.89, $P > 0.001$), ALT (19.00 ± 2.07, $P = 0.021$), and Apo B (0.65 ± 0.13, $P = 0.040$), with higher values for Group 2 (PE > NBP).

Extreme groups (Group 1—PE > HTA and Group 4—NBPP > NBP) differ significantly with higher levels for Group 1 in BMI (27.22 ± 5.00, $P = 0.016$), WC (90.56 ± 18.96, $P = 0.010$), systolic (145.88 ± 16.11, $P < 0.001$), diastolic (98.90 ± 16.26, $P < 0.001$) blood pressures, MPO (82.74 ± 11.04, $P = 0.010$), nitrites (23.04 ± 13.07, $P = 0.037$), and ALT (19.00 ± 1.85, $P = 0.031$) (Table 6).

We evaluated the distribution of the Hp phenotypes among the four subgroups and we did not find differences between them ($P = 0.273$), even within subgroups of previously preeclamptic or normotensive women considering separately ($P = 0.130$ and 0.185, resp.) (Table 7).

In order to study the influence of the Hp phenotypes (1.1 plus 2.1 versus 2.2) in cardiovascular risk, we analyse in these newly identified four groups the levels of biomarkers and their variation according to Hp phenotype (see Supplementary table in Supplementary Material available online at http://dx.doi.org/10.1155/2014/361727). Relative to individual groups, we found significant differences only in Group 4 (NBPP > NBP, previously normotensive pregnant women that maintain normotensive) with higher levels of Apo A (0.89 ± 0.17 versus 1.07 ± 0.23, $P = 0.003$) and slightly elevated differences for HDL (49.00 ± 1.46 versus 54.20 ± 2.04, $P = 0.068$) associated with Hp 2.2 phenotype.

Considering only the Hp 1.1 plus 2.1 phenotypes, we observed between Groups 1 and 2 (PE > HTA versus PE > NBP) differences for HDL cholesterol with higher values at Group 2 (46.00 ± 1.69 versus 53.00 ± 1.39, $P = 0.053$), and between Groups 2 and 3 (PE > NBP versus NBPP > HTA) we found differences in nitrites (17.90 ± 2.89 versus 9.00 ± 0.00, $P < 0.001$) with higher values for PE > NBP, and between Groups 3 and 4 (NBPP > HTA versus NBPP > NBP) differences were found for BMI (28.71 ± 5.11 versus 24.45 ± 3.22, $P = 0.010$), systolic blood pressure (140.00 ± 6.23 versus 115.50 ± 11.06, $P < 0.001$), diastolic blood pressure (86.00 ± 5.87 versus 70.47 ± 10.26, $P = 0.001$), pulse pressure (54.00 ± 9.53 versus 45.03 ± 7.12, $P = 0.011$), and CRP (0.70 ± 0.24 versus 0.30 ± 0.17, $P = 0.029$), but for WC (89.00 ± 15.11 versus 81.20 ± 8.48, $P = 0.078$) differences were slight. Between Groups 2 and 4 (PE > NBP versus NBPP > NBP) we found significantly mean higher levels for BMI (26.88 ± 5.23 versus 24.45 ± 3.44, $P = 0.026$), WC (88.93 ± 12.51 versus 24.45 ± 3.22, $P = 0.005$), systolic blood pressure (124.56 ± 9.02 versus 115.50 ± 11.06, $P = 0.001$), MPO (96.93 ± 45.84 versus 54.38 ± 30.75, $P = 0.009$), nitrites (17.90 ± 2.89 versus 8.99 ± 2.32, $P < 0.001$), Apo A (0.99 ± 0.15 versus 0.89 ± 0.17, $P = 0.011$), and ALT (18.00 ± 1.65 versus 15.00 ± 1.34, $P = 0.025$). Finally for extreme Groups 1 and 4 (PE > HTA versus NBPP > NBP) there were significant differences in WC (92.74 ± 22.68 versus 81.20 ± 8.47, $P = 0.022$), systolic blood pressure (147.56 ± 19.17 versus 115.50 ± 11.06, $P < 0.001$), diastolic blood pressure (100.92 ± 18.48 versus 70.47± 10.26, $P < 0.001$), and MPO (80.33 ± 6.42 versus 54.38 ± 30.75, $P = 0.014$), as well as a trend in BMI (29.97 ± 5.93 versus 24.45 ± 3.22, $P = 0.063$) and ALT (0.45 ± 0.19 versus 0.30 ± 0.17, $P = 0.055$) (supplementary table).

By other hand, when consider only the Hp 2.2 phenotype, we obtained differences between Groups 1 and 2 (PE > HTA versus PE > NBP) with higher values for systolic (143.41 ± 10.12 versus 126.14 ± 8.66, $P < 0.001$) and diastolic (95.94 ± 12.24 versus 72.71 ± 10.37, $P < 0.001$) blood pressures. Between Groups 1 and 4 (PE > HTA versus NBPP > NBP) we found differences in nitrites with higher values in Group 1 (17.53 ± 1.89 versus 11.54 ± 5.06, $P = 0.052$) (data not shown).

Table 6: Characterization of four distinguished groups in conformity of hypertension classification and the anthropometric, hemodynamic, cardiovascular risk biomarkers and other biochemical parameters.

	[PE > HTA] (1)	[PE > NBP] (2)	[NBPP > HTA] (3)	[NBPP > NBP] (4)	*P* value					
					(1)* versus (2)	(1) versus (3)	(2) versus (3)	(2) versus (4)	(3) versus (4)	(1) versus (4)
Age (years)†	42 (36.64 ± 5.16)	46 (33.50 ± 5.29)	6 (36.33 ± 4.97)	52 (35.50 ± 5.78)	**0.008**	0.891	0.220	0.079	0.737	0.320
BMI (Kg/m^2)†	42 (27.22 ± 5.00)	45 (26.85 ± 4.69)	6 (28.71 ± 5.11)	51 (24.97 ± 3.83)	0.830	0.500	0.373	**0.033**	**0.033**	**0.016**
WC (cm)†	42 (90.56 ± 18.96)	45 (88.38 ± 12.01)	6 (89.00 ± 15.11)	49 (82.06 ± 9.04)	0.516	0.848	0.908	**0.005**	0.107	**0.010**
Systolic BP (mmHg)†	42 (145.88 ± 16.11)	46 (125.04 ± 8.85)	6 (140.00 ± 6.23)	52 (116.44 ± 11.73)	**<0.001**	0.384	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Diastolic BP (mmHg)†	42 (98.90 ± 16.26)	46 (74.09 ± 10.22)	6 (86.00 ± 5.87)	52 (70.62 ± 9.23)	**<0.001**	0.062	**0.008**	0.080	**<0.001**	**<0.001**
Pulse pressure†	42 (46.98 ± 14.68)	46 (50.96 ± 8.38)	6 (54.00 ± 9.53)	52 (45.83 ± 8.90)	0.144	0.263	0.413	**0.004**	**0.040**	0.658
CRP (mg/L)††	38 (0.60 ± 0.13)	44 (0.60 ± 0.07)	6 (0.70 ± 0.24)	49 (0.40 ± 0.12)	0.388	0.350	0.404	0.079	0.055	0.188
MPO (ng/mL)†	7 (82.74 ± 11.04)	25 (86.49 ± 44.39)	3 (86.83 ± 24.08)	20 (60.86 ± 29.78)	0.781	0.710	0.990	**0.032**	0.167	**0.010**
Nitrites (mol/L)†	7 (23.04 ± 13.07)	25 (18.02 ± 3.89)	3 (9.00 ± 0.00)	21 (9.84 ± 3.56)	0.190	0.110	**<0.001**	**<0.001**	0.693	**0.037**
NO_x (mol/L)†	6 (109.70 ± 40.96)	23 (96.77 ± 39.62)	3 (91.47 ± 63.01)	21 (78.63 ± 35.86)	0.474	0.610	0.839	0.120	0.600	0.134
AST (UI/L)††	42 (19.00 ± 0.84)	46 (20.00 ± 1.19)	6 (17.50 ± 1.25)	52 (18.00 ± 0.66)	0.589	0.190	0.188	0.108	0.564	0.230
ALT (UI/L)††	42 (19.00 ± 1.85)	46 (19.00 ± 2.07)	6 (15.50 ± 1.01)	52 (15.50 ± 1.17)	0.809	0.110	0.121	**0.021**	0.878	**0.031**
t-Cholesterol (mg/dL)†	42 (202.48 ± 42.02)	46 (210.35 ± 37.72)	6 (205.17 ± 14.10)	52 (207.48 ± 36.36)	0.267	0.878	0.739	0.701	0.879	0.538
Non HDL cholesterol†	42 (154.98 ± 38.86)	46 (159.80 ± 37.72)	6 (154.17 ± 15.03)	51 (158.16 ± 37.66)	0.392	0.960	0.721	0.830	0.799	0.690
LDL (mg/dL)†	42 (136.54 ± 37.97)	46 (137.74 ± 40.55)	6 (133.87 ± 10.29)	51 (140.25 ± 34.05)	0.632	0.866	0.818	0.741	0.326	0.690
HDL (mg/dL)††	42 (47.00 ± 1.29)	46 (53.00 ± 1.24)	6 (52.00 ± 3.54)	51 (50.00 ± 1.21)	0.172	0.367	0.878	0.580	0.677	0.130
Apo A (mg/dL)†	40 (0.97 ± 0.18)	45 (1.01 ± 0.16)	6 (0.94 ± 0.17)	50 (0.95 ± 0.21)	0.320	0.698	0.370	0.128	0.952	0.548
Apo B (mg/dL)†	40 (0.63 ± 0.14)	45 (0.65 ± 0.13)	6 (0.60 ± 0.06)	50 (0.59 ± 0.14)	0.704	0.584	0.387	**0.040**	0.866	0.159

†Independent sample *t*-test; and values are means ± standard deviation (SD); ††Mann-Whitney *U* test; and values are median ± standard error (SE). Relative to *P* value of (1) versus (2)*, values were adjusted for age (regression binary logistic).

Preeclamptic women (PE); hypertension after pregnancy (HTA), normal blood pressure in pregnancy (NBPP), normotensive after pregnancy (NBP), waist circumference (WC), Body mass index (BMI), systolic blood pressure (systolic BP), diastolic blood pressure (diastolic BP), c-reactive protein (CRP), myeloperoxidase (MPO), nitrites, total nitric oxide (NO_x), aspartate transaminase (AST); alanine transaminase (ALT), low density lipoprotein (LDL) and high density lipoprotein (HDL), and apolipoprotein A and B (Apo A and Apo B).

Table 7: Comparison of haptoglobin polymorphism between the subgroups.

	Hp 1.1 *n* (%)	Hp 2.1 *n* (%)	Hp 2.2 *n* (%)	*P* value
[PE > HTA] [1]	9 (21.4)	16 (38.1)	17 (40.5)	0.130
[PE > NBP] [2]	5 (10.9)	27 (58.7)	14 (30.4)	
[NBPP > HTA] [3]	1 (16.7)	5 (83.3)	0 (0.0)	0.185
[NBPP > NBP] [4]	9 (17.3)	25 (48.1)	18 (34.6)	

PE: Preeclamptic women; HTA: hypertension after pregnancy; NBP: normal blood pressure in pregnancy; NBP: normotensive after pregnancy.

4. Discussion

Cardiovascular disease in pre- and postmenopausal women is the most prevalent cause of morbidity including metabolic syndrome with abdominal obesity, dyslipidaemia, insulin resistance, and hypertension.

In the last 10 years, several studies demonstrate that history of preeclampsia increases the risk for development of cardiovascular disease [2, 5]. Hypertensive disease of pregnancy in particular preeclampsia (PE) is characterized by a proinflammatory state of low intensity initiated in the placenta after under-perfusion, hypoxia, and local oxidative stress. This state leads to endothelial dysfunction and secondarily the clinical symptoms of PE [27]. The initial phenomena of ischemia reperfusion of placenta give places probability to the formation and release of advanced glycation end products (AGEs) that secondarily activates the AGE-RAGE (receptor of AGE) axis [28, 29].

AGE-RAGE axis activates an acute phase response locally in placenta or systemically in liver where one of its the components is haptoglobin (Hp) that initiates the axis Hp-CD163-heme oxygenase (HO) that leads to the switch of Th1 to Th2 of acquired immune response [12, 20, 30].

In our present study we did not observe a clear association of the Hp phenotypes with susceptibility to preeclampsia or to its long-term prognosis. But the presence of Hp allele 1 seems to be a protective factor for these outcomes, as it was observed by the other authors [31–33]. For some authors, this can be due to the great immune tolerance potential of the Hp 2.1 phenotype [34, 35]. However, this subject is controversial [36, 37]. The early PE, more characteristics of placenta dysfunction versus late PE, linked to endothelial dysfunction due to constitutional factors such as body mass index (BMI) and metabolic syndrome, cannot be explained by Hp polymorphism (Table 2).

In our cohort, we observed independently of age, significant higher BMI, WC, and systolic and diastolic blood pressure in previously preeclamptic women. The same happens for more elevated MPO, nitrites, ALT, and Apo B concentrations in blood. These results are in accordance with those of other authors [3, 38].

When we analysed those biomarkers (anthropometric, haemodynamic, and circulatory) stratified by Hp phenotypes (Hp 1.1 plus 2.1 versus 2.2), we found significant differences between previously PE versus normotensive (Table 5), respectively, for WC, MPO, ALT, and Apo A (more elevated in carriers of Hp 1.1 plus 2.1 phenotypes). For lipid profile biomarkers, Hp 2.2 in both NBPP and PE groups has higher values than Hp allele 1 carriers. This can be explained by great expression of Apo A in oxidative condition [21]. Elevated MPO probably is related to NO bioavailability through its oxidation into nitrites, which were also more elevated in previously PE women of both Hp phenotypes [39]. MPO free in plasma or serum represents that one which is mobilized from the vessel wall to the lumen affecting NO bioavailability [40]. After reclassification according to actual blood pressure of previously PE women, in two groups with (Group 1) or without (Group 2) actual hypertension and using the same criteria for previously normotensive women we could have a more real picture of risk of the women having hypertensive disease, years after pregnancy and the natural history of cardiovascular disease in premenopausal women (Figure 2). Between the two subgroups of previously PE women there is a difference in age, with a mean age lower in NBP (Table 6). These women probably became hypertensive later. The same situation relative to age was observed between the two normotensive Groups 3 and 4. Group 3 seems to have characteristics of metabolic syndrome features, like WC, pulse pressure, and CRP. This situation is also observed comparing Group 4 with Group 2 (PE > NBP) and similarly comparing with Group 1 (PE > HTA) as is observed in Table 6.

Finally, haptoglobin polymorphism also did not influence apparently the natural history of previously preeclamptic and normotensive Groups 1 and 2, premenopausal one (Table 7). After our trial to clarify the influence of that polymorphism in some circulating risk biomarkers (supplementary table), in women with Hp 1 allele (Hp 1.1 plus 2.1), we observe a trend for higher values of HDL cholesterol in Group 2 (PE > NBP), compared with women PE > HTA (Group 1), even after adjusting for age.

The difference between groups previously with PE that became hypertensive (Group 1) or yet normotensive (Group 2) and also Group 3 (NBPP > HTA), as compared with Group 4 (NBPP > NBP, previously normotensive pregnant women that maintain normotensive) depends on surrogate biomarkers of metabolic syndrome and NO bioavailability, sustained by Hp 2.2 phenotype.

5. Conclusions

Women with previous preeclampsia and premenopausal, even if became normotensive, presented significant differences compared with previous normotensive women during pregnancy in some classic cardiovascular risk biomarkers as well as in some others, associated with metabolic syndrome, NO bioavaibility and inflammatory process. These biomarkers variation may be modulated by haptoglobin functional genetic polymorphism more relevant in the carriers of haptoglobin 1 allele. The history of hypertensive disease in pregnancy may be relevant, in association with these biomarkers including genetic ones, to the prevention of cardiovascular disease in particular of postmenopausal women.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Andreia Matos and Alda Pereira da Silva contributed equally to the work.

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Research Article

Preeclampsia and Future Cardiovascular Risk: Are Women and General Practitioners Aware of This Relationship? The Experience from a Portuguese Centre

Pedro Viana Pinto,[1] Mariana Rei,[1] Ana Paula Machado,[1] and Nuno Montenegro[1,2]

[1] *Serviço de Ginecologia-Obstetrícia, Centro Hospitalar São João, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal*
[2] *Faculdade de Medicina da Universidade do Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal*

Correspondence should be addressed to Pedro Viana Pinto; pedrovianapinto@gmail.com

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Objective. To evaluate the impact of preeclampsia in the modification of lifestyle habits and decreasing cardiovascular risk factors in a population of women at least 6 months after having the diagnosis of preeclampsia. *Methods*. Cross-sectional observational study. Data included 141 cases of preeclampsia and chronic hypertension with superimposed preeclampsia on singleton births diagnosed in our institution between January 2010 and December 2013. From the cases diagnosed over 6 months a standardized questionnaire evaluating lifestyle changes was applied. *Results*. We reviewed 141 cases, of which 120 were diagnosed for more than 6 months. An overall participation rate in the questionnaire of 65% was yielded. A slight increase from the mean BMI before pregnancy was found. No statistical significant association was established between postpregnancy mean BMI, weight variation, and the frequency of aerobic exercise with the severity of preeclampsia. Only 28% of our cases were practising aerobic exercise at least weekly. The majority of women assessed blood pressure at least monthly (45/78), but only 25 assessed glycaemia at least once/year. *Conclusion*. This study shows that the majority of our patients and general practitioners do not take into consideration a previous pregnancy affected by preeclampsia as a risk factor for future cardiovascular disease.

1. Introduction

The hypertensive disorders of pregnancy remain one of the most important causes of maternal and fetal morbidity and mortality all over the world. Preeclampsia, either alone or superimposed on preexisting hypertension, affects around 5 to 8% of all pregnancies and is responsible for approximately 50,000 maternal deaths annually [1]. Although appropriate perinatal care has reduced the number and extent of poor outcomes, serious maternal and fetal morbidity and mortality still occur [2].

Preeclampsia is now clearly associated with an anomaly of the placentation and incomplete remodelling of the uteroplacental spiral arteries [3]. Trophoblast invasion is often defective in preeclampsia, particularly in early-onset preeclampsia, affecting the endovascular, but not the interstitial, invasion pathway. The resulting abnormal uteroplacental flow is associated with placental oxidative and endoplasmic reticulum stress, probably from ischemia-reperfusion injury, which stimulates the release of proinflammatory cytokines and imposes an excessive inflammatory stress on the maternal circulation [4, 5]. This systemic inflammation may result from a variety of circulating factors such as pro- and antiangiogenic proteins (sFLT1, placental growth factor or soluble endoglin), proinflammatory cytokines, and activating autoantibodies against the AT1-receptor [4, 6–8]. Recently, transcription factors (like HIF-1α and NF-kappaB) and cell stress induced genes like GADD45α have been established as linking points between the hypoxic aggression and the release of antiangiogenic factors [9, 10]. The key target of these factors is

the maternal vascular endothelium, which plays an important role in smooth muscle tone control and regulation of the coagulation and fibrinolytic systems. Alterations in the concentration of circulating markers of endothelial dysfunction have been consistently reported in women with preeclampsia, highlighting the role of the endothelium in the pathogenesis of this disease [11, 12].

Acute atherosis is a vascular lesion observed in approximately 20 to 40% of the maternal spiral arteries. These lesions, mainly affecting the downstream of the unremodelled spiral arteries, strongly resemble atherosclerosis and have also been implied in the pathogenesis of preeclampsia [4, 8]. An immune mediated reaction may be responsible for the development of these lesions with maternal immune recognition of foreign fetal HLA-C leading to a switch from the anti-inflammatory milieu of normal pregnancy to a more proinflammatory status, triggering the formation of lipid-filled foam cells and vascular fibrinoid necrosis within the uterine arteries vascular wall [4, 13–15]. These findings enhance the idea that alloreactivity between maternal decidual immune cells and fetal extravillous trophoblasts may also contribute to the pathogenesis of preeclampsia [14, 15].

Several studies have clearly demonstrated that women with a history of preeclampsia have an increased risk of 2–4-fold cardiovascular diseases (CVD) later in life, at least equalling the risk attributed to obesity and smoking [16–19]. This situation is important to such an extent that led the American Heart Association, in 2011, to consider preeclampsia as a major risk factor for cardiovascular diseases, mainly hypertension, myocardial infarction, stroke, and diabetes [2, 20]. The probability seems to be higher if it is recurrent or early-onset preeclampsia or when it is associated with preterm birth and fetal growth restriction [18, 19, 21]. Possible explanations for this cardiovascular profile include the following: (1) both cardiovascular disease and preeclampsia share risk factors including dyslipidemia, increased insulin resistance, hypertension, obesity, and endothelial dysfunction, turning pregnancy into a "stress test" with the development of hypertensive disorders during pregnancy identifying a woman destined to develop cardiovascular disease; (2) pregnancy, and especially preeclampsia, may induce permanent arterial changes—the proatherogenic stress of pregnancy, excessive in many women with preeclampsia, could activate arterial wall inflammation that fails to resolve after delivery, increasing the risk for future cardiovascular disease [4, 19].

Therefore, women with a history of preeclampsia should be encouraged to have a more rigorous follow-up and adopt a healthier lifestyle. Patient and healthcare provider education is essential for the successful assessment and management of cardiovascular risk and prevention of the long term burden associated with preeclampsia.

The aim of this study was to evaluate the impact of the diagnosis of preeclampsia in the modification of lifestyle habits and decreasing cardiovascular risk factors in a population of women at least 6 months after having the diagnosis of preeclampsia, in a tertiary hospital for a 4-year period. Furthermore, we intended to evaluate the patient and general practitioner knowledge of the cardiovascular risks associated with a history of preeclampsia.

2. Methods

The 141 cases of preeclampsia and chronic hypertension with superimposed preeclampsia with singleton births diagnosed in our institution from January 2010 to December 2013 were retrospectively reviewed. Patients with multiple pregnancy were excluded.

We defined preeclampsia as the new onset of hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation in a previously normotensive woman. Superimposed preeclampsia was defined as preeclampsia complicating chronic hypertension, according to The American College of Obstetricians and Gynecologists (ACOG) criteria. Systolic blood pressure of 160 mmHg or higher or diastolic blood pressure of 110 mmHg or higher in two occasions, thrombocytopenia (less than 100,000/microliter), impaired liver function (elevated blood concentrations of liver enzymes to twice normal), or severe refractory epigastric pain, progressive renal insufficiency (serum concentration greater than 1.1 mg/dL or a doubling concentration), pulmonary edema, or new onset cerebral/visual disturbances were considered severe features of preeclampsia. The Mississippi classification was used to define HELLP syndrome: hemolysis (increased LDH level and progressive anemia), hepatic dysfunction (LDH level > 600 IU/L, AST > 40 IU/L, ALT > 40 IU/L or both), and thrombocytopenia (platelet nadir less than 150,000 cells/mm^3). The term fetal growth restriction was used to describe fetuses with an estimated weight less than the 10th percentile for gestational age.

Demographic and outcome data were collected from the computerised hospital database, VCIntegrator Obscare, which records all the final diagnoses by patient, and a systematic search using preeclampsia, superimposed preeclampsia, and HELLP syndrome as keywords was carried out. Demographic variables collected included woman's age at delivery, prepregnancy maternal body mass index (BMI), parity, education, past obstetric history (including previous preeclampsia, gestational diabetes, preterm birth, and fetal death), the indication for labour induction, and the mode of delivery (vaginal birth or caesarean section). Pregnancy adverse outcomes as fetal growth restriction, gestational diabetes, preterm birth, abruption placentae, and HELLP syndrome were also collected.

A standardized telephonic questionnaire was applied to 120 women who were diagnosed with preeclampsia or superimposed preeclampsia between January 2010 and October 2013. We excluded the 21 cases that delivered in the last six months, to better evaluate women lifestyle after hospital's follow-up and maternal license conclusion. Forty-two women not answering after four telephonic calls in three consecutive days were considered nonresponders. For those who were contacted successfully, the purpose of the study was explained and an invitation was given to participate in the evaluation.

The questions included current age, weight, medication (including antihypertensive drugs, insulin or oral antidiabetic drugs, antidyslipidemic drugs, aspirin, or others), and contraception method (none, barrier, combined hormonal, progestin-only pills, subdermal implant, vaginal ring,

intrauterine device, and female sterilization). We inquired about the mean meals per day, healthy nutrition behaviour, and attendance to nutritional counselling and to general medicine consultation and if an explanation of preeclampsia subject was addressed. Aerobic exercise practice before and after pregnancy was graded as (i) none, (ii) once per month, (iii) once per week, (iv) twice weekly, and (v) more than twice weekly. The monitoring of tensional values and glycemic levels were graded as (i) never, (ii) once per year, (iii) once per month, and (iv) once per week.

Study data were collected, validated, and entered into a dedicated study database by trained personnel. A descriptive analysis was performed using SPSS 20.0 software and the STATISTICA FOR WINDOWS statistical package, version 10.0. Chi-square test was used to compare categorical variables and one-way ANOVA test was applied to compare the means BMI between women with preeclampsia with or without severe features. No adjustment for confounders was made. A P value of less than 0.05 was considered significant.

3. Results

From January 2010 to December 2013 our institution admitted 141 cases of preeclampsia (22 cases of chronic hypertension with superimposed preeclampsia), with 120 cases having more than 6 months after delivery. A total of 78 women with previous preeclampsia answered the questionnaire, resulting in an overall participation rate of 65%. The remaining women did not answer the questionnaire.

Concerning the demographic characteristics (Table 1), the median (range) maternal age was 31 years (15–46). The mean BMI before pregnancy was 27.73. Seventy-five women were nulliparous (53.2%) and, from the multiparous women, 23 had a previous preeclamptic pregnancy. Along with preeclampsia, 37 women had suspected intrauterine growth restriction (all of them gave birth to small for gestational age newborns) and 64 newborns were preterm; the mean weight of newborns was 2533.77 g (400–4170 g). During the study period 47 women suffered from severe preeclampsia (29 before 34 weeks of gestation) and 16 from HELLP syndrome. Labour induction was performed in 93 deliveries (66%), from which 37 (39%) ended up in a caesarean section, nonreassuring fetal tracing (14 cases), failed induction of labour and arrested labour (both with 8 cases) being the most common reasons. The overall caesarean section rate was 52%.

Regarding the questionnaire (Table 2), the mean time from preeclampsia diagnosis was 2.02 years. Most women were taking combined hormonal pills as their contraceptive method. Eight women were trying to conceive again and all of them replied not knowing that they required a more rigorous follow-up during their next pregnancy.

The mean BMI was 26.7, demonstrating a slight increase from the mean BMI before being pregnant (26.07). Notably, 29 women diminished their weight while 35 increased weight (mean increase of 6,1 Kg). We could not find any statistical significant difference (Table 3) in postpregnancy mean BMI between women with severe preeclampsia and those with preeclampsia without severe features. Moreover, a statistical significant association could not be established between the severity of preeclampsia and the weight variation from pre- to postpregnancy (Figure 1). However, when comparing women with preeclampsia with women with chronic hypertension with superimposed preeclampsia there was a statistically significant reduction ($P = 0.006$) in weight in women with superimposed preeclampsia. The mean number of meals per

Table 1: Participant baseline characteristics during pregnancy.

Participant baseline characteristics during pregnancy	
Age (mean)	30.82
Body mass index before pregnancy (mean)	27.73
Education (%)	
Primary school	16 (11.3)
Secondary school	63 (44.6)
University	61 (43.6)
Conception (%)	
Spontaneous	135 (95.7)
Medically assisted	6 (4.3)
Parity (%)	
Primiparous	75 (53.2)
Multiparous	66 (46.8)
Past obstetric history	
Previous preeclampsia	23
Gestational diabetes	3
Fetal death	4
Preterm birth	12
Pregnancy adverse outcomes	
Fetal growth restriction	37
Severe preeclampsia	47
Gestational diabetes	16
HELLP syndrome	16
Placenta abruption	3
Preterm birth	64
Gestational age at birth (mean)	35.82
Type of labor	
Induced	93
Obstetric cholestasis	1
Fetal death	4
Preeclampsia	72
Severe preeclampsia	15
HELLP syndrome	1
Spontaneous	48
Mode of delivery	
Vaginal birth	68
Caesarean section	73
Severe preeclampsia/HELLP syndrome	20
Nonreassuring fetal tracing	18
Failed induction of labor	8
Arrested labor	12
Fetal malpresentation	7
Previous caesarean section	6
Fetal anomaly	2

Table 2: Baseline characteristics of women answering the questionnaire.

Baseline characteristics of women answering the questionnaire	
Age (mean)	25.46
Current body mass index (mean)	26.7
Contraception	
None	8
Barrier	10
Combined hormonal	29
Progestin-only pills	9
Subdermal implant	7
Vaginal ring	1
Intrauterine device	10
Female sterilization	4
Mean meals per day	4.7
Aerobic exercise before pregnancy	
None	41
Once per month	3
Once per week	7
Twice weekly	6
>twice weekly	21
Aerobic exercise after pregnancy	
None	54
Once per month	2
Once per week	6
Twice weekly	7
>twice weekly	9
Appointments with healthcare provider per year (mean)	2.44
Approach to preeclampsia by healthcare provider	
Yes	24
No	54
Blood pressure assessment	
Never	7
Once per year	26
Once per month	28
Once per week	17
Glycemia assessment	
Never	53
Once per year	19
Once per month	5
Once per week	1
Chronic hypertension after pregancy	10

Table 3: Association between preeclampsia severity and lifestyle modifications.

	Severe preeclampsia		
	Yes	No	
BMI postpregnancy	25.2	26.4	$P = 0.323$
Aerobic exercise after pregnancy			$P = 0.837$
(i) Increased	3	3	
(ii) Decreased	9	18	
(iii) Did not change	14	31	
Weight variation-Kg (%)			$P = 0.541$
(i) > −10	3 (12.5)	4 (7.8)	
(ii) −10 to −6	1 (4.2)	2 (3.9)	
(iii) −5 to 0	10 (41.7)	19 (37.3)	
(iv) 1 to 5	4 (16.7)	19 (37.3)	
(v) 6 to 10	4 (16.7)	4 (7.8)	
(vi) >10	2 (8.3)	3 (5.9)	

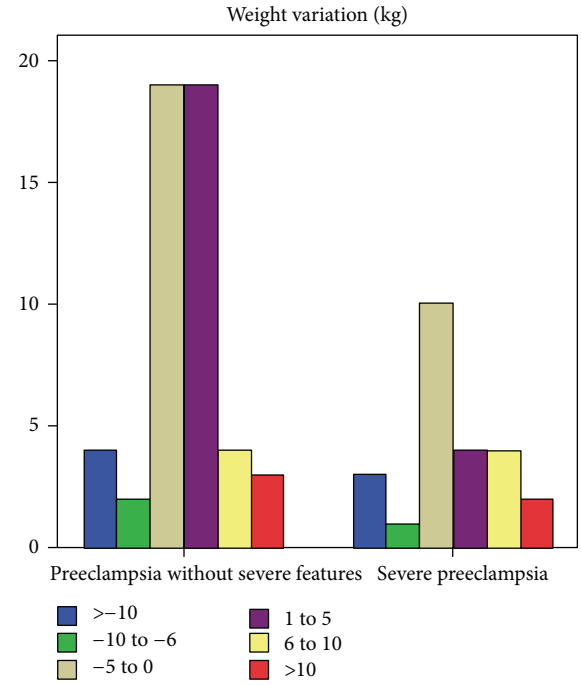

Figure 1: Weight variation distribution in women with preeclampsia without severe features and with severe preeclampsia.

day per patient was 4.74, ranging from 2 (1 woman) to 8 (3 women). Thirty-four women claimed a healthy change in diet, mostly salt intake reduction (considering less relevant the need for other adjustments) by their own initiative (only 11 had nutritional counselling).

Regarding aerobic exercise, only 6 women reported having increased the frequency of aerobic exercise practice comparing to before pregnancy, while 45 did not alter the frequency of exercise after having a pregnancy complicated by preeclampsia. Consistently, women affirmed that they knew about the importance of regular exercise practice but they did not change their habits. Only 28% of our cases were doing aerobic exercise at least weekly, with 9 women reporting exercise more than twice a week (whereas 21 were engaged in exercise with this frequency before the case index). Fifty-four women stated not doing any exercise at all. Regarding the frequency of aerobic exercise practice, no significant statistical difference was found between women with severe preeclampsia and those without severe features.

Lastly, women reported having a mean of 2.44 appointments per year with their basic healthcare provider, ranging from 0 (8 women) to 10 (5 women), with the majority (33) having one appointment per year. Furthermore, 24 women stated that their basic healthcare provider had addressed the item preeclampsia and future cardiovascular risks implied. The majority of women feared the possibility of developing chronic hypertension, with 45 women assessing their blood pressure at least every month (10 women remained hypertensive after pregnancy).

Most women did not find it important to assess the fasting blood glucose, with 53 women not doing it once a year. Not surprisingly, women with previous gestational diabetes were more sensitized to this issue, with 71% assessing fasting blood glucose at least once a year against 28% with preeclampsia and without gestational diabetes.

4. Discussion

Cardiovascular disease (CVD) is the leading cause of death in women in all developed countries [19]. Despite being more frequent in male, the disease in women is now looked at differently all over the world. In 2007, CVD caused one death per minute among women in the United States [22]. In Portugal, during 2010, the mortality rate attributable to CVD in women was 342,7/100 000, making it the leading cause of death in this gender [23]. Pregnancy is being regarded as a cardiovascular risk "stress test" and so more emphasis is being paid to past obstetric history. It is now quite established that a hypertensive disorder occurring during pregnancy, particularly preeclampsia, identifies a subset of women with increased risk of developing CVD. A recent large meta-analysis found that women with a history of preeclampsia have an increased risk for subsequent ischemic heart disease, stroke, and venous thromboembolic events over 5 to 15 years after pregnancy [24]. Risk factors for preeclampsia, resembling those for atherosclerosis, are increasing in prevalence, stressing its importance as a future CVD predictor. This is highlighted in the 2011 update of the American Heart Association "effectiveness-based guidelines for the prevention of cardiovascular disease in women," with preeclampsia being classified as a major risk factor for future CVD [20]. The European Society of Cardiology also states the importance of a pregnancy complicated by preeclampsia as a risk factor, recommending annual vigilance of blood pressure and metabolic factors as well as lifestyle modifications. The Portuguese Society of Cardiology has introduced these recommendations in practice guidelines in 2011 [25, 26]. The American College of Obstetricians and Gynecologists recommends a yearly assessment of blood pressure, lipids, fasting blood glucose, and body mass index after having a preeclampsia [2].

An aim of this study was to highlight the value of lifestyle modifications and to encourage clinicians to consider cardiovascular risk assessment in women with a previous preeclampsia. Awareness of a history of preeclampsia might allow the identification of cases not previously recognized as at-risk for CVD, allowing the implementation of measures to prevent the occurrence of these events. Our population did not appear sensitized to adopt a healthier lifestyle, as shown by a slight increase on their mean BMI with a decrease in the practice of aerobic exercise. Also, their diet was similar as before pregnancy, and when a change on the diet was reported, the only modification was a reduction in salt intake without any professional counselling. Besides the reduction in salt intake, based on the dietary approaches to stop hypertension (DASH diet) introduced in 1998, the ACOG advocates a diet rich in fibers, vegetables, and fruits and low in fat [2, 27]. We believe that professional counselling may improve the adhesion to a healthier diet, reducing patient's cardiovascular risk.

The majority of our patients are not engaged in regular exercise, with a great number of them stating a decrease in the practice of regular physical exercise. From the 21 women engaged in regular aerobic exercise (more than twice per week) before pregnancy only 6 remained practicing exercise with the same regularity after having a preeclampsia. This probably reflects a trend towards a sedentary lifestyle in the Portuguese women. The implementation of strategies to increase the time spent doing exercise seems crucial to improve health and quality of life of these women, reducing the burden imposed by this disease.

In Portugal, regular medical follow-up is provided by general practitioners, including the great majority of women during and after pregnancy. From our study we can assume that the majority of general practitioners (70%) do not take into consideration the preeclampsia issue, probably meaning that they are not aware of the future implications of preeclampsia in CVD, and are not taking into consideration previous obstetric history when assessing cardiovascular risk profiles. Furthermore, the association between preeclampsia and future development of diabetes is seriously undervalued, both by general practitioners and by patients, as shown by the number of women not making any fasting blood glucose assessment after pregnancy. On the other hand, women are more conscious of the future risk of developing hypertension, with 17 women assessing blood pressure once a week. This probably reflects an association established on an individual basis, reflecting the more straightforward connection between preeclampsia and hypertension.

Much has to be done in order to improve the follow-up of these patients. As a beginning step, in our institution we implemented a specialized postpartum appointment for all women with a pregnancy complicated by a hypertensive disorder with the aim of explaining the risks for a future pregnancy, the lifestyle modifications, and the surveillance that should be implemented in order to reduce the risk of future CVD.

To our knowledge there is not much information in our country regarding the follow-up of women with a history of a pregnancy complicated by preeclampsia. Although the results were basically what we expected, our study proves that much has to be done in order to guarantee the ideal monitoring of these patients. We found satisfactory the overall participation rate of 65%, chiefly because every woman answering the phone call accepted to participate in our study.

Some limitations of the study should be addressed. Above all, the small number of years of follow-up (mean time from preeclampsia diagnosis was 2.02 years) prevents us from

evaluating long term outcomes for these women. The implications for the future cardiovascular profile are long term rather than short term, precluding us from taking strong inferences regarding future risk for these patients. However, lifestyle modifications and adequate follow-up by general practitioners should be initiated right away in order to prevent CVD, supporting our conclusions. Also, although prepregnancy weight and height were obtained from birth certificates with reliable information, after pregnancy weight was obtained by a telephone call, this information may have suffered from some bias, as estimates of obesity prevalence based on self-reported weight tend to be lower than those based on measured weight. Therefore, if we underestimated the rate of obesity, we have also underestimated our conclusions; the same goes for aerobic exercise. Another limitation of our study regarding its retrospective nature is that we might have missed some diagnosis, especially due to coding errors, but, most likely, no cases of severe preeclampsia, with a major impact on future CVD, were missed.

5. Conclusion

CVD is the leading cause of women mortality. Considering preeclampsia as a risk factor for CVD it is of uppermost importance to take it into consideration when assessing for cardiovascular risk in women. It is also important for these women to adopt a healthier lifestyle, including a balanced diet, more regular exercise, and losing weight as mainstays for preventing future cardiovascular events. With this study we demonstrate that most of our patients previously affected by preeclampsia are not aware of the risks for their future life. Although most of them are aware of the probability of developing hypertension, they are not inclined to change their lifestyle. As a consequence, the majority of our cases have failed to change their routines and in some cases they have even implemented a worse lifestyle. It is imperative to pay more attention to these women in order to provide the best assessment according to the currently considered ideal standards. This study aims to highlight the value of lifestyle modifications and to encourage clinicians to consider cardiovascular risk assessment and active management in women with a previous preeclampsia.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

First Trimester Aneuploidy Screening Program for Preeclampsia Prediction in a Portuguese Obstetric Population

Cláudia Teixeira,[1,2,3] Eduardo Tejera,[3] Helena Martins,[1] António Tomé Pereira,[4] Altamiro Costa-Pereira,[2,5] and Irene Rebelo[3,6]

[1] *Department of Pathology, Porto Hospital Center, 4099-001 Porto, Portugal*
[2] *Department of Health Information and Decision Sciences (CIDES), Faculty of Medicine, University of Porto, 4200-450 Porto, Portugal*
[3] *Institute for Molecular and Cell Biology (IBMC), University of Porto, 4150-180 Porto, Portugal*
[4] *Department of Women, Porto Hospital Center, 4099-001 Porto, Portugal*
[5] *Center for Research in Health Technologies and Information Systems (CINTESIS), Faculty of Medicine, University of Porto, 4200-450 Porto, Portugal*
[6] *Department of Biochemistry, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal*

Correspondence should be addressed to Cláudia Teixeira; claudiateixeira@med.up.pt

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Objective. To evaluate the performance of a first trimester aneuploidy screening program for preeclampsia (PE) prediction in a Portuguese obstetric population, when performed under routine clinical conditions. *Materials and Methods*. Retrospective cohort study of 5672 pregnant women who underwent routine first trimester aneuploidy screening in a Portuguese university hospital from January 2009 to June 2013. Logistic regression-based predictive models were developed for prediction of PE based on maternal characteristics, crown-rump length (CRL), nuchal translucency thickness (NT), and maternal serum levels of pregnancy-associated plasma protein-A (PAPP-A) and free beta-subunit of human chorionic gonadotropin (free β-hCG). *Results*. At a false-positive rate of 5/10%, the detection rate for early-onset (EO-PE) and late-onset (LO-PE) PE was 31.4/45.7% and 29.5/35.2%, respectively. Although both forms of PE were associated with decreased PAPP-A, logistic regression analysis revealed significant contributions from maternal factors, free β-hCG, CRL, and NT, but not PAPP-A, for prediction of PE. *Conclusion*. Our findings support that both clinical forms of EO-PE and LO-PE can be predicted using a combination of maternal history and biomarkers assessed at first trimester aneuploidy screening. However, detection rates were modest, suggesting that models need to be improved with additional markers not included in the current aneuploidy screening programs.

1. Introduction

Preeclampsia (PE) is a prevalent clinical entity in pregnancy, which is responsible for substantial maternal-fetal morbidity and mortality [1–4]. Prediction of PE could offer a window of opportunity for intervention during pregnancy, making it potentially possible to prevent adverse obstetric and neonatal outcomes.

In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) has delivered clinical guidelines recommending the evaluation of maternal risk factors for PE at the first prenatal visit for all pregnant women [5]. However, screening for PE based only on maternal history has shown to be insufficient [6].

In this context, measurement in early pregnancy of a variety of markers implicated in the pathophysiology of PE has been proposed to predict its development. These included tests for aneuploidy screening, renal and endothelial dysfunction, oxidative stress, and fetal-derived products [7]. Because any single biomarker is unlikely to be effective in prediction of the onset of a disorder as heterogeneous as PE, it is under investigation which combinations of tests, such as ultrasound and serum markers, would raise the effectiveness of history and physical-based screening [7].

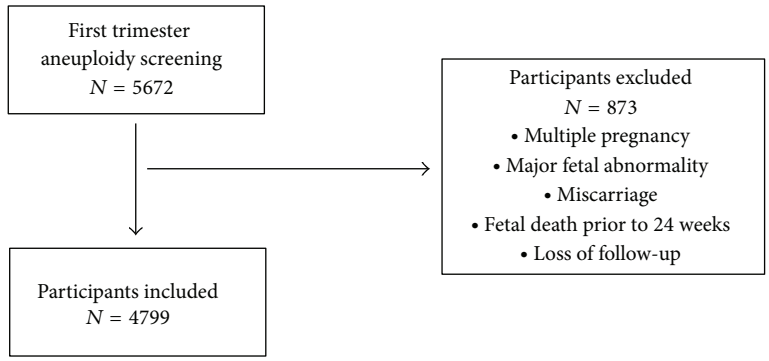

Figure 1: Flow chart of the study population.

The accuracy of models for PE prediction, either maternal history-based or combined with biomarkers, is unknown in the Portuguese population. Therefore, we aim to evaluate the performance of a first trimester aneuploidy screening program for preeclampsia prediction in a Portuguese obstetric population, when performed under routine clinical conditions.

2. Materials and Methods

2.1. Design, Setting, and Participants. This is a retrospective cohort study of 5672 pregnant women who underwent routine first trimester aneuploidy screening in a Portuguese university hospital (Centro Hospitalar do Porto) from January 2009 to June 2013. All singleton pregnancies between 9 weeks and 0 days and 13 weeks and 6 days of gestation were considered for inclusion in the study. Cases of multiple pregnancy, major fetal chromosomal or structural abnormalities, miscarriage, fetal death prior to 24 weeks, or loss of follow-up were excluded ($n = 873$) (Figure 1). All participants were followed from first trimester combined aneuploidy screening until delivery. The study protocol has been approved by the local ethics committee and institutional review boards.

2.2. Maternal Evaluation. Combined screening for aneuploidies was performed between 9 weeks and 0 days and 13 weeks and 6 days of gestation ($n = 4799$). Participants were asked to provide information on age, ethnicity, method of conception, weight, smoking status, chronic conditions, parity and previous pregnancy complications. Blood samples were collected and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free beta-subunit of human chorionic gonadotropin (free β-hCG) were measured using routine automated analyzers. During the study period, the analytical platform used by the clinical chemistry laboratory for measuring these biochemical markers was changed from IMMULITE 2000 system ($n = 1634$) to DELFIA XPRESS analyzer ($n = 3165$); this event was taken into consideration in the statistical analysis of data. An ultrasound examination was performed between 11 weeks and 0 days and 13 weeks and 6 days of gestation, including the measurement of crown-rump length (CRL) and nuchal translucency thickness (NT); gestational age was estimated on the basis of CRL measurements. These clinical data were systematically collected into an integrated electronic form in order to perform combined first trimester risk assessment.

2.3. Outcome Measures. Data on pregnancy outcome were collected from maternal and pediatric records. PE cases were defined by the new onset of hypertension (>140/90 mmHg) developed after 20 weeks of gestation in a woman with previously normal blood pressure, associated by coexisting significant proteinuria, according to the definition of the American College of Obstetricians and Gynecologists (ACOG) [3]. Chronic hypertension cases were defined as known high blood pressure before conception or new onset of hypertension before 20 weeks of gestation [3]. In the cases in which PE was superimposed on chronic hypertension, there was significant proteinuria development after 20 weeks of gestation in women with known chronic hypertension [3]. Cases of new onset of hypertension after 20 weeks of gestation in the absence of accompanying proteinuria were considered as gestational hypertension [3]. These outcome diagnoses were made by the treating physician and registered in maternal records at hospital discharge. Preeclampsia cases were classified as early-onset (EO-PE) or late-onset (LO-PE), depending on when findings first become apparent, before or after 34 weeks of gestation. We also included obstetric and neonatal outcomes in our analysis, such as gestational age at delivery, delivery by cesarean section, stillbirth occurrence, and birth weight. The adopted definition of low birth weight (LBW) was birth weight below 2500 grams.

2.4. Statistical Analysis. A descriptive analysis of maternal characteristics was conducted, separating the unaffected group from the women affected by preeclampsia according to their PE status, as described in the previous section. The maternal weight, PAPP-A, and β-hCG were expressed as multiples of the median (MoM) and log transformed for logistic regression analysis. Considering that two distinct analytical platforms were used for PAPP-A and β-hCG measurement, we adjusted these differences by performing the MoM transformation with the median values of the samples of both assays. The MoM values distribution obtained by

this procedure were not statistically different when compared by analytical method using ANOVA analysis. We performed Mann-Whitney U Test and Pearson χ^2 for single categorical and quantitative variables analysis across groups. Moreover, the Kruskal-Wallis test was also used to compare the quantitative variables across multiples groups with subsequent pairwise analysis.

ROC (Receiver Operating Characteristic) analysis was performed to evaluate models performances and estimate predictive values, which were presented as the estimated detection rate (DR) at fixed false-positive rate (FPR) of 5% and 10%. All the binomial logistic models were obtained using stepwise backward algorithm for variable selection and a P-value cutoff of 0.05. We also presented the Nagelkerke R^2 for each model.

The statistical software package SPSS 21.0 [8] was used for data analyses.

3. Results and Discussion

3.1. Results. First trimester aneuploidy screening was carried out in 5672 pregnant women between January 2009 and June 2013. We excluded 873 cases because of missing outcome data ($n = 715$) or pregnancies resulting in miscarriage, fetal death prior to 24 weeks, or major fetal chromosomal or structural abnormalities ($n = 158$).

In the remaining 4799 cases, 140 developed PE (2.9%) and 4659 were pregnancies unaffected by PE. In the PE group, 35 (25%) developed early-onset PE and 105 (75%) developed late-onset PE. Biomarkers included in first trimester combined aneuploidy screening were available in all cases. A descriptive analysis of maternal characteristics, aneuploidy screening biomarkers results, and pregnancy outcomes is presented in Table 1.

In the PE group, compared to unaffected pregnancies, there was a higher median maternal age and weight as well as a higher prevalence of nulliparous women and history of chronic hypertension or diabetes mellitus. There were no significant differences in maternal ethnic origin, smoking habits, type of conception and infant gender between groups. In both the EO-PE and LO-PE groups PAPP-A were lower compared to unaffected pregnancies; there were no significant differences in free β-hCG, CRL, and NT. Median gestational age at delivery was lower in PE group compared to unaffected pregnancies and in EO-PE group compared to LO-PE group. Delivery by cesarean section was carried out in 70.5% of PE cases compared to 34.1% in pregnancies unaffected by PE. There was a lower median birth weight in PE group compared to unaffected pregnancies and in EO-PE group compared to LO-PE group, as well as a higher prevalence of LBW.

Although EO-PE and LO-PE were associated with decreased PAPP-A (0.93 MoM and 0.85 MoM), logistic regression analysis demonstrated that there were significant contributions from maternal factors, free β-hCG, CRL and NT, but not PAPP-A, for prediction of PE (Table 2). The R^2 values obtained were 10.0%, 9.4%, and 10.3% for PE, EO-PE and LO-PE, respectively. As expected, maternal history of PE, chronic hypertension, or diabetes mellitus contributed to the increase of the risk of PE, even when the last was not found significant for early expression of the disease. Similarly, higher maternal age and weight as well as nulliparous condition were also significant risk factors for PE.

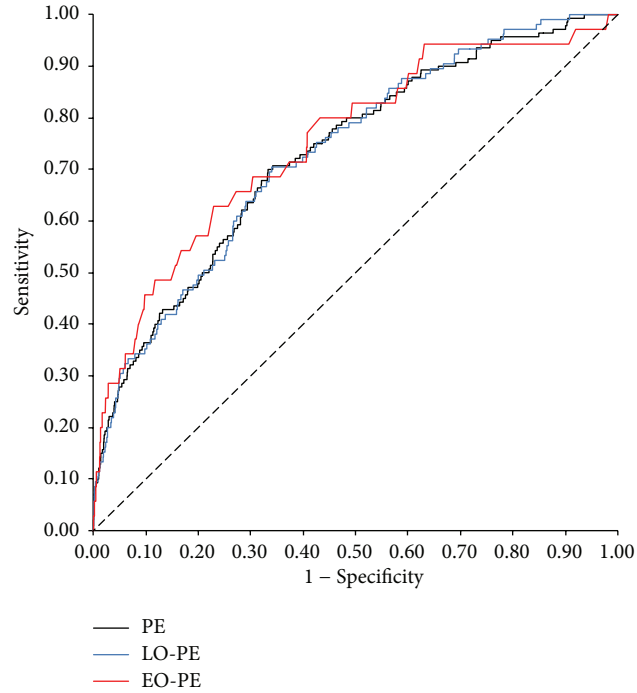

Figure 2: ROC curves of logistic regression models for prediction of PE, EO-PE, and LO-PE by maternal characteristics and aneuploidy screening biomarkers. PE, preeclampsia; EO-PE, early-onset preeclampsia; LO-PE, late-onset preeclampsia.

Our logistic regression models for PE prediction estimate that 27.9%, 31.4%, and 29.5% of PE, EO-PE, and LO-PE cases, respectively, could be detected with a 5% false-positive rate (Table 3). The model for EO-PE prediction presented the best performance (Figure 2), with detection rates of 31.4% and 45.7% at false-positive rates of 5% and 10%.

A univariate analysis of PAPP-A and free β-hCG according to fetal weight at delivery shows lower median PAPP-A in LBW group but no significant differences of free β-hCG (Figure 3). Moreover, when we considered a logistic regression model for LBW, including all the previous variables, the final obtained model is 1.886 − 1.013 (if chronic hypertension) + 0.658 (if caucasian) − 0.570 (if smoker) + 0.196 (if multiparous) + 1.155 ∗ PAPP-A (MoM, Log) + 3.381 ∗ Maternal Weight (MoM, Log). This suggests that, unlike in PE prediction models, PAPP-A is related to LBW when other variables are included in a logistic regression model.

3.2. Discussion. Our cohort study of 4799 pregnant women who underwent routine first trimester aneuploidy screening in a Portuguese university hospital found a prevalence of PE of 2.9%, which is consistent with the reported epidemiologic data available in the literature [1–4, 9–11].

Table 1: Demographic characteristics of the study population.

Variable	Unaffected pregnancy (n = 4659)	PE (n = 140)	EO-PE (n = 35)	LO-PE (n = 105)
Maternal age, years, median (IQR)*[a]	29.9 (25.8–33.0)	31.0 (27.7–33.6)	30.0 (25.0–34.9)	31.0 (28.0–33.0)
Maternal weight, median (IQR)				
Kg*[a]	63.5 (57.0–72.0)	70.0 (60.9–82)	73.0 (64.5–82.0)	69.3 (60.6–83.4)
MoM*[a]	0.99 (0.89–1.13)	1.10 (0.95–1.28)	1.14 (1.01–1.28)	1.07 (0.94–1.30)
Ethnicity, n (%)				
White	4529 (97.2)	138 (98.6)	34 (97.1)	104 (99.0)
Black	82 (1.8)	1 (0.7)	1 (2.9)	0 (0.0)
Other	48 (1.0)	1 (0.7)	0 (0.0)	1 (1.0)
Nulliparous, n (%)[b]	2843 (61.0)	98 (70.0)	27 (77.1)	71 (67.6)
Medical history, n (%)				
Chronic hypertension[b]	104 (2.2)	12 (8.6)	5 (14.3)	7 (6.7)
Renal disease	5 (0.1)	1 (0.7)	1 (2.9)	0 (0.0)
Diabetes mellitus[b]	47 (1.0)	9 (6.4)	1 (2.9)	8 (7.6)
Smoking during pregnancy, n (%)	975 (20.9)	21 (15.0)	6 (17.1)	15 (14.3)
Spontaneous conception, n (%)	4486 (96.3)	130 (92.9)	33 (94.3)	97 (92.4)
Ultrasound markers, median (IQR)				
CRL, mm	62.9 (56–70)	64.5 (58–70)	63.2 (56–68.9)	65.0 (59–70.5)
NT, mm	1.5 (1.2–1.8)	1.5 (1.2–1.8)	1.5 (1.2–1.9)	1.5 (1.1–1.8)
Maternal serum, median (IQR)				
PAPP-A, MoM*[a]	1.01 (0.63–1.60)	0.85 (0.56–1.35)	0.93 (0.33–1.39)	0.85 (0.58–1.33)
Free β-hCG, MoM	1.00 (0.66–1.54)	1.10 (0.66–1.64)	0.93 (0.53–1.38)	1.17 (0.70–1.76)
Obstetric outcomes				
Gestational hypertension, n (%)	57 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Cesarean section, n (%)[b]	1589 (34.1)	98 (70.5)	31 (88.6)	67 (64.4)
Gestational age at delivery, weeks, median (IQR)*[a]	39 (38–40)	37 (35–38)	34 (29–36)	37 (36–39)
Neonatal outcomes				
Male, n (%)	2367 (50.8)	67 (48.2)	19 (54.3)	48 (46.2)
Stillbirth, n (%)	14 (0.3)	2 (1.4)	2 (5.7)	0 (0.0)
Birth weight, g, median (IQR)*[a]	3165 (2873–3440)	2670 (2150–3055)	1910 (1050–2440)	2830 (2481–3158)
LBW, n (%)[b]	354 (7.6)	55 (39.6)	27 (77.1)	28 (26.9)

PE: preeclampsia; EO-PE: early-onset preeclampsia; LO-PE: late-onset preeclampsia; IQR: interquartile range; CRL: crown-rump length; NT: nuchal translucency thickness; β-hCG: beta-subunit of human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein-A; MoM: multiple of the median; LBW: low birth weight. Significant comparisons between unaffected pregnancies and preeclampsia cases ($P < 0.05$) using: *Mann-Whitney U test, [a]Kruskal-Wallis test, and [b]Pearson χ^2.

Our study provides evidence that both clinical forms of EO-PE and LO-PE can be predicted using a combination of maternal history and biomarkers assessed at first trimester aneuploidy screening, in agreement with previous publications [9–15]. As expected, regression models applied for prediction of the two forms of PE differed regarding which variables were included and performance achieved for each clinical form. However, these detection rates were modest, suggesting that models need to be improved with new information.

At false-positive rates of 5% and 10%, the detection rates for EO-PE were 31.4% and 45.7%, respectively, which are close to similar reported models [10, 12, 15]. Though EO-PE prediction presented a better performance compared to LO-PE, we must notice that its regression model only includes maternal clinical data, excluding biochemical and ultrasound markers. On the other hand, for LO-PE and overall PE prediction, logistic regression analysis revealed significant contributions from maternal factors, free β-hCG, CRL, and NT, but not from PAPP-A.

Although EO-PE and LO-PE were associated with decreased PAPP-A in the univariate analysis, this biomarker was not included in any of the logistic models for PE prediction. This could mean that the inclusion of PAPP-A in the models did not add further significant information to the one already provided by the others variables combined, hence the potential added value of PAPP-A measurement could be virtually negligible when used in combination with other biomarkers. These results suggest that a combination of free β-hCG, NT, and CRL could be more useful in PE prediction

Table 2: Logistic regression models for prediction of PE, EO-PE and LO-PE by maternal characteristics and aneuploidy screening biomarkers.

Variable	PE		EO-PE		LO-PE	
	B	*P*-value	*B*	*P*-value	*B*	*P*-value
Chronic hypertension [if true]	0.870	0.014	1.519	0.004	0.050	0.012
Diabetes mellitus [if true]	1.428	0.000			1.649	0.000
Parity [if multiparous]	−0.787	0.000	−1.201	0.008	−0.623	0.008
History of PE [if true]	3.952	0.000	3.201	0.001	3.668	0.000
Maternal age	0.039	0.026				
Maternal weight (MoM, log)	6.159	0.000	7.108	0.000	5.834	0.000
CRL	0.027	0.010			0.036	0.003
NT	−0.483	0.036			−0.592	0.026
Free β-hCG (MoM, log)	0.766	0.018			1.046	0.004
Constant	−5.723	0.000	−4.951	0.000	−8.248	0.000

Note: Missing values or any variable not included in the table indicate that those variables were not selected for the final regression models by absence of statistical significance. PE: preeclampsia; EO-PE: early-onset preeclampsia; LO-PE: late-onset preeclampsia.

Table 3: Detection rates and ROC results of logistic regression models for prediction of PE, EO-PE, and LO-PE by maternal characteristics and aneuploidy screening biomarkers.

Variable	ROC AUC	DR (FPR = 5%)	DR (FPR = 10%)
PE	0.732	27.9	36.4
EO-PE	0.754	31.4	45.7
LO-PE	0.734	29.5	35.2

PE: preeclampsia; EO-PE: early-onset preeclampsia; LO-PE: late-onset preeclampsia; AUC: area under the curve; DR: detection rate; FPR: false-positive rate.

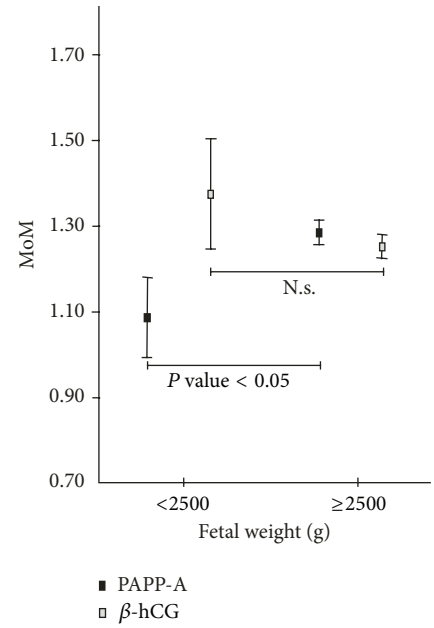

Figure 3: Variation of PAPP-A and β-hCG according to fetal weight at delivery (LBW).

than PAPP-A alone. Our findings are supported by other studies [11, 16, 17] that also found a significant association between PE and PAPP-A that lost its significance when combined with others biomarkers and therefore did not contribute to PE prediction. Moreover, PAPP-A was significantly related to LBW, unlike free β-hCG, NT, and CRL; previous publications have shown inconsistent results regarding the association of birth weight with these biomarkers, as some studies reported a significant correlation [18, 19] and others did not [14, 20, 21].

Our study presents some limitations related to its retrospective nature. First, serum measurement of PAPP-A and β-hCG was not performed by the same assay method for all participants due to change of the analytical platform used by the clinical chemistry laboratory during the study period; however, this event was taken into consideration in the statistical analysis of data. Additionally, although several studies [9–11, 15] have shown that mean arterial pressure (MAP) is an important predictive variable for PE, data on maternal arterial pressure at first trimester screening were not available in clinical records. Furthermore, diagnosis of PE cases was made by the treating physician, which could constitute a potential source of bias. Nevertheless, it is the first study of its kind conducted under routine clinical conditions in a Portuguese obstetric population, reflecting the reality of nearly five years of performing a first trimester prenatal screening program.

As the traditional approach for PE screening based only on maternal demographic characteristics and medical history has shown to be insufficient [6], it is under investigation which combinations of markers would improve the performance of history-based screening. Ideal markers for PE screening should be easily measured and integrated within routine testing currently used as a part of prenatal screening. Furthermore, it would be helpful to integrate PE screening into existing analytical platforms to reduce costs, equipment, and human resources. Moreover, those markers should predict the risk in the first trimester of pregnancy, thus creating a wide window of opportunity to implement preventive or prophylactic treatment strategies which may facilitate normal placental development [22]. In this

regard, biomarkers measured concurrently with testing for aneuploidies meet these requirements.

This study was conducted in a large unselected population under routine clinical care conditions, which supports the idea that screening for PE is feasible in obstetric populations with low *a priori* risk. However, our results suggest that the single inclusion of biomarkers currently used for aneuploidy screening in the prediction models for PE cannot achieve satisfactory detection rates and predictive values. Nevertheless, first trimester combined aneuploidy screening could be improved by inclusion of other biomarkers implicated in the pathophysiology of PE. Recent evidence suggests that serum placental growth factor (PlGF) and uterine artery pulsatility index (UtA Doppler) can be successfully included in preeclampsia prediction models with promising results [9–13, 15]. Although those results may be encouraging, it is difficult to achieve generalizable conclusions and standardized cut-points at specific gestational ages due to divergent study designs, population characteristics, and statistical approaches. Therefore, performance of PE screening should be validated in further large prospective studies.

Although the performance of such approach in Portuguese population is unknown, we believe that screening for PE could be successfully incorporated into routine prenatal care for assessment of patient-specific risk for PE and therefore offer a window of opportunity for intervention in early pregnancy.

4. Conclusion

Our findings support that both clinical forms of EO-PE and LO-PE can be predicted using a combination of maternal history and biomarkers assessed at first trimester aneuploidy screening. However, detection rates were modest, suggesting that the models need to be improved with additional markers not included in current aneuploidy screening programs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Contemporary Clinical Management of the Cerebral Complications of Preeclampsia

Stefan C. Kane,[1,2] Alicia Dennis,[3,4] Fabricio da Silva Costa,[1,2,5] Louise Kornman,[2,6] and Shaun Brennecke[1,2]

[1] *Department of Perinatal Medicine, The Royal Women's Hospital, Cnr Grattan Street and Flemington Road, Parkville, VIC 3052, Australia*
[2] *Department of Obstetrics and Gynaecology, The University of Melbourne, Parkville, VIC 3010, Australia*
[3] *Department of Anaesthetics, The Royal Women's Hospital, Cnr Grattan Street and Flemington Road, Parkville, VIC 3052, Australia*
[4] *Department of Obstetrics and Gynaecology and Department of Pharmacology, The University of Melbourne, Parkville, VIC 3010, Australia*
[5] *Monash Ultrasound for Women, 15 Murray Street, Clayton, VIC 3170, Australia*
[6] *Ultrasound Department, The Royal Women's Hospital, Cnr Grattan Street and Flemington Road, Parkville, VIC 3052, Australia*

Correspondence should be addressed to Stefan C. Kane; stefan.kane@thewomens.org.au

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The neurological complications of preeclampsia and eclampsia are responsible for a major proportion of the morbidity and mortality arising from these conditions, for women and their infants alike. This paper outlines the evidence base for contemporary management principles pertaining to the neurological sequelae of preeclampsia, primarily from the maternal perspective, but with consideration of fetal and neonatal aspects as well. It concludes with a discussion regarding future directions in the management of this potentially lethal condition.

1. Scope of the Problem

Preeclampsia (new onset proteinuria and hypertension during pregnancy [1]) is the commonest serious medical disorder of human pregnancy, complicating around 3-4% of pregnancies worldwide [2, 3]. It remains a leading cause of maternal mortality, with 12% of such deaths being attributable to the sequelae of this condition [3], the majority of which occur in the developing world [4]. Even in developed countries, despite an apparent decline in its incidence in some regions [5], preeclampsia is responsible for a significant proportion of maternal deaths: between 2006 and 2008, its mortality rate was 0.83 per 100,000 maternities in the UK, accounting for 18% of direct maternal deaths [6]. Neurological events, such as eclampsia (the pathognomonic convulsive endpoint of preeclampsia) and intracranial haemorrhage, are some of the primary mechanisms by which preeclampsia exerts its fatal maternal influence [7], along with acute pulmonary oedema and hepatic rupture.

In addition to mortality, the maternal morbidity associated with preeclampsia is significant in both the short and long terms. Again, it is the neurological manifestations of this condition that result in a major proportion of this morbidity, including blindness, persistent neurological deficits secondary to stroke, and later cognitive impairment [8]. Effects on the offspring of preeclamptic mothers are no less significant. These infants are commonly born preterm and/or growth restricted, and those who do not succumb to the twofold-increased risk of neonatal mortality [9] are susceptible to long-term neurological disability, as well as cardiovascular and metabolic diseases in later life [10].

The pathogenesis of preeclampsia remains incompletely understood, but is thought to involve a maternal genetic predisposition [11] which leads to defective placentation

in early pregnancy, followed by a hyperinflammatory state resulting in widespread endothelial dysfunction [12]. The only curative treatment is delivery of the fetus and placenta [13]. Other current therapies are aimed at the prevention of maternal seizures and severe hypertension, thereby mitigating the effects of this disease without fundamentally altering its course. Trials of therapies that target the pathological processes underlying preeclampsia (e.g., statins [14] and melatonin [15]) are ongoing, with a view to improving neonatal outcome, primarily through prolongation of gestation and improved fetal growth, without unduly compromising maternal health. Similarly, research attention has been paid to identifying agents effective at preventing the development of preeclampsia [16]. Thus far, only aspirin [17] and calcium [18] have demonstrated this benefit, although many other potential agents are under active investigation. Furthermore, the improved prediction of those destined to develop preeclampsia, especially its early onset and severe forms, may lead to better clinical outcomes through the initiation of preventive therapies or enhanced surveillance [19]. Predictive testing strategies using various combinations of maternal factors, serum biomarkers, and ultrasonographic parameters have been studied in the first [20], second [21], and third trimesters [22], with encouraging results.

This paper provides an overview of management principles specific to the neurological complications of preeclampsia. Its focus is primarily on those affecting the woman with this condition, although fetal and neonatal considerations are also briefly addressed.

2. Headache/Visual Disturbance

Headache is a relatively common symptom in pregnancy, although its incidence is far greater among those with preeclampsia, with one case-control study having determined an odds ratio of 4.95 (95% CI 2.47–9.92) [23]. No single headache phenotype is typical in preeclampsia: throbbing pain, generalised pressure, or needle-/knife-like sensations have all been reported, although a common attribute is a generally poor response to nonopioid analgesics [24]. Headache is generally considered a premonitory symptom for eclampsia, although it is only present in 56% of patients who develop eclamptic seizures [25], and most preeclamptic patients with headache will not progress to eclampsia. Transcranial Doppler ultrasound studies of the middle cerebral artery in preeclamptic women have demonstrated a strong association between headache and abnormal cerebral perfusion pressure [26]. Adequate control of hypertension may lead to symptomatic improvement in such headaches, although this symptom is also a relatively common side effect of antihypertensive therapy, particularly nifedipine.

The visual disturbance associated with preeclampsia can also take many forms, including scotomata, photopsia, diplopia, blurry vision, and amaurosis fugax [27]. Such symptoms herald seizures in 23% of eclamptic patients [19] and may in part be related to retinal vasospasm [28] and cerebral autoregulatory dysfunction [27]. A wide range of pathologies has been associated with visual disturbance in preeclampsia (relating to different aspects of the visual pathway), including

(i) *cortical blindness*, which affects up to 15% of patients with eclampsia [29] and is thought to be related to the posterior reversible encephalopathy syndrome (see the following). It may rarely be the presenting feature of preeclampsia and generally resolves completely postpartum. Uncommon variants include Balint's syndrome (simultanagnosia, optic ataxia, and ocular apraxia), and Anton syndrome (visual anosognosia) [27];

(ii) *serous retinal detachment* which has been identified in 1–3% of patients with preeclampsia, although it is much more common following eclampsia [30]. It generally resolves spontaneously, with 75% of cases resolving within one week of ophthalmoscopic diagnosis;

(iii) the rare entities of *Purtscher-like retinopathy*, *central retinal vein occlusion*, and *retinal/vitreous haemorrhages*, which have only been associated with preeclampsia in case reports [27].

Assuming that preeclampsia is the cause of a patient's headache and/or visual disturbance, treatment of the former will usually result in resolution of the latter. Atypical presentations, persistent symptomatology, or focal neurological signs should prompt careful consideration of alternative diagnoses, both related to preeclampsia (e.g., intracerebral haemorrhage [31]) and unrelated (e.g., tumour). In these instances, a low threshold for performing neuroimaging and seeking specialist neurological and/or ophthalmological opinion is advisable.

3. Eclampsia

Eclampsia is the occurrence of tonic-clonic seizures in pregnancy or the puerperium that cannot be explained by another cause, such as epilepsy—the commonest reason for seizures in pregnant women. Eclamptic convulsions occur in around 2-3% of patients with preeclampsia [5, 32] and may be the presenting feature of this condition. Premonitory symptoms and signs—including headache, visual changes, hypertension, epigastric discomfort, and proteinuria—are present in up to four-fifths of subsequently eclamptic patients [19], although most patients with these features will not fit. Eclampsia remains difficult to predict, as evidenced by the relatively large numbers-needed-to-treat in trials of prophylactic therapy [33]. It remains a potentially lethal complication, with US data indicating a fatality rate of 71.6 per 10,000 cases [7].

3.1. Pathogenesis. The pathogenic mechanisms underlying eclamptic seizures remain to be elucidated, although endothelial dysfunction is likely to make a significant contribution [34]. Two theories have been proposed, based on different

hypotheses regarding the cerebrovascular response to systemic hypertension:

(i) cerebral "overregulation," leading to vasospasm, ischaemia, and intracellular (cytotoxic) oedema [35],

(ii) loss of cerebral autoregulation, leading to hyperperfusion, extracellular (vasogenic) oedema [36], and the posterior reversible encephalopathy syndrome (PRES) [34], also known as reversible posterior leukoencephalopathy syndrome (RPLS) [37].

PRES is not unique to either eclampsia or pregnancy and can occur in a wide range of hypertensive states. It is a clinico(neuro)radiological entity typified by the appearance of symmetrical lesions of vasogenic oedema, predominantly in the parietooccipital lobes [38]. Coexistent evidence of ischaemia/infarction has been reported, potentially as a result of vasoconstriction secondary to pressure from oedema [39]. The term PRES is perhaps a misnomer, given that the condition is not always reversible [40] and can affect any part of the brain.

Cerebral autoregulatory dysfunction in preeclampsia has been assessed using MRI [41] and transcranial Doppler ultrasound [26], generally of the middle cerebral artery. A recent cohort study utilised the latter to determine cerebral autoregulation among twenty women with untreated preeclampsia and twenty controls and found that, although the study group had a significantly reduced autoregulation index, there was no correlation between blood pressure or clinical features of disease and impaired cerebral autoregulation [42]. This potentially explains why predicting eclampsia remains challenging.

3.2. Prophylaxis. The Magpie (magnesium sulphate for prevention of eclampsia) trial [33] and subsequent meta-analyses [43] have confirmed the superiority of magnesium sulphate ($MgSO_4$) over other anticonvulsants in the prevention of eclampsia. Its use halves the rate of eclampsia overall, with a number-needed-to-treat of 63 for women with severe preeclampsia and 109 for those without [33]. Cost-benefit analyses would suggest that maximal utility is achieved through reserving $MgSO_4$ for cases of severe preeclampsia [44]. The number-needed-to-treat could only be reduced through better prediction of those destined for eclampsia, which remains an area for further research.

There is no agreement on the optimal dose, timeframe, or route of administration of $MgSO_4$, resulting in divergent local policies. The regimen used in the Magpie trial (4 g loading dose followed by 1 g per hour) has the advantage of not requiring assessment of serum magnesium levels, as the risk of toxicity is low and can be predicted by clinical examination [13]. Women with renal impairment do, however, require monitoring of serum levels, and the drug is contraindicated in those with myasthenia gravis. The general safety profile of $MgSO_4$ was confirmed in a recent integrative review of use of this agent in (pre)eclampsia, which found low rates of absent patellar reflexes (1.6%), respiratory depression (1.3%), and use of calcium gluconate to reverse the effect of $MgSO_4$ (<0.2%), with only one maternal death (in 9556 women) directly attributable to its use [45]. Magnesium sulphate can lower the baseline fetal heart rate and reduce variability on cardiotocography but does not seem to influence the fetal biophysical profile [46] and in fact has neuroprotective effects for the fetus as well.

The mechanism of action of $MgSO_4$ in preventing eclampsia is unclear. It may have a direct effect on the cerebrovasculature [47] or may elevate the seizure threshold through membrane stabilisation or other central effects [48]. Given the putative role of impaired cerebral autoregulation in the pathogenesis of eclampsia, it has been postulated that antihypertensive therapy (such as labetalol) could be an effective, more easily administered, and less costly alternative to $MgSO_4$ for seizure prophylaxis [49]. Support for this approach is derived from the observation that eclampsia remains a rare event in centres with high utilisation of antihypertensive therapy and minimal use of $MgSO_4$, and although pilot trial data were promising [50], adequately powered prospective studies designed to test this hypothesis have proven to be difficult to conduct in the post-Magpie era [51].

3.3. Treatment. Eclampsia is an obstetric and medical emergency that necessitates immediate involvement of a consultant-level multidisciplinary team, including obstetricians and obstetric anaesthetists [52], in addition to senior midwifery or obstetric nursing staff. Failure to provide this level of care has consistently been identified in maternal deaths associated with eclampsia [6], and it is inappropriate for more junior staff to make the complex clinical decisions this scenario demands.

The treating team's first priority is supportive care of the fitting woman, with a view to prevent injury and to maintain oxygenation through protection of the airway and application of oxygen by mask. Eclamptic seizures are usually self-limiting, generally lasting only one to two minutes. As with prophylaxis, $MgSO_4$ has a clearly established role in the treatment of eclamptic seizures and prevention of their recurrence, having been shown to be superior to both diazepam and phenytoin [53, 54]. Use of magnesium sulphate is associated with a significantly lower rate of recurrent seizures (RR 0.41; 95% CI 0.32–0.51) and lower rate of maternal death (RR 0.62; 95% CI 0.39–0.99) than is achieved with other anticonvulsants [55]. Again, a range of regimens for $MgSO_4$ exists: it is generally administered as a loading dose followed by an infusion and is continued for 24 hours postpartum or following the last seizure. Recurrent seizures can be treated with a further bolus of $MgSO_4$, necessitating careful attention to the possibility of toxicity. Seizures unresponsive to $MgSO_4$ can be treated with benzodiazepines (diazepam or lorazepam) or sodium amobarbital [56] and should raise the prospect of an alternative (or additional) causative pathology.

By definition, eclampsia represents a manifestation of severe preeclampsia, and so assessments of other potential complications of this multisystem disorder must be initiated after the seizure has ceased. Particular attention must be paid to the management of concomitant severe hypertension (see the following), which often (but not always) accompanies

eclampsia [57]. Haematological and biochemical tests for preeclampsia should be performed urgently, to establish baseline parameters and assess for disseminated intravascular coagulopathy (DIC), the presence of which requires specialist haematology input. Eclampsia may be complicated by acute pulmonary oedema, and so an in-dwelling catheter should be placed to permit strict fluid balance and pulse oximetry used to identify evolving hypoxaemia.

Fetal bradycardia is common during the eclamptic seizure, followed by a reactive tachycardia on cardiotocography. More concerning fetal heart rate patterns should prompt consideration of abruptio placentae, which occurs in 7–10% of cases [58]. Eclampsia is generally considered an indication for delivery, although this should only occur once the patient is stable, with an adequate airway and oxygenation, controlled seizures, stabilised blood pressure, and treatment of any coagulopathy initiated. These measures also allow for in-utero fetal resuscitation, thereby improving the condition of the infant at delivery. The mode of delivery need not necessarily be caesarean section but should be determined by gestation, cervical favourability, and maternal/fetal status. The risk of intra- and postpartum haemorrhage is increased, especially in the context of DIC or thrombocytopaenia and should be anticipated. Ergometrine and its derivatives should not be used for uterine atony in the patient with preeclampsia, as it can cause severe hypertension and intracranial haemorrhage [6].

Complicating all aspects of the management of eclampsia is morbid obesity, which is strongly associated with preeclampsia [59]. It is incumbent upon hospitals to ensure that clinical infrastructure is adequate for these patients, including bariatric beds and large blood pressure cuffs. Additionally, policies should be implemented that anticipate the potential complications faced by obese pregnant women, who often have difficult airways and intravenous access [60].

After delivery, high dependency care is indicated for all patients after eclampsia, with close monitoring of renal and respiratory function and appropriate referral for psychological support, given the increased risk of postnatal depression and associated psychopathology [61]. Postnatal patients who have been delivered in the context of severe preeclampsia or who have developed this complication after delivery, remain at risk of eclampsia, with 36% of initial eclamptic seizures occurring postpartum [25]. As such, these patients require close clinical observation in the early puerperium and should be treated with prophylactic $MgSO_4$ if features premonitory for eclampsia ensue [62]. Neuroimaging is only required for those with an atypical seizure pattern, recurrent seizures, prolonged coma, or focal neurological signs [34].

4. Intracranial Haemorrhage/Stroke

The incidence of both ischaemic and haemorrhagic strokes is increased in preeclampsia/eclampsia (OR 4.4, 95% CI 3.6–5.4) [63], with 36% of strokes in pregnancy occurring in women with this concomitant diagnosis [64]. Strokes in women with preeclampsia are more likely to be haemorrhagic [65], with 89% being classified thus in one series [66], and are often (but not always) associated with eclampsia. In addition to permanent neurological deficits, these episodes carry a significant risk of mortality: of the 19 maternal deaths in the UK between 2006 and 2008 attributable to preeclampsia, nine (47%) occurred as a result of intracerebral bleeds [6]. Outcomes of strokes sustained in pregnancy appear to be worse than those in nonpregnant patients, possibly reflecting physiological differences or variations in standards of care [67]. As with eclampsia, the pathogenic processes leading to stroke in preeclampsia are incompletely understood, but are likely to involve endothelial dysfunction and disturbance to cerebral autoregulation [64].

4.1. Prevention. The recognition and prompt treatment of severe hypertension in pregnancy remain the mainstay of preventing intracerebral haemorrhage [68]. Failure to provide this care is consistently implicated in otherwise potentially preventable maternal deaths in the context of preeclampsia [6]. Guidelines generally recommend immediate antihypertensive therapy for blood pressures consistently equal to or greater than a systolic of 160 mmHg and/or diastolic of 110 mmHg, equating to a mean arterial pressure (MAP) of around 130 mmHg [69–73]. However, a significant proportion (up to 25% in a US series) [66] of patients may sustain an intracerebral bleed at MAPs lower than 130 mmHg, and there is evolving evidence to suggest that rapidity of change in blood pressure [74], and the absolute level of systolic blood pressure, may be of greater clinical relevance. In light of this, the development of point-of-care tests for the improved identification of those at greatest risk of the neurological effects of hypertension may permit better targeted therapy than that which relies on sphygmomanometry alone.

A range of agents in a variety of preparations is available for the treatment of severe hypertension in pregnancy, including intravenous hydralazine and labetalol and oral labetalol and nifedipine. The Cochrane systematic review of their use in this context found insufficient evidence to recommend one over another, suggesting that choice of agent should be determined by clinician familiarity and side effect profile [75]. The review did, however, recommend against the use of high-dose diazoxide, ketanserin, and nimodipine, and found the antihypertensive effect of magnesium sulphate to be too modest to support its use for this purpose alone. Given regional variations in the availability of these products, local protocols that take these into consideration should be followed, with care taken to avoid "overshoot" hypotension that can lead to abruptio placentae and maternal and fetal compromise.

4.2. Diagnosis and Treatment. Strokes may present clinically with headache, altered consciousness, seizures, focal neurology, or visual disturbance [63]. As with eclampsia, a stroke is a clinical emergency. Management is optimised through the early involvement of a senior multidisciplinary team, including neurologists, neurosurgeons, and anaesthetists. The team approach is especially important in the context of the complicating factors of pregnancy and preeclampsia. The primary aims of treatment include preservation of brain tissue, avoidance of further complications (including aspiration and those of preeclampsia), control of blood pressure, and

long-term rehabilitation [58]. In the acute phase, the patient requires airway support with maintenance of respiration and positioning to avoid aortocaval compression. Urgent investigations are required to assess for DIC or thrombocytopaenia, which may have contributed to intracranial bleeding.

Where required, intravenous antihypertensive agents should be used to control severe hypertension, with a suggested blood pressure target of ≤160/110 [58]. This is in contrast to ischaemic strokes in the non-pregnant population, in which control of blood pressure is only indicated if severe (≥220/120) or if thrombolysis is to be considered (target ≤180/105) [76, 77]. Control of hypertension in patients with haemorrhagic stroke is necessary to minimise further bleeding, although this benefit must be balanced against the risk of cerebral ischaemia. Evidence for target blood pressure ranges is limited [78], and trials are ongoing in the non-pregnant population to determine optimal blood pressure management in this context [79]. Labetalol has been suggested as the first-line agent for hypertension accompanying stroke in preeclampsia [64], in the light of evidence that it lowers cerebral perfusion pressure without affecting cerebral perfusion [80]. A low threshold should be observed for commencing $MgSO_4$ for eclampsia prophylaxis.

Neuroimaging is indicated in all pregnant patients whose clinical condition is suggestive of a cerebrovascular event, with MRI preferred on account of its superior multiplanar resolution and soft-tissue contrast [34]. Such imaging should only be performed once the patient has been stabilised. The timing of delivery will be influenced by fetal condition, gestation and severity of the associated preeclampsia. Choice of mode of delivery requires detailed anaesthetic, neurological, and obstetric input to minimise maternal risk.

Evidence regarding specific treatment strategies for stroke in the context of preeclampsia is limited. Haemorrhagic strokes resulting from ruptured aneurysms or arteriovenous malformations are rare [81] but are amenable to neurosurgical intervention, as are extra-axial haemorrhages secondary to head trauma following eclampsia in the context of coagulopathy. Ischaemic cerebrovascular events are generally treated by anticoagulation, with limited data supporting the safety of thrombolysis in pregnancy [82], especially in the context of coexisting preeclampsia.

In the rehabilitative phase, despite clear evidence of benefit in the non-pregnant population [83], admission to a stroke unit is achieved for only a minority of those with strokes related to pregnancy [84]. Use of such resources may aid in closing the gap in outcomes between these groups.

5. Confounders

Pregnancy-related conditions that mimic aspects of preeclampsia may also present with neurological symptoms and signs [85]. For example, TTP-HUS (thrombotic thrombocytopaenic purpura—haemolytic uraemic syndrome) may present with confusion, headache, or seizures [86], and acute fatty liver of pregnancy (AFLP) can be associated with hepatic encephalopathy [87]. Differentiation of these pathologies—although potentially difficult—is important, as specific treatments may be indicated. TTP-HUS does not improve following delivery, whereas preeclampsia does, and hypoglycaemia in the context of deranged liver function tests is suggestive of AFLP.

6. Long-Term Maternal Outcomes

The risk of recurrence of preeclampsia in a subsequent pregnancy ranges from 11.5 to 65%, depending on preexisting maternal risk factors and the gestation of disease onset in the prior pregnancy [88]. Women with a history of eclampsia face a 2% overall risk of this complication returning in a subsequent pregnancy, with higher risks for those whose eclampsia was of early onset [89]. The risk of preeclampsia recurring can be reduced by optimising maternal weight and preexisting conditions such as chronic hypertension and diabetes, and commencing calcium supplementation and low-dose aspirin from early gestation in a subsequent pregnancy. Close antenatal surveillance is required for early identification of recurrent preeclampsia, in addition to those complications of which such women remain at risk even in the absence of preeclampsia, such as fetal growth restriction and preterm birth [88].

There is increasing evidence that previously preeclamptic women face increased lifetime risks of ill health, predominantly due to cardiovascular events and metabolic disease. Such women have a relative risk of overall mortality at 14.5 years of 1.49 (95% CI 1.05–2.14), a relative risk of stroke of 1.81 (95% CI 1.45–2.27) after 10.4 years [90], and double the risk of any cerebrovascular event [91]. Later neuroimaging of women with prior preeclampsia [92] and eclampsia [93] demonstrates a greater incidence and severity of cerebral white matter lesions, which have been associated with an increased risk of Alzheimer's disease, vascular dementia, cognitive impairment, and stroke [94]. It is not clear whether preeclampsia simply portends these events, which would have happened anyway, or whether it plays a role in their pathogenesis, although commonality of risk factors for preeclampsia and cardiovascular events (such as obesity, diabetes, and chronic hypertension) and evidence of a shared genetic predisposition [95] suggest a unified causal mechanism. Specific guidelines for the mitigation of these long-term risks in this population are yet to be established, although earlier adoption of proven preventive health strategies would seem reasonable in the meantime.

7. Fetal and Neonatal Considerations

As a disease mediated by the placenta, preeclampsia has a significant association with fetal growth restriction and confers a relative risk of 4.2 (95% CI 2.2–8) for delivery of a small-for-gestational-age infant [96]. Overall, up to 12% of fetal growth restriction arises in the context of this maternal diagnosis [97]. Preeclampsia also contributes significantly to rates of preterm birth [32], both spontaneous and iatrogenic on maternal and/or fetal grounds [98]. Growth restriction and prematurity are leading causes of perinatal mortality and morbidity, with neurological disability comprising much of the latter. Additionally, such infants are at increased risk of developing cardiovascular and metabolic disease in later life,

as evidenced by the increasing volume of epidemiological data [99] in support of the Barker hypothesis [100].

Given that preeclampsia is cured by delivery, the maternal benefit derived from prolonging such pregnancies is limited to facilitation of transfer to an appropriate care facility and an increased chance of successful induction of labour with advancing gestation. The primary rationale for the expectant management of preeclampsia is to improve neonatal outcomes, by allowing administration of corticosteroids for fetal lung development (if prior to 35 weeks) [101] and achieving greater maturity and growth. Such a policy is generally employed with mild preeclampsia [102], with a randomised trial reporting that delivery ≥37 weeks rather than expectant management beyond this gestation is associated with optimal maternal outcomes without increasing the risk of neonatal complications [103]. A trial to determine the optimal timing of delivery for women with mild preeclampsia between 34 and 37 weeks' gestation is ongoing [104].

Severe preeclampsia is generally regarded as an indication for delivery at any gestation above 34 weeks, although uncertainty remains regarding management at earlier gestations. The Cochrane review of interventionist versus expectant care for severe preeclampsia between 24 and 34 weeks' gestation identified lower rates of neonatal morbidity in pregnancies managed expectantly, although there were insufficient data from which conclusions can be drawn regarding perinatal mortality [105]. In contrast, a subsequent trial involving 264 patients with severe preeclampsia from eight tertiary centres in South America comparing expectant care with delivery following corticosteroid administration at gestations of 28 to 33 weeks found no neonatal or maternal benefit with prolongation of pregnancy, with increased rates of small-for-gestational-age infants and abruptio placentae in this group [106]. These disparate results may reflect variations in care between high and low resource settings [107].

The relationship between fetal exposure to preeclampsia and subsequent development of cerebral palsy is complex. Recent birth registry data from Norway indicate that exposure to preeclampsia is associated with an increased risk of cerebral palsy (OR 2.5, 95% CI 2.0–3.2), mediated through prematurity or being born small-for-gestational-age or both [108]. Among children born at term, preeclampsia is a risk factor for cerebral palsy only among small-for-gestational-age infants. Of note is that normally grown infants delivered before term in the setting of preeclampsia have lower rates of cerebral palsy than infants born prematurely for other reasons, such as intrauterine infection, although these rates are still greater than those for infants born at term [109]. This suggests that, in the absence of growth restriction, preeclampsia is less detrimental to (but not protective of) the fetal brain than other causes of preterm birth [110]. An additional consideration is the fetal neuroprotective effect of maternally administered magnesium sulphate, with early observational data suggesting potential benefit [111] having now been confirmed in a Cochrane review of randomised trials: preterm infants exposed to $MgSO_4$ prior to birth have a relative risk of cerebral palsy of 0.68 (95% CI 0.54–0.87), with 63 mothers requiring treatment to avert this outcome in one infant [112]. In light of this evidence, regional guidelines for the use of $MgSO_4$ in this context have been developed [113, 114], although further research is required to determine optimal dosage and gestational timeframes [115].

8. Future Directions

As this review demonstrates, the implications of preeclampsia can be wide ranging and significant, and much remains to be established about the optimal management of this condition. Research priorities in this area might include:

(i) improved delineation and prediction of the complications of preeclampsia in established disease, especially those of a neurological nature, allowing better targeted maternal therapies;

(ii) an expanded evidence base to support decisions regarding timing of delivery in the fetal interest in preterm preeclampsia; and

(iii) strategies to mitigate the long-term risks of cardiovascular and metabolic diseases in previously preeclamptic women.

Notwithstanding the need for further research, the consistent application of evidence-based management principles outlined in this paper—most of which are simple and relatively inexpensive—would reduce the burden of preeclampsia significantly. Energy expended in discovering new diagnostic and therapeutic strategies for this disease needs to be matched by systematic efforts toward ensuring that existing evidence is applied reliably by all involved in the care of preeclamptic women. Indeed, such an approach is the mainstay of exhortations to improve outcomes in preeclampsia, in both the developed [6] and the developing [116] world alike, and would have a substantial impact on this condition and its potentially devastating consequences—neurological and otherwise.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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