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Prediction of Preeclampsia by Uterine Artery Doppler at 20–24 Weeks' Gestation

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Key Words
Preeclampsia · Uterine artery Doppler · Second trimester · Pyramid of pregnancy care

Abstract
Objectives: To determine maternal characteristics affecting uterine artery pulsatility index (PI) in normal pregnancies at 20–24 weeks' gestation and examine in pregnancies with preeclampsia (PE) the relation between uterine artery PI multiple of the median (MoM) and severity of disease. ***Methods:*** Uterine artery PI was measured at 20–24 weeks in 50,490 singleton pregnancies, including 1,442 (2.9%) that developed PE. Uterine artery PI was expressed as MoM after adjustment for maternal characteristics and corrected for adverse pregnancy outcomes. In PE, the correlation between uterine artery PI MoM with gestational age at delivery and birth weight Z-score was determined. ***Results:*** In the normal group there were significant independent contributions to uterine artery PI from gestational age, racial origin and prior history of PE, and/or small for gestational age (SGA). In the PE group, there was an inverse significant association between uterine artery PI MoM and both gestational age at delivery and birth weight Z-score ($p < 0.0001$). Uterine artery PI was above the 95th percentile (1.509 MoM) in 72.7, 36.1 and 14.9% of cases of PE requiring delivery at <34, 34–37 and ≥38 weeks, respectively, and the percentages for PE with SGA were 80.2, 55.6 and 37.4%. ***Conclusions:*** In a normal pregnancy, uterine artery PI is affected by maternal characteristics, and in PE, uterine artery PI MoM is related to the severity of the disease.

Introduction

Preeclampsia (PE), which is a major cause of maternal and perinatal morbidity and mortality [1–3], is the consequence of impaired placentation manifested in increased impedance to flow in the uterine arteries in the first, second and third trimesters of pregnancy [1–11]. Several uterine artery Doppler studies have reported that in pregnancies that develop PE, especially in those requiring early delivery and in those associated with birth of small for gestational age (SGA) neonates, the pulsatility index (PI) is increased [7–11].

Most of the Doppler studies were carried out during the second trimester and the high-risk group was identi-

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fied by values in PI, or some other index of impedance to flow, above a certain cutoff. For example, in the largest study, which involved 30,639 singleton pregnancies examined at 22–24 weeks' gestation, the uterine artery PI of 1.58, which was the 95th percentile of the normal range, was used [9]. In our recent studies, however, we adopted an approach, widely used in biochemical screening, of expressing the measured PI as a multiple of the median (MoM) after adjustment for those maternal characteristics that influence the measurement in the normal outcome group. In normal pregnancies at 11–13 weeks' gestation, uterine artery PI decreases with gestational age, increases with maternal weight and is higher in women of Afro-Caribbean origin than in other racial groups [7]. At 30–33 weeks, uterine artery PI increases with maternal age and weight, decreases with height, and is higher in women of Afro-Caribbean racial origin than in other racial groups [10].

The objectives of this screening study were (1) to determine the maternal characteristics that affect uterine artery PI in normal pregnancies at 20–24 weeks' gestation, and (2) to examine in pregnancies with PE the relation between uterine artery PI MoM and the severity of the disease, defined by the gestational age at delivery and the presence of fetal growth restriction.

Methods

The study population consisted of singleton pregnancies undergoing a routine ultrasound examination at 20–24 weeks' gestation, which was preceded by combined screening for aneuploidies at 11–13 weeks' gestation between 2006 and 2013 at three hospitals in and around London (King's College Hospital, University College London Hospital, Medway Maritime Hospital in Kent) [12]. All women delivered alive or dead phenotypically normal babies at or after 24 weeks' gestation. Gestational age at screening was calculated from the measurement of the fetal crown-rump length at 11–13 weeks [13].

The scan included examination of the fetal anatomy and growth by transabdominal sonography and measurement of uterine artery PI by transvaginal sonography [8]. The scans were carried out by sonographers who had received the Certificate of Competence in Doppler of The Fetal Medicine Foundation (http://www.fetalmedicine.com). Women with a mean uterine artery PI greater than 1.6 were followed up with growth scans, blood pressure measurements and urinalysis for protein at 28, 32 and 36 weeks. Women with normal uterine artery Doppler received routine antenatal care.

We prospectively examined 53,160 singleton pregnancies. We excluded 2,670 (5.0%) pregnancies because they had missing outcome data (n = 2,269), there was a major fetal defect or aneuploidy (n = 304), the pregnancy resulted in miscarriage between 20 and 24 weeks' of gestation (n = 87) or the pregnancy was terminated for psychosocial reasons (n = 10). In the remaining 50,490 cases, there were 1,442 (2.9%) that developed PE, 1,437 (2.8%) with gestational hypertension, 2,595 (5.1%) that delivered SGA neonates (without hypertension in pregnancy), 2,629 (5.2%) that delivered large for gestational age neonates and 42,387 (83.0%) that were unaffected by these outcomes.

Maternal History and Characteristics

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or in vitro fertilisation), cigarette smoking during pregnancy (yes or no), history of chronic hypertension (yes or no), history of type 1 or 2 diabetes mellitus (yes or no), history of systemic lupus erythematosus or antiphospholipid syndrome (yes or no), family history of PE in the mother of the patient (yes or no) and obstetric history including parity (parous or nulliparous if no previous pregnancies at or after 24 weeks), previous pregnancy with PE (yes or no), previous pregnancy with SGA babies (yes or no), and interpregnancy interval (from the previous delivery or miscarriage to the estimated date of conception of the current pregnancy). The questionnaire was then reviewed by a doctor together with the patient. The maternal weight and height were recorded.

Outcome Measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or non-proteinuric gestational hypertension.

The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [14]. The systolic blood pressure should be 140 mm Hg or more and/or the diastolic blood pressure should be 90 mm Hg or more on at least two occasions 4 h apart developing after 20 weeks' gestation in previously normotensive women, and there should be proteinuria of 300 mg or more in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 weeks' gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

The neonatal birth weight was expressed as a Z-score (difference between observed and expected divided by fitted SD) and percentile corrected for gestational age of a reference range derived from our population [15]. The definitions of SGA and large for gestational age were birth weight below the 5th percentile and above the 95th percentile, respectively.

Statistical Analysis

Comparisons of maternal characteristics between the outcome groups were made using a χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. The distribution of the mean uterine artery PI was made gaussian after logarithmic transformation. Backward stepwise multiple regression analysis was used to determine which of the factors

Table 1. Characteristics in the study population

	Normal (n = 42,387)	PE (n = 1,442)	p
Maternal age, years	30.8 (26.2–34.6)	31.0 (26.2–35.6)	0.01
Maternal weight, kg	69.8 (63.0–79.6)	76.4 (67.2–90.0)	<0.0001
Maternal height, cm	164 (160–169)	163 (159–168)	<0.0001
Gestation at screening, weeks	22.3 (22.0–22.7)	22.3 (22.0–22.9)	0.202
Racial origin			
Caucasian	30,258 (71.4)	782 (54.2)	<0.0001
Afro-Caribbean	8,024 (18.9)	544 (37.7)	<0.0001
South Asian	1,978 (4.7)	60 (4.2)	0.405
East Asian	1,062 (2.5)	22 (1.5)	0.023
Mixed	1,065 (2.5)	34 (2.4)	0.777
Past obstetric history			
Nulliparous	21,731 (51.3)	873 (60.5)	<0.0001
Parous with no prior PE and SGA	18,101 (42.7)	313 (21.7)	<0.0001
Parous with prior PE no SGA	1,015 (2.4)	176 (12.2)	<0.0001
Parous with prior SGA no PE	1,398 (3.3)	42 (2.9)	0.464
Parous with prior PE and SGA	142 (0.3)	38 (2.6)	<0.0001
Interpregnancy interval, months	29.1 (17.4–46.7)	33.5 (18.6–61.7)	<0.0001
Cigarette smoker	4,157 (9.8)	101 (7.0)	0.0005
Patients' mother had PE	1,659 (3.9)	112 (7.8)	<0.0001
Conception			
Spontaneous	41,020 (96.8)	1,364 (94.6)	<0.0001
Ovulation drugs	435 (1.0)	20 (1.4)	0.231
In vitro fertilisation	932 (2.2)	58 (4.0)	<0.0001
Chronic hypertension	473 (1.1)	182 (12.6)	<0.0001
No medication	229 (0.5)	75 (5.2)	<0.0001
Medication	244 (0.6)	107 (7.4)	<0.0001
Pre-existing diabetes mellitus	253 (0.6)	33 (2.3)	<0.0001
Type 1	117 (0.3)	14 (1.0)	<0.0001
Type 2	136 (0.3)	19 (1.3)	<0.0001
Systemic lupus erythematosus/APS	79 (0.2)	10 (0.7)	<0.0001
Gestation at delivery, weeks	40.1 (39.1–40.9)	38.5 (36.5–40.0)	<0.0001
Birth weight, g	3,400 (3,111–3,685)	2,968 (2,293–3,420)	<0.0001
Birth weight centile	46.7 (25.3–69.8)	26.7 (7.1–61.9)	<0.0001

Values represent medians (interquartile range) or n (%). Significance set at $p < 0.05$. APS = Antiphospholipid syndrome.

amongst the maternal characteristics and gestation were significant predictors of the $\log_{10}$ uterine artery PI, adjusting for the adverse pregnancy outcomes as specified (PE, gestational hypertension, SGA and large for gestational age). Variables were not considered to be significant predictors if the p value was >0.05 or if the ratio of the regression coefficients to the SD of the uterine artery PI $\log_{10}$ MoM was less than 0.1. Gestational age at screening was centred by subtracting 22 weeks, maternal weight was centred by subtracting 70 kg and maternal height was centred by subtracting 165 cm. The distribution of $\log_{10}$ uterine artery PI was then expressed as MoM in all cases, correcting for the significant predictors as defined in the multiple regression. Linear regression analysis was used to determine the significance of association between uterine artery PI $\log_{10}$ MoM with gestational age at delivery and birth weight Z-score in the cases of PE. The proportions of SGA in cases of PE with uterine artery PI MoM above the 90th and 95th percentiles were determined.

The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM, Armonk, N.Y., USA) was used for the data analyses.

Results

The characteristics of the study population are presented in table 1. In the PE group, compared to the normal group, there was a higher median maternal age and

Table 2. Fitted regression model for $\log_{10}$ uterine artery PI at 20–24 weeks

Coefficient	Estimate	Standard error	LCL	UCL	p
Intercept	0.0126703	0.00063842	0.011419	0.013922	<0.0001
(GA – 22 weeks)	–0.013572	0.00055559	–0.014661	–0.012483	<0.0001
Racial origin					
Afro-Caribbean	0.013824	0.0012790	0.011318	0.016331	<0.0001
South Asian	–0.011404	0.0023909	–0.016091	–0.0067181	<0.0001
East Asian	–0.014171	0.0032668	–0.020574	–0.0077678	<0.0001
Past obstetric history					
Parous – previous SGA no PE	0.0078398	0.0027477	0.0024542	0.013225	0.004
Parous – previous PE no SGA	0.015575	0.0029777	0.0097385	0.021411	<0.0001
Parous – previous PE and SGA	0.042149	0.0073388	0.027765	0.056533	<0.0001

GA = Gestational age; LCL = lower confidence limit; UCL = upper confidence limit.

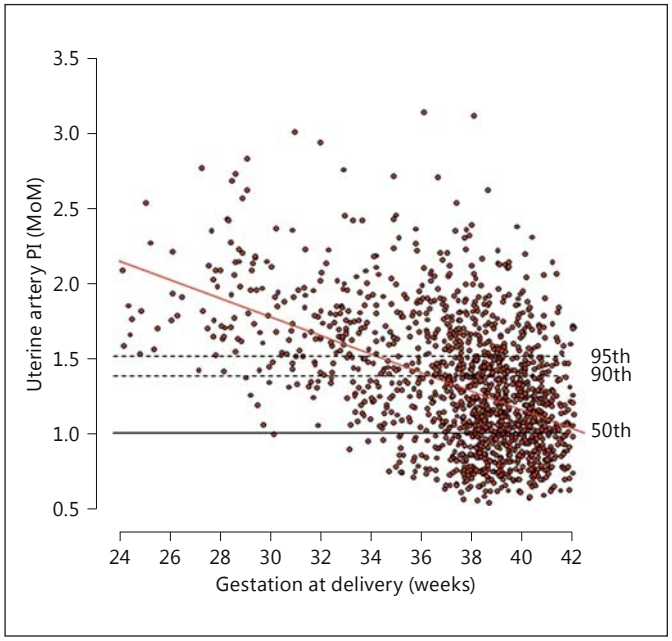

Fig. 1. Relationship between gestational age at delivery and mean uterine artery PI MoM in women who developed PE. The three horizontal lines represent the 50th, 90th and 95th percentiles of mean uterine artery PI MoM.

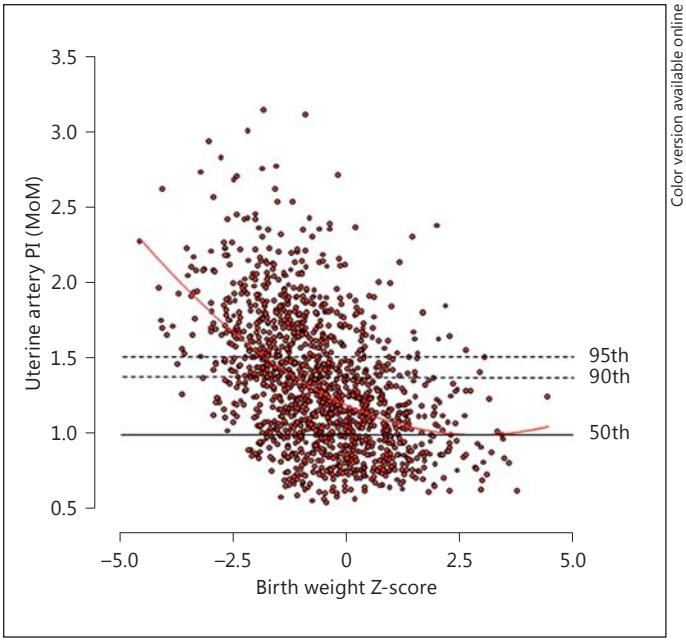

Fig. 2. Relationship between birth weight Z-score and mean uterine artery PI MoM in women who developed PE. The three horizontal lines represent the 50th, 90th and 95th percentiles of mean uterine artery PI MoM.

weight; a longer interpregnancy interval; a higher prevalence of Afro-Caribbean racial origin, personal history of PE with and without associated SGA, family history of PE, women who conceived with in vitro fertilisation, history of chronic hypertension, pre-existing diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome; a lower maternal height, and a lower prevalence of East-Asian racial origin and smokers. The median gestational age at delivery and neonatal birth weight were significantly lower in the PE group than in the normal group.

Multiple regression analysis demonstrated that for the prediction of the mean $\log_{10}$ uterine artery PI, significant independent contributions were provided by

Table 3. Fitted regression model for $\log_{10}$ MoM uterine artery PI at 20–24 weeks' gestation at the time of delivery and neonatal birth weight Z-score for pregnancies with PE

	Coefficient	Standard error	LCL	UCL	p
Intercept	0.60035	0.039084	0.52368	0.67701	<0.0001
Gestational age at delivery	–0.014080	0.0010196	–0.016080	–0.012080	<0.0001
Neonatal birth weight Z-score	–0.036278	0.0026150	–0.041408	–0.031149	<0.0001

LCL = Lower confidence limit; UCL = upper confidence limit.

Table 4. Mean uterine artery PI MoM above the 90th and 95th percentiles in women who subsequently developed PE with or without associated SGA according to gestational age (GA) at delivery

GA, weeks	Total PE					PE with SGA				
	Total, n	Uterine artery PI MoM >90th percentile		Uterine artery PI MoM >95th percentile		Total, n	Uterine artery PI MoM >90th percentile		Uterine artery PI MoM >95th percentile	
		n	% (95% CI)	n	% (95% CI)		n	% (95% CI)	n	% (95% CI)
24–25	11	11	100.0 (74.1–100.0)	11	100.0 (74.1–100.0)	7	7	100.0 (64.6–100.0)	7	100.0 (64.6–100.0)
26–27	17	17	100.0 (81.6–100.0)	15	88.2 (65.7–96.7)	9	9	100.0 (70.1–100.0)	8	88.9 (56.5–98.0)
28–29	44	40	90.9 (78.8–96.4)	38	86.4 (73.3–93.6)	29	27	93.1 (78.0–98.1)	26	89.7 (73.6–96.4)
30–31	46	36	78.3 (64.4–87.7)	27	58.7 (44.3–71.7)	17	16	94.1 (73.0–99.0)	11	64.7 (41.3–82.7)
32–33	87	69	79.3 (69.6–86.5)	58	66.7 (56.2–75.7)	34	29	85.3 (69.9–93.6)	25	73.5 (56.9–85.4)
34–35	118	64	54.2 (45.3–63.0)	47	39.8 (31.5–48.8)	41	31	75.6 (60.7–86.2)	25	61.0 (45.7–74.3)
36–37	261	116	44.4 (38.5–50.5)	90	34.5 (29.0–40.4)	67	47	70.1 (58.3–79.8)	35	52.2 (40.5–63.7)
38–39	508	143	28.1 (24.4–32.2)	84	16.5 (13.6–20.0)	63	40	63.5 (51.1–74.3)	25	39.7 (28.5–52.0)
≥40	350	73	20.9 (16.9–25.4)	44	12.6 (9.5–16.5)	28	13	46.4 (29.5–64.2)	9	32.1 (17.9–50.7)
Total	1,442	569	39.5 (37.0–42.1)	414	28.7 (26.4–31.3)	295	219	74.2 (69.0–78.9)	171	58.0 (52.3–63.5)

gestational age at screening, racial origin (Afro-Caribbean, South Asian and East Asian) and prior history of PE and/or SGA (R^2 = 0.050; table 2), but not maternal weight (p = 0.106), height (p = 0.218), age (p = 0.277), method of conception (p = 0.973), chronic hypertension (p = 0.644), pre-existing diabetes mellitus (p = 0.854) and systemic lupus erythematosus or antiphospholipid syndrome (p = 0.106) due to insignificant p values, and smoking and family history of PE as the ratio of the regression coefficients to the SD of the uterine artery PI $\log_{10}$ MoM was less than 0.1.

In the PE group, there was an inverse significant association between the uterine artery PI $\log_{10}$ MoM and gestational age at delivery (r = −0.458, p < 0.0001; fig. 1) and between the uterine artery PI $\log_{10}$ MoM and neonatal birth weight Z-score (r = −0.473, p < 0.0001; fig. 2). Multiple regression analysis demonstrated significant independent contributions from both gestational age at delivery and neonatal birth weight Z-score in cases of PE (r = –0.550; table 3).

In 295 (20.5%, 95% CI: 18.5–22.6) of the 1,442 cases of PE, there was SGA and the incidence of SGA was inversely related to the gestational age at delivery decreasing from 46.8% (95% CI: 40.1–53.7) before 34 weeks to 28.5% (95% CI: 24.2–33.2) at 34–37 weeks and 10.6% (95% CI: 8.7–12.8) at or after 38 weeks.

The median, 90th and 95th percentiles of uterine artery PI MoM were 0.996, 1.377 and 1.509, respectively. The uterine artery PI MoM was above the 95th percentile in 72.7% (95% CI: 66.2–78.3) of women who developed PE requiring delivery before 34 weeks, in 36.1% (95% CI: 31.5–41.1) of those delivering at 34–37 weeks and in 14.9% (95% CI: 12.7–17.5) of those delivering at or after 38 weeks (table 4; fig. 3). The respective percentages for PE with SGA were 80.2% (95% CI: 71.1–86.9), 55.6% (95% CI: 46.2–64.6) and 37.4% (95% CI: 28.1–47.6), and 66.1% (95% CI: 56.8–74.3), 28.4% (95% CI: 23.4–34.1) and 12.3% (95% CI: 10.1–14.8) for PE without SGA.

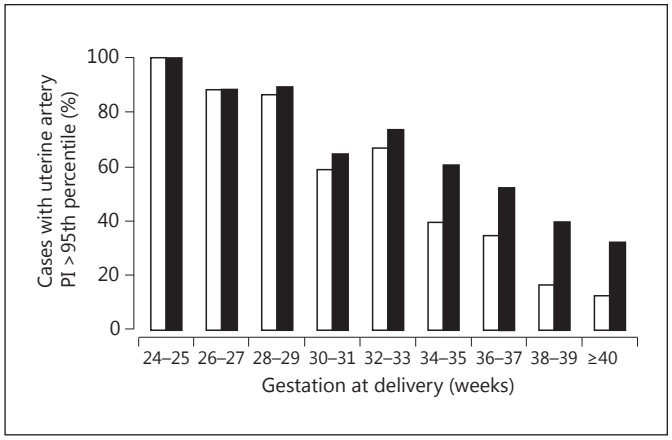

Fig. 3. Percentage of pregnancies that developed PE with mean uterine artery PI MoM above the 95th percentile according to gestational age at delivery. The white histograms are for all cases of PE and the black ones are for PE with delivery of SGA neonates.

Discussion

The findings of this study demonstrate that in normal singleton pregnancies at 20–24 weeks' gestation, uterine artery PI decreases with gestational age, is higher in women of Afro-Caribbean racial origin than in Caucasians, is decreased in South and East Asians, and is increased in multiparous women who developed PE and/or delivered SGA neonates in previous pregnancies. Consequently, adjustments should be made for these maternal characteristics before valid comparisons can be carried out between normal and pathological pregnancies.

In women who develop PE, uterine artery PI at 20–24 weeks' gestation is increased and the increase is particularly marked in those with early PE and in PE with SGA. The uterine artery PI MoM was above the 95th percentile in about 73, 36 and 15% of PE cases requiring delivery at <34, 34–37 and ≥38 weeks, respectively. The percentages for PE with SGA were 80, 56 and 37%, and for PE without SGA the percentages were 66, 28 and 12%. These findings are compatible with the results of previous Doppler studies [7–11, 16] and pathological studies which reported that the prevalence of placental lesions in women with PE is inversely related to the gestational age at delivery [17–19]. The findings are also important in relation to the objectives of screening because there is evolving evidence that the incidence of adverse fetal and maternal short-term and long-term consequences of PE is inversely related to the gestational age at onset of the disease [20–22]. Consequently, the endpoint in screening for PE should not be total disease but rather severe disease, reflected in the need for early delivery and the association with fetal growth restriction.

In our initial studies aiming to capture this gestational age-related severity of disease, we subdivided the condition into early PE and late PE. However, such subdivision could lead to the erroneous conclusion that early PE and late PE are different diseases with different biomarker profiles. As demonstrated by the MoM values of uterine artery PI in pregnancies with PE, the distribution with gestational age is not bimodal. Consequently, PE could be considered as 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. We have therefore proposed a new approach in screening for PE that is based on a survival time model, and the gestation at the time of delivery for PE is treated as a continuous rather than a categorical variable [7, 8]. We are now developing a model in which both the gestation at delivery and the coincidence with SGA are treated as a categorical variable.

The current approach to prenatal care, which involves visits at 16, 24, 28, 30, 32, 34 and 36 weeks' gestation and then weekly until delivery, was established more than 80 years ago [23]. The high concentration of visits in the third trimester implies that (1) most complications occur at this late stage of pregnancy and (2) most adverse outcomes are unpredictable during the first or the second trimester. Extensive research in the last 20 years has shown that many pregnancy complications, including PE, can now be predicted at an integrated first hospital visit at 11–13 weeks combining data from maternal characteristics and history with findings of biophysical and biochemical tests. It is therefore proposed that the traditional pyramid of care should be inverted with the main emphasis placed in the first rather than the third trimester of pregnancy [24]. Early estimation of patient-specific risks for pregnancy complications would improve pregnancy outcome by shifting prenatal care from a series of routine visits to a more individualized patient and disease-specific approach both in terms of the schedule and content of such visits.

The value of early screening for PE is derived from the evidence that the prophylactic use of low-dose aspirin can result in a major reduction in the prevalence of preterm PE and the associated perinatal mortality, provided the onset of treatment is before rather than after 16 weeks' gestation [25–27]. In the context of the new pyramid of pregnancy care [24], the value of a clinic at 20–24 weeks is to modify the individual patient and disease-specific

estimated risk from the initial assessment at 11–13 weeks and to provide risks for those women who did not have prior screening. In the high-risk group, intensive maternal monitoring for earlier diagnosis of PE and fetal growth restriction could improve outcome by selecting the best time and place for delivery. At present there is no useful pharmacological intervention after 16 weeks that can reduce the prevalence or modify the severity of the disease, but identification of the high-risk group would form the basis of future research that could achieve these objectives.

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